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Hereditary Stochastic Hybrid Systems

Application to *E. coli* Movement

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Hereditary Stochastic Hybrid Systems

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Ph.D Thesis

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Abstract

A stochastic hybrid system (SHS) is a dynamic system that exhibits both a continuous and a discrete dynamical behavior. In the scientific literature on SHS the principle of causality is commonly assumed, but more realistic models should account on history dependence. In this thesis we developed and analyze a new mathematical model called Hereditary Stochastic Hybrid System which, with the help of a generalization of stochastic time change, allows for general history dependence. We apply the above model to the study of the movement of the bacterium E. coli: when these bacteria swim in a field of chemoattractant molecules, they perform a random walk characterized by a run-and-tumble motion. This random walk is biased towards regions of higher concentration of the chemoattractant. These bacteria are, however too small to sense spatial gradients along their body axis. Instead they developed a history-dependent strategy to search of food, namely the use of memory of previous measurements of chemical concentrations. In this way the bacteria are able to infer whether they swim up or down a chemical gradient. By using our framework we are able to generalize the existing models for E. coli movement and have a better fitting of the experimental data. We developed also a software that simulates and compares the different models existing in the literature, with special care for high performance and usability.

Zusammenfassung

Ein stochastisches Hybrid-System (SHS) ist ein dynamisches System, welches sowohl kontinuierliches als auch diskretes dynamischen Verhalten zeigt. In der wissenschaftlichen Literatur zu SHS wird allgemein das Prinzip der Kausalität angenommen, aber realistischere Modelle sollten auch eine Abhängigkeit von längeren vorhergehenden Zeitsegmenten einbeziehen. In dieser Arbeit wird ein neues mathematisches Modell entwickelt und analysiert, welches wir hereditäres stochastisches Hybrid-System nennen. Dieses erlaubt durch eine Generalisierung der stochastischen Zeitdynamik eine allgemeine Abhängigkeit von der Vergangenheit des Systems. Mit Hilfe dieses Modells beschreiben wir den Bewegungsprozess von E. coli Bakterien. Diese bewegen sich in einer Lösung chemischer Lockstoffe in Form eines Random Walks, welcher einen Bias in Richtung höherer chemischer Konzentrationen des Lockstoffs aufweist. Da E. coli Bakterien zu klein sind, um räumliche Gradienten entlang des Zellkörpers wahrzunehmen, entwickelten sie eine Gedächtnis-basierte Strategie für die Nahrungssuche. Dafür wird in einem intrazellulären Signalpfad, der auch das Bewegungsverhalten steuert, die Lockstoffkonzentration früherer Zeitschritte gespeichert. Durch den Vergleich der derzeitigen zur vorherigen Konzentration können die Bakterien nun entscheiden, ob sie entlang oder entgegen eines Gradienten schwimmen. Mit Hilfe unseres Modells können wir bestehende Modelle für die Bewegung von E. coli Bakterien verallgemeinern, und eine bessere übereinstimmung mit experimentellen Daten erreichen. Desweiteren entwickelten wir eine Software die die verschiedenen Bewegungsmodelle simuliert und vergleicht, mit besonderem Fokus auf hohe Effizienz und Benutzerfreundlichkeit.

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I would like to express my gratitude towards professors W. Jäger, V. Capasso and F. Matthäus, especially for their advice, patientce and encouragement throughout my research. I am especially thankful to professor F. Matthäus for the great deal of freedom I have been allowed in the choice of the methods to investigate the research topic. The same goes for professor V. Capasso, whom I would like to thank for his advice and sharing with me his encyclopaedic knowledge and experience, for is valuable references to existing contributions and to relevant literature. Professor Jäger has been a tremendous mentor for me. I would like to thank him for encouraging my research and for allowing me to grow as a research scientist. His advice on both research as well as on my career have been priceless. I can not omit to thank the secretaries of professor Jäger, Ina Scheid and Gabriele Schocke, and Dorothea Heukäufer of the Dekanat of Mathematic and Informatics who always helped me with the bureaucratic jungle. I would also like to thank all of my friends who supported me in writing, and incented me to strive towards my goal

Warm thanks to my family. The one I left behind in Italy, who has been supporting me throughout my life in general without asking anything in return and is still doing so. The family I found and founded in Germany: my wife Жанна and my daughter Emilia, who have been constantly a reason to keep going on. Words cannot express how grateful I am for their patience and their encouragement ... to all of them.

Contents

List of Symbols & Abbreviations

Symbol		Description
I	.....	The interval [-r,0]
I^0	.....	The interval [-r,0)
D^N	.....	Malliavin derivative of order N
$\nabla_{F,g}^{[t-r\mapsto t]} c_t$	.....	Temporal gradient
$\mathbf{W}_E(t)$	.....	Wiener Process with value in E
x_t	.....	Segment process
$\overline{\sum}$	.....	Sum on the sphere
$\mathcal{S}^{d-1}$	.....	d-dimensional sphere
$c(t,x)$	.....	Chemical concentration of chemoattractant
$\mathcal{A}^\Lambda$	.....	Infinitesimal generator for the process Λ
$\mathcal{N}(t)$	.....	Integer valued cádlág process
$\mathcal{N}_\nu(t)$	.....	Fractional poisson process with index ν
$\mathcal{N}_1(t) := \mathcal{N}(t)$	.....	Poisson process
$\mathbf{E}[\cdot]$	.....	Mathematical expectation
$\mathbf{E}[\cdot\|\mathcal{G}]$	.....	Conditional expectation with respect to $\mathcal{G}$
$\mathbb{P}[\cdot\|\mathcal{G}]$	.....	Conditional probability with respect to $\mathcal{G}$
$\delta(u)$	.....	Skorohod integral of u
$S\phi(\eta)$	.....	Shift operator
$\mathscr{C}$	.....	Segment operator
A^*	.....	Adjoint of the operator A
H	.....	Hilbert space
$\mathbb{D}^{N,p}$	.....	Malliavin-Sobolev Space
$\mathbf{1}_A$	.....	Indicator of the set A
$\mathcal{D}_t$	.....	Dupin-Comt-Fournier vertical derivative
∇_x	.....	Gradient in $\mathbb{R}^d$
$\nabla_x^{\mathcal{D}}$	.....	Dupin-Comt-Fournier horizontal derivative
$\Phi(z)$	.....	Cumulative distribution of a normal random variable
ϵ_A	.....	Dirac measure of the set A
$\mathcal{M}_I$	.....	Internal state infinitesimal generator
	.....	Memory map
*	.....	Stochastic memory map
$\mathcal{B}(A)$	.....	Borel σ-algebra for the set A
$\mathcal{L}_{\mathscr{C}}$	.....	Space of bounded linear functionals

$\mathcal{B}_{\mathscr{C}}$	.....	Space of bounded bilinear functionals
$\mathcal{D}(A)$	.....	Domain of the operator A
$\mathcal{M}(t)$	.....	Martingale
$\mathscr{C}(A,B)$	.....	Continuous functions from set A valued in set B
$\mathscr{D}(A,B)$	.....	Cádlág functions from set A valued in set B
[G.R. $x.y.z$]	.....	Formula $x.y.z$ from [58]
$\mathbf{M}_W^p[\alpha,\beta]$	.....	L^p space between the stopping time α and β

Acronyms		**Meaning**
CTRW	.....	Continuous Time Random Walk
PDMP	.....	Piecewise Deterministic Markov Process
SFDE	.....	Stochastic Functional Differential Equation
SHS	.....	Stochastic Hybrid System
HSHS	.....	Hereditary Stochastic Hybrid System
HSHSEcoli	.....	Hereditary Stochastic Hybrid System For *E. coli*
LW	.....	Lévy Walk
RV	.....	Random Variable
BW	.....	Brownian Motion
PP	.....	Poisson Process
FPP	.....	Fractional Poisson Process
cádlág	.....	French *continue á droite, limite á gauche*, see RCLL
RCLL	.....	right continuous with left limits

INTRODUCTION

***E. coli* and Chemotaxis.** Micro-organisms that live in liquids have developed several strategies to explore their environment in order to find regions that are more favorable for their development. One of the most studied organisms, in this respect, is the *petrichously flagellated bacterium Escherichia coli* (*E. coli*), a bacterium with flagella that can be grown easily and inexpensively in a laboratory setting, and has been intensively investigated for over 60 years.

The 4-8 flagella of *E. coli* are distributed over the entire cell surface. Each one of the flagella is anchored to a motor, which can rotate counterclockwise (CCW) or clockwise (CW). When all the flagella rotate CCW, they form a flagellar bundle and the bacterium is pushed forward in an almost straight line with a characteristic speed $u \sim 16 - 30\frac{\mu m}{s}$. This phase of the motion is called *run*, and it is interrupted when at least one flagellum rotates CW. In this phase, called *tumble*, the bundle unravels, the bacterium stops and starts to reorientate its swimming direction: the average duration of a *tumbling* is approximately 0.1 s [45]. *E. coli*, to survive, searches for nutrients in space by maintaining a remarkable system of biochemical reactions inside the cell, called the chemotaxis-signaling pathway. Chemotaxis allows each bacterium to move toward the nutrient and to avoid poisonous substances with great precision, and it is robust against external and internal fluctuations [87].

In the last 40 years, bacterial chemotaxis has been an area of increasing interest to both experimentalists and theoreticians. This interest has been stoked by ever-increasing experimental insight into the behavior of bacteria, both on the population and individual scale, coupled with insight provided by new and more detailed mathematical models, at various scales. The fundamental challenges today are in seeking to provide an appropriate description on the macro-scale population level while accounting for variation of specific characteristics amongst individual cells.

The *E. coli* bacterium belongs to the species that are unable to sense spatial chemoattractant gradients reliably due to their small size. In evolution therefore it has then developed a history-dependent strategy for food searching, mainly based on the use of memories of previous chemical concentrations. As reported by Brown, the question of whether cells respond to spatial or temporal stimuli had been considered earlier in a simpler way by [82]. These experiments showed that *E. coli* senses temporal stimuli. In this way the bacterium is able to infer whether the swimming is done up or down a chemical gradient [106]
In the presence of chemoattractants, the duration of the runs is modulated by a chemotactic

pathway. The chemotaxis signaling pathway of *E. coli* has been extensively studied and modeled on various levels of microscopic detail. The first attempt to quantitatively model the chemotaxis signaling pathway was the two-state model by Asakura and Honda [4], which was later extended and improved several times leading to the identification of an optimal reaction network, which satisfies the requirements of robustness and adaptivity.
Although the chemotaxis signaling network has a relatively simple topology, when it comes to the study and simulation of a great number of cells computation becomes demanding. It is convenient and necessary to describe the chemotaxis signaling pathway via a cartoon model that captures the essential structure of the dynamics of the run-and-tumble strategy [2, 22, 45]. In this way it is possible to derive macroscopic equations for the dynamics of the bacterial density.
Understanding the behavior of chemotactic bacterial populations is interesting for a number of reasons. While bacteria behave independently, populations exhibit a collective behavior. In the natural environment, bacterial populations are generally found to exist in the form of biofilms which can have substantial impact upon industry and medicine [35]. Hence, understanding the comparative importance of mechanisms which affect and cause the observed behavior within bacterial populations, for example chemotaxis and diffusion, would greatly facilitate in the prediction of bacterial behavior in the natural environment. To this aim continuum models (particularly early models of bacterial populations) have generally used the Keller-Segel model of chemotaxis, originally devised by Keller and Segel [70, 71] in modeling the movement of slime molds.

Brief Review of the Existing Literature. A growing number of approaches have been taken in modeling and understanding the impact that microscopic (individual) behavior has on the macro-scale (population) level.
The derivation of a stochastic description, incorporating individual cell behavior, was the focus of work by Alt [2]. Alt undertook asymptotic analysis of the governing equations and considered small limits of certain parameters affecting run lengths and turn angles of the bacteria. It is interesting to notice that this model differs substantially from the others presented in the literature since the distribution of runs is not exponentially distributed: the probability rate to tumble for an individual running in a specific direction depends on the chemical ligand as well as on the run time, counted from the beginning of the run. Recently, two further pieces of work (De Gennes [39], Clark, Damon A., and Lars C. Grant [28]) have considered the effect that internal delays within the intracellular signaling cascade have on the bacterial response. De Gennes [39] considered the motion of a single bacterium during one run, i.e. a counter-clockwise (CCW) rotation of its flagella, and related the response function (the receptor to motor response) describing the bacterial movement to the macroscopic scale chemotactic coefficient.
Other recent work on developing multi-scale models of bacterial chemotaxis using equation-free methods has been undertaken by Setayeshgar et al. [13, 113] and Erban and Othmer [45]. Bialek, William, and Sima Setayeshgar [13] describe the microscopic behavior of a single bacterium using a system of ordinary differential equations for the internal state variables of the bacterium describing for instance, the pathway molecule concentration. Applying this theory, Setayeshgar et al. [113] propose a simplified model of excitation and adaptation.
Erban and Othmer [45] incorporated the above microscopic description into a macroscopic

description of bacterial chemotaxis as defined by the telegraph process. The turning rates were assumed to depend on the concentration of CheYP. By use of appropriate scalings and moment closure techniques, they derive both a hyperbolic system of equations and the classical parabolic Keller-Segel description of chemotaxis. Expressions for the form of the chemotactic coefficient in terms of individual state variables are derived.
Vergassola and Celani [22] exploited the regularity of some kernel function for the memory of the bacteria to derive refined macroscopic equations for the population dynamics. This model was generalized a year later in collaboration with T. S. Shimizu [21]. This work is of fundamental importance and can be pointed as a great synthesis of years of studying: it can be considered as a generalization of [22] and [126]: they propose that *E. coli* adopts the strategy called minimax, i.e. a decision rule used for minimizing the possible loss for a worst case (maximum loss) scenario, against the environment. They show that this optimization principle provides a systematic possibility to get around the need to know precisely the statistics of environmental fluctuations.

Hypotheses. In all the literature we have consulted about *E.coli* models the run phase follows an exponential distribution. By considering the data in [12] we noticed that the mean and the variance of the distribution of the runs are incompatible with respect to an exponentially distributed random variable. We can still use exponentially distributed random variables as a first approximation: they will, though, underestimate the variance of the distribution of the runs. There are, however, lots of reason why one might keep using such a distribution and why it is so popular in the literature: first of all, the memoryless property which simplifies the Kolmogorov equation related to the stochastic process that describes the bacterial movement. In this case the tumble and run events are generated by a Poisson process. In the present work we propose a microscopic description of the dynamics of the bacterium via a subordinated diffusion process, which models the internal state of the bacterium: this allows to weaken the assumption that the bacterial tumbling process obeys a Poisson distribution. The core of the thesis is the description of a new mathematical model which generalizes a great number of published models mentioned in this introduction. We call this model Hereditary Stochastic Hybrid System (HSHS). We consider the bacterium as a system which can switch between two discrete states, namely *running* and *tumbling*, and we force the jumping from one state to the other via appropriate hitting times of a stochastic process. In this sense it is an extension of the theory of stochastic hybrid systems (SHS) [63], into which we introduce functional (hereditary) dependency in the controlling dynamics. It represents a bridge between SHS of the theory of stochastic differential equations with Markovian switching [84].
The model makes use of the theory of subordinated diffusion processes to model the internal state of the system. With this approach we weaken the assumption that the probability distribution to switch between different states follows an exponential distribution.

The second model (*One-Point Memory Model*) that we propose is a generalization of the work of Stroock [119]: in the framework of Piecewise Deterministic Markov Processes (PDMP) [36] we allow a weak dependence of the turning rate with respect to the level of chemoattractant measured at the beginning of the run.

The last model (*Moderately Interacting Particles Model*) exploits the theory of moderately interacting multi-particle systems [97, 98, 92, 38, 115]. We introduce functional dependences in the governing equations and undertake heuristic analysis.

Additionally we develop a software written in C++ to simulate and analyze data relative to the movement of *E. coli* with the following characteristics:

i) platform independent;

ii) fast to perform simulation, visualization and statistical analysis of the data;

iii) implementation of different models in the literature to easily compare them;

iv) freedom to set a great number of parameters;

v) versatile to include easily and with minimum effort new models.

Results and Contributions. The results and new contributions of this thesis are the following:

- the study of *E. coli* movement leads to the structure of a dynamical system that goes behind the mere application to bacteria movement and chemotaxis. In this sense:
  - we propose a new mathematical model which generalizes HHS [19], velocity-jump models [45] including functional dependency in the coefficient of the leading equations;
  - we generalize the Feynman-Kac formula for SFDE in [130] and study the exit-time distribution for SFDE from a bounded domain;
- we apply the general framework to the special case of *E. coli* movement.
  - we generalize the large-scale approximation of generalized velocity-jump models [122], considering that between two tumble events, the direction of the bacterium follows a Brownian motion on the sphere;
  - we study and conjecture a new limit theorem for moderately interacting particles in presence of a memory term;
  - we develop a portable and easy-to-use software to compare and analyze existing models for the dynamics of *E. coli*.

Overview of the thesis

The **first part** of the thesis is devoted to the biology of the microorganism *E. coli*, by reviewing the approaches that have already been taken to model the *E. coli* movement and introducing the mathematical model *Hereditary Hybrid Stochastic System* as well as the *One-Point Memory Model* and *Moderately Interacting Particle Model*.

In **Chapter 1: Biological Background**, we start with the physical and biological description of the bacterium *E. coli*. In **Section 1.1** we set the problem of *gradient sensing*;

Section 1.2 deals with the signaling pathway that controls the communication between the receptors and the flagellar motors, and **Section 1.3: Memory and Signaling Pathway** is devoted to describe the connection between temporal gradient and signaling pathway.

In **Chapter 2: Hereditary Hybrid Stochastic Model** we introduce, develop and analyze the mathematical model Hereditary Hybrid Stochastic System. In **Section 2.2** we give the formal definition of the model: the system is characterized by two components. The discrete component can have values in a discrete set (at most numerable). The jump between the discrete states is described via a given probability kernel. The continuous component evolves following a system of stochastic functional differential equations (SFDE). The moment in which the system jumps to a new state is given by an appropriate stopping time depending on the state of the system as well as on its configuration during a temporal window in the past. **Section 2.3** focuses on the analysis of the basic properties of the model: we investigate under which hypotheses the system HSHS has a unique well defined solution, study the regularity of the solution with respect to the initial conditions and examine in which sense we may speak of the Markov property for this system with memory. In **Section 2.4.2** we investigate the probabilistic properties of the duration of the time spent by the system in a given state: we study the associated martingale problem, generalize the Feynman-Kac representation problem for SFDE [130] and the related exit time distributions from a bounded domain.

In **Chapter 3: Mathematical Model for *E. coli*,** we apply the model developed in Chapter 2 to study the *E. coli* motion. We first briefly review three fundamental papers [119, 2, 22] that have stimulated the present work, and then focus on describing the application of the model HSHS to the case of the *E. coli* movement. In **Section 3.3** we have a closer look at the hypothesis that the distribution of runs follows an exponential distribution: by studying the confidence intervals of the involved distributions, we motivate our approach to use a more general distribution. The following **Section 3.4** deals with the study of the macroscale limit of the model in case the environment is constant in space and time and extends the results obtained in [56]. In **Section 3.5** we specialize the general model to the memory kernel derived in [21] and [22]: we study the generalized Fokker-Plank equation for the model on a line and the general formulation with non-zero tumbling time [6]. We consider an approximating set of equations for the general model and conjecture the form of the macroscopic equation for the dynamics of the bacterial density at scales larger than the length of a single run.

In **Chapter 4** various simplifications of the models are considered. In **Section 4.1** we present a scheme that links HSHS to existing literature, showing that it generalizes many existing models and find the connection between them: we find that the underlying structure refers to the theory of *random time change processes* and briefly recall it. In **Section 4.2** we consider a random time change performed via a functional of the Brownian motion and link HSHS to the theory of Fractional Poisson processes and Lévy Walks [8, 123]. **Section 4.3** deals with Stochastic Hybrid Systems, while **Section 4.4** offers an overview of *Poisson Time Change*: in this context we show that HSHS generalizes the classical *Velocity-Jump process* [102, 45, 128] as well as the process described in [22].

In **Chapter 5** we introduce a new model called *One-Point Memory Model*: the bacterium follows a *run and tumble* random walk in which the duration of a tumble is negligible and the time spent swimming along a given direction follows an exponential distribution, whose parameter depends on the difference of the current ligand concentration and the one recorded at the beginning of a current run. **Section 5.1** deals with the standard PDMP setting, where the new direction (selected instantaneously during a *tumble*) is selected from an at most countable set of values: we investigate its infinitesimal generator and propose a related process to study the performance of the model. In **Section 5.2** we generalize the content of the previous chapter to the case of a continuous range of values for the direction and study the parabolic limit in distribution of the rescaled process.

In the **second part** of the thesis, we concentrate on the simulation of the model described in the **first part**. We describe the software **E.coli_Simulator** written to simulate, compare and analyze the models presented in the literature and the ones proposed in this work.

Chapter 6 is devoted to computer simulation of the model using methods of non-parametric estimation to derive the density distribution of the population. We performed simulations for different landscapes of the ligand concentrations. In **Chapter 7** we give a detailed description of the software we have developed: the requirements, mode of use, structure and outputs.

Chapter 8 we summarize the results of the thesis and in **Section 8.2** we propose a new model which takes inspiration from the theory of moderately interacting multi-particle systems [97, 98, 92, 38, 115]. We introduce functional dependence in the governing equations and undertake a heuristic analysis. The functional calculus in this section follows the approach in [32].

The **third part** contains **Appendix A: Probabilistic Zibaldone,** where we provide the reader with the definitions needed to formulate the problem, as well as some results from the literature we need throughout the text, and **Appendix B**, where we present in detail the paper [22].

Part I

Mathematical Models

Chapter 1

BIOLOGICAL BACKGROUND

This chapter gives a brief introduction to the biological background of the present thesis, with particular attention to the meaning of temporal gradient and memory in the context of the the random walk performed by *E. coli*.

1.1 The bacterium *Escherichia coli*

Escherichia coli (*E. coli*), originally known as *bacterium coli commune*, was identified in 1885 by the German pediatrician, Theodor Escherich [46]. *E. coli* is a member of the family Enterobacteriaceae [49], which includes many genera, such as the known pathogens *Salmonella*, *Shigella*, and *Yersinia* [52]. *E. coli* is a gram-negative, rod-shaped bacterium propelled by long, rapidly rotating flagella. It is part of the normal flora of the mouth and gut and helps protect the intestinal tract from bacterial infection, aids in digestion, and produces small amounts of vitamins B12 and K [80].The bacterium, which is also found in soil and water, is widely used in laboratory research and is often referred to as the best or most-studied free-living organism [44].

As we may read in [11], "[if you happen to look] through a microscope at a suspension of cells of motile *E. coli*, [you might be impressed] by the intense activity. Nearly every organism moves at speeds of order 10 body lengths per second. [A cell swims in a direction roughly parallel to its body axis for more or less a second], moves erratically for a small fraction of a second, reorienting itself, and then swims steadily again in a different direction. [...]. A few just seem to fidget". Although the movement appears as a random walk, or better a random swim, we can observe that the environment influences the behavior of the bacterium. More precisely, when a nutrient or a chemorepellent are added to the liquid, *E. coli* bacteria bias their motion towards high nutrient concentrations and away from regions where the chemorepellent concentration is high. In this case we talk about *bacterial chemotaxis*, i.e. the ability of bacteria to sense changes in their extracellular environment and to bias their motility towards favorable stimuli (attractants) and away from unfavorable stimuli (repellents).

A typical *E. coli* cell is propelled by a bundle composed of multiple flagella which are located at random points on the bacterial membrane. Each flagellum is controlled by a rotary motor that can switch between clockwise (CW) and counter-clockwise (CCW) rotation.

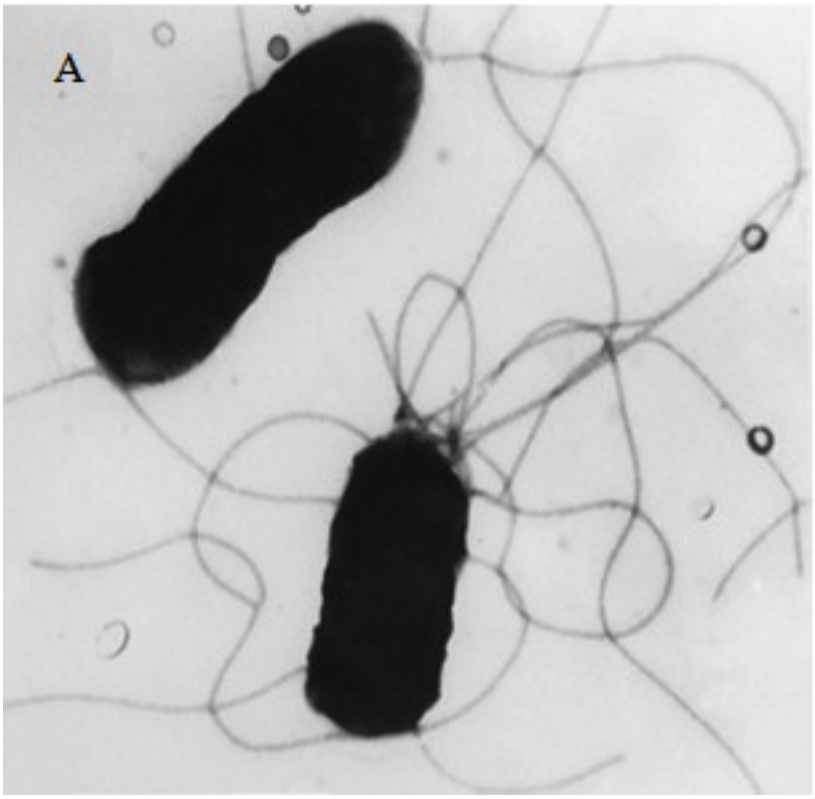


Figure 1.1: The polar flagella of *E. coli* viewed by transmission electron microscopy. (B) A scheme of the organization of the components associated with the flagella in *E. coli* [1]-> Adler, J. (1975). "Chemotaxis in Bacteria." Annual Review of Biochemistry 44(1): 341-356.

When flagella on a cell rotate CCW, they collectively bundle together to propel the bacterium through the medium along an approximately straight path. This behavior is called a *run*. When some of the flagella rotate CW, the bundle disintegrates causing an abrupt change in the direction. This behavior is called a *tumble* [83, 12]. *E. coli* modulates the probability of being in one of these two swimming states in response to its environment, allowing it to navigate in chemical, temperature, and light gradients [12, 11]. At any point in time, the probability that a flagellar motor rotates CW is determined by the concentration of phosphorylated signaling protein CheY (CheY-P). By coupling CheY phosphorylation to chemicals from the environment the cell is able to bias its random walk and migrate towards more favorable conditions [89].

1.1.1 Temporal gradient

When the cells are swimming along a positive gradient of attractant, CCW rotation is favored resulting in longer running intervals. This rises the question whether cells respond to spatial or temporal stimuli. That is, is a favorable run extended because the cell finds more attractant near its nose than near its tail (spatial gradient), or because the concentration goes up as it moves along (temporal gradient)?

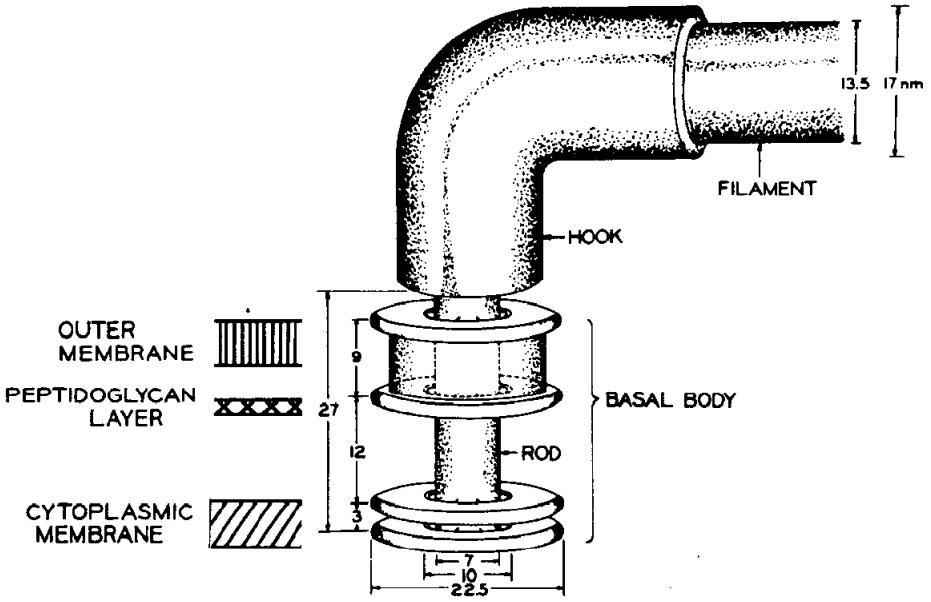


Figure 1.2: The polar flagella of *E. coli* viewed by transmission electron microscopy (B) A schematic of the organization of the components associated with the flagella in *E. coli* [1]

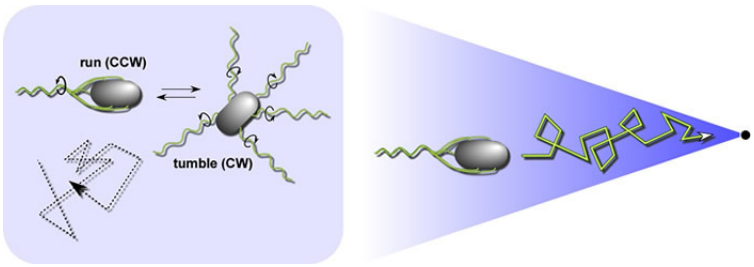


Figure 1.3: Left: A random walk in isotropic environments. When the cell's motors rotate CCW, the flagellar filaments form a trailing bundle that pushes the cell forward. When one or more of the flagellar motors reverses to CW rotation, that filament undergoes a shape change (owing to the torque reversal) that disrupts the bundle. Until all motors turn again in the CCW direction, the filaments act independently to push and pull the cell in a chaotic tumbling motion. Tumbling episodes enable the cell to try new, randomly-determined swimming directions. Right: A biased walk in a chemo-effector gradient. Sensory information suppresses tumbling whenever the cell happens to head in a favorable direction. The cells cannot head directly up-gradient because they are frequently knocked off course by Brownian motion. [79]

Experiments [82] showed that *E. coli* senses temporal stimuli. Cells suddenly exposed to a positive step of serine swam smoothly (without tumbling) for up to 5 minutes. Cells exposed to a negative step tumbled incessantly for about 12 seconds. The finding was supported

by another experiment of Berg et al. [17], who found an alternative way to not expose cells to spatial inhomogeneities. They found an enzyme, available commercially, that would convert an innocuous substance into a chemical attractant. The reaction was reversible, so alternatively the attractant could be destroyed. Thus, no matter where a cell might be or where it might be headed, it would always find the concentration of the attractant rising or falling. The experiments showed that when the attractant was generated, all the runs got longer. When it was destroyed, the cells failed to respond. The response to the positive temporal gradient was large enough to account for the results obtained in spatial gradients [17].

We have to notice that *E. coli* does not encounter temporal stimuli of this magnitude when swimming in spatial gradients in nature. Unless there is a strong source and a strong sink, spatial gradients are rapidly smoothed out by diffusion [11]. In any event, cells do not swim fast enough to generate large temporal stimuli. Such stimuli saturate the response: in the mixing experiments, cells either swam without tumbling or tumbled incessantly, although much longer in the former than in the latter case. What one measures is the time required for the cells to recover (i.e., to return to a mode in which they run and tumble). However, such stimuli have proved quite useful for probing the chemotaxis machinery [11].

It is possible to infer that, unable to sense a change in extracellular gradient along their own length due to the small dimension of the cell body ($\sim 0.7 - 1.4\mu m$ diameter, $\sim 2 - 4\mu m$ length, $\sim 0.5 - 5\mu m^3$ in volume [94, 59, 93, 74]), bacteria use a system of membrane receptors and intracellular signals to sense, adapt, and respond to changes in their environment and developed a history-dependent strategy in order to find region of high density chemoattractant [124].

The following are common characteristics to be taken into account when bacterial systems are under investigations:

Adaptation: Many bacterial systems show an inherent ability to adapt to local changes in the levels of extracellular attractant or repellent over quite wide ranges (approximately five orders of magnitude) of background concentrations. Exact adaptation in a bacterial chemotaxis context means the ability to respond to changes in the external environment and return the intracellular protein phosphorylation levels to their pre-stimulus levels. Adaptation is not necessarily always exact as in the case of *E. coli* responding to serine. Following this process, the bacteria are then able to detect any further changes in the attractant concentration [124].

Sensitivity: Studies have shown that even small changes in the local extracellular environment of bacteria, as small as ten attractant molecules per cell, can initiate a chemotactic response from the bacteria [124].

Gain: The ability to sense small changes in the extracellular environment means that the bacterium must be able to amplify the received signal, in order to modulate the intracellular signaling cascade. Gain is generally defined as the change in motor bias with respect to the change in occupancy of the receptors [124].

Robustness: In order to cope with cell-to-cell variations in levels of the signal transduction proteins the intracellular signaling network must be robust [124].

All of the above concepts are closely interwoven. For instance, gain requires the sensitivity of the system to be high enough to initiate the downward cascade of biochemical signals. The system must be robust to cope with variability in levels of the signal transduction proteins

between cells in order to be able to adapt across an extremely wide range of background concentrations. It is important to note that these events all occur on different timescales. In strong contrast, adaptation can take up to seconds or minutes dependent on the magnitude of the stimulus [124].

1.2 The chemotaxis signaling pathway

The signal transduction between the receptors and the flagellar motors is controlled by a set of well defined intracellular protein-protein interactions. In the case of *E. coli*, one of the most common attractants used to study the bacterial response is aspartate. A number of intracellular proteins (known as chemotaxis (Che) proteins) provide the necessary signaling cascade which links the membrane receptors to the flagellar motor.

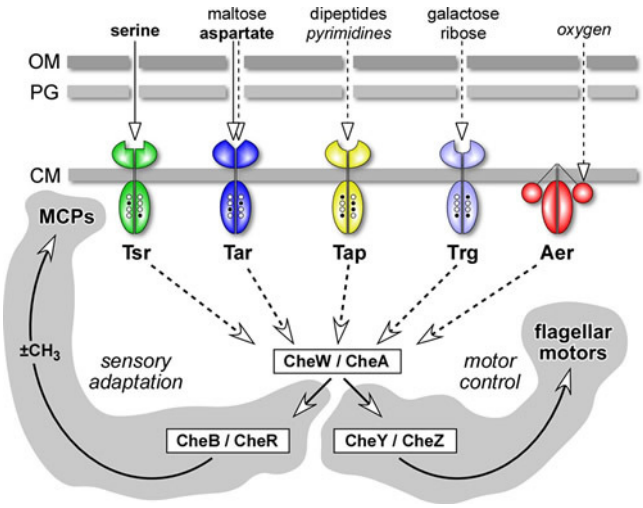


Figure 1.4: Signaling components and circuit logic. *E. coli* receptors employ a common set of cytoplasmic signaling proteins: CheW and CheA interact with receptor molecules to form stable ternary complexes that generate stimulus signals; CheY transmits those signals to the flagellar motors, CheZ controls the lifetime of CheYp. CheR (methyltransferase) and CheB (methylesterase) regulate receptor complex. Abbreviations: OM (outer membrane); PG (peptidoglycan layer of the cell wall); CM (cytoplasmic membrane).

E. coli senses chemo-effector gradients in a temporal fashion by comparing current concentrations to those encountered over the past few seconds. *E. coli* has four transmembrane chemoreceptors, known as methyl-accepting chemotaxis proteins (MCPs), that have periplasmic ligand binding sites and conserved cytoplasmic signaling domains. MCPs record the cell's recent chemical past in the form of reversible methylation of specific glutamic acid residues in the cytoplasmic signaling domain. Whenever the current ligand occupancy state fails to coincide with the methylation record, the MCP initiates a motor control response and a feedback circuit that updates the methylation record to achieve sensory adaptation

and cessation of the motor response. A fifth MCP-like protein, Aer, mediates aerotactic responses by monitoring redox changes in the electron transport chain. Aer undergoes sensory adaptation through a poorly-understood, methylation-independent mechanism.

The five MCP-family receptors in *E. coli* utilize a common set of cytoplasmic signaling proteins to control flagellar rotation and sensory adaptation. CheW and CheA generate receptor signals; CheY and CheZ control motor responses; CheR and CheB regulate the MCP methylation state.

1.2.1 Molecular implementation of chemotaxis signaling

A population of receptors at the cell surface binds chemo-effector ligands and affects the rate at which an intracellular kinase, CheA, hydrolyzes ATP on a time scale of ~ 0.1 s. The phosphate group produced in this hydrolysis reaction is then passed to a response regulator protein, CheY, which affects stochastic switches in the direction of motor rotation (CCW or CW) on a time scale ~ 1 s [21].

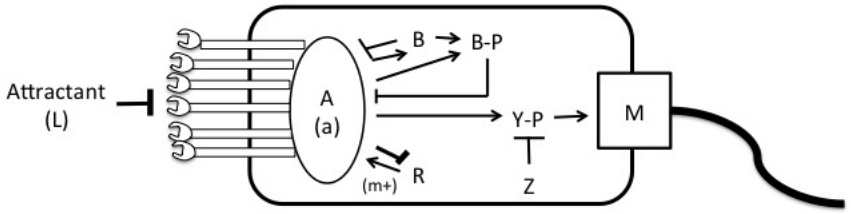


Figure 1.5: The *E. coli* Chemotaxis signaling network. The input ligand concentration, L, is sensed by the membrane-associated receptor-kinase complex, A, to regulate its autophosphorylation activity, a. A then transfers phosphate to the response regulator, CheY (Y), the phosphorylated form of which (Y-P) interacts with the flagellar motor (M), to control swimming behavior. The feedback loop is closed by the methyltransferase CheR (R) and the methylesterase/deamidase CheB (B), by regulation of the receptor methylation level, m. CheZ (Z), the phosphatase for CheY-P, decreases the signal lifetime, thus accelerating the response of the pathway. Redraw from [21]

- The receptor-kinase complex is stable on the time scale of the response, and hence can be considered a single molecular species in signaling function. In addition to the input ligand concentration, L, the receptor-kinase activity, a, is modulated by chemical modifications at specific amino acid residues of the receptors cytoplasmic domains. These covalent modifications are catalyzed by two enzymes: CheR, which adds methyl groups, and CheB, which removes them. The balance between the activity of these two enzymes determines the average methylation level, m, which can take values between 0 and a maximal value, M, corresponding to the number of modification sites per

receptor monomer (4 for the aspartate receptor Tar). Thus, the kinase activity, a, is determined by a function of both of these variables [21]:

$$a = G(m, L).$$

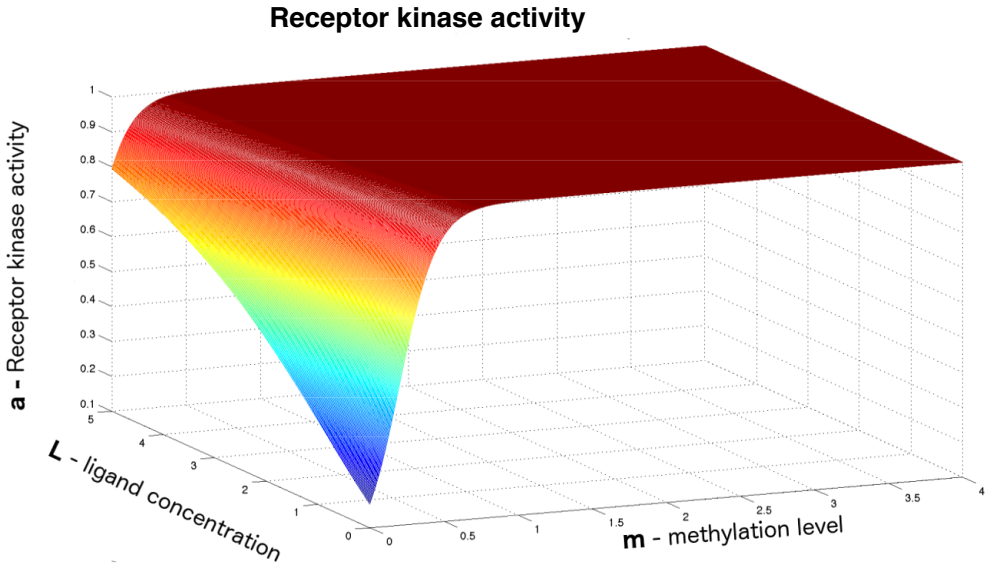


Figure 1.6: Shape of the function used to model the receptor kinase activity.

- Kinase activity decreases with attractant ligand concentration and increases with methylation. The activities of both CheR and CheB, which determine the dynamics of m, in turn, depend on the kinase activity, a, in a manner that provides negative feedback. These reactions occur on a much slower time scale ($\sim 10s$.) than that of the modulation of a, so these dynamics must be considered explicitly, and in general can be written as [21]:

$$\frac{d}{dt}m = F(a, m).$$

- Transmission of changes in a to the motor is accelerated by CheZ, which shortens the lifetime of the signal by accelerating the dephosphorylation of CheY-P back to CheY. The equation for the phosphorylation/dephosphorylation cycle of CheY then reads [21]

$$\frac{d}{dt}y = k_a a(1 - y) - k_z y.$$

- The equilibrium probability of the motor being in the CCW state (run mode) is called the CCW bias, and is a function of y [21]:

$$h(y) = \frac{1}{1 + \left(\frac{y}{y_0}\right)^H}.$$

where y_0 is the CheY-P concentration at which the bias is $1/2$, and the parameter H accounts for the steepness of the sigmoidal response [29]. It follows that the ratio of the probabilities for the CW state and the CCW state is $(y/y_0)^H$.

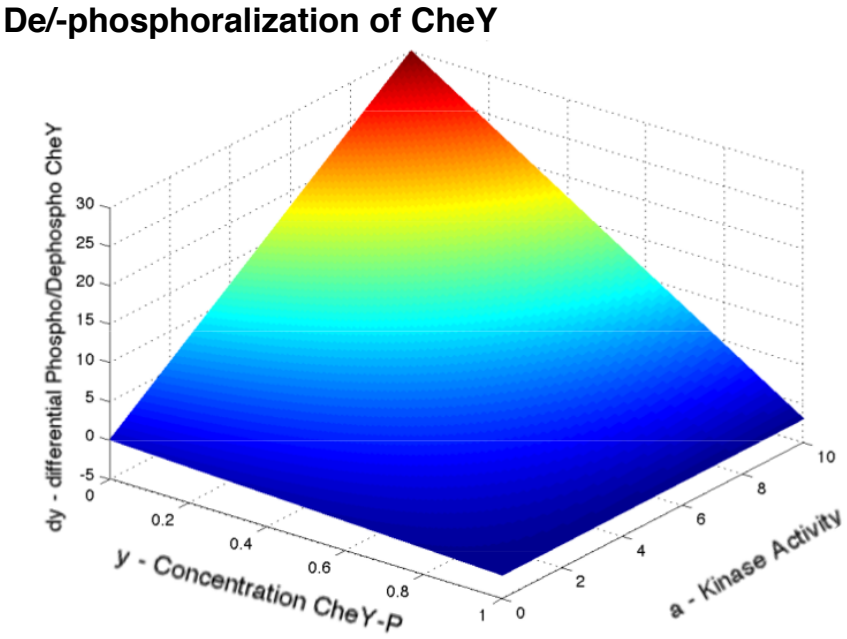


Figure 1.7: De/-phosphoralization of CheY.

The chemotactic transduction pathway is conveniently modeled by the following set of mean-field equations [126]:

$$a = G(m, L), \tag{1.2.1}$$

$$\frac{d}{dt}m = F(a, m), \tag{1.2.2}$$

$$\frac{d}{dt}y = k_a a(1 - y) - k_z y, \tag{1.2.3}$$

$$\frac{d}{dt}p_r = \frac{1 - \frac{p_r}{h(y)}}{\tau_t}. \tag{1.2.4}$$

The detailed expressions for the functions that appear above are

$$G(m, L) = \frac{1}{1 + e^{f(m,L)}},$$

$$f(m, L) = n_a \alpha_m (m_0 - m) + n_a \ln \frac{1 + \frac{L}{K_{off}}}{1 + \frac{L}{K_{on}}},$$

$$F(a, m) = k_r[\text{CheR}](1 - a)\frac{M - a}{M - m + K_R} - k_b[\text{CheB}]a\frac{m}{m + K_B};$$

$$h(y) = \frac{1}{1 + \left(\frac{y}{y_0}\right)^H}.$$

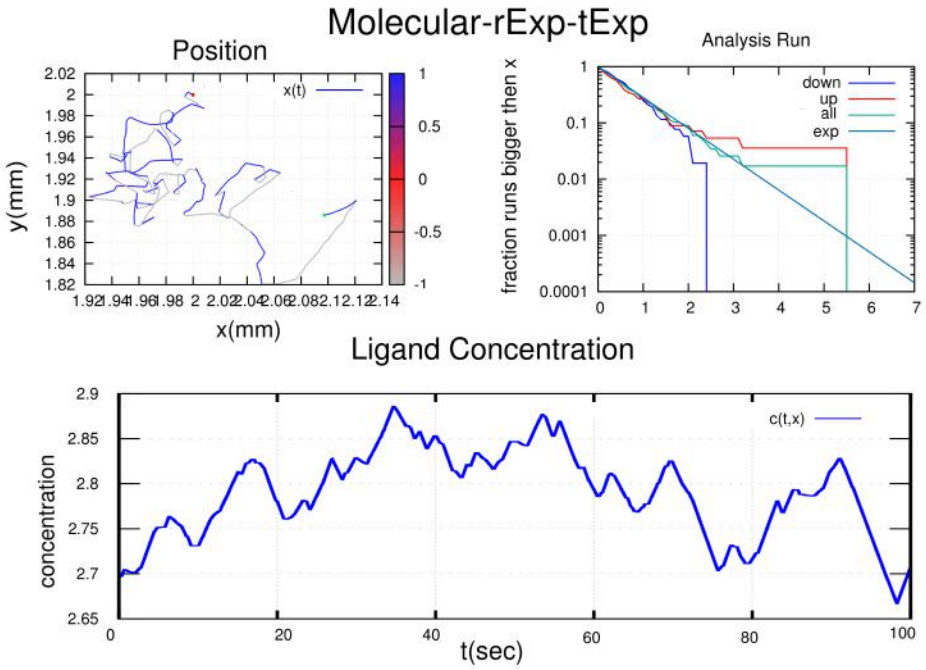


Figure 1.8: Simulation of the random walk of *E. coli* implementing the chemotaxis signaling pathway in [126]. **Top left:** trajectory: the initial position is marked red. The trajectory is colored blue if the run goes up the gradient, red if the ligand concentration remains constant, gray in all other cases. **Top right:** distribution of the length of the runs in plot with logarithmic scale on the y-axes: the abrupt behavior in the tails is due to the limited amount of data. we simulated a single trajectory for a time interval of 100 seconds. **Bottom:** plot of the ligand concentration measured during the random walk. The simulation was performed using the program **EcoliSimulator** discussed in **Chapter 7**.

1.3 Memory and signaling pathway

As pointed out, the bacteria are too small to measure any spatial gradient: they have developed a strategy based on the comparison of the current level of a chemical substance and the one measured and memorized in the past to measure the *temporal gradient*.
In mathematical terms this translates to the following formulations: bacteria continuously modulate their instantaneous probability of tumbling as a function of a weight of past measurements of chemoattractant concentration. The differential weight constitutes the chemotactic response function [28].
We may have many different functions and hypotheses on how the temporal sensing is performed. Here we consider the following simple and heuristic cases:

$$\nabla_{F,\mu}^{[t-r\mapsto t]} c(X) := F\Big(c(X(t),t) - \int_{-r}^{0} c(X(t+s),t+s)\mu(ds)\Big)$$

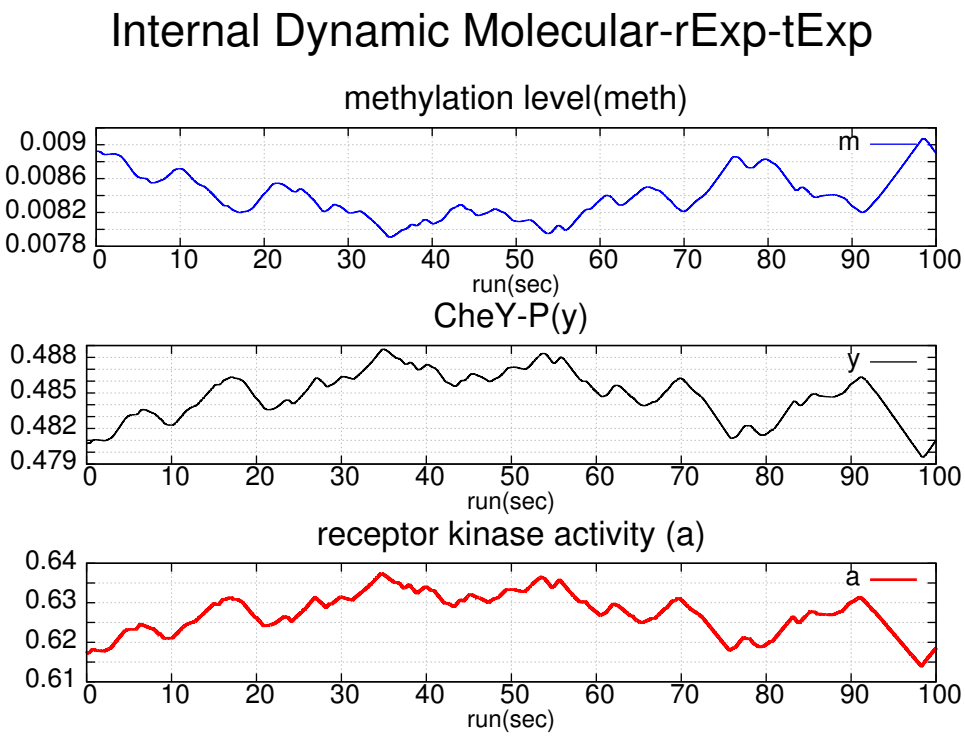


Figure 1.9: Evolution of the functions $m(t)$, $y(t)$ and $a(t)$ of the system 1.2.1 during the simulation of the random walk of *E. coli* implementing the chemotaxis signaling pathway in [126] (see **Figure 1.8**). We started the simulation from the steady state for the internal variable. We notice that the receptor kinases activity (a) and CheY-P (y) proceed parallel, while the methylation level m has the opposite growth pattern. The simulation was performed using the program **EcoliSimulator** discussed in **Chapter 7**.

and the discrete-time analog:

$$\delta_{F,\mu}^{[t-r\mapsto t]}c(X) := F\Big(c(X(t),t)^{\smile}\sum_{k=0}^{N}c(X(t+s_k),t+s_k)\cdot\mu_k\Big), \tag{1.3.1}$$

where $\{s_k\}_{k=0\ldots N}$ is a partition of the interval $[-r,0]$.
The bacterium senses a certain average via the weight function μ (resp. for the discrete case the weights μ_k):

$$\int_{-r}^{0}c(X(t+s),t+s)\mu(ds)\quad(\text{resp. }\sum_{k=0}^{N}c(X(t+s_k),t+s_k)\cdot\mu_k)$$

and compares it to the concentration currently measured, i.e. $c(X(t),t)$.

The obtained result, say $c-\mathbf{E}[c]$, which is a real number, is given to the function F, which is the response function for such stimuli. The function F generally takes the form of

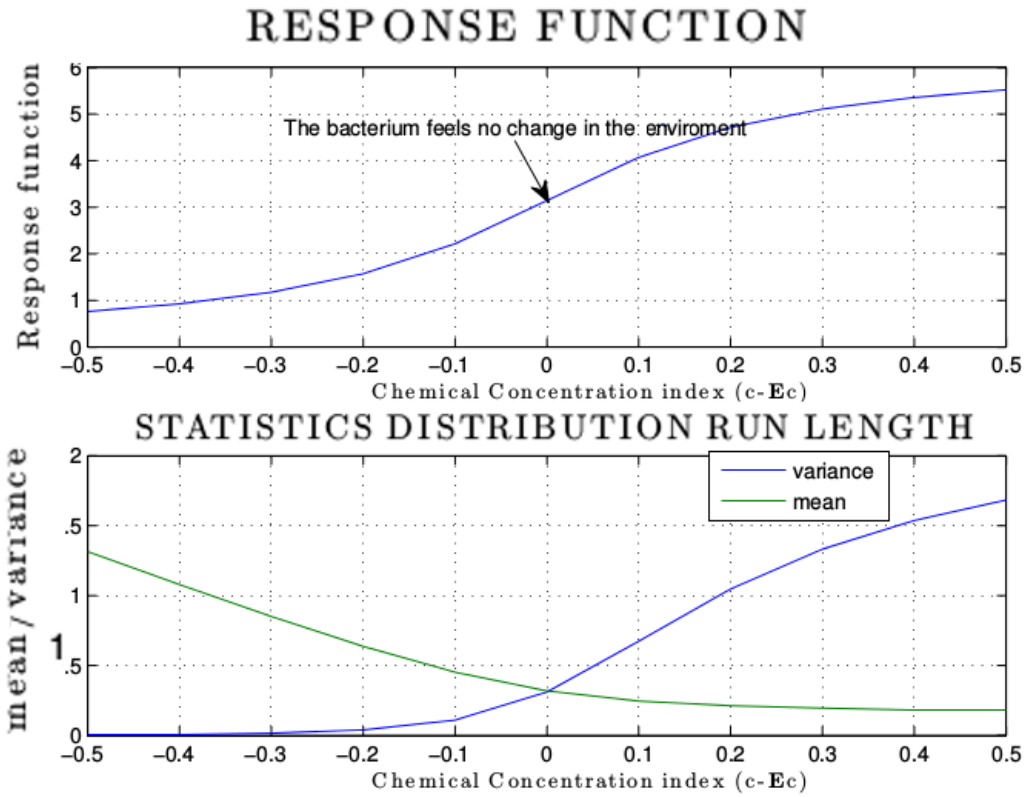


Figure 1.10: Response function $\nabla_{F,\mu}^{[t-r\mapsto t]}c(X)$. The response function is the link between the environment and the strategy of the bacterium, i.e. it modulates the duration of runs and tumbles. We notice that the response function does not assume the value 0 at the point where the bacterium does not sense a change in the environment: in all the models that we discuss and analyze the response function is related to the mean duration of a run for a given scenario, more precisely it is the inverse of this mean. For a deeper explanation we refer to **Chapter 2**, in particular **subsection 2.2.1** and *Remark 2.2.1.*

a arctan-type function.

$$F(c) := \gamma + \beta \cdot \arctan\Big(\phi_\epsilon(\alpha_+ \cdot c^+ + \alpha_- c^-)\Big),$$

where $\phi_\epsilon(\cdot)$ is a mollifier, $c^\pm$ is the positive $(+)$ or negative(-) part of c, $\alpha_\pm$, γ and β are constants.

1.3.1 Memory kernel and signaling pathway

In the presence of a uniform distribution of chemoattractant, the average duration of runs can be obtained by looking at the stationary solutions of the model equations [21] and will be indicated with a $\star$: in this case any mild variation in the concentration can be decomposed as the superposition of responses to elementary stimuli.

In the linear response limit, the evolution of the running probability p_r takes the customary form of a two-state inhomogeneous Poisson process: following [21] we develop the expression of this probability around the equilibrium value and obtain:

$$\frac{dp_r}{dt} = \frac{1}{\tau_t}(1-p_r) - \frac{1-h}{\tau_t h}p_r \sim \frac{1}{\tau_t}(1-p_r) - \frac{1}{\tau_{r,\star}}\Big(1 - \frac{h'_\star \Delta y}{h_\star(1-h_\star)}\Big)p_r$$

Introducing a linear response function $K(t)$ we obtain the rate of conversion between run to tumble as follows:

$$Q(t) := \frac{h'_\star \Delta y}{h_\star(1-h_\star)} = \int_{-\infty}^{t} K(t-s)L(s)ds$$

The explicit form of this response function is obtained by integrating the linearized dynamical equations and can be found in [21] pages 237 - 239. In conclusion the expression is given by:

$$K(t) = k_a \frac{h'(y_\star)(1-y^\star)}{h(y_\star)(1-h(y_\star))}\Big(\frac{\partial G}{\partial L}\Big)_\star \cdot \frac{1}{\tau_y^{-1} - \tau_m^{-1}}\Big[(\tau_y^{-1}e^{-t/\tau_y} - \tau_m^{-1}e^{-t/\tau_m}) - \Big(\frac{\partial F}{\partial m}\Big)_\star (e^{-t/\tau_y} - e^{-t/\tau_m})\Big]$$

where $\tau_y^{-1} = k_z + k_a a_\star$ and $\tau_m^{-1} = -(\frac{\partial F}{\partial a}\frac{\partial G}{\partial m} + \frac{\partial F}{\partial m})_\star$.

We adopt, however, another option for the response to an impulsive stimulus. We follow [22] and we will refer to the expression

$$\nabla_t^K c(X,s) = \frac{1}{\tau_r}\Big[1 - \int_{-\infty}^{s} K(s-r)c(X(r),r)ds\Big],$$

with $K(t) = \lambda e^{-\lambda t}\sum_{k=1}^{k_M}\beta_k(\lambda t)^k \cdot \mathbf{1}_{\{t\geq 0\}}$, since it it more general and readable.

These functions are the bridge between the information coming from the environment and the decision to *tumble*, it is the modulation of the rate of transition from run to tumble.

Chapter 2

HEREDITARY STOCHASTIC HYBRID SYSTEMS

In this chapter we are going to develop a general mathematical model which can be considered as a generalization of Hybrid Systems and of Stochastic Functional Differential Equations with Markovian Switching (SFDEwMS) [84].

2.1 Introduction

A hybrid system is a dynamic system that exhibits both a continuous and a discrete dynamical behavior: in other words it is a system that can both flow (described by a differential equation) and jump (described by a difference equation). Although the deterministic framework captures many characteristics of the real systems in practice, in other cases, the missing favor of randomness will indeed be a fatal flaw because of the inherent uncertainty in the environment of most real world applications [63]. One obvious choice is to replace the deterministic jumps between discrete states by random jumps governed by some prescribed probabilistic law. Another choice is to replace the deterministic dynamics inside the invariant set of each discrete state by a stochastic differential equation [63, 19]. We talk in this case of stochastic hybrid systems (SHS): intuitively, a SHS can be described as an interleaving between a finite or countable family of diffusion processes and jump processes [19].

The features of stochastic hybrid processes can be summarized as follows [73]:

- The time t is measured continuously. The state of the system is represented by a continuous variable x and a discrete variable i. The continuous variable evolves in some open set in the Euclidean space and the discrete variable belongs to a countable set $\mathbb{Q}$. The intrinsic difference between the discrete and continuous variables consists in the way that they evolve through time.
- **switching diffusion**: between the random switches of the discrete valued component, the Euclidean valued component evolves as a diffusion;
- **random hybrid jumps**: switches of discrete and Euclidean valued components can be driven by a Poisson random measure;

- **boundary hybrid jumps**: simultaneous and dependent jumps and switches of discrete and Euclidean valued components are initiated by boundary hittings;
- **mode dependent dimension**: the dimension of the Euclidean state space depends on the discrete valued component measure.

The abstract structure of the movement of *E. coli* described in the previous chapter can be seen as an example of a SHS, in the following sense:

- the bacterium undergoes two different modes: *run* and *tumble*, the discrete component in the hybrid space;
- during a run the system evolves following a differential equation (ordinary/ stochastic/ partial differential equation) which incorporates some *memory term*;
- during a tumble we have a change in the direction: the velocity jumps to a new value;
- the duration of a run and the one of a tumble is random.

This analogy leads us to develop a generalization of Hybrid Systems in the direction of Stochastic Functional Differential Equations with Markovian Switching [84]. We call it Hereditary Stochastic Hybrid Model/Systems (HSHM, HSHS) and think it might find wider applicability then the random movement of bacteria. For a review of SSS we refer to [19, 63, 73] and the **Appendix**.

2.2 Hereditary Stochastic Hybrid Systems

In the following we make use of some standard notions from Markov process theory, (Stochastic) Functional Differential Equations, Malliavin Calculus and Martingale Theory. For more details see **Appendix A**.
We will start by giving a short description of the Hereditary Stochastic Hybrid Systems (HSHS) in the context of the specific application we have in mind, to justify some assumption and notation, i.e. *E .coli* movement.
Bacteria are characterized by position X, direction θ, internal dynamics ζ, a satisfaction index Λ and a variable indicating in which state the bacterium is, i.e. *rum* or *tumble*. We have that X and ζ take value in $\mathbb{R}^d$ and $\mathbb{R}^n$, while θ is a process living on the sphere $\mathcal{S}^{d-1}$. The process Λ behaves like a time-change process and has its value in $\mathbb{R}$.

- θ is defined as the solution of a jump-diffusion process on the sphere: the direction of the bacterium evolves following a Brownian motion on the sphere during a run and jumps to a new position when the *E. coli* performs a tumble.
- X and ζ satisfy a stochastic differential equation with values in $\mathbb{R}^d$: because in this chapter we are interested in the general structure of the model, we are going to merge the two processes and call it again ζ, i.e. let X and ζ satisfy

$$dX(t) = F_X dt + G_X dW_X(t),$$

$$d\zeta(t) = F_\zeta(t)dt + G_\zeta(t)dW_\zeta.$$

We redefine ζ as the vector in $\mathbb{R}^{d+n}$ given by

$$\zeta(t) := (X(t), \zeta(t)),$$

which satisfies

$$d\zeta(t) = F(t)dt + G(t)dW(t),$$

with

$$F := (F_X, F_\zeta),$$
$$W := (W_X, W_\zeta),$$

and the matrix G is given by

$$G := \begin{bmatrix} G_X & 0 \\ 0 & G_\zeta \end{bmatrix}.$$

2.2.1 Definition of HSHS

Let $(\Omega, \mathfrak{F}, \mathbf{P})$ be a probability space where $\mathfrak{F}$ is a filtration that satisfies the *usual assumptions*. If E is a Banach space, the space $L^2(\Omega, E)$ consists of all $\mathfrak{F}$-measurable maps $x : \Omega \mapsto E$ such that

$$\|x\|_{L^2(\Omega,E)} = \Big[\int_\Omega \|x(\omega)\|_E^2 \, d\mathbf{P}(\omega) \Big]^{\frac{1}{2}} = \sqrt{\mathbf{E}[x]_E^2} < \infty.$$

If $r > 0$, let $I := [-r, 0]$ and $\mathscr{C} := \mathscr{C}(I, \mathbb{R}^n)$ the space of continuous functions from T to $\mathbb{R}^n$ with the sup-norm $\|\gamma\|_{\mathscr{C}} := \sup_{s\in\overline{J}} |\gamma(s)|$, where $|\cdot|$ denotes the Euclidean norm on $\mathbb{R}^n$. As a metric space we associate with $\mathscr{C}(I, \mathbb{R}^n)$ its Borel σ-algebra $\mathfrak{B}_{\mathscr{C}(I,\mathbb{R}^n)}$. The space $L^2(\Omega, \mathscr{C})$ is complete when endowed with the semi-norm

$$\|\eta\|^2_{L^2(\Omega,\mathscr{C})} := \mathbf{E}[\|\eta\|^2_{\mathscr{C}}].$$

We will use for the segment process the notation in [61]:

Let $x : [0, \infty) \to E$, then for all $t \in [0, \infty)$ we write x_t for the r-segment process

$$x_t(u) := x(t + u) \quad u \in [-r, 0].$$

We are ready to introduce and define the general model. Now we describe briefly the stochastic processes appearing in the definition of the model.

- Let $\mathcal{Q}(t)$ be a stochastic process with values in an at most countable space M_Q: it describes the state of the system: in case of *E. coli* the cardinality of M_Q is two, i.e. $M_Q = \{q_r, q_t\}$, *run*, *tumble*.
- Let us define a process $\mathcal{N}(t)$ on $(\Omega, \mathfrak{F}, \mathbf{P})$ as follows: it is a piecewise constant càdlàg process a.s. bounded on compact intervals given by

$$\mathcal{N}(t) := \sum_{j=-1}^{\infty} \mathbf{1}_{[\tau_j,\infty)}(t),$$

with $\tau_{-1} = -r$, $\tau_j = \tau_{j-1} + a_j$ where $\{a_j\}_{j\in\mathbb{N}}$ can be deterministic quantities or $\mathcal{F}_0$-measurable random variables.

Remark 2.2.1. In order to have a better understanding on the meaning of this process let us explain in what sense it is a generalization of the standard Poisson process.
Let $\{a_j\}_{j\in\mathbb{N}}$ be a sequence of independent exponentially distributed random variables. As before, let τ_j be recursively defined by $\tau_{-1} = -r$, $\tau_j = \tau_{j-1} + a_j$.
If we consider the counting process

$$\mathcal{N}(t) := \sum_{j=-1}^{\infty} \mathbf{1}_{[\tau_j,\infty)}(t),$$

we have that $\mathcal{N}(t)$ is a Poisson process. We can immediately obtain a non-homogenous Poisson process by performing a stochastic time change. In fact let Λ be defined as

$$\Lambda(t) = \int_0^s \lambda(s)ds,$$

where λ is some positive function. If we consider now the stochastic process

$$\mathcal{N}_\lambda(t) := \sum_{j=-1}^{\infty} \mathbf{1}_{[\tau_j,\infty)}(\Lambda(t)), \tag{2.2.1}$$

we have that $\mathcal{N}_\lambda$ is a non-homogenous Poisson process with parameter $\lambda(t)$. In general we have that the time of jump for the Poisson process are given as the hitting time of the barrier τ_j by the process Λ.
We borrow this idea in order to construct the process that drive the system to a new state: more precisely we use a monotonic functional of the solution of a stochastic functional differential equation to model the time-change process Λ and force a jump to a new state, whereby the jump is recorded by the process $\mathcal{N}(t)$.

- Let us consider the following Wiener processes:
  - $\{W(t)\}_{t\in[-r,T]}$ be a one dimensional Wiener process [20] such that for $u \leq 0$ $W(u) = 0$ a.s.;
  - $\{W_\zeta(t)\}_{t\in[-r,T]}$ a m-dimensional Wiener process [20] such that for $u \leq 0$ $W(u) = 0$ a.s;
  - $\{W_{\mathcal{S}^{d-1}}(t)\}_{t\in[-r,T]}$ be a Wiener process on the sphere $\mathcal{S}^{d-1}$ [131, 16, 118].

  We suppose for simplicity that these stochastic objects are independent of each other.

- The system under investigation does not react to the change of the environment directly, but the informations gathered from the outside are processed internally: the output of this elaboration is used to decide if the system will jump to a new state. Let ζ be this internal process: we underline that this process has values in $\mathbb{R}^d$. We will call it *internal dynamics* and is defined as the solution of a a stochastic differential equation, whose general form can be expressed as

$$\zeta(t) = x_0 + \int_0^t \phi_X(s)ds + \int_0^t \mu_X(s)\delta\mathcal{N},$$

with a noise source $\delta\mathcal{N}$.
In the present general context, the process ζ has no special meaning, apart from the binding between the system and the external environment. As mentioned in the introduction, if we, instead, look at the particular application we have in mind, i.e. the study of the movement of *E. coli*, we are better off separating the vector ζ in two components: let the first one be the position of the bacterium, say $X(t)$, and the second one the *internal dynamic*, i.e. the description of the processes happening inside the cell which influence the run and tumble behavior of the bacterium. For this particular case we refer to the next chapter.

- On the space $(\Omega, \mathfrak{F}, \mathbf{P})$ let $(Y_n)_{n\in\mathbb{N}}$ be a sequence of i.i.d. $\mathcal{F}_0$-measurable $L^2(\Omega)$ random variables with values on the sphere $\mathcal{S}^{d-1}$: these random variables represent the reorientation of the direction of a bacterium.
Let the law of Y_k be μ^Y, i.e. $Y_k \sim \mu^Y$ and write $\overline{\sum}$ for the sum of elements on the sphere $\mathcal{S}^{d-1}$.

- Let $c : [-r, \infty) \times \mathbb{R}^3 \to (0, \infty)$ be a given (*deterministic*) function, sufficiently regular. The function $c(t, x)$ describes the density of attractant for the bacterium - we can consider it to be of class $\mathscr{C}^\infty([-r, T] \times \mathbb{R}^r, \mathbb{R}_+)$.

The dynamics of a bacterium is governed by the following system of stochastic functional differential equations, namely in the sequel (**HSHS**).

$$\begin{aligned}
\theta(t) &= \theta_0(0) + \int_0^t D_\theta(\mathcal{Q}(s)) \cdot dW_{\mathbb{S}^{d-1}}(s) + \overline{\sum}_{j=0}^{\Psi(t)} Y_j, \\
\zeta(t) &= \zeta(0) + \int_0^t F(\mathcal{Q}(s)), s, c(\zeta(s), s), \theta(s))ds + \int_0^t G(\mathcal{Q}(s), s, c(\zeta(s), s), \theta(s))dW_\zeta(t), \\
\Lambda(t) &= \Lambda_0 + \int_0^t \lambda(\mathcal{Q}(s), s, \zeta(s), \zeta_s, \Lambda_s, \theta(s))ds + \int_0^t \sigma(\mathcal{Q}(s), s, \zeta(s), \zeta_s, \Lambda_s, \theta(s))dW(s).
\end{aligned} \tag{2.2.2}$$

where we have for $0 \le t \le T$,

$$\begin{aligned}
\mathcal{Q}(t) &= \mathcal{H}(\Psi(t), \mathcal{Q}(t^-)); \\
\Psi(t) &= \mathcal{N}(\Xi(t^-)); \\
\Xi(t) &= \beta(\Lambda(t-s)|_{s\le t}),
\end{aligned} \tag{2.2.3}$$

and for $t \in [-r, 0]$ supposed that the following initial conditions are given:

$$(\theta(t))_{t\in[-r,0]}, \quad (\Lambda_0(t))_{t\in[-r,0]}, \quad (\zeta_0(t))_{t\in[-r,0]}.$$

The coefficients of the equations presented above are here reported with special attention on the spaces they take value in:

$$\begin{aligned}
&\lambda : M_Q \times [0, \infty) \times \mathbb{R} \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathcal{S}^{d-1} \to \mathbb{R}; \\
&\sigma : M_Q \times [0, \infty) \times \mathbb{R} \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathcal{S}^{d-1} \to (0, \infty); \\
&F : M_Q \times [0, \infty) \times \mathbb{R} \times \mathcal{S}^{d-1} \to \mathbb{R}^n; \\
&G : M_Q \times [0, \infty) \times \mathbb{R} \times \mathcal{S}^{d-1} \to \mathbb{R}^{n\times m};
\end{aligned}$$

$$\begin{aligned}\mathcal{H} &: \Omega \times [0,\infty) \times M_Q \to M_Q;\\ D_\theta &: M_Q \to (0,\infty);\\ \beta &: M_Q \times \mathscr{C}([-\infty,0],\mathbb{R}) \to (0,\infty),\end{aligned}$$

where β has to be a monotonic function in the following sense: if $t \leq s$, then

$$\beta(\cdot,\Lambda(\cdot))|_t \leq \beta(\cdot,\Lambda(\cdot))|_s.$$

An example of such a function is the premium of the process Λ. We notice the dependency on the infinite dimensional space $\mathscr{C}([-r,0],\mathbb{R})$.

Remark 2.2.2. The three stochastic processes $(\theta(t),\zeta(t),\Lambda(t))$ in (2.2.2) have specific analytics and topological characteristics:

- $\theta(t)$ is a stochastic process on the sphere composed by overlapping a Brownian motion (with constant diffusion coefficient D_θ for every discrete state the process is in) and a jump process. It might be possible to include mode general processes and more general spaces:

  - we might substitute the sphere with a Lie group [65];
  - me might also substitute the Brownian motion on the sphere with a more general Itô's diffusion with jumps [27].

  For clarity and simplicity of exposition and analytical details we confine ourself to this setting.

- the process $\zeta(t)$ represents the link between the environment (the function $c(x,t)$) and the of the system. It is a classical Itô diffusion with values in $\mathbb{R}^n$: we call it *internal variable*.

- $\Lambda(t)$ is the process which drives the time-change: it is a one dimensional SFDE which is coupled with the process $\mathcal{N}(t)$ to produce a jump in the process $\theta(t)$: we call it *generalized subordinator*, since it can be seen as a generalization of the concept of subordinator. We recall that a subordinator is a stochastic process of the evolution of time within another stochastic process, the subordinated stochastic process: we define a *subordinator* as an (a.s.) increasing Lèvy process. In our general framework we do not deal with Lèvy processes.

Equation (2.2.3) describes what happens to the system at the time-points of discontinuity and the nature of the functional dependency:

- $\mathcal{H}$ is a probability kernel that controls the probability distribution of the state into which the system will jump. We might add a probability kernel that performs a discontinuity in the process ζ as well, but we have to be careful when we study existence of the system due to the coupling of the segment process ζ_t with Λ.

- $\Xi(t)$ represents the functional dependency that links the process Λ to the counting process $\mathcal{N}(t)$: we obtain an inhomogeneous Poisson process $\mathcal{N}(t)$ with intensity $\Lambda(t)$ when we impose the following :

$$\sigma(\cdot) \equiv 0, \quad \beta(\Lambda(t-s)_{s\leq t}) \equiv \Lambda(t), \quad \lambda(\cdot) > 0,$$

  and $\{a_j\}_j$ is a i.i.d. sequence of exponential random variables (RV).

- Ψ counts the number of jumps: we perform the same trick as in (2.2.1), by changing the time of the counting process.

Remark 2.2.3. We begin underlying that the process θ takes values in the group $\mathcal{S}^{d-1}$. If the jump part has a Lévy measure, θ reduce to a diffusion process with jumps with values in a group: a well studied problem in the theory of Lévy processes [3, 81].
The process that drives the time change is a one dimensional SDFE, while the process ζ is a multidimensional SFDE. We could have combined these last two processes, but for readability we decided to keep them separate.

Remark 2.2.4. The model (HSHS) is different from the standard setting of HHS in the following sense:

i) the continuous component evolves according to a Stochastic Functional Differential Equation (SFDE), a discontinuity during the transition between different states might be present.;

ii) in the standard setting the transition between different states can be due to a controlled Markov Chain or forced when the continuous component reaches the boundary of its domain. We adapt, instead, the idea of a random time change: one of the component of the continuos time will be used to stretch and shrink the time-scale; in this sense the time of transition will be defined as the time when this (one dimensional) process hits a certain threshold. We stress that the nature of this barrier (whether deterministic or stochastic) is fixed for every particular state. We could have had the possibility of the coexistence of these two different sources of noise, but for clarity of the theory we decided to separate them.

iii) we explicitly separate the different components of the continuous part of the hybrid system according to their analytical and topological properties.

Remark 2.2.5. There's a great deal of modification that can be done to the system of equations for other practical applications: here we point out one with respect to the functional dependency of the coefficient of the functions.
Let the system be in the state q_i: we might assume that the functional dependency of the process Λ is confined only to the time windows, during which the system is in the current state, i.e. the system is renewed when a discrete transition is performed.
Let τ be the last transition time, then the expression X_s will indicate the segment process $X(t-s)_{s\in[\tau,t]}$. In this case it may be useful to adopt the functional stochastic calculus developed by Dupire [42, 32].

2.3 Basic Analysis of the Mathematical Model

In this section we focus on the analysis of the system of equations (2.2.2) based on its stochastic and analytical properties, i.e. existence and uniqueness of a solution, Markov properties, extended generators, associated martingale problems etc.

2.3.1 Existence of Solution

In order to prove the existence of a solution and its uniqueness, we will first state some lemmas and specify what is meant in the present context with the term *solution* of the system (2.2.2).

We begin with a simple result to illustrate the nature of the problem: the process Λ is strongly related to an Itô diffusion and in particular, due to the hypotheses of Lipschitz continuity, to one with constant coefficients: because of its pedagogical value we analyze it here.

Lemma 2.3.1. *Let Z^* be the stochastic process $Z^*(t) = \eta(0) + H^* \cdot t + \sigma^* \cdot W(t)$. If $\tau^k_{Z^*}$ is defined as $\tau^k_{Z^*} := \inf\{t > 0 : Z^*(t) = k\}$, then for all $T \geq 0$*

$$\lim_{k\to\infty} \tau^k_{Z^*} > T, \quad a.s.$$

that is

$$\mathbf{P}(\omega \in \Omega : \lim_{k\to\infty} \tau^k_{Z^*}(\omega) = \infty) = 1.$$

Proof. The distribution of the k^{th}-stopping time follows an Inverse Gaussian distribution: $\tau^k_{Z^*} \sim \mathcal{IG}\Big(\frac{k}{H^*}, \frac{k^2}{\sigma^{*2}}\Big)$, i.e.

$$\mathbf{P}\Big(\omega \in \Omega : \tau^k_{Z^*}(\omega) \leq T\Big) := \Phi\Big(\frac{TH^* - k}{\sigma^*\sqrt{T}}\Big) + e^{2k\frac{H^*}{\sigma^{*2}}} \cdot \Phi\Big(\frac{-TH^* - k}{\sigma^*\sqrt{T}}\Big).$$

To prove that

$$\mathbf{P}\Big(\omega \in \Omega : \tau^k_{Z^*}(\omega) \leq T, \text{ infinitely often}\Big) = 0,$$

one can appeal to Borel-Cantelli's lemma. So what we have to check is that

$$\sum_{k=1}^{\infty} \mathbf{P}\Big(\omega \in \Omega : \tau^k_{Z^*}(\omega) \leq T\Big) < \infty.$$

From the standard upper bound for the cumulative normal distribution, $x > 0$:

$$\Phi(-x) = 1 - \Phi(x) \leq \frac{1}{\sqrt{2\pi}} \frac{1}{x} e^{-\frac{x^2}{2}},$$

by using the monotonicity of $\Phi(x)$:

$$\begin{aligned}\sum_{k=1}^{\infty}\mathbf{P}\Big(\omega\in\Omega:\tau_{Z^*}^k(\omega)\le T\Big)&=\sum_{k=1}^{\infty}\Big[\Phi\Big(\frac{TH^*-k}{\sigma^*\sqrt{T}}\Big)+e^{2k\frac{H^*}{\sigma^{*2}}}\cdot\Phi\Big(\frac{-TH^*-k}{\sigma^*\sqrt{T}}\Big)\Big]\\&\le\sum_{k}^{\infty}\Phi\Big(\frac{TH^*-k}{\sigma^*\sqrt{T}}\Big)(1+e^{2k\frac{H^*}{\sigma^{*2}}})\\&\le Const+\sum_{k=N(H)}^{\infty}(1+e^{2k\frac{H^*}{\sigma^{*2}}})\frac{1}{\sqrt{2\pi}}\frac{\sigma^*\sqrt{T}}{|TH^*-k|}e^{-\frac{(TH^*-k)^2}{2\sigma^{*2}T}},\end{aligned}$$

which converges.

Since it holds for all $T\ge 0$, we have: $\lim_{k\to\infty}\tau_{Z^*}^k=\infty$, a.s. □

The following lemma [127] is a very powerful result to guarantee the non-explosion of the process Λ: if we decompose a process into the sum of a martingale part and a finite variation process, the control over the finite variation part of the process guarantees the non-explosion of the process.

Lemma 2.3.2. *Let τ be a stopping time such that $\lim_{s\to\tau}\Lambda(s)=\infty$ and let $\lambda(s)$ be a function such that $\int_0^\infty\lambda(s)^{-1}ds=\infty$. If it holds*

$$\Lambda(t)\le\int_0^t\lambda(\sup_{u\le s}Z(u))ds+\mathcal{M}(t)+C,$$

then $\tau=\infty$ almost surely.

Proof. For the proof we refer to [127]. □

Lemma 2.3.3. *Let $\Lambda(\cdot):[0,T]\times\Omega\to\mathbb{R}_+$ be an $\mathcal{F}_t$-adapted stochastic process a.s. continuous and let $N(\cdot):[0,\infty)\times\Omega\to\mathbb{R}_+$ be a càdlàg stochastic process almost surely bounded for every compact interval. Then the stochastic process*

$$N\Big(\sup_{s\le t}\Lambda(s)\Big)$$

is well defined, i.e. is $\mathcal{F}_t$-adapted and is not exploding in a finite time.

Proof. The structure of the process is that of a *stochastic time change*. It is necessary to prove that the map

$$t\mapsto T_t:=\sup_{s\le t}\{\Lambda(s)\}$$

is $\mathcal{F}_t$-adapted. One has the following chain of equality:

$$\begin{aligned}\{\omega|T_t^\omega\le u\}&=\{\omega|\sup_{s\le t}\Lambda(s;\omega)\le u\}\\&=\Big\{\omega|t\le\inf\{r\in[0,T]:\Lambda(r;\omega)\ge u\}\Big\}\\&=\{\omega|t\le\tau_u^{\Lambda;\omega}\}\in\mathcal{F}_{u^+},\end{aligned}$$

where τ_u^Λ is the hitting time for the process Λ at the level u. □

Once the system of equations we are dealing with is fixed, we focus on the spaces where we look for a solution and the meaning of such a *solution*.

Definition 2.3.4. Let α and β be two stopping times such that a.s. $\alpha \leq \beta$ and consider the spaces, for $1 \leq p < \infty$,

$$\mathbf{M}_W^p[\alpha, \beta] := \Big\{ f \in L_W^0[\alpha, \beta] : \|f\|_p^p := \mathbf{E}^W \Big[\int_\alpha^\beta |f(t)|^p dt \Big] < \infty \Big\},$$

where $\mathbf{E}^W[]$ is the expectation w.r.t. W, $L_W^0[\alpha, \beta]$ is the set of non-anticipating processes indistinguishable on (α, β) with values in an appropriate subspace $\mathcal{D}$ of $\mathbb{R}^n$, e.g. if we study the process $(\zeta(t), \theta(t), \Lambda(t))$, we have $\mathcal{D} := \mathbb{R}^d \times \mathbb{S}^{d-1} \times \mathbb{R}$.

The following result guarantees that the chosen spaces have good geometrical and analytical properties:

Proposition 2.3.5. *The space $\mathbf{M}_W^p[\alpha, \beta]$ is a Banach space equipped with the norm*

$$\|f\|_p^p := \mathbb{E}^W \Big[\int_\alpha^\beta |f(t)|^p dt \Big].$$

We have now all the tools to give the definition of a solution for the system of equations (2.2.2):

Definition 2.3.6. We say that the random object

$$(\zeta(\cdot), \Lambda(\cdot), \theta(\cdot), (\tau_n)_{n \in \mathbb{N}})$$

is a *strong* (resp. *weak*)*solution* of the system (2.2.2), if

$$(\zeta(\cdot), \Lambda(\cdot), \theta(\cdot)) \in \bigoplus_{n \in \mathbb{N}} \mathbf{M}_W^2[\tau_n \wedge T, \tau_{n+1} \wedge T]$$

and each component is a *strong* (resp. *weak*) solution of the corresponding SFDE [91] on $[\tau_n \wedge T, \tau_{n+1} \wedge T]$.

The problem **HSHS** is actually well posed, as guaranteed by the following:

Theorem 2.3.7. *Let us assume that the following hypotheses are satisfied:*

- *suppose that there exists a Lipschitz continuous function $c : [0, T] \times \mathbb{R}^n \to \mathbb{R}$;*
- *the stochastic process $W(\cdot)$ is a $\mathbf{P}$-Wiener process and $\mathcal{N}(\cdot)$ as before;*
- *the functions*
  $\lambda : [0, T) \times \mathbb{R} \times L^2(\Omega, \mathscr{C}([-r, 0], \mathbb{R})) \times L^2(\Omega, \mathscr{C}([-r, 0], \mathbb{R})) \times \mathbb{S}^2 \to L^2(\Omega, L(\mathbb{R}^m, \mathbb{R}^n))$,
  $\sigma : [0, T) \times \mathbb{R} \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathbb{S}^2 \to L^2(\Omega, L(\mathbb{R}^m, \mathbb{R}^n))$
  $G : M_Q \times [0, \infty) \times \mathbb{R} \times \mathbb{S}^2 \to (0, \infty)$;
  $H : M_Q \times [0, \infty) \times \mathbb{R} \times \mathbb{S}^2 \to (0, \infty)$
  $u : M_Q \times [0, \infty] \times \mathbb{R} \times \mathbb{S}^2 \to (0, \infty)$;
  $D : M_Q \times \to (0, \infty)$;

are continuous, uniformly bounded in all variables and are also uniformly Lipschitz in the second and third variable with respect to the first [1]

- *for all adapted processes* $y_1, y_2 \in \mathscr{C}([0,T], L^2(\Omega, \mathscr{C}(\overline{J}, \mathbb{R}^n))$*, the processes*

$$[0,T] \mapsto \lambda(t, y_1(t), y_2(t)),$$

$$[0,T] \mapsto \sigma(t, y_1(t), y_2(t))$$

are also adapted to $(\mathfrak{F})_{t\in[0,T]}$ *(similarly for the other coefficients).*

- *The function* $\beta(\cdot)$ *is a either a bounded function or* $\beta(x(t-\cdot)) := \sup(x(s) : s < t)$.

*Then the system of equations (**HSHS**) has a unique solution.*

Remark 2.3.8. The proof of the theorem uses the decomposition $\bigoplus_{n\in\mathbb{N}} \mathbf{M}_W^2[\tau_n \wedge T, \tau_{n+1} \wedge T]$ presented in the definition of the solution for (**HSHS**):

- we can construct a unique *local solution* in every random interval $[\tau_n \wedge T, \tau_{n+1} \wedge T]$ using standard results in the theory of SFDE (see **Appendix**);
- we use the compactness and the boundedness of the interval $[0,T]$ to avoid explosion;
- we conclude by glueing the different *local solutions* together.

Proof. By the hypotheses on the process $\mathcal{N}(t)$ there exists a sequence of $\mathcal{F}_0$-measurable random variables $\{\tau_j\}_{j\in\mathbb{N}}$ such that a.s. $\tau_j < \tau_{j+1} \to \infty$. Consider now the stopping time

$$\tau_j^\Lambda := \inf\{t \in [\tau_{j-1}, T] : \Lambda(t) \geq \tau_j\} \wedge T.$$

We have that the processes involved in the system of equations on the stochastic interval $[0, \tau_1^\Lambda]$ are bounded:

- $\theta(t)$ for $t \in [0, \tau_1^\Lambda]$ is a pure diffusive process on the sphere and since this random interval is a.s. bounded, the process $\theta(t)$ a.s. does not leave the sphere.
- By Theorem 2.1 on page 36 in [91] the stochastic functional differential equation for Λ has for $t \in [0, \tau_1^\Lambda]$ a unique solution.

  - If β is a bounded function, we have clearly no explosion of the counting process in a finite time.

[1] i.e. there exists $L > 0$ such that, with $\psi = (\eta, \zeta)$

$$\sup_{(t,x,\eta,\zeta,\theta)\in[0,T)\times\mathbb{R}\times\mathscr{C}([-r,0],\mathbb{R})\times\mathscr{C}([-r,0],\mathbb{R})\times\mathbb{S}^2} \lambda(t,x,\eta,\zeta,\theta) \leq \Lambda^*$$

$$\sup_{(t,x,\eta,\zeta,\theta)\in[0,T)\times\mathbb{R}\times\mathscr{C}([-r,0],\mathbb{R})\times\mathscr{C}([-r,0],\mathbb{R})\times\mathbb{S}^2} \sigma(t,x,\eta,\zeta,\theta) \leq \sigma^*$$

$$\|\lambda(t,\psi_1,\eta_1) - \lambda(t,\psi_2,\eta_2)\|_{L^2} \leq L(\|\psi_2 - \psi_1\|_{L^2(\Omega,\mathscr{C})} + \|\eta_2 - \eta_1\|_{L^2(\Omega,\mathscr{C})})$$

$$\|\sigma(t,\psi_1,\eta_1) - \sigma(t,\psi_2,\eta_2)\|_{L^2} \leq L(\|\psi_2 - \psi_1\|_{L^2(\Omega,\mathscr{C})} + \|\eta_2 - \eta_1\|_{L^2(\Omega,\mathscr{C})})$$

for all $t \in [0,T]$, for all $\psi_1, \psi_2 \in \mathscr{C}(\overline{J}, \mathbb{R})$ and for all $\eta_1, \eta_2 \in \mathscr{C}(\overline{J}, \mathbb{R}^n)$

– If β is the function $\beta(a(t)) := \sup\{a(s) : s < t\}$ we have to be more careful: we can invoke **Lemma 2.3.2** to ensure that the process Λ does not explode in a finite time. It implies that

$$\mathbf{P}\Big(\omega \in \Omega : \sup_{t\in[0,T]} \Lambda(\omega) = \infty\Big) = 0.$$

- A similar argument as for Λ holds for the process $\zeta(t)$.

We next consider the equations on $t \in [\tau_1^\Lambda, \tau_2^\Lambda]$. Again we know that the system of equations has a unique continuous solution on this random interval. Repeating this procedure we have the existence of a solution as long as we can show that

$$\mathbf{P}\Big\{ \sup\{j : \tau_j < \sup_{t\in[0,T]} \Lambda(t)\} = \infty\} = 0,$$

i.e. that there are non infinite jumps in finite time for the process $\theta(t)$. Combining the results of the previous lemmas, the property that $\sup_{k>0} \tau_k > T$ a.s. and that a.s. $\sup_{t\in[0,T]} |\Lambda(t)| < \infty$, we obtain the result. □

2.3.2 Continuous Dependence of the Generalized Subordinator with respect to the Internal Variable

In this section we concentrate our attention on the regularity of the system of equations (2.2.2), in a sense to be clarified in what follows. Let us consider the case in which the thresholds for the process Λ are deterministic quantities. In this case, due to the nature of forced jumps, there is no hope to have some kind of continuity property with respect to the initial data for the process solution $(\zeta(t), \theta(t), \Lambda(t))_{t\in[-r,T]}$ [6]. We study the relationship between the trajectory and the process Λ. We will first study a particular case of the process (2.2.2).

Let us consider the system of equations defined on a probability space $(\Omega, \mathfrak{F}, (\mathfrak{F})_{t\in[0,T]}, \mathbf{P})$ satisfying the property stated above:

$$\Lambda(t) = \begin{cases} \eta_0(t) & -r \le t < 0 \\ \eta_0(0) + \int_0^t \lambda(\Lambda_s, c(\zeta_s, \cdot_s), s)ds + \int_0^t \sigma(\Lambda(s), c(\zeta(s), s), s)dW(s) & 0 \le t \le T \end{cases}$$

$$\zeta(t) = \begin{cases} \zeta(t) & -r \le t < 0 \\ \zeta_0(0) + \int_0^t \theta(s)ds & 0 \le t \le T \end{cases}$$

$$\theta(t) = \begin{cases} \theta_0(t) & -r \le t < 0 \\ \theta_0(0) + \sum_{j=0}^{N(t)} Y_j & 0 \le t \le T \end{cases}$$

where

$$N(t) = \begin{cases} n_0(t) = \sup\{n \in \mathbb{N} : n \le \sup_{s\in[0,t]} \Lambda(s)\} & -r \le t < 0 \\ N(t) = n_0 + \sum_{k=1}^{\infty} \chi_{[\tau_{n_0+k},\infty)}(s) & 0 \le t \le T \end{cases}$$

$$\tau_n = \begin{cases} 0 & n = 0 \\ \inf\{s > \tau_{n-1} : \Lambda(s) = \tau_n^{\mathcal{N}}\} & n \geq 1 \end{cases}$$

One may consider the following system into which our problem seems to be naturally immersed, with $\phi \in \Phi$ given by

$$\Phi := W_T^{1,2} := \{f \in W^{1,2}[0,T] : f(0) = 0 \text{ and } |f(T)|_{\mathbb{R}} \leq T\},$$

where $W^{1,2}[0,T]$ is the Sobolev space[2] endowed with the usual norm.

$$\Lambda(t) = \begin{cases} \eta_0(t) & -r \leq t < 0 \\ \eta_0(0) + \int_0^t \lambda(\Lambda_s, c(\zeta_s, \cdot_s), s)ds + \int_0^t \sigma(\Lambda_s, c(\zeta_s, \cdot_s), s)dW(s) & 0 \leq t \leq T \end{cases}$$

$$\zeta(t) = \begin{cases} \zeta_0(t) & -r \leq t < 0 \\ \zeta_0(0) + \phi(s) & 0 \leq t \leq T \end{cases}$$

Let us consider the following operator:

$$T_t : L^2(\Omega, \Phi) \to L^2(\Omega, \mathscr{C}(J, \mathbb{R}; \mathcal{F}_t)$$

$$T_t(\phi) := \Lambda_t^\phi \in \mathscr{C}(J, \mathbb{R}).$$

Where Λ_t^ϕ is the unique solution guaranteed by the previous results.

Remark 2.3.9. Notice that for all the processes ϕ, ζ^0 is the same, i.e. the initial path for the process ζ is the same. We investigate how the internal dynamics is influenced by similar trajectories.

The functions λ and σ are continuous, uniformly bounded in all variables and are also uniformly Lipschitz in the second and third variable with respect to the first, i.e. there exists $L > 0$ such that

$$\|H(t, \psi_1, \eta_1) - H(t, \psi_2, \eta_2)\|_{L^2} \leq L(\|\psi_2 - \psi_1\|_{L^2(\Omega, \mathscr{C})} + \|\eta_2 - \eta_1\|_{L^2(\Omega, W_T^{1,2}(J))}),$$

$$\|\sigma(t, \psi_1, \eta_1) - \sigma(t, \psi_2, \eta_2)\|_{L^2} \leq L(\|\psi_2 - \psi_1\|_{L^2(\Omega, \mathscr{C})} + \|\eta_2 - \eta_1\|_{L^2(\Omega, W_T^{1,2}(J))}),$$

for all $t \in [0,T]$, for all $\psi_1, \psi_2 \in \mathscr{C}(\overline{J}, \mathbb{R})$ and for all $\eta_1, \eta_2 \in L^2(\Omega, W_T^{1,2}(J))$, where $W_T^{1,2}(J) := \{f : J \to \mathbb{R}^d, f \in W_T^{1,2}\}$.

[2]This particular space has been used since one has:

- a.s it is valid the fundamental theorem of integral calculus with the weak derivatives
- The Poinacré's inequality guarantees that the L^2-norm of the gradient alone is equivalent to the "complete" norm
- the form of the straightforward estimation due to the properties of λ and σ which leads to

$$\mathbf{E}\int_0^t \|\cdot_s\|_{W_T^{1,2}} ds$$

Proposition 2.3.10. *Under all the hypotheses stated above, for the operator T_t defined we have*

$$T_t \in \mathscr{C}\Big(L^2(\Omega, W_T^{1,2}), L^2(\Omega, \mathbb{C}(J, \mathbb{R}; \mathcal{F}_t)\Big);$$

in particular we have

$$\big\|T_t(\phi^1) - T_t(\phi^2)\big\|_{L^2(\Omega,\mathbb{C}(J,\mathbb{R};\mathcal{F}_t)} \leq C_1 \left\|\phi^1 - \phi^2\right\|_{L^2(\Omega,W_T^{1,2})} e^{C_2 t}.$$

Proof. Let[3] $s + t \geq 0$, by writing $[H(\cdot), \sigma(\cdot)] := \mathbb{H}(\cdot)$ and $\xi(u) := [u, W(u)]^T$ one has

$$\begin{aligned}
\big\|T_t(\phi^1) - T_t(\phi^2)\big\|_{L^2(\Omega,\mathbb{C}(J,\mathbb{R};\mathcal{F}_t)} &= \mathbb{E}\Big[\sup_{s\in J}\Big|\int_0^{s+t} [\mathbb{H}(T_s(\phi^1), \phi_s^1, s) - \mathbb{H}(T_s(\phi^2), \phi_s^2, s)] d\xi(s)\Big|^2\Big] \\
&\leq M_1 \int_0^t \mathbb{E}\left\|\mathbb{H}(T_s(\phi^1), \phi_s^1, s) - \mathbb{H}(T_s(\phi^2), \phi_s^2, s)\right\|^2 ds \\
&\leq M_2 \int_0^t \big\|T_s(\phi^1) - T_s(\phi^2)\big\|_{L^2(\Omega,\mathbb{C}(J,\mathbb{R};\mathcal{F}_t)} ds \\
&+ M_2 \int_0^t \left\|\phi_s^1 - \phi_s^2\right\|_{L^2(\Omega,W_T^{1,2}(J))} ds.
\end{aligned}$$

To use in a profitable way Gronwall's lemma it is important to try to write and estimate the last integral in term of $\|\phi^1 - \phi^2\|_{L^2(\Omega,W_T^{1,2})}$.

Since $\phi \in W^{1,2}$, with $\phi(0) = 0$, then it is possible to write $\phi(t) := \int_0^t \partial_t^w[\phi](s)ds$, so we have with $g(\cdot) := \left|\partial_t^w[\phi^1](\cdot) - \partial_t^w[\phi^2](\cdot)\right|^2$, where ∂_t^w is the weak derivative w.r.t. t:

$$\begin{aligned}
\int_0^t \left\|\phi_s^1 - \phi_s^2\right\|_{L^2(\Omega,W_T^{1,2}(J))} ds &= \mathbb{E}\int_0^t \left\|\phi_s^1 - \phi_s^2\right\|_{W_T^{1,2}(J)} ds \\
&\leq C_{W^{1,2}} \cdot \mathbb{E}\int_0^t \left\|\partial_t^w[\phi^1]_s - \partial_t^w[\phi^2]_s\right\|_{L^2(J)} ds \\
&\leq C_{W^{1,2}} \cdot \mathbb{E}\int_0^t \Big[\int_{-r}^0 \left|\partial_t^w[\phi^1](s+u) - \partial_t^w[\phi^2](s+u)\right|^2 du\Big] ds \\
&= C_1 \cdot \mathbb{E}\int_0^t \Big[\int_{-r}^0 g(s+u) du\Big] ds \\
&= C \cdot \mathbb{E}\int_0^t g(s) \cdot \mathcal{L}eb\{[\max(t-s, -r), 0]\} ds \\
&\leq C_2 \cdot \mathbb{E} \cdot \int_0^t g(s) ds.
\end{aligned}$$

[3] the case $s + t < 0$ leads to the above norm being 0 since the starting path - $\zeta^0(t + s)$ - is the same for all ϕ

then,

$$\begin{aligned}\int_0^t \left\|\phi_s^1 - \phi_s^2\right\|_{L^2(\Omega, W_T^{1,2}(J))} ds &= C_2 \cdot \mathbb{E} \int_0^t \left|\partial_t^w[\phi^1](s) - \partial_t^w[\phi^2](s)\right|^2 ds \\ &= C_2 \cdot \mathbb{E} \left\|\partial_t^w[\phi^1](\cdot) - \partial_t^w[\phi^2](\cdot)\right\|_{L^2(0,t)}^2 \\ &\leq C_3 \cdot \mathbb{E} \left\|\phi^1(\cdot) - \phi^2(\cdot)\right\|_{W^{1,2}(0,t)}^2 \\ &= C_3 \cdot \left\|\phi^1(\cdot) - \phi^2(\cdot)\right\|_{L^2(\Omega, W^{1,2}(0,t))}^2.\end{aligned}$$

Hence,

$$\begin{aligned}\left\|T_t(\phi^1) - T_t(\phi^2)\right\|_{L^2(\Omega, \mathbb{C}(J,\mathbb{R};\mathcal{F}_t)} &\leq C_1 \left\|\phi^1 - \phi^2\right\|_{L^2(\Omega, W^{1,2}(0,t))} \\ &\quad + C_2 \cdot \int_0^t \left\|T_s(\phi^1) - T_s(\phi^2)\right\|_{L^2(\Omega, \mathbb{C}(J,\mathbb{R};\mathcal{F}_t)} ds,\end{aligned}$$

which implies, through Gronwall's inequality, the desired relation, i.e.

$$\left\|T_t(\phi^1) - T_t(\phi^2)\right\|_{L^2(\Omega, \mathbb{C}(J,\mathbb{R};\mathcal{F}_t)} \leq C_1 \left\|\phi^1 - \phi^2\right\|_{L^2(\Omega, W^{1,2}(0,t))} e^{C_2 t}.$$

□

2.3.3 Markov Property

In this section we investigate the Markov property of the solution process. In some cases, apparently non-Markovian processes may still have Markovian representations, constructed by expanding the concept of the *current* and *future* states. The process $\Lambda(t)$ is clearly non-Markovian when the dependence involves the segment process Λ_t. In order to obtain some kind of Markov property it is necessary to enlarge the spaces in the same fashion as it is done in the standard SFDE [91].

Since the notation for the full system might lead to a quite unreadable result, we decide to perform explicitly the analysis on a simpler version of our model.

We concentrate our attention on the following system of equations:

$$\begin{aligned}\theta(t) &= \theta_0(0) + \overline{\sum}_{j=0}^{N(t)} Y_j \\ \Lambda(t) &= \Lambda_0 + \int_0^t \lambda(\mathcal{Q}(s), s, \Lambda_s, \theta(s)) ds + \int_0^t \sigma \cdot dW(s),\end{aligned} \tag{2.3.1}$$

where for $0 \leq t \leq T$, we have

$$N(t) = \begin{cases} n_0(t) = \sup\{n \in \mathbb{N} : n \leq \sup_{s\in[0,t]} \Lambda(s)\} & -r \leq t < 0 \\ N(t) = n_0 + \sum_{k=1}^{\infty} \chi_{[\tau_{n_0+k}, \infty)}(s) & 0 \leq t \leq T \end{cases}$$

$$\tau_n = \begin{cases} 0 & n = 0 \\ \inf\{s > \tau_{n-1} : \Lambda(s) = \tau_n^{\mathcal{N}}\} & n \geq 1, \end{cases}$$

and for $t \in [-r, 0]$ assuming the initial processes:

$$(\theta(t))_{t\in[-r,0]}, \quad (\Lambda_0(t))_{t\in[-r,0]}, \quad (n_0(t))_{t\in[-r,0]}.$$

Theorem 2.3.11. *Assume that the condition of existence and uniqueness for the system (2.3.1) stated in Theorem 2.3.7 holds. Let us consider the space F, that takes into account the space where the segment for each components lives, i.e.*

$$F := \mathscr{C}([-r, 0], \mathbb{R}) \times \mathscr{C}([-r, 0], \mathbb{R}) \times \mathscr{C}([-r, 0], \mathbb{N}).$$

Let $\Phi^{\phi_0}(t) = (\Lambda(t), \theta(t), N(t))$ be a stochastically continuous *solution of the system (2.3.1) with initial value $\phi_0 := (\Lambda_0, \theta_0, n_0) \in \mathbf{M}_F^2$. For each of such ϕ_0, Φ^{ϕ_0} describes a Markov process on F. That means that for all $B_F \in \mathcal{B}(F)$*

$$\mathbf{P}\Big(\Phi_t \in B_F \Big| \mathcal{F}_s\Big) = \mathbf{P}\Big(\Phi_t \in B_F \Big| \sigma\{\Phi_s\}\Big).$$

In order to proof this result, we need the following

Lemma 2.3.12 (Factorization Lemma, [33])**.** *Let $T : \Omega \to \Omega'$ be a function of a set Ω in a measure space $(\Omega', \mathcal{A}')$ and let $f : \Omega \to \overline{\mathbb{R}}$ be a scalar function on Ω. Then f is measurable with respect to the σ-algebra $\sigma(T) = T^{-1}(\mathcal{A}')$ generated by T in Ω if and only if there exists a measurable function $g : (\Omega', \mathcal{A}') \to (\overline{\mathbb{R}}, \mathcal{B}(\overline{\mathbb{R}}))$ such that $f = g \circ T$, where $\mathcal{B}(\overline{\mathbb{R}})$ denotes the Borel set of the real numbers. If f only takes finite values, then g takes only finite values, too.*

Proof of Theorem 2.3.11. Let us fix $u \geq 0$ and consider for $t \geq u$ the system of equations (2.3.1) with initial condition for $t \in [u - r, u]$ the vector $\phi_0 := (\Lambda_0, \theta_0, n_0) \in \mathbf{M}_F^2$, which is $\mathcal{F}_u$-measurable.
Let us denote by ${}^{(\psi,u}\Phi(t))_{t\in[u-r,T]} := (\Lambda(t), \theta(t), N(t))_{t\in[u-r,T]}$ the unique solution. We will be using the usual notation for the segment process, i.e ${}^{(\psi,u}\Phi_t)_{t\in[u,T]}$.
Let us define $\mathcal{G}_u$ as $\mathcal{G}_u := \sigma\{W(s) - W(u) : s \geq u\}$. We have from Theorem 2.3.7 that this σ-algebra is independent of $\mathcal{F}_u$. From the *stochastic continuity* and $\mathcal{G}_u$-measurability of the process solution for $t \geq u$ one has by Lemma 3.2 in [108] the $\mathcal{G}_u$-measurability of the segment process as well.
The uniqueness of the solution implies that, with probability one,

$${}^{\Phi_u,u}\Phi(s) = \Phi(s), s \geq u - r,$$

and thus

$${}^{\Phi_u,u}\Phi_t = \Phi_t, t \geq u.$$

By construction the solution process is, via a Borel-measurable map, the image of the (Borel-measurable) initial condition.
Let us consider the function:

$$A : F \times \Omega \to \mathbb{R},$$

$$(\psi, \omega) \mapsto \chi_{B_F}\Big({}^{\psi,u}\Phi(\omega)\Big).$$

This function is measurable for all $B_F \in \mathcal{B}(F)$ and is independent of $\mathcal{F}_u$ for a fixed ψ.

An application of the factorization lemma concludes the proof of the result.
Let $B := B_F$, then from the following equalities

$$\mathbf{P}\Big(\Phi_t \in B\Big|\mathcal{F}_u\Big) = \mathbb{E}\Big[\chi_B\Big(^{\Phi_u,u}\Phi_t\Big)\Big|\mathcal{F}_u\Big] = \mathbb{E}\Big[A(\Phi_u,\cdot)\Big|\mathcal{F}_u\Big] = \mathbb{E}\Big[A(\psi,\cdot\Big]\Big|_{\psi=\Phi_u},$$

we conclude the proof, since the right hand side is $\sigma(\Phi_u)$-measurable. □

2.4 Distribution of the time spent in a specific state

In this section we investigate the distribution of the time spent by the system in a specific state, i.e. we will study the distribution of the following random variable:

$$\alpha^j_\Lambda := \inf\{s > \alpha^{j-1}_\Lambda : \Lambda(s) > \tau_j\}.$$

In the next subsection we will start investigating some special cases in order to show how complex the problem might become. We will then approach the problem from another prospective and related the random time α^j_Λ with a martingale problem associated with the system of equations HSHS.

2.4.1 Distribution of the time of the first state-change in various scenarios

The analysis of the stochastic system described in the previous sections is far too complicated for us to be treated in a general way: in the present section some special cases and some associated distributions are considered. Let $\lambda, \sigma > 0$ and constant. In what follows we show that special values of the parameters and the distribution of the random variables a_j, which define the process $\mathcal{N}(t)$ might lead to an interesting situation:

Exponential Barrier

Let $a_j \sim \mathcal{E}xp(\beta)$ then the probability of the first jump for the process $N(\sup(\Lambda^*))$ is given by a random variable X whose distribution can be called *Compound-Exponential-Inverse Gaussian Distribution.*

$$\frac{d}{dt}\mathbf{P}\Big(\inf\{s>0 : \Lambda := \lambda s + \sigma W(s) = a_1\} < t\Big) = \int_0^\infty f_{IG}\Big(\frac{\alpha}{\lambda}, \frac{\alpha^2}{\sigma^2}\Big) f_E(\alpha) d\alpha,$$

where $f_{IG}(a,b)$ is the density function of an inverse Gaussian distribution and f_E the one of an exponential distribution with parameter β, explicitly using formula [G.R. 3.462.5][4]

$$f_X(t) = \beta e^{-\frac{\lambda^2}{2\sigma^2}t}\Big\{\frac{\sigma}{\sqrt{2\pi t}} - \frac{\sigma^2}{2}\Big(\beta - \frac{\lambda}{\sigma^2}\Big)e^{\frac{\sigma^2}{2}\left(\beta-\frac{\lambda}{\sigma^2}\right)^2 t}\Big[1 - \Phi\Big(\sqrt{\frac{\sigma^2}{2}\Big(\beta - \frac{\lambda}{\sigma^2}\Big)}\Big)\Big]\Big\},$$

[4] $\int_0^\infty x e^{-\mu x^2 - \nu x} dx = \frac{1}{2\nu} - \frac{\mu}{4\nu}\sqrt{\frac{\pi}{\mu}} e^{\frac{\nu^2}{4\mu}}\Big[1 - \Phi\Big(\frac{\nu}{2\sqrt{\mu}}\Big)\Big]$

whose moment generating function is given by

$$M(u) = \beta\sigma^2 \frac{1}{\sqrt{\lambda^2 - 2\sigma^2 u}} \Big[1 - \Big(\beta - \frac{\lambda}{\sigma^2}\Big) \frac{\sigma^2}{\sigma^2(\beta - \frac{\lambda}{\sigma^2}) + \sqrt{\lambda^2 - 2\sigma^2 u}} \Big].$$

Pareto-Type Barrier

Let the random variable a_1 follow a Pareto distribution with parameters (x_m, α), i.e.

$$F_{a_1}(x) = \Pr(a_1 > x) = \begin{cases} \left(\frac{x_{\mathrm{m}}}{x}\right)^{\alpha} & x \geq x_{\mathrm{m}}, \\ 1 & x < x_{\mathrm{m}}. \end{cases}.$$

In this case we were not able to obtain an explicit formula for the density. We specialize it to a Pareto distribution starting from the level $x_m = 1$ and parameter β.
We obtain

$$f_X(t) = \frac{\beta}{\sigma\sqrt{2\pi t^3}} e^{-\frac{\lambda^2}{2\sigma^2}t} \int_1^{\infty} \alpha^{-\beta} e^{\frac{\lambda}{\sigma^2}\alpha - \frac{1}{2\sigma^2 t}\alpha^2}.$$

In this case not all the moments of the distribution are finite. Using Fubini's Theorem and the properties of the modified Bessel function of the second kind, it can be shown that if $\lambda = \sqrt{2}\sigma$, then $X_\beta \notin L^1$ for $\beta \in (0,1)$, $X_\beta \in L^1/L^2$ for $\beta \in (1,2)$ and $X_\beta \in L^n$ for all the other β.

For the mean of this random variable let us consider:

$$\begin{aligned} \mathbb{E}[X] = \int_\Omega X P_X(d\omega) &= \int_0^{\infty} dt \int_1^{\infty} d\alpha \Big[\beta \frac{1}{\alpha^\beta} \frac{t}{\sigma\sqrt{2\pi t^3}} \exp\Big\{ -\frac{\lambda^2}{2\sigma^2}t - \frac{\alpha^2}{2\sigma^2 t} + \frac{\lambda}{\sigma^2}\alpha \Big\} \Big] \\ &= \int_1^{\infty} d\alpha \frac{\beta}{\alpha^\beta} e^{\frac{\lambda}{\sigma^2}\alpha} \int_0^{\infty} dt \Big[\frac{1}{\sigma\sqrt{2\pi t}} \exp\Big\{ -\frac{\lambda^2}{2\sigma^2}t - \frac{\alpha^2}{2\sigma^2 t} \Big\} \Big]. \end{aligned}$$

From formula [G.R. 3.471.9][5] it follows that:

$$\mathbb{E}[X] = \int_1^{\infty} \frac{\beta}{\alpha^\beta} e^{\frac{\lambda}{\sigma^2}\alpha} \frac{1}{\sigma\sqrt{2\pi}} 2\sqrt{\frac{\alpha}{\lambda}} K_{1/2}\Big(2\frac{\alpha}{\lambda}\Big) d\alpha.$$

We were not able to find the explicit formula for this integral, but only conditions on convergence or divergence.

By employing formulae for the modified Bessel functions of the second kind with index of multiple of half order:

$$K_\nu(z) = \sqrt{\frac{\pi}{2}} \sum_{j=0}^{[|\nu|-1/2]} \frac{(j + |\nu| - \frac{1}{2})!}{j!(-j + |\nu| - \frac{1}{2})!} (2z)^{-j}, \quad \nu - \frac{1}{2} \in \mathbb{Z}.$$

In particular for $\nu = \frac{1}{2}$

$$K_{\frac{1}{2}}(z) = \sqrt{\frac{\pi}{2}} \frac{e^{-z}}{\sqrt{z}}.$$

[5] $\int_0^{\infty} x^{\nu-1} e^{-\frac{\beta}{x} - \gamma x dx} = 2\Big(\frac{\beta}{\gamma}\Big)^{\frac{\nu}{2}} K_\nu(2\sqrt{\beta\gamma})$

So the integral

$$\mathbb{E}[X] \sim C \int_0^\infty \alpha^{-\beta} \exp\Big\{\Big(\frac{\lambda}{\sigma^2} - \frac{2}{\lambda}\Big)\alpha\Big\} d\alpha \Rightarrow \begin{cases} \mathbb{E}[X] = \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} > 0 \wedge \forall \beta \\ \mathbb{E}[X] = \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} = 0 \wedge \beta \leq 1 \\ \mathbb{E}[X] < \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} < 0 \wedge \forall \beta \\ \mathbb{E}[X] < \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} = 0 \wedge \beta > 1 \end{cases}.$$

In a similar way it is possible to check the second moment: employing formula [G.R. 3.471.9] for $\mathbb{E}[X^2]$, one has

$$\begin{aligned} \mathbb{E}[X^2] = \int_\Omega X^2 P_X(d\omega) &= \int_0^\infty dt \int_1^\infty d\alpha \Big[\beta \frac{1}{\alpha^\beta} \frac{t^2}{\sigma\sqrt{2\pi t^3}} \exp\Big\{ - \frac{\lambda^2}{2\sigma^2} t - \frac{\alpha^2}{2\sigma^2 t} + \frac{\lambda}{\sigma^2}\alpha \Big\}\Big] \\ &= \int_1^\infty \frac{2\beta}{\alpha^{\beta-1}} e^{\frac{\lambda}{\sigma^2}\alpha} \frac{1}{\sigma\sqrt{2\pi}} 2\Big(\frac{\alpha^2}{\lambda^2}\Big)^{\frac{3}{4}} K_{3/2}\Big(2\frac{\alpha}{\lambda}\Big) d\alpha. \end{aligned}$$

And from the formulae above stated for $K_{3/2}(z)$, which reads

$$K_{3/2}(z) = \sqrt{\frac{\pi}{2}} \frac{e^{-z}}{\sqrt{z}} \Big(1 + C\frac{1}{z}\Big)$$

one obtains

$$\mathbb{E}[X^2] \sim C \int_0^\infty \alpha^{-\beta+\frac{5}{2}} \exp\Big\{\Big(\frac{\lambda}{\sigma^2} - \frac{2}{\lambda}\Big)\alpha\Big\} \frac{1}{\sqrt{\alpha}} \Big(1 + \frac{C}{\alpha}\Big) d\alpha \Rightarrow \begin{cases} \mathbb{E}[X^2] = \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} > 0 \wedge \forall \beta \\ \mathbb{E}[X^2] = \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} = 0 \wedge \beta \leq 2 \\ \mathbb{E}[X^2] < \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} < 0 \wedge \forall \beta \\ \mathbb{E}[X^2] < \infty & \frac{\lambda}{\sigma^2} - \frac{2}{\lambda} = 0 \wedge \beta > 2 \end{cases}.$$

Deterministic Barrier

Let us suppose that the process Λ needs to reach a deterministic level $a_1 = 1$. In this case the distribution jumps of the process $\mathcal{N}$ is connected with the supremum of the stochastic process Λ: more precisely with the supremum of a Brownian motion with drift.
Let T_j be the time of the j-th jump, then

$$\mathbf{P}\Big(N(t) = 0\Big) = \mathbb{P}\Big(\tau_1^\Lambda \leq t\Big) = 1 - \Phi\Big(\frac{\lambda(t - 1/\lambda)}{\sigma\sqrt{t}}\Big) - e^{2\frac{\lambda}{\sigma^2}} \Phi\Big(- \frac{\lambda(t + 1/\lambda)}{\sigma\sqrt{t}}\Big)$$

$$\begin{aligned} \mathbf{P}\Big(N(t) = 1 | T_1 = s\Big) &= \mathbf{P}\Big(\tau_2^\Lambda \geq t | T_1 = s\Big) = \mathbb{P}\Big(\tau_1^\Lambda > t - s\Big) \\ &= 1 - \Phi\Big(\frac{\lambda(t - s - 1/\lambda)}{\sigma\sqrt{t-s}}\Big) - e^{2\frac{\lambda}{\sigma^2}} \Phi\Big(- \frac{\lambda(t - s + 1/\lambda)}{\sigma\sqrt{t-s}}\Big). \end{aligned}$$

similarly

$$\mathbf{P}\Big(N(t) = k | T_{k-j} = s\Big) = \mathbf{P}\Big(\tau_j^\Lambda \geq t - s\Big)$$

$$= 1 - \Phi\Big(\frac{\lambda(t-s-j/\lambda)}{\sigma\sqrt{t-s}}\Big) - e^{2\frac{\lambda}{\sigma^2}}\Phi\Big(-\frac{\lambda(t-s+j/\lambda)}{\sigma\sqrt{t-s}}\Big),$$

and in particular

$$\mathbf{P}\Big(N(t)=1|T_1\le s\Big) = \int_0^s \mathbf{P}\Big(\tau_1^\Lambda \ge t-u\Big)\mathbf{P}_{\tau_1^\Lambda}(du).$$

Remark 2.4.1. We notice that an opportune choice of the parameters can lead to very different behavior:

- the distribution of the first jump belongs to $\mathcal{L}^2$: in this case we might infer that a Central Limit result can be applied
- the distribution of the first jump does not belong to $\mathcal{L}^2$: in this case we have to consider fractional processes when we investigate the limit distribution of the rescaled process.

2.4.2 Distribution of the time of the first state-change and a related martingale problem

The structure of the system is intimately connected with the one of the cádlág processes

$$\begin{aligned}\theta(t) &= \begin{cases}\theta_0(t) & -r\le t<0\\ \theta_0(0)+\overline{\sum}_{j=0}^{\Psi(t)}Y_j & 0\le t\le T\end{cases}\\ \Psi(t) &= \mathcal{N}(\Xi(t^-)),\\ \Xi(t) &= \sup_{s\le t}\Lambda(s).\end{aligned}$$

In order to deal with this quite difficult problem in what follows we assume that $\mathcal{N}$ is defined, for a fixed a_0, as follows:

$$\mathcal{N}(t) = \sum_{k\in\mathbf{N}} k\cdot a_0\mathbf{1}_{[k,k+1[}(t).$$

Now the jumping points for the cádlág part are determined by the hitting times of the underlying functional diffusion $\Lambda(t)$.
Let us define

$$\mu(dt,dx) = \sum_{n=1}^{\infty}\mathbf{1}_{\{T_n<\infty\}}\epsilon_{(T_n,Z_n)}(dt,dx).$$

By following [68], and denoting by $G_n(\omega,ds,dx)$ the regular version of the conditional distribution of (T_{n+1},Z_{n+1}) with respect to $\mathcal{G}(n)$ then

Theorem 2.4.2. *Under suitable conditions on the filtration a version of the compensator of the E-valued multivariate point process μ is*

$$\nu(dt,dx) = \sum_{n=1}^{\infty}\frac{1}{G_n([t,\infty],E)}\mathbf{1}_{\{t\le T_{n+1}\}}G_n(dt,dx).$$

The problem now moves to the determination of the probability distribution of these stopping times. The idea is to follow the approach in [55, 104] connecting the desired probability distribution to the solution of a certain differential equation: this approach can be considered as a generalization of the classical Feynman-Kac formula.

2.4.3 The Feynman-Kac Formula

In this section we prove the Feynman-Kac Formula for SFDE and extend the results in [64] and [26].
Let us consider the following autonomous SFDE:

$$dX(s) = H(X(s), X_s)ds + G(X(s), X_s)dW(s), \quad s \in [0, T], \tag{2.4.1}$$

with the initial condition $\eta \in L^2(\Omega, L^2([-r, 0], \mathbb{R}^d))$, at time $t = 0$.

Assumption A: $H \in \mathbb{L}^{1,2}$ and $G \in \mathbb{L}^{1,2}$ are adapted functions that satisfy the hypothesis of Lipschitz continuity with respect to both arguments.

Remark 2.4.3. We stress that **Assumption A** guarantees existence and uniqueness of the solution of equation (2.4.1) (see [91]).

2.4.4 Representation Formula

The following theorem extends Theorem 9.5 in [64].

Theorem 2.4.4. *Suppose $f \in \mathcal{D}(\mathcal{A}_w)$ and $c : L^2([-r, 0]) \times \mathbb{R}^d \to \mathbb{R}_+$ bounded and Lipschitz continuous. If u solves weakly*

$$\frac{\partial}{\partial t}u(t) + \mathcal{A}_w(u(t)) + c \cdot u(t) = 0,$$

$$u(T, \eta, x) = f(\eta, x),$$

with $\mathcal{A}_w$ as defined in Theorem A.3.2, then

$$u(t, \eta, x) := \mathbb{E}_{(t,\eta,x)}\Big[f({}^{\eta}X_T, {}^{\eta}X_T(0))e^{\int_t^T c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big].$$

Proof. Let us suppose that u is a solution of the above FPDE.

Fix $0 \le t_0 < T$. Define for all $t_0 \le t \le T$

$$q(t) := \mathbf{E}\Big[u(t, X_t, X_t(0))e^{\int_{t_0}^t c(X_s, X_s(0))ds} \| \mathcal{F}_{t_0}\Big].$$

Now we calculate the right derivative (if it exists) of $q(t)$.
Since the process $(X_t, X(t))$ is a Markov process, the following equality holds:

$$\begin{aligned} q(t_2) - q(t_1) &= \mathbf{E}\Big\{\mathbf{E}\Big[u(t_2, X_{t_2}, X_{t_2}(0))e^{\int_{t_0}^{t_2} c(X_s, X_s(0))ds} \\ &\qquad - u(t_1, X_{t_1}, X_{t_1}(0))e^{\int_{t_0}^{t_1} c(X_s, X_s(0))ds} \| \mathcal{F}_{t_1}\Big] \| \mathcal{F}_{t_0}\Big\} \\ &= \mathbf{E}\Big\{\mathbf{E}\Big[u(t_2, X_{t_2}, X_{t_2}(0))e^{\int_{t_1}^{t_2} c(X_s, X_s(0))ds} - u(t_1, X_{t_1}, X_{t_1}(0)) \| \mathcal{F}_{t_1}\Big] \\ &\qquad \cdot e^{\int_{t_0}^{t_1} c(X_s, X_s(0))ds} \| \mathcal{F}_{t_0}\Big\}. \end{aligned}$$

Consider the process

$$Y(t) = e^{\int_{t_1}^t c(X_s, X_s(0))ds},$$

solution of the following stochastic integral equation:

$$Y(t) = 1 + \int_{t_1}^t c(X_s, X_s(0))Y(s)ds.$$

The idea is to apply now the Itô-Mohammed-Yan formula (Theorem A.3.2) to the process

$$h(t, X_t, X_t(0), Y(t)) = u(t, X_t, X(0)) \cdot Y(t)$$

and calculate explicitly the right derivative of the projection of the random variable $h(t)$ on the space $L^2(\mathcal{F}_{t_1})$. We have that the processes involved are adapted (see [91]), in particular for the process Y, $D_s Y(\alpha) = 0$. A straightforward use of the formula leads to

$$\begin{aligned}
h(t, X_t, X_t(0), Y(t)) = \; & h(t_1, X_{t_1}, X_{t_1}(0), Y(t_1)) \\
(i) = & \int_{t_1}^t c(X_s, X_s(0))u(s, X_s, X(s))e^{\int_{t_1}^s c(X_u, X_u(0))du}ds \\
(ii) + & \int_{t_1}^t \frac{\partial u}{\partial s}(s, X_s, X(s))e^{\int_{t_1}^s c(X_u, X_u(0))du}ds \\
(iii) + & \int_{t_1}^t \langle \frac{\partial u}{\partial \eta}(s, X_s, X(s))e^{\int_{t_1}^s c(X_u, X_u(0))du}, dX_s \rangle_V \\
(iv) + & \int_{t_1}^t \frac{\partial u}{\partial x}(s, X_s, S(s))e^{\int_{t_1}^s c(X_u, X_u(0))du}dX(s) \\
(v) + & \int_{t_1}^t \frac{\partial^2 u}{\partial \eta^2}(s, X_s, X(s))(\Theta_s)e^{\int_{t_1}^s c(X_u, X_u(0))du}ds \\
(vi) + & \int_{t_1}^t \frac{\partial^2 u}{\partial \eta \partial x}(s, X_s, X(s))[(G\Lambda)_s X(s)]e^{\int_{t_1}^s c(X_u, X_u(0))du}ds \\
(vii) + & \int_{t_1}^t \frac{\partial^2 u}{\partial x \partial \eta}(s, X_s, X(s))[G(s)D_s X_s]e^{\int_{t_1}^s c(X_u, X_u(0))du}ds \\
(viii) + & \frac{1}{2}\sum_{i=1}^d \int_{t_1}^t e^{\int_{t_1}^s c(X_u, X_u(0))du}\frac{\partial^2 u}{\partial x^2}(s, X_s, X(s))[(\nabla_+^i X)(s) \otimes G^i(s)]ds,
\end{aligned}$$

where

$$\Theta_s(\alpha, \beta) = \frac{1}{2}((G\Lambda)_s X_s(\alpha, \beta) + (G\Lambda)_s X_s(\beta, \alpha))$$

$$(G\Lambda)_s X_s(\alpha, \beta) = \mathbf{I}_{\{0 \le s+\alpha\wedge\beta\}} G(s+\alpha) D_{s+\alpha} X(s+\beta)$$

$$(\nabla_+^i X)(s) = \lim_{\epsilon \to 0}(D_t^i X(t+\epsilon) + D_t^i X(t-\epsilon)).$$

We treat now every single term (identified by the Roman number (α)), calculating the limit for t approaching t_1 of the quantity $\frac{1}{t-t_1} \cdot \mathbb{E}[(\alpha) \| \mathcal{F}_{t_1}]$.

Since we consider the limit of the projection on the σ-algebra $\mathcal{F}_{t_1}$, we consider for $t > t_1$ the SFDE with B a Brownian motion s.t. $B(t) = 0$ in $[-r, t_1]$ and $Z(t) = X(t)$,

$$Z(t) = X_{t_1}(0) + \int_{t_1}^{t\vee t_1} H(Z_s, Z(s))ds + \int_{t_1}^{t\vee t_1} G(Z_s, Z(s))dB(s),$$

so that $\|\Theta_s\|_{(V\otimes V)^*} \to 0$.
In this case it follows that the addends (v),(vi) and (vii) converge to 0.
A straightforward calculation for the terms (i), (ii), (iv), using the boundedness and Lipschitz continuity of the function c, leads to:

- for the term (i):

$$\lim_{t_2\searrow t_1} \mathbf{E}\Big[\frac{1}{t_2 - t_1}\int_{t_1}^{t_2} c(X_s, X_s(0))u(s, X_s, X(s))e^{\int_{t_1}^{s} c(X_u, X_u(0))du}\|\mathcal{F}_{t_1}\Big]$$
$$= c(X_{t_1}, X_{t_1}(0))u(t_1, X_{t_1}, X(t_1));$$

- for the term (ii):

$$\lim_{t_2\searrow t_1} \mathbf{E}\Big[\frac{1}{t_2 - t_1}\int_{t_1}^{t_2} \frac{\partial u}{\partial s}(s, X_s, X(s))e^{\int_{t_1}^{s} c(X_u, X_u(0))du}ds\|\mathcal{F}_{t_1}\Big]$$
$$= \frac{\partial u}{\partial t}(t_1, X_{t_1}, X(t_1));$$

- for the term (iv):

$$\lim_{t_2\searrow t_1} \mathbf{E}\Big[\frac{1}{t_2 - t_1}\int_{t_1}^{t_2} \frac{\partial u}{\partial x}(s, X_s, S(s))e^{\int_{t_1}^{s} c(X_u, X_u(0))du}dX(s)\|\mathcal{F}_{t_1}\Big]$$
$$= \lim_{t_2\searrow t_1} \mathbf{E}\Big[\frac{1}{t_2 - t_1}\int_{t_1}^{t_2} \frac{\partial u}{\partial x}(s, X_s, S(s))e^{\int_{t_1}^{s} c(X_u, X_u(0))du}$$
$$\cdot H(X_s, X_u(s))ds\|\mathcal{F}_{t_1}\Big] + 0$$
$$= H(X_{t_1}, X(t_1))\frac{\partial u}{\partial x}(t_1, X_{t_1}, X(t_1));$$

- we now concentrate our attention on the third term (iii).

This term contains an integral with respect to the *segment process* (we refer to the Appendix for its definition and properties).
We have to check that for the function

$$g(t) := \int_{t_0}^{t} \langle\frac{\partial u}{\partial \eta}(s, X_s, X(s)e^{\int_0^t c(X_u, X_u(0))du}, dX_s\rangle_V,$$

it holds:

$$\lim_{t_2\searrow t_1} \mathbf{E}\Big[\frac{g(t_2) - g(t_1)}{t_2 - t_1}\|\mathcal{F}_{t_1}\Big] = \langle\frac{\partial u}{\partial \eta}(t_1, X_{t_1}, X_{t_1}(0), dX_{t_1}\rangle_V \cdot e^{\int_{t_0}^{t_1} c(X_u, X_u(0))du}.$$

By taking into account that c is Lipschitz continuous and bounded, by the stochastic Fubini's theorem (Lemma 4.2 in [64]) and the definition of segment integral, we may compute the following limit: Let us define $(*)$, as follow

$$\lim_{t_2 \searrow t_1} \mathbf{E}\Big[\frac{g(t_2)-g(t_1)}{t_2-t_1}\|\mathcal{F}_{t_1}\Big] = (*),$$

then we have

$$\lim_{t_2 \searrow t_1} \mathbf{E}\Big[\int_r^0 \int_{t_1}^{t_2} e^{\int_{t_1}^{t_2} c(X_u, X_u(0))du} \frac{\partial u}{\partial \eta}(s, X_s, X(s))(\alpha) dX(\alpha+s) d\alpha \Big\| \mathcal{F}_{t_1}\Big] e^{\int_{t_0}^{t_1} c(X_u, X_u(0))du}.$$

We omit in what follows the factor $e^{\int_{t_0}^{t_1} c(X_u, X_u(0))du}$.

$$\begin{aligned}
(*) = \lim_{t_2 \searrow t_1} \mathbf{E}\Big[\int_r^0 \frac{1}{t_2-t_1}\int_{t_1}^{t_2} e^{\int_{t_1}^{s} c(X_u, X_u(0))du} \\
\cdot \frac{\partial u}{\partial \eta}(s, X_s, X(s))(\alpha)\mathbf{1}_{\{s+\alpha \geq t_1\}} dX(\alpha+s)d\alpha \Big\| \mathcal{F}_{t_1}\Big] \\
+ \lim_{t_2 \searrow t_1} \mathbf{E}\Big[\int_r^0 \frac{1}{t_2-t_1}\int_{t_1}^{t_2} e^{\int_{t_1}^{s} c(X_u, X_u(0))du} \\
\cdot \frac{\partial u}{\partial \eta}(s, X_s, X(s))(\alpha)\mathbf{1}_{\{s+\alpha > t_1\}} H(\alpha+s) ds d\alpha \Big\| \mathcal{F}_{t_1}\Big]
\end{aligned}$$

$$\begin{aligned}
+ \lim_{t_2 \searrow t_1} \mathbf{E}\Big[\int_r^0 \frac{1}{t_2-t_1}\int_{t_1}^{t_2} e^{\int_{s}^{t_2} c(X_u, X_u(0))du} \\
\cdot \frac{\partial u}{\partial \eta}(s, X_s, X(s))(\alpha)\mathbf{1}_{\{s+\alpha > t_1\}} G(s+\alpha) dW(\alpha+s) d\alpha \Big\| \mathcal{F}_{t_1}\Big] \\
= \langle \frac{\partial u}{\partial \eta}(t_1, X_{t_1}, X_{t_1}(0), dX_{t_1}\rangle_V = Su(t_1, X_{t_1}, X_{t_1}(0),
\end{aligned}$$

since the second and third integrals are 0. From the hypothesis

$$\Big(\frac{\partial}{\partial t} + \mathcal{A}_w + c\cdot \mathbb{I}\Big) u(t, \eta, \eta_{t_1}(0)) = 0,$$

so that we can conclude that on $\mathcal{F}_{t_0}$

$$\lim_{t_2 \searrow t_1} \frac{q(t_2)-q(t_1)}{t_2-t_1} =$$

$$= \mathbf{E}\Big\{\mathbf{E}\Big[\Big(\frac{\partial}{\partial t} + \mathcal{A}_w + c\cdot \mathbb{I}\Big) u(t_1, X_{t_1}, X_{t_1}(0)) \|\mathcal{F}_{t_1}\Big] e^{\int_{t_0}^{t_1} c(X_s, X_s(0))ds} \|\mathcal{F}_{t_0}\Big\} \equiv 0.$$

Thus the function q is continuous and has continuous right derivatives. By a well-known Lemma ([131], p. 239), q is differentiable and hence a constant. We conclude that

$$\begin{aligned}
q(t_0) = q(T) &= \mathbf{E}\Big[u(T, X_T, X(T)) e^{\int_{t_0}^{T} c(X_s, X_s(0))ds} \|\mathcal{F}_{t_0}\Big] \\
&= \mathbf{E}\Big[f(X_T, X(T)) e^{\int_{t_0}^{T} c(X_s, X_s(0))ds} \|\mathcal{F}_{t_0}\Big].
\end{aligned}$$

□

This theorem can be generalized to the case where c is time in-homogenous by using the same approach.

Corollary 2.4.5. *Suppose $f \in \mathcal{D}(\mathcal{A}_w)$ and $c : [-r, T] \times L^2([-r, 0]) \times \mathbb{R}^d \to \mathbb{R}_+$ bounded and (*maybe *Lipschitz) continuous: if u solves weakly*

$$\frac{\partial}{\partial t}u(t) + \mathcal{A}_w(u(t)) + c(t, \cdot) \cdot u(t) = 0,$$

$$u(T, \eta, x) = f(\eta, x),$$

with $\mathcal{A}_w$ as defined in Theorem A.3.2, then

$$u(t, \eta, x) := \mathbb{E}_{(t,\eta,x)}\Big[f({}^{\eta}X_T, {}^{\eta}X_T(0))e^{\int_t^T c(s, {}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big]$$

In what follows, we assume that **Assumption A** is satisfied. Consider the following SFDE:
Set $\eta_0 : [-r, t] \to \mathbb{R}^d$, with $\eta_0(s) = \eta_0(0)$ for $s \geq 0$ and $t_s^{t,\eta} = t - s$. If $s \in [-r, t]$

$$X^{t,\eta}(s) = \eta_0(s) + \int_0^{s\vee 0} H(t_s^{t,\eta}, X_u^{t,\eta}, X^{t,\eta}(u))ds + \int_0^{s\vee 0} G(t_s^{t,\eta}, X_u^{t,\eta}, X^{t,\eta}(u))dW(u).$$

In accordance with the previous section, it is possible to define a Markov family

$$\Big(t_s^{t,\eta}, {}^{\eta}X_s, {}^{\eta}X_s(0)\Big) \in \mathbb{R} \times L^2([-r, 0], \mathbb{R}^d) \times \mathbb{R}^d.$$

In this case the infinitesimal generator is given by $\mathcal{A}_w^-$, defined as

$$\begin{aligned}\widetilde{\mathcal{A}}_w^-\Phi(t, \phi) = &- \frac{\partial}{\partial t}\Phi(t, \phi_t) + S(\Phi)(t, \phi_t) + \overline{D\Phi(t, \phi_t}(H(t, \phi_t)\mathbf{1}_{\{0\}}) \\ &+ \frac{1}{2}\sum_{j=1}^{m} \overline{D^2\Phi(t, \phi_t}(G(t, \phi_t)(\mathbf{e}_j)\mathbf{1}_{\{0\}}, G(t, \phi_t)(\mathbf{e}_j)\mathbf{1}_{\{0\}}).\end{aligned}$$

If the coefficients are homogenous in time, then we have the following result:

Corollary 2.4.6. *Suppose $f \in \mathcal{D}(\mathcal{A}_w^-)$. If u solves weakly*

$$\frac{\partial}{\partial t}u(t) = \widetilde{\mathcal{A}}_w^-(u(t)),$$

$$u(0, \eta, x) = f(\eta, x),$$

then

$$u(t, \eta, x) = \mathbb{E}_{(0,\eta,x)}\Big[f({}^{\eta}X_t, {}^{\eta}X_t(0))\Big]$$

Proof. Let $u(t, \eta, x)$ be a solution of $\frac{\partial}{\partial t}u(t) = \mathcal{A}_w(u(t))$, $u(0, \eta, x) = f(\eta, x)$. Consider now, for a fixed but arbitrary T, the function $v(t, \eta, x) := u(T - t, \eta, x)$. Let us consider now the random variable

$$q(t) := \mathbb{E}[v(t, X_t, X(t))\|\mathcal{F}_0].$$

Exactly as before $\frac{d}{dt^+}q(t) = 0$ on $\mathcal{F}_0$, one has the equalities:

$$\begin{aligned} q(0) = q(T) &= \mathbf{E}\Big[v(T, X_T, X(T))\|\mathcal{F}_0\Big] \\ &= \mathbf{E}\Big[v(0, X_0, X(0))\|\mathcal{F}_0\Big] \\ &= \mathbf{E}\Big[u(0, X_T, X(T))\|\mathcal{F}_0\Big] \\ &= \mathbf{E}\Big[f(X_T, X(T))\|\mathcal{F}_0\Big] = u(t, \eta, x). \end{aligned}$$

□

2.4.5 Viscosity Solution

To state the reverse result we need to introduce the concept of a viscosity solution.

Definition 2.4.7. Let $V \in \mathscr{C}([0,T]\mathscr{C})$. We say that V is a viscosity sub-solution of

$$\frac{\partial}{\partial t}u(t) + \mathcal{A}_w(u(t)) + c \cdot u(t) = 0,$$

$$u(T, \eta, x) = f(\eta, x),$$

with $\mathcal{A}_w$ as defined in Theorem A.3.2, if, for every $\Gamma \in \mathscr{C}^{1,2}_{lip}([0,T], \mathscr{C}) \cap \mathcal{D}(S)$, and for $(t, \psi) \in [0,T] \times \mathscr{C}$ satisfying $\Gamma \geq V$ on $[0,T] \times \mathscr{C}$ and $\Gamma(t, \psi) = V(t, \psi)$, we have

$$\frac{\partial}{\partial t}\Gamma(t) - SV + \Big[H(\Gamma(t)) \cdot \nabla_x + \frac{1}{2}tr(\langle G, D^2(\cdot)G\rangle)\Big](\Gamma(t)) \leq 0.$$

It is a super-solution if the analogous condition is met: $\Gamma \leq V$ on $[0,T] \times \mathbb{C}$, $\Gamma(t, \psi) = V(t, \psi)$ and we have

$$\frac{\partial}{\partial t}\Gamma(t) - SV + \Big[H(\Gamma(t)) \cdot \nabla_x + \frac{1}{2}tr(\langle G, D^2(\cdot)G\rangle)\Big](\Gamma(t)) \geq 0.$$

A function V is called a viscosity solution if it is simultaneously a sub-solution and a super-solution.

We are ready to state the reverse of Theorem 2.4.4.

Theorem 2.4.8. *Suppose $f \in \mathcal{D}(\mathcal{A}_w)$ and $c : L^2([-r, 0]) \times \mathbb{R}^d \to \mathbb{R}_+$ bounded and Lipschitz continuous. The function*

$$u(t, \eta, x) := \mathbb{E}_{(t,\eta,x)}\Big[f({}^{\eta}X_T, {}^{\eta}X_T(0))e^{-\int_t^T c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big]$$

is a viscosity solution of

$$\frac{\partial}{\partial t}u(t) + \mathcal{A}_w(u(t)) - c \cdot u(t) = 0,$$

$$u(T, \eta, x) = f(\eta, x).$$

In order to prove this result we need first a lemma that emphasizes the concept of Markovianity of the solution of the SFDE $(X(t), X_t)$.

Lemma 2.4.9. *For $s,t \in [0,T]$ with $t \leq s$, we have*

$$u(t,\eta,x) := \mathbb{E}_{(t,\eta,x)}\Big[u({}^{\eta}X_s, {}^{\eta}X_s(0))e^{-\int_t^s c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big].$$

Proof. Let $s,t \in [0,T]$ such that $t \leq s$. Then the following equality holds:

$$\begin{aligned} u(s, X_s, X_s(0)) =& \mathbb{E}\Big[f(X_T, X_T(0))e^{-\int_u^T c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big\|X_u, X_u(0)\Big] \\ =& \mathbb{E}\Big[f(X_T, X_T(0))e^{-\int_u^T c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big\|\mathcal{F}_u\Big]. \end{aligned}$$

Since $({}^{\eta}X_u, {}^{\eta}X_u(0))$ is Markovian, it follows from the Tower Property of the conditional expectation

$$\begin{aligned} \mathbb{E}_{(t,\eta,x)}\Big[u({}^{\eta}X_s, {}^{\eta}X_s(0))e^{-\int_t^u c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big] =& \\ \mathbb{E}_{(t,\eta,x)}\Big[\mathbb{E}\Big[f(X_T, X_T(0))e^{-\int_u^T c(X_s, X_s(0))ds}\Big\|\mathcal{F}_u\Big]e^{-\int_t^u c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big] =& \\ \mathbb{E}\Big[e^{-\int_u^T c(X_s, X_s(0))ds}e^{-\int_t^u c(X_s, X_s(0))ds}\mathbb{E}\Big[f(X_T, X_T(0))\Big\|\mathcal{F}_u\Big]\Big\|\mathcal{F}_t\Big] =& \\ \mathbb{E}\Big[f(X_T, X_T(0))e^{-\int_t^T c(X_s, X_s(0))ds}\Big\|\mathcal{F}_t\Big] = u(t,\eta,x).& \end{aligned}$$

□

Proof of the Theorem. We will be using the notation

$$\mathbb{E}_{\eta^x}[\cdot] := \mathbb{E}[\cdot \| X_t = \eta, X_t(0) = x].$$

Let $\Gamma \in C^{1,2}_{lip}$ in the domain of the shift operator. For $0 \leq t \leq t_1 \leq T$, following Theorem 3.1 in [91], we have that

$$\begin{aligned} &\mathbb{E}_{\eta^x}\Big[e^{-\int_t^{t_1} c(X_s, X_s(0))ds}\Gamma(t_1, X_{t_1}, X_{t_1}(0))\Big] - \Gamma(t,\eta,x) \\ &= \mathbb{E}_{\eta^x}\Big[\int_t^{t_1} e^{-\int_t^u c(X_s, X_s(0))ds}\Big(\frac{\partial}{\partial t}\Gamma(u) + \mathcal{A}_w(\Gamma(u)) - c\cdot\Gamma(u)\Big)\Big], \end{aligned}$$

where we have used the notation $\Gamma(u) = \Gamma(u, X_u, X_u(0))$.
From the previous lemma, for any $t_1 \in [t,T]$

$$u(t,\eta,x) \geq \mathbb{E}_{(t,\eta,x)}\Big[u({}^{\eta}X_s, {}^{\eta}X_s(0))e^{-\int_t^s c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big].$$

By using $\Gamma \geq u$ the previous formula leads to

$$\begin{aligned} 0 &\geq \mathbb{E}_{\eta^x}\Big[e^{-\int_t^{t_1} c(X_s, X_s(0))ds}u(t_1, X_{t_1}, X_{t_1}(0))\Big] - u(t,\eta,x) \\ &\geq \mathbb{E}_{\eta^x}\Big[e^{-\int_t^{t_1} c(X_s, X_s(0))ds}\Gamma(t_1, X_{t_1}, X_{t_1}(0))\Big] - u(t,\eta,x) \\ &\geq \mathbb{E}_{\eta^x}\Big[\int_t^{t_1} e^{-\int_t^u c(X_s, X_s(0))ds}\Big(\frac{\partial}{\partial t}\Gamma(u) + \mathcal{A}_w(\Gamma(u)) - c\cdot\Gamma(u)\Big)\Big]. \end{aligned}$$

By dividing by $(t_1 - t)$ and letting t_1 towards t in the previous inequality, it follows

$$\frac{\partial}{\partial t}\Gamma(t) - SV + \Big[H(\Gamma(t)) \cdot \overline{\nabla}_x + \frac{1}{2} tr(\langle G, \overline{\Delta}(\cdot) G\rangle)\Big](\Gamma(t)) \geq 0.$$

In a similar fashion the other inequality is obtained. For any $t_1 \in [t, T]$

$$u(t, \eta, x) \leq \mathbb{E}_{(t,\eta,x)}\Big[u({}^{\eta}X_s, {}^{\eta}X_s(0)) e^{-\int_t^s c({}^{\eta}X_s, {}^{\eta}X_s(0))ds}\Big].$$

Now set $\Gamma \geq u$, and thus

$$\begin{aligned} 0 &\leq \mathbb{E}_{\eta^x}\Big[e^{-\int_t^{t_1} c(X_s, X_s(0))ds} u(t_1, X_{t_1}, X_{t_1}(0))\Big] - u(t, \eta, x) \\ &\leq \mathbb{E}_{\eta^x}\Big[e^{-\int_t^{t_1} c(X_s, X_s(0))ds} \Gamma(t_1, X_{t_1}, X_{t_1}(0))\Big] - u(t, \eta, x) \\ &\leq \mathbb{E}_{\eta^x}\Big[\int_t^{t_1} e^{-\int_t^u c(X_s, X_s(0))ds} \Big(\frac{\partial}{\partial t}\Gamma(u) + \mathcal{A}_w(\Gamma(u)) - c \cdot \Gamma(u)\Big)\Big]. \end{aligned}$$

Let us divide the previous inequality by $(t_1 - t)$ and let t_1 towards t: it follows

$$\frac{\partial}{\partial t}\Gamma(t) - SV + \Big[H(\Gamma(t)) \cdot \overline{\nabla}_x + \frac{1}{2} tr(\langle G, \overline{\Delta}(\cdot) G\rangle)\Big](\Gamma(t)) \leq 0.$$

And the conclusion of the theorem follows. □

The following result implies the uniqueness of the solution.

Theorem 2.4.10. *Comparison principle. Assume that $V_1(t, c)$ and $V_2(t, c)$ are both continuous with respect to the argument (t, c) and are respectively viscosity sub-solution and super-solution of the FPDE with at most a polynomial growth. Then*

$$V_1(t, c) \leq V_2(t, c) \forall (t, c) \in [0, T] \times C[-r, 0].$$

Proof. The proof follows the same argument as in *Chang et al.* [25]. □

2.4.6 The Feynman-Kac Formula - Boundary Value problem.

In this section we develop the Feynman-Kac's formula for the solution of a SFDE constrained to a domain D. Let us consider an open bounded domain D of $\mathbb{R}^d$ and the set of continuous functions $A = \mathscr{C}([-r, 0], D)$ bounded uniformly by M. Let us consider the random time

$$\tau_{\eta,x}^t := \inf\{s \in [0, T] : ({}^{\eta}X_s, {}^{\eta}X(s)) \in \partial(A \times D)\} \wedge t,$$

and the stopped process

$$X^{\tau_{\eta,x}^t}(t) = \eta_0(t) + \int_0^{\tau_{\eta,x}^t \vee 0} H(X_s, X(s))ds + \int_0^{\tau_{\eta,x}^t \vee 0} G(X_s, X(s))dW(s),$$

where η is defined as in the previous section and $H \in \mathbb{L}^{1,2}$ and $G \in \mathbb{L}^{1,2}$ are $\mathcal{F}_t$-adapted functions that satisfy the hypothesis of Lipschitz continuity with respect to both arguments that implies existence and uniqueness.

Let us confine ourselves to the class of quasi-tame functions [91].

Definition 2.4.11. A function $\phi : \mathscr{C}([-r,0],\mathbb{R}^m) \to \mathbb{R}$ is *quasi-tame* if there is an integer $k > 0$, $\mathscr{C}^\infty$ maps $f_j : \mathbb{R}^m \to \mathbb{R}^m$, $h : \mathbb{R}^{n\times k} \to \mathbb{R}$ and a piece-wise $\mathscr{C}^1$ function $g_j : [-r,0] \to \mathbb{R}$, with $1 \geq j \geq k-1$, such that for all $\eta \in \mathscr{C}([-r,0],\mathbb{R}^m)$ we have

$$\phi(\eta) = h\Big((\int_{-r}^{0} f_j(\eta(s))g_j(s)ds)_{j=1}^{k-1}; \eta(0)\Big).$$

Theorem 2.4.12. *Suppose $\psi \in L^2(\Omega,\mathscr{C})$ and the operator $\mathcal{A}_q$ defined in Theorem A.3.2 applied to the class of quasi-tame functions. Then the martingale problem for $(\mathcal{A}_q,\psi)$ is well posed.*

Lemma 2.4.13. *Suppose $f \in \mathcal{D}(\mathcal{A}_w)$ and $\mathbb{E}[\tau^D_{x,\eta}] < \infty$. If u solves classically*

$$\mathcal{A}_w(u(x,\eta)) - c(x,\eta)u(x,\eta) = f(x,t) \quad (\eta,x) \in A \times D,$$

$$u(\eta,x) = g(\eta,x) \quad (\eta,x) \in \partial(A \times D),$$

where $g(\eta,x)$ belongs to the class of quasi tame functions, then

$$u(\eta,x) = -\mathbb{E}_{(0,\eta,x)}\Big[\int_0^{\tau^t_{x,\eta}} f({}^\eta X_s, {}^\eta X(s))e^{-\int_0^s c({}^\eta X_u, {}^\eta X(0))du}\Big],$$

$$+\mathbb{E}_{(0,\eta,x)}\Big[g({}^\eta X_{\tau^t_{\eta,x}}, {}^\eta X(\tau^t_{\eta,x}))e^{-\int_0^{\tau^t_{\eta,x}} c({}^\eta X_u, {}^\eta X(u))du}\Big].$$

Proof. The proof can be done following the proof in [55], Theorem 2.1 page 127, using the Itô formula for quasi-tame functions. □

Similarly as in the previous section, let us suppose that **Assumption A** is satisfied. Consider the following SFDE:

Set $\eta_0 : [-r,t] \to \mathbb{R}^d$, with $\eta_0(s) = \eta_0(0)$ for $s \geq 0$. Let us define $t^{t,\eta}_s = t - s$.

If $s \in [-r,t]$

$$X^{t,\eta}(s) = \eta_0(s) + \int_0^{s\vee 0} H(t^{t,\eta}_s, X^{t,\eta}_u, X^{t,\eta}(u))ds + \int_0^{s\vee 0} G(t^{t,\eta}_s, X^{t,\eta}_u, X^{t,\eta}(u))dW(u).$$

In accordance with the previous section, it is possible to define a Markov family

$$\Big(t^{t,\eta}_s, {}^\eta X_s, {}^\eta X_s(0)\Big) \in \mathbb{R} \times L^2([-r,0],\mathbb{R}^d) \times \mathbb{R}^d.$$

In this case the infinitesimal generator is given by $\mathcal{A}^-_w$, defined as

$$\begin{aligned}\widetilde{\mathcal{A}}^-_w\Phi(t,\phi) = &-\frac{\partial}{\partial t}\Phi(t,\phi_t) + S(\Phi)(t,\phi_t) + \overline{D\Phi(t,\phi_t}(H(t,\phi_t)\mathbf{1}_{\{0\}}) \\ &+ \frac{1}{2}\sum_{j=1}^m \overline{D^2\Phi(t,\phi_t}(G(t,\phi_t)(\mathbf{e}_j)\mathbf{1}_{\{0\}}, G(t,\phi_t)(\mathbf{e}_j)\mathbf{1}_{\{0\}}).\end{aligned}$$

The following theorem holds:

Theorem 2.4.14. *Suppose $f \in \mathcal{D}(\mathcal{A}_w)$. If u solves weakly*

$$\frac{\partial}{\partial t}u(t) = \mathcal{A}_w(u(t)) + c(x,\eta)u(x,\eta) \quad (t,\eta,x) \in [0,T]\times A \times D,$$
$$u(0,\eta,x) = f(\eta,x) \quad (\eta,x) \in A \times D,$$
$$u(t,\eta,x) = g(t,\eta,x) \quad (\eta,x) \in \partial(A \times D),$$

then

$$\begin{aligned} u(t,\eta,x) =& \mathbb{E}_{(0,\eta,x)}\Big[f({}^{\eta}X_t, {}^{\eta}X_t(0))\mathbf{1}_{\{\tau^t_{\eta,x}=t\}}e^{-\int_0^t c({}^{\eta}X_u, {}^{\eta}X(u))du}\Big] \\ &+ \mathbb{E}_{(0,\eta,x)}\Big[g(\tau^t_{\eta,x}, {}^{\eta}X_t, {}^{\eta}X_t(0))\mathbf{1}_{\{\tau^t_{\eta,x}\neq t\}}e^{-\int_0^{\tau^t_{\eta,x}} c({}^{\eta}X_u, {}^{\eta}X(u))du}\Big]. \end{aligned}$$

The reverse holds for viscosity solutions of the FPDE.

Theorem 2.4.15.

$$\begin{aligned} u(t,\eta,x) =& \mathbb{E}_{(0,\eta,x)}\Big[f({}^{\eta}X_t, {}^{\eta}X_t(0))\mathbf{1}_{\{\tau^t_{\eta,x}=t\}}e^{-\int_0^t c({}^{\eta}X_u, {}^{\eta}X(u))du}\Big] \\ &+ \mathbb{E}_{(0,\eta,x)}\Big[g(\tau^t_{\eta,x}, {}^{\eta}X_t, {}^{\eta}X_t(0))\mathbf{1}_{\{\tau^t_{\eta,x}\neq t\}}e^{-\int_0^{\tau^t_{\eta,x}} c({}^{\eta}X_u, {}^{\eta}X(u))du}\Big] \end{aligned}$$

is a viscosity solution of the system

$$\frac{\partial}{\partial t}u(t) = \mathcal{A}_w(u(t)) + c(x,\eta)u(x,\eta) \quad (t,\eta,x) \in [0,T]\times A \times D,$$
$$u(0,\eta,x) = f(\eta,x) \quad (\eta,x) \in A \times D,$$
$$u(t,\eta,x) = g(t,\eta,x) \quad (\eta,x) \in \partial(A \times D).$$

2.4.7 First Exit Time Probability for SFDE

Let us denote by τ_D the first exit time of $X^{x,\eta}(t)$, where $X^{x,\eta}(t)$ is the solution of the SFDE with initial conditions x,η. Let $\mathbf{Q}(t,x,\eta)$ be the probability that $X^{x,\eta}$ starting from x,η did not exit the domain $D \subset \mathbb{R}^d \times C([-r,0],\mathbb{R}^d)$ before t, i.e.

$$\mathbf{Q}(t,\eta,x) = 1 - \mathbf{P}_{x,\eta}\Big(\tau_A < t\Big).$$

2.4.8 First Exit Time Probability as a Viscosity Solution

Let us consider the process solution of the SFDE:

$$X(t) = \eta_0(t) + \int_0^{t\vee 0} H(X_s, X(s))ds + \int_0^{t\vee 0} G(X_s, X(s))dW(s).$$

Throughout this section we impose the following stringent hypothesis about the FPDE:

$$\begin{cases} \frac{\partial}{\partial t}u(t) = \mathcal{A}_w(u(t)) & (t,\eta,x) \in [0,T]\times D \\ u(0,\eta,x) = 1 & (\eta,x) \in D \\ u(t,\eta,x) = 0 & (t,\eta,x) \in]0,T[\times \partial D \end{cases}. \tag{2.4.2}$$

Hypothesis B: the variational problem (2.4.2) belongs to

$$u \in \mathscr{C}^0\Big([0,T];\mathscr{C}^2([0,T],D)\cap\mathscr{C}^2(\overline{D})\Big).$$

It is then possible to state the following result:

Theorem 2.4.16. *Under* ***Hypothesis B****, the function*

$$\mathbf{Q}(t,\eta,x) = 1 - \mathbf{P}_{x,\eta}\Big(\tau_A < t\Big)$$

is a viscosity solution of the problem:

$$\begin{cases} \frac{\partial}{\partial t}u(t) = \mathcal{A}_w(u(t)) & (t,\eta,x)\in[0,T]\times D \\ u(0,\eta,x) = 1 & (\eta,x)\in D \\ u(t,\eta,x) = 0 & (t,\eta,x)\in]0,T[\times\partial D \end{cases}.$$

Chapter 3

MATHEMATICAL MODELS FOR *E. COLI*

This chapter deals with the application of the HSHS Model developed in Chapter 2 to the special case of modeling of *E. coli* movement.

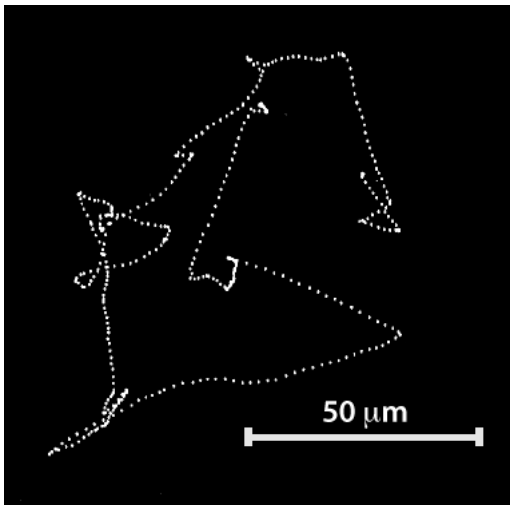
3.1 Introduction

The study of *E. coli* traces back to the end of the 17th century: since then the knowledge of this little and simple microorganism developed so deep that nowadays we have a good understanding of almost every single process that happens in the cell. The immense scientific literature related to *E. coli* underlines that it is a paradigmatic example of how nature works and evolves. For an organic review we invite to have a look at the paper [124]. Despite of this deep knowledge, though, there are still open problems and interesting questions that this little bacterium is able to rise.

A very popular branch of research connected with *E. coli* is chemotaxis: the evolutionary and functional reasons for the experimentally observed response to chemoattractants remain a riddle [22]. In general regular environmental conditions allow for the evolution of specifically adapted responses, whereas complex environments usually lead to conflicting requirements upon the organism's response. Sensing and motility requirements are in fact optimized by different responses, which strongly depend on the chemoattractant profile in the environment. It is not clear then how those conflicting requirements quantitatively combine and compromise in shaping the chemotaxis response [22].

The work of Berg and colleagues [17, 11, 12] has conclusively demonstrated that *E. coli* employ a temporal sensing mechanism, engaging in a biased random walk consisting of alternating periods of straight runs and random tumbles. When the concentration of chemoattractant (L) is increasing in time ($dL/dt > 0$), the bacteria tend to have longer runs (i.e., the probability of a tumble decreases), thus allowing the bacteria to move up the gradient. If the chemoattractant concentration is decreasing ($dL/dt < 0$), then the bacteria are more likely to reorient their direction by tumbling.

In what follows we summarize three articles [119, 2, 22], which have, in various senses, inspired the present work.



3.1.1 Model by Daniel W. Stroock

D.W.Stroock [119] modeled the data of the experiments in [12] and proposed the following model for the movement of a single *E. coli*:

- the bacterium performs a *run&tumble* random walk, in which the speed is constant and the direction is a process which lives on the sphere $\mathbb{S}^2$.
- the duration of a twiddle is negligible and therefore it is possible to talk about the direction of the bacterium at a given instant;
- the motion is Markovian in the phase space. This leads to the conclusion that the direction of the bacterium (say $\theta(t)$) is a Poisson-type process on the sphere $\mathbb{S}^{d-1}, d = 3$ whose intensity depends not only on its position in $\mathbb{S}^2$ but also on the time and location (say $x(t)$) of the bacterium. Then a temporally inhomogeneous Markov process $(x(t), \theta(t))$ on $\mathbb{R}^3 \times \mathbb{S}^2$ is constructed with the property that

  $$x(t) - x(s) = (t - s) \cdot \theta(s),$$

  if $\theta(\cdot)$ is constant during $[s, t)$;
- the conditional probability of $\theta(\cdot)$ being constant during $[t, s)$ given the past up to time s is

  $$\mathbf{P}\Big(\theta(u) = \theta(s), u \in [s, t) \| \mathcal{F}_s\Big) = \exp\Big[- \int_s^t \lambda(u, x + (u - s)\theta, \theta) du\Big],$$

  where λ is a given function

  $$\lambda : [0, \infty) \times \mathbb{R}^3 \times \mathbb{S}^2 \to (0, \infty);$$

- the conditional distribution of the first place at which $\theta(\cdot)$ jumps after time s given the past up to time s is given by $\mu_{\theta(s)}$, a probability measure on $\mathbb{S}^2$.

Those assumptions give rise to a temporally inhomogeneous Lèvy-type diffusion on $\mathbb{R}^3 \times \mathbb{S}^2$ whose backward equation is

$$\frac{\partial u(t,x,\theta)}{\partial t} + \theta \cdot \nabla_x u(t,x,\theta) + \lambda(t,x,\theta) \int_{\mathbb{S}^2} [u(t,x,\eta) - u(t,x,\theta)]\mu_\theta(d\eta) = 0,$$

$$u(t,x,\theta) = \mathbb{E}_{t,x,\theta}[f(x(T),\theta(T))] = \mathbb{E}[f(x(T),\theta(T))\|x(t) = x, \theta(t) = \theta], \quad t \leq T,$$

where f is a generic function of class $\mathscr{C}^{1,1}([0,T] \times \mathbb{R}^3, \mathbb{R})$.

Remark 3.1.1. This model (as well as [103] of the following year) contains many of the features of a piecewise deterministic Markov Process described by Davis in [36].

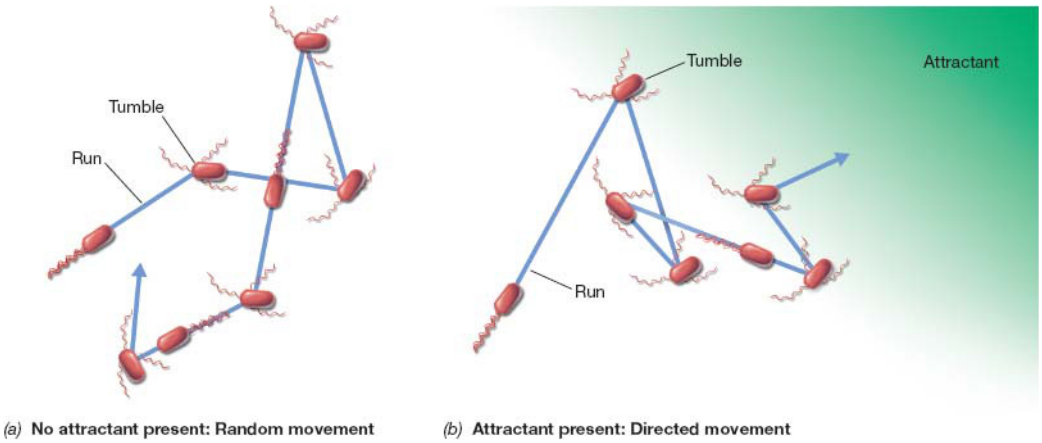


Figure 3.1: Chemotaxis in a peritrichously flagellated bacterium such as *Escherichia coli*. (a) In the absence of a chemical attractant the cell swims randomly in runs, changing direction during tumbles. (b) In the presence of an attractant runs become biased, and the cell moves up the gradient of the attractant.

This model has various properties that make it very interesting and a solid base for all the developments that have followed during the last 40 years.

- although wrapped in a quite technical set-up [1] the underling idea is rather simple and intuitive and is able to catch most (but not all) of the characteristics of the movement of *E. coli*; it developed in what in the literature is commonly referred to as *velocity-jump model* (see for example [102, 128, 45]);
- in the last section he developed the parabolic scaling of the process leading to a diffusive approximation with space-dependent coefficients using a limit theorem for random processes with values in a group [102].

[1] First of all the existence of the process by Martingale properties, merging of regular-probabilities conditional distributions, ergodic theorem for Poisson processes on a commutative group etc.

We have underlined many times that *E. coli* builds up its strategy to find food with the use of some kind of temporal gradient, and this is absent in the work by Stroock: it turns out to be the key ingredient to add to Stroock's model to make it more realistic.

The other important hypothesis is that run lengths are exponentially distributed. It can be viewed as a first approximation of the real distribution: it makes the model analytically tractable and is still able to capture many features. We will have a closer look to this aspect in **Section 3.3**.

3.1.2 Model by Wolfgang Alt

A partial answer to the unsolved question in Stroock's paper was given by Alt in 1980 [2]. In his approach, which is a generalization of Stroock's model [53], he considers the locomotion of individuals, moving independently of each other in the following way:

- the motion of each individual or of a well defined observable part of it (the nucleus of a cell, for instance) is piecewise linear, where the (mean) speed of such a linear *run* equals $c(t,x)$, depending on time t and position x of the individual;
- supposed that an individual at (t,x) has been running in direction θ for a time τ (counted from the beginning of the run): it will then stop at (t,x) to tumble with a probability rate given by $\beta(t,x,\tau,\theta)$;
- if an individual stops a run with direction θ at (t,x), then after a negligibly short time it chooses a new direction η of motion with a given probability $k(t,x,\theta;\eta)$ (*tumble* of bacteria).

Alt assumed that the density $\sigma(t,x,\theta,\tau)$ of individuals, moving at (t,x) in direction θ and having started their run a time τ ago is a smooth function of its variables. With the aid of Gauss' theorem applied to suitable test domains one concludes that σ satisfies the following differential-integral system:

$$\begin{aligned} &\frac{\partial}{\partial t}\sigma(x,t,\theta,\tau)+\frac{\partial}{\partial \tau}\sigma(x,t,\theta,\tau)+\theta\cdot\nabla_x\Big(c(t,x)\sigma(x,t,\theta,\tau)\Big)=-(\beta\sigma)(x,t,\theta,\tau)\\ &\sigma(x,t,\eta,0)=\int_0^\infty\int_S(\beta\sigma)(x,t,\theta,\tau)k(t,x,\theta;\eta)d\theta d\tau, \end{aligned} \tag{3.1.1}$$

where we use the notation $(\beta\sigma)(x,t,\theta,\tau)$ to shorten the product $\beta(x,t,\theta,\tau)\sigma(x,t,\theta,\tau)$.

Remark 3.1.2. If β is independent of the run time τ, then the system for the time-space-velocity density

$$\bar\sigma(t,x,\theta):=\int_0^\infty\sigma(t,x,\theta,\tau)d\tau$$

directly gives the differential integral equation obtained by Stroock.

One has to notice that, while Stroock works with backward Kolmogorov equations, Alt deals with the Fokker-Plank equation directly for the density of the process, assuming its smooth existence. In case of an unbounded domain, one obtains that the probability $P(t,x,\theta)$ satisfies the equation for the adjoint of the backward Kolmogorov operator [51].

Remark 3.1.3. The model by Alt is really interesting also from an analytic point of view. We refer to the problem of the definition of a stochastic process by its infinitesimal generator and the Kolmogorov equations [51].
In [51] arises the important issue that the general Fokker-Planck equation is not a differential equation. In this respect we may adapt the framework of PDMP (see Appendix A Section A.4) and derive that the infinitesimal generator $\mathcal{A}^{\Phi}$ associated with the process Φ discussed in [2] is given by:

$$\mathcal{A}^{\Phi} f(t,x,\theta,\tau) := -\frac{\partial}{\partial \tau} f(t,x,\theta,\tau) + \theta \cdot \nabla_x f(t,x,\theta,\tau) + \int_{\mathbb{S}^{d-1}\times\mathbb{R}} \Big[f(t,x,\eta,\tau') - f(t,x,\theta,\tau) \Big] dk(t,x,\eta,\tau') \otimes \delta_0(d\tau').$$

When we derive the corresponding Fokker-Plank equation we end up with the differential-integral system (3.1.1).

Remark 3.1.4. We may consider the model by Alt as a special case of the Velocity-Jump models (see for example [128]): In Alt's model the *internal variable* (here τ) satisfies the differential equation $\dot{\tau} = -1$ and is reset to the value 0 at every arrival time of a non-homogenous Poisson process.

Alt undertook multilayer analysis and ended up with a generalization of the Keller-Segel equation; he managed to express the macroscopic coefficients as functions of the microscopic parameters: he thus obtained the Patlak-Keller-Segel diffusion equation:

$$\frac{\partial}{\partial t} u(t,x) = \nabla_x \Big(\frac{\mu}{c} \nabla_x (c \cdot u(t,x)) - \chi u(t,x) \nabla_x \rho(t,x) \Big).$$

where the coefficients are related to the microscopic parameters (*Proposition 2* on page 164 in [2]). That paper is quite technical and presents non trivial calculations. It is a first attempt to introduce the memory in the model. Because of the chosen chemical reaction which takes place inside the cell and influences the run length, this memory term is somehow smoothed out. What Alt could not capture, is the main feature of the work by Celani and Vergassola [22]: they simplify the form of the underlying jump process, turning it into a non-homogenous Poisson process [119].

3.1.3 Model by Celani & Vergassola

Celani and Vergassola [22] investigate what might be the strategy followed by *E. coli* in the search for food: they show that the experimental bacterial response corresponds to the maxmin strategy that ensures the highest minimum uptake of chemoattractants for any profile of concentration. They consider a quite complete model which can be considered a generalization of the *velocity-jump model* [45].

Bacteria are supposed to run at (fixed) velocity u in the direction θ, and the transition rate from the running to the tumbling phase at time t depends on the detection history experienced by the bacterium via the quantity $Q(t) = \int_{-\infty}^{t} K(t-s) c(X(s), s) ds$. Here the convolution kernel is the one presented in the first chapter;

- $X(t)$ is the trajectory followed by the bacterium;
- $c(x,t)$ is the chemoattractant concentration field;
- τ_r is the running time in the absence of chemoattractants.

We refer to the **Appendix** for a deeper review of their article.

They use homogenization methods to analyze the hydrodynamic limit of the distribution of the population. They rescale $x \mapsto \epsilon x$ and $t \mapsto \epsilon^2 t$, and obtain the final form of the effective diffusion equation:

$$\frac{\partial}{\partial t} n(x,t) + \nabla \cdot \Big(\chi \cdot n(x,t) \nabla c(x,t) \Big) = D_0 \Delta \Big[\Big(1 + \gamma c(x,t) \Big) n(x,t) \Big],$$

where

$$\gamma := \frac{\alpha}{\sigma} \int_0^\infty K(t)dt \text{ and } \chi := D_0 \frac{\alpha}{\sigma} \int_0^\infty e^{-\sigma t} K(t)dt.$$

3.1.4 Our Proposed Model

We are ready to present our model and analyze it.

> *In order to have a model that at the population level predicts the desired properties of the system, one must first have a detailed model of a single cell, and then lift it to the collective behavior of the population of individuals: we can understand the qualitative behavior of the continuous equations in order to obtain a better understanding of how parameters in the microscopic movement rules translate into macroscopic parameters in the integro-partial differential equations.*
>
> freely adapted from [117]

Guided by this principle, the model we propose tries to describe as many features as possible of the complex dynamics of this simple bacterium, with particular attention to the memory-dependence.
We introduce a dissatisfaction index, denoted by Λ, which is a stochastic process satisfying a functional stochastic differential equation. The moment when this process crosses a threshold determines the moment when a run ends and a tumble begins. This dissatisfaction index controls only the transition from *run* to *tumble*: the reverse transition is controlled by a Poisson process. The process Λ depends on the previous measurements of chemical concentrations and, in order not to loose generality, we make it dependent on the process itself and all the other random objects that build the model.

We can say that the swimming bacterium will discover the environment around it via recording and memorizing the concentration of the chemical substance during the movement. Via a comparison between the current concentration and the one previous measured, the bacterium realizes whether it is going up or down the gradient, adjusting consequently its strategy. This is controlled by a simple signaling pathway. We try to be as general as possible and talk abstractly of *internal dynamics*, which measure the level of dissatisfaction of the bacterium. The dissatisfaction will grow at a high rate, if the comparison leads to the

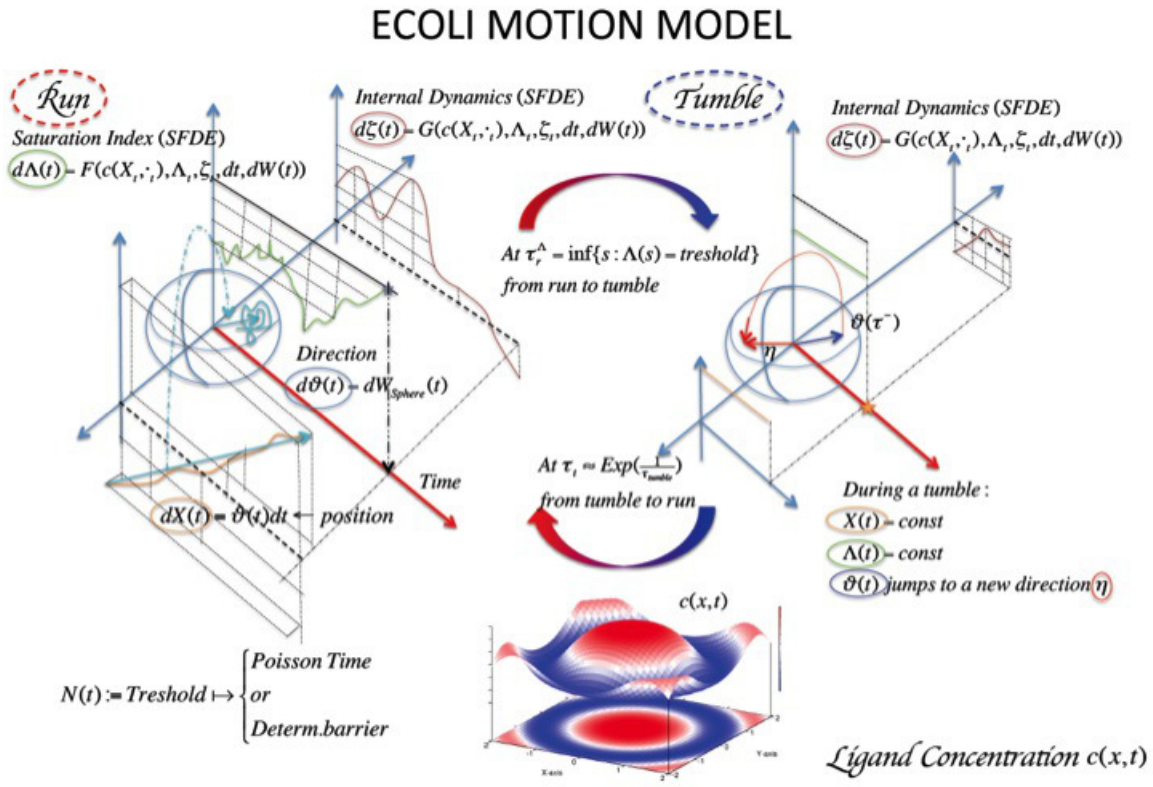


Figure 3.2: Hereditary Hybrid Stochastic Model for the Movement of *E. coli*: the bacterium switches between two states: *run* (left) and *tumble* (right)

conclusion that it is swimming against the gradient, it will grow at a low rate in the opposite situation. In this chapter we assume that the growth rate for the process Λ is always positive, since even in a favorable environment, the bacterium will eventually turn.

The dynamics of a bacterium is described via five different stochastic processes, whose explicit description is postponed to the next section:

- the position, X;
- the swimming direction, θ;
- the internal dynamics, ζ
- the *dissatisfaction index*, Λ, which depends on the difference of the level of chemical concentration measured in the past and the one registered at the present time;
- the levels of saturation or threshold, $\{\tau_j\}_{j\in\mathbb{N}}$.

In what follows we consider that the chemical concentration (or the ligand), $c(x,t)$, is a given function which is sensed by the bacterial population but not produced or ingested.

We shall assume that the locomotion of individuals, moving independently of each other, is characterized as follows:

- the bacterium follows a run-and-tumble strategy;
- the duration of the tumbling is not negligible;
- during the run of the bacterium, the direction is characterized by a Brownian motion around the direction selected at the tumbling;
- the distribution of a run lengths depends on the memory (whose length is r) of previous measurements of chemical concentrations and is not *a priori* exponentially distributed.
- the new swimming directions are supposed to be independent and identically distributed random variables, say $Y_j, j = 1, 2, \dots$.

The above assumptions give rise to the following algorithm in order to simulate one realization of the stochastic processes controlling the swim of the bacterium:

0 Initial condition: $x_0(t)$, $\theta_0(t)$ and $\Lambda_0(t)$, for $t \in [-r, 0]$, and the function of chemical concentration $c(x, t)$ for $t \in [-r, T]$ and $x \in \mathbb{R}^d$.

1 - run: the bacterium swims in direction $\theta_j(t) := \theta(\tau_{j-1}) + D_\theta W_S(t)$ until the process Λ reaches the next level τ_j at time τ_j^Λ.

3 - tumble: when the level is reached the bacterium stops for a random time, exponentially distributed, and the swimming direction is updated to $\theta_{j+1} = \theta_j + Y_j$

4 while $\tau_j^\Lambda < T$, restart from step 1 with $j \mapsto j + 1$.

3.2 General Mathematical Model

The dynamic of a bacterium is governed by the following system of stochastic functional differential equations. Let us call it **HHSEcoli**.

$$
\begin{aligned}
X(t) &= \begin{cases} x_0(t) & t \in [-r, 0[\\ x_0(0) + \int_0^t u(\Omega(s)) \cdot \theta(s) ds + \sigma_X W(t) & t \in [0, T] \end{cases} \\
\theta(t) &= \begin{cases} \theta_0(t) & t \in [-r, 0[\\ \theta_0(0) + D_\theta(\Omega(t)) \cdot W_{\mathbb{S}^{d-1}} + \overline{\sum}_{j=0}^{\Psi(t)} Y_j & t \in [0, T] \end{cases} \\
\zeta(t) &= \begin{cases} \zeta_0(t) & t \in [-r, 0[\\ \zeta(0) + \int_0^t F(\Omega(s)), s, c(X(s), s), \theta(s)) ds & \\ \qquad + \int_0^t G(\Omega(s), s, c(X(s), s), \theta(s)) dW_\zeta(t) & t \in [0, T], \end{cases} \\
\Lambda(t) &= \begin{cases} \Lambda_0(t) & t \in [-r, 0[\\ \Lambda_0 + \int_0^t \lambda(\Omega(s), s, \zeta(s), \zeta_s, \Lambda_s, \theta(s)) ds & \\ \qquad + \int_0^t \sigma(\Omega(s), s, \zeta(s), \zeta_s, \Lambda_s, \theta(s)) dW(s) & t \in [0, T], \end{cases}
\end{aligned}
\tag{3.2.1}
$$

where we have for $0 \leq t \leq T$,

$$\begin{aligned} \mathcal{Q}(t) &= \mathcal{H}(\Psi(t), \mathcal{Q}(0)), \\ \Psi(t) &= \mathcal{N}(\Xi(t^-)), \\ \Xi(t) &= \beta(\Lambda(t-s)_{s\leq t}). \end{aligned} \tag{3.2.2}$$

$\mathcal{H}(\psi, q)$ is a function that governs the transition of the discrete component $Q(t)$: more precisely if we know the initial state of the bacterium, say $Q(0)$, then the value of $\Psi(t)$ tells us if we are now performing a *run* or a *tumble*.
We may suppose that the jumps of the function $\mathcal{N}$ are exponentially distributed if the current phase is a *tumble*; in this case $\sigma \equiv 0$.
We may also consider that the process ζ and Λ might be reset during a the transition from two phases via a deterministic as well as stochastic reset map.

Remark 3.2.1. The form of the dependency is general: due to the biological explanation stated in the introduction, it may be given by:

$$\nabla_{F,g}^{[t-r\mapsto t]} c(X) := F\Big(c(X(t),t) - \int_{-r}^{0} c(X(t+s), t+s) g(ds)\Big),$$

or in case $r = \infty$,

$$\nabla_t^K c(X,s) = \frac{1}{\tau_r}\Big[1 - \int_{-\infty}^{s} K(s-r) c(X(r), r) ds\Big],$$

with $K(t) = \lambda e^{-\lambda t} \sum_{k=1}^{k_M} \beta_k (\lambda t)^k \cdot \mathbf{1}_{\{t\geq 0\}}$

Remark 3.2.2. When we impose $u \equiv 1$, $\sigma \equiv 0$ and $\lambda(s, \zeta(s), \zeta_s, \theta) \equiv \lambda(s, \zeta(s), \theta)$, $D_\theta \equiv 0$, instantaneous reorientation and $\{a_j\}_{j\in\mathbb{N}}$ exponentially distributed, we obtain Stroock's model, i.e.

- (X, θ) is a Markov Process
- the backward equation is

$$\frac{\partial}{\partial t} u(t,x,\theta) + \theta \cdot \nabla_x u(t,x,\theta) + \lambda(t, c(x,t), \theta) \int_{\mathbb{S}^2} [u(t,x,\eta) - u(t,x,\theta)] \mu_\theta(d\eta) = 0,$$

$$u(t,x,\theta) = \mathbb{E}_{t,x,\theta}[f(x(T), \theta(T))] = \mathbb{E}[f(x(T), \theta(T)) \| x(s) = x, \theta(s) = \theta], \quad s \leq T.$$

It follows from [119, paragraph 3, Example 2], , that if $\lambda(x)$ is continuously differentiable and uniformly positive, then the distribution of $X_\epsilon(t) := X(0) + \epsilon(X(\frac{t}{\epsilon^2}) - X(0))$ as ϵ goes to zero tends to the distribution of a diffusion whose generator on $C^2(\mathbb{R}^d)$ is given by $\nabla_x\Big(\frac{1}{\lambda(x)}\nabla_x\Big)$. In particular, if $\lambda(x)$ is constant, then $X_\epsilon(t)$ tends to a Brownian motion. In other words, if the medium is homogeneous, then the limiting behavior of the bacterium with this scaling is that of a Brownian particle in $\mathbb{R}^3$.

Remark 3.2.3. We are recast into the model by Alt if $\zeta(t)$ records the time when the bacterium jumps; more precisely let $\zeta(t)$ be evolving as $\dot{\zeta}(t) = -1$ during a run and let it jump back to 0 at the time of a tumble.

3.3 Model vs. Data

If we look at the literature the distribution for the run lengths of *E. coli* is usually considered to be exponential [22, 21, 45, 128]. We decided to have a general approach which allows the distribution of runs and tumbles to be different from the exponential distribution.

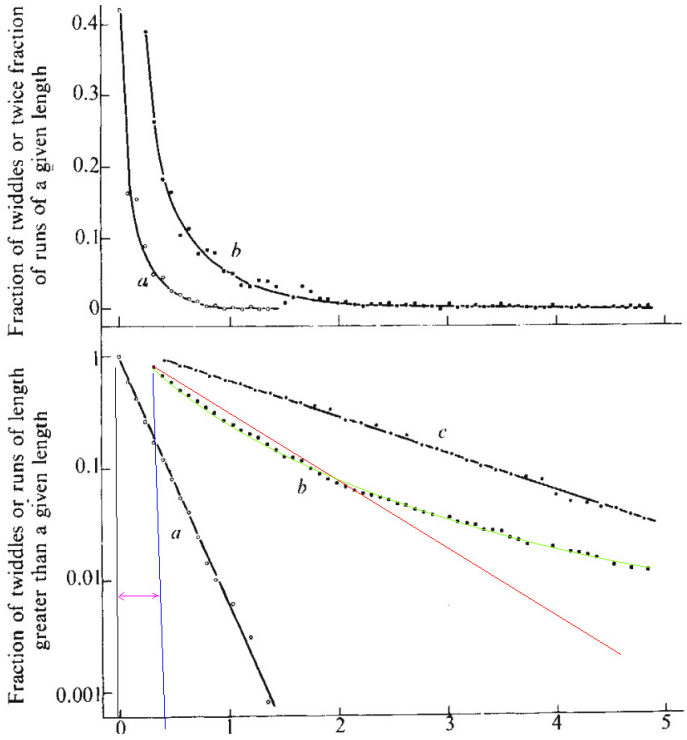


Figure 3.3: The black and white part of the picture is taken from [12]: **Top**: the fractional number of tumbles (a) or runs (b) of different lengths. There were 1201 data points for each state. **Bottom**: For the same data: number of tumbles (a) and runs (b) greater than a given length, displayed on semi-logarithmic axes. Curve c was obtained by scaling the run lengths of each bacterium so that its mean run length was equal to the ensemble mean. The red curve is the distribution of an exponential with mean given by the experiments, and the green one is the distribution obtained by an inverse gaussian interpolation. The pink arrow underlines that the gap between the smallest run and zero is not zero.

This choice is motivated by two observations (see Figure 3.3):

1. the minimum length of a run is much larger then 0: of course it might be ascribed to the modality of how the run length was measured, but this time interval should be taken into account. In the large scale approximation it might have implications on the

	AW405	Unc 602	CheC 497
Number of bacterial tracked	35	10	14
Total tracking time (min)	20	3.0	2.7
Mean speed ($\mu m/2$)	14.2±3.4	14.4±3.9	20.0±4.9
Mean twiddle length (s)	0.14 ± 0.19	0.14 ± 0.24	0.10 ± 0.13
Mean run length (s)	0.86 ± 1.18	0.42 ± 0.27	6.3 ± 5.2

Table 3.1: Statistics of runs and tumbles reported in [12]: the datapoint were generated at the rate of 12.6 per seconds. The experiments were done with three different cultures. The value *mean speed, mean twiddle and mean run length* for homogenous environment are so formatted: $\mathbf{E}[X] \pm \sqrt{\mathrm{Var}[X]}$

magnitude of the diffusion coefficient: in fact after a tumble there will be some kind of *persistent interval*, during which the bacterium will not turn its swimming direction;

2. in the of Table 3.1 we report the statistics of runs and tumbles [12]: By having a closer look at it, we may notice that the mean and the variance of the distribution of the runs are *incompatible* with exponentially distributed random variables:
   More precisely, let X be an exponentially distributed random variable with parameter α. We would have
   $$\mathbf{E}[X] = \frac{1}{\alpha} = \sqrt{\mathrm{Var}[X]} = \frac{1}{\alpha}.$$
   This is in contrast with the data in Table 3.1.
   As an answer to the last remark, one might impute error estimation and confidence intervals for the statistics of the first two moments of the distribution of runs. Although we are aware of the validity of this hypothesis we decide, however, to undertake a more general analysis: we believe it to be interesting both from a purely theoretical point of view and a modeling one.

Remark 3.3.1. We mentioned that the discrepancies between the theoretical values and the sample mean and variance might find a justification considering confidence intervals of the estimated parameters: we now look closely in this direction. There are several ways to obtain confidence intervals for a random variable which is exponentially distributed:

First Method: The $100 \cdot (1-\beta)\%$ confidence interval for the rate parameter of an exponential distribution is given by [109]:

$$\frac{2n}{\widehat{\alpha}\chi^2_{1-\frac{\beta}{2},2n}} < \frac{1}{\alpha} < \frac{2n}{\widehat{\alpha}\chi^2_{\frac{\beta}{2},2n}}, \tag{3.3.1}$$

which is also equal to:

$$\frac{2n\overline{x}}{\chi^2_{1-\frac{\beta}{2},2n}} < \frac{1}{\alpha} < \frac{2n\overline{x}}{\chi^2_{\frac{\beta}{2},2n}},$$

where $\chi^2_{p,v}$ is the percentile of the chi-squared distribution with v degrees of freedom, n is the number of observations of inter-arrival times in the sample, and $\bar{x}$ is the sample average. A simple approximation of the exact interval endpoints can be derived using a normal approximation of the $\chi^2_{p,v}$ distribution. This approximation gives the following values for a 95% confidence interval:

$$\alpha_{low} = \widehat{\alpha}\left(1 - \frac{1.96}{\sqrt{n}}\right) \quad \alpha_{upp} = \widehat{\alpha}\left(1 + \frac{1.96}{\sqrt{n}}\right).$$

This approximation may be acceptable for samples containing at least 15 to 20 elements [60]. If we substitute the value given in [12] we obtain that the confidence intervals for a sample of 100 and 1000 measurements [2] are given by:

$$I^{\alpha}_{100} = [0.78, 0.93] \quad I^{\alpha}_{1000} = [0.83, 0.89].$$

Second Method: The Maximum Likelihood estimator for the parameter α of an Exponential distribution is given by $\widehat{\alpha}_{ML} = \frac{n}{\sum_{i=1}^{n} x_i}$. We can calculate the asymptotic variance of $\widehat{\alpha}_{ML}$: first of all we need the Fisher Information

$$I(\alpha) = -\mathbf{E}[\frac{d^2}{d\alpha^2} \ln f(x, \alpha)] = \frac{1}{\alpha^2},$$

where f is the pdf of a exponential random variable. The asymptotic variance of $\widehat{\alpha}_{ML}$ is given by $\mathbf{Var}\left(\widehat{\alpha}_{ML}\right) = \frac{1}{nI(\lambda)} = \frac{\lambda^2}{n}$. For large n we have asymptotic normality, i.e.

$$\widehat{\alpha}_{ML} \sim \mathcal{N}(\lambda, \frac{\lambda^2}{n}).$$

Therefore the 95% confidential Interval is given by:

$$I_{95} = \Big(\frac{\sqrt{n} - 1.96}{\sqrt{n}}\widehat{\alpha}_{ML}, \frac{\sqrt{n} + 1.96}{\sqrt{n}}\widehat{\alpha}_{ML}\Big).$$

Remark 3.3.2. There are variants that can increase the degree of freedom of the statistics of the distribution; we consider a variant based on the following simple consideration: when the *E. coli* swims in a homogeneous and constant environment for a sufficiently long time, then the run length distribution will be stationary, in the following sense: the dynamics will be influenced only by the dissatisfaction index and the equation that the dissatisfaction index solves is of the following form:

$$\Lambda(t) = \lambda dt + \sigma dW(t).$$

If the threshold for the tumble level is a deterministic quantity, then the distribution of a run follows an inverse Gaussian distribution with parameters:

$$\mathcal{IG}(\frac{n}{\lambda}, \frac{n^2}{\sigma^2}),$$

[2] The number of data is not explicitly given in [12] but from the table we can infer it accounts more the 1000 measurements.

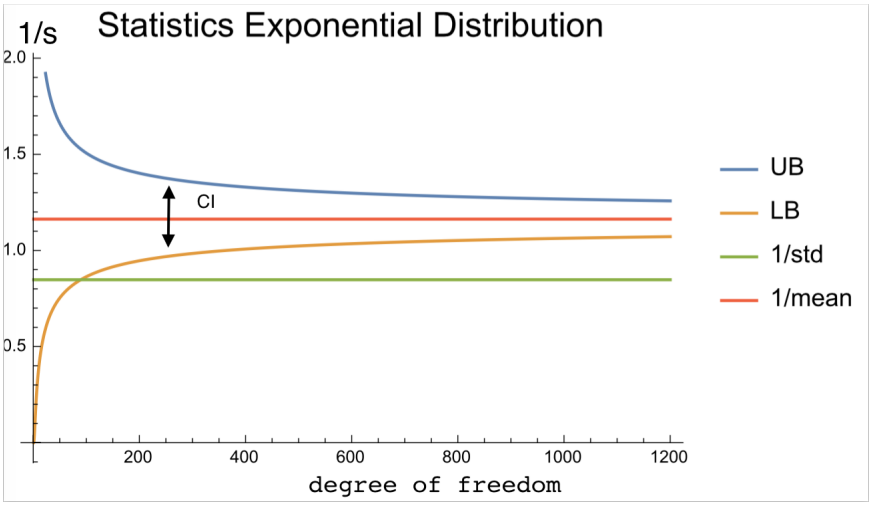


Figure 3.4: Plot of the statistics for the parameter α of an exponentially distributed random number [similar to the sample given in [12]]: **UB** (resp. **LB**) is the upper (resp. lower) bound for the confidential interval (**CI**) for the parameter α, *std* is the standard deviation (1.18) and mean is the mean of the measurements (0.86). We notice that the value of the inverse of the standard deviation lies outside the CI for the parameter of the exponential distribution. From the formula (3.3.1) we have that the number of samples is equal to half of the degrees of freedom. From [12] the number of data are above 200. The plot is drawn for a level $\beta = 0.05$.

where n is the magnitude of the threshold. For an inverse Gaussian distribution $X \sim \mathcal{IG}(\mu, \lambda)$ it holds:

$$\mathbf{E}[X] = \mu \quad \mathbf{Var}[X] = \frac{\mu^3}{\lambda}.$$

We can now solve the relation to find stationary λ^* and σ^* in **HHS**. In the next section we will study the case of a constant environment in greater detail.

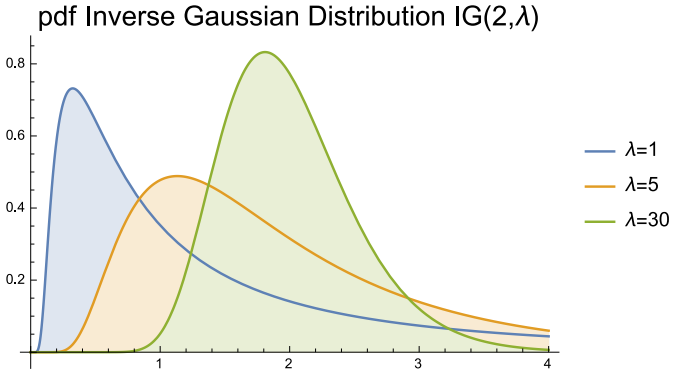


Figure 3.5: Plot of the pdf of inverse Gaussian random variable with parameters given by $\mathcal{IG}(2, \lambda)$ and $\lambda = 1, 5, 30$

3.4 Constant Environment in Space and Time

We now consider a simplified problem, where we assume that the external stimulus is constant in space and time.

$$\begin{cases} \Lambda(t) = \eta_0 + H \cdot t + \sigma \cdot W(t) \quad 0 \le t \le T \\ N(t) = \sum_{k=1}^{\infty} \chi_{[\tau_k,\infty)}(s) \quad 0 \le t \le T \\ X(t) = x_0 + \int_0^t \theta(s)ds \quad 0 \le t \le T \\ \theta(t) = \theta_0 + \sum_{j=0}^{N(t)} Y_j \quad 0 \le t \le T \\ \tau_n = \begin{cases} 0 & n = 0 \\ \inf\{s > \tau_{n-1} : \Lambda(s) = n\} & n \ge 1 \end{cases} \end{cases} . \tag{3.4.1}$$

The aim now is to write explicitly the transition probability for the vector $\Phi = (\Lambda(t), N(t))_{t\in[0,T]}$. Let $(\eta_0, n_0) \in \mathbb{R} \times \mathbb{N}$ and $A := B \times \{k\} \in \mathcal{B}(\mathbb{R} \times \mathbb{N})$, $k \in \mathbb{N}, \eta_0 \le n_0$

$$\mathbf{P}(t, (\eta_0, n_0); t+h, A) = \mathbf{P}\Big((\Lambda, N)(t+h) \in A \Big| (\Lambda, N)(t) = (\eta_0, n_0)\Big)$$
$$\mathbf{P}\Big(\Lambda_{\eta_0}(t+h) \in B, \sup_{s\in[t,t+h]} \Lambda_{\eta_0}(s) \in [k, k+1) \Big| N(t) = n_0\Big).$$

Let us consider now $k \ge n_0$ and $B \cap [k+1, \infty) \ne \emptyset$, with $\Lambda^*_{t,t+h} = \sup_{s\in[t,t+h]} \Lambda_{\eta_0}(s)$

$$\mathbf{P}\Big(\Lambda_{\eta_0}(t+h) \in B, \sup_{s\in[t,t+h]} \Lambda_{\eta_0}(s) \in [k, k+1) \Big| N(t) = n_0\Big)$$
$$= \mathbb{E}^{\eta_0,n_0}\Big[\chi_{B,[k,k+1]}\Big(\Lambda(t+h), \Lambda^*_{t,t+h}\Big)\Big]$$
$$= \mathbb{E}^{\eta_0,n_0}\Big\{\mathbb{E}\Big[\chi_{B,[k,k+1]}\Big(\Lambda(t+h), \Lambda^*_{t,t+h}\Big)\Big|\Lambda(t+h)\Big]\Big\}$$
$$= \int_B \mathbf{P}\Big(\Lambda^*_{t,t+h} \in [k, k+1)\Big|\Lambda_{\eta_0}(t+h) = x\Big)\mathbf{P}_{\Lambda_{\eta_0}(t+h)}(dx)$$
$$= 2\int_B d\alpha \int_{[k,k+1)} d\beta\Big\{\frac{2\beta - \eta_0 - \alpha}{\sigma\sqrt{2\pi h^3}} \exp\Big(-\frac{(\alpha - Hh - \eta_0)^2 + 4\sigma^2(\beta - \eta_0)(\beta - \eta_0 - \alpha)}{2\sigma^2 h}\Big)\Big\}.$$

The last passage is justified by [15], where it is proven that for $B^{0,y}_{t+h}(s)$ being a Brownian Bridge one has:

$$\mathbf{P}\Big(\Lambda^*_{t,t+h} > x\Big|\Lambda_{\eta_0}(t+h) = y\Big) = \mathbf{P}\Big(\sup_{s\in[t,t+h]} B^{0,y}_{t+h}(s) > x\Big),$$

and

$$\mathbf{P}\Big(\sup_{s\in[0,t_0]} B^{x,y}_{t+h}(s) > z\Big) = \begin{cases} \exp\Big(-2\frac{(z-x)(z-y)}{t_0}\Big), & z > \max(x, y) \\ 1 & \text{otherwise} \end{cases}.$$

To calculate the generator, one should then proceed to the calculus of the following limit, where f is a sufficiently regular function:

$$\lim_{h\to 0} 2\sum_{k\geq n_0}^{\infty}\int_B\int_{[k,k+1)}\Big\{\frac{f(\alpha,\beta)-f(\eta_0,n_0)}{h}\frac{2\beta-\alpha-\eta_0}{\sigma\sqrt{2\pi h^3}} \cdot e^{-\frac{(\alpha-Hh-\eta_0)^2+4\sigma^2(\beta-\eta_0)(\beta-\eta_0-\alpha)}{2\sigma^2 h}}\Big\}d\beta d\alpha.$$

But it seems to be quite prohibitive.

3.4.1 Negligible Tumble Time

In this section we make use of the methods developed in [56, 122, 48]. In the next section we will extend the results to the case of a finite tumble time.
In the case of a constant environment, the distribution of the jumps can be considered as a sequence of independent and identically distributed random variables, say $\mathcal{W}(\tau)$, where $\mathcal{W}(\tau)d\tau$ represents the probability that a tumble occurs in the time interval $[\tau, \tau + d\tau]$.
In what follows we suppose that the density function of the random vector representing the marginals of the system for the variable (x, θ), $p(t, x, \theta)dtdxd\theta$ and the distribution of the system just starting a new *run*, $f(t, x, \theta)dtdxd\theta$ exist and are smooth in all their components. After a random time τ, distributed as $\mathcal{W}(\tau)d\tau$, the bacterium changes direction according to the probability distribution $\mu(\theta)$. The corresponding conditional probability shall be called $q(t+\tau, y, \eta|x, \theta)dyd\eta d\tau$. We suppose, in addition to [56] and [122], that during the *run* phase the direction follows a diffusion process on the sphere with constant diffusion coefficient D_θ. We can now write the integral equations for the evolution of the quantities described above:

$$f(t, x, \theta) - f(0, x, \theta) = \int_0^t \int_{\mathbb{R}^d}\int_{\mathbb{S}} q(t - s, x, \theta|y, \eta)f(s, y, \eta)dxd\theta.$$

The evolution of the components (x, θ) satisfies the following system of equations

$$\frac{\partial}{\partial h}\mathbf{E}[g(t + h, x(t + h), \theta(t + h))|(t, x, \theta)]\big|_{h=0} = \Big(\frac{\partial}{\partial t} + \theta\cdot\nabla_x + D_\theta\Delta_\theta\Big)g(t, x, \theta).$$

In what follows we indicate with $e^{-(t-s)(\eta\cdot\nabla_x+D_\theta\Delta_\eta)}$ the semigroup generated by the operator:

$$\mathcal{A} := \eta\cdot\nabla_x + D_\theta\Delta_\eta.$$

We obtain then that

$$\begin{aligned} f(t, x, \theta) - f(0, x, \theta) &= \int_0^t\int_{\mathbb{R}^d}\int_{\mathbb{S}} q(t - s, x, \theta|y, \eta)f(s, y, \eta)dxd\eta \\ &= \int_0^t\int_{\mathbb{S}} \mathcal{W}(t - s)e^{-(t-s)(\eta\cdot\nabla_x+D_\theta\Delta_\eta)}f(s, y, \theta)\mu_\eta(\theta)dxd\eta. \end{aligned}$$

We can now study the joint position-velocity distribution function, say $p(t, x, \theta)$. Using the notation $w(t) = 1 - \int_0^t W(s)ds$ we have

$$p(t,x,\theta) = \int_0^t \int_{\mathbb{S}} w(t-s) e^{-(t-s)(\eta\cdot\nabla_x - D_\theta\Delta_\eta)} f(s,y,\theta)\mu_\eta(\theta) dx d\eta.$$

We can then write the Laplace transform of this equation and proceed as in [56], Equations (15-22). We have only to take care of the presence of the Laplacian for the evolution of the direction between two jumps; for Example eq. (15) becomes in our case:

$$\mathcal{L}\{p\}(\lambda,x,\theta) = f(0,x,\theta) + \int_{\mathbb{S}} \mu_\eta(\theta)\mathcal{L}\{\mathcal{W}\}(\lambda + \eta\cdot\nabla_x + D_\theta\Delta_\eta)\mathcal{L}\{f\}(\lambda,y,\eta),$$

where we use the notation

$$\mathcal{L}\{p\}(\lambda,x,\theta) := \int_0^\infty e^{-\lambda s} p(s,x,\theta) ds.$$

We obtain the master equation

$$\begin{aligned}\Big[\frac{\partial}{\partial t} + \theta\cdot\nabla_x - D_\theta\Delta_\theta\Big]p(t,x,\theta) = &\int_0^t \int_{\mathbb{S}} e^{-(t-s)(\eta\cdot\nabla_x - D_\theta\Delta_\eta)} p(s,y,\eta)\mu_\eta(\theta)\Phi(t-s) ds \\ &- \int_0^t e^{-(t-s)(\eta\cdot\nabla_x - D_\theta\Delta_\eta)} f(s,y,\theta)\Phi(t-s)(\theta) ds,\end{aligned}$$

where the kernel $\Phi(t)$ is defined via the equation for the Laplace transform:

$$\mathcal{L}\{\Phi\}(\lambda) = \frac{1-\lambda\cdot\mathcal{L}\{w\}(\lambda)}{\mathcal{L}\{w\}(\lambda)}.$$

We can follow [122] to investigate the limit of the parabolically rescaled equation for large time, i.e. for $t \mapsto \frac{t}{\epsilon^2}$ and $x \mapsto \epsilon x$ as $\epsilon \to 0$.

By expanding the kernel for small λ, which corresponds to large time, we have the equation:

$$(1+\Phi'(0))\Big(\frac{\partial}{\partial t} + \theta\cdot\nabla_x - D_\theta\Delta_\theta\Big)p(t,x,\theta) = \mathcal{T}_0[p(t,x,\theta)] + \mathcal{T}_1[p(t,x,\theta)],$$

where

$$\mathcal{T}_0[p(t,x,\theta)] = -\Phi(0)\Big(p(t,x,\theta) + \int_{\mathbb{S}} \mu_\eta(\theta)p(t,x,\eta)d\theta\Big),$$

$$\mathcal{T}_1[p(t,x,\theta)] = \Phi'(0)\int_{\mathbb{S}} \mu_\eta(\theta)\Big(\frac{\partial}{\partial t} + \eta\cdot\nabla_x + D_\theta\Delta_\eta\Big)p(t,x,\eta)d\theta.$$

Suppose that the turning kernel satisfies the relations:

$$\int_{\mathbb{S}}\int_{\mathbb{S}} \mu_\eta(\theta)p(t,x,\eta)d\theta d\eta = 0,$$

$$\int_{\mathbb{S}} \theta\mu_\eta(\theta)d\theta = \psi_d\cdot\theta,$$

and using the *Cattaneo Approximation* (see [122]) we obtain for the moments

$$M(t,x) = \int_{\mathbb{S}} p(t,x,\theta)d\theta) \text{ and } J(t,x) = \int_{\mathbb{S}} \theta \cdot p(t,x,\theta)d\theta),$$

the following two equations:

$$\frac{\partial}{\partial t}M(t,x) + \nabla_x \cdot J(t,x) = 0,$$

$$\frac{\partial}{\partial t}J(t,x) + \frac{u^2}{d}\Big(1 + \Phi'(0) - \psi_d \cdot \Phi'(0)\Big)\nabla_x M(t,x) + \Phi(0)\Big(1 - \psi_d + D_\theta\Big)J(t,x) = 0.$$

Now using standard hydrodynamics theory, with the transformations $\frac{\partial}{\partial t} \mapsto \epsilon^2 \frac{\partial}{\partial t}$ and $\nabla_x \mapsto \epsilon \nabla_x$ we derive the parabolic limiting equation. We suppose that it is possible to expand the functions in powers of ϵ:

$$f(t,x,) = \sum_{k=1}^{\infty} f^{(k)}(t,x) \cdot \epsilon^k.$$

By comparing terms of the same order in ϵ we have

$$\frac{\partial}{\partial t}M^{(0)}(t,x) = D \cdot \Delta_x M^{(0)}(t,x).$$

Let μ be the mean of the distribution of the waiting time and σ its standard deviation, then the constant D is given by

$$D = \frac{1 + (1-\psi_d) \cdot \Phi'(0)}{(1-\psi_d)\Big(\Phi(0) + \Phi'(0) \cdot D_\theta(d-1)\Big) + D_\theta(d-1)}.$$

3.4.2 Equation with Finite Tumble Time

Using the same technique as above it is possible to extend the results in [122] to the case in which during a run the direction performs a diffusion on the sphere. In this case we obtain a diffusion coefficient which depends also on the mean of the *tumble* time: we have

$$\frac{\partial}{\partial t}M^{(0)}(t,x) = D \cdot \Delta_x M^{(0)}(t,x),$$

with the constant D given by

$$D = \frac{u^2}{d}\frac{\Phi_\tau(0)}{\Phi(0) + \Phi_\tau(0)}\frac{1 + (1-\psi_d) \cdot \Phi'(0)}{(1-\psi_d)\Big(\Phi(0) + \Phi'(0) \cdot D_\theta(d-1)\Big) + D_\theta(d-1)}.$$

If we use the relations

$$\lim_{\lambda \to 0} \Phi_i(\lambda) = \frac{1}{\mu_i} \quad \lim_{\lambda \to 0} \Phi_i'(\lambda) = \frac{\sigma_i}{2\mu_i} - 1,$$

we obtain that

$$D = \frac{u^2}{d}\frac{\mu_r}{\mu_t + \mu_r}\frac{2\mu_r^2\psi_d + (1-\psi_d)\sigma_r^2}{2\mu_r(1-\psi_d) + (d-1)D_\theta(2\mu_r\psi_d + (1-\psi_d)\sigma_r^2)}. \tag{3.4.2}$$

We notice that this formula is consistent with previous publications, in fact if we impose $D_\theta = 0$ we obtain the result in [122]. We notice also that if $\psi_d \sim 1$, then the contribution of the variance of the duration of a run disappears.

3.5 Infinite Fading Memory

The introduction of an explicit dependency upon the segment process in the SDE that drives the internal dynamics destroys many nice properties in comparison with the *standard* setting: in one word we have not not been able to describe the *infinitesimal generator* of the model **HHSEcoli** and the related *Kolmogorov's equation*. This makes impossibility to use all the tools and techniques to shift from the microscopic scale to the macroscopic one [2, 45, 22].

In the following section we will incorporate the memory term in a less general way [22]: the memory term is identified as the solution of a particular system of ODEs, leading to a process which is Markov without the need of enlarging the state space and adding infinite dimensional Hilbert spaces. We say it is *less general* since it can be seen as a particular case of **HHSEcoli** in a sense made clearer in the following section.

3.5.1 Mathematical Model

We make use of the same notation and hypotheses as in the general mathematical model. The dynamic of a bacterium is governed by the following system of stochastic differential equations; let $t \in [0, T]$
for $t \in [\tau_n, \tau_{n+1}]$

$$\begin{aligned} Q(t) &\in \{0, 1\} \\ X(t) &= x_{\tau_n} + \int_{\tau_n}^{t} u(\mathcal{Q}(s)) \cdot \theta(s) ds \\ \theta(t) &= \theta_{\tau_n} + D_\theta(\mathcal{Q}(t)) \cdot W_{\mathbb{S}^{d-1}}(t - \tau_n) \\ \Lambda(t) &= \Lambda_{\tau_n} + \int_{\tau_n}^{t} \lambda(\mathcal{R}(s)) ds + \int_{\tau_n}^{t} \sigma(\mathcal{R}(s)) dW(s), \end{aligned} \tag{3.5.1}$$

where $\sigma(2n) = 0$,

$$\tau_n = \inf\{s > \tau_{n-1} : \Lambda(s) \geq a_n\},$$

where a_n is a sequence such that a_{2n} is an exponentially distributed random variable and a_{2n+1} may either be deterministic or stochastic quantities. The memory term is given by the expression [22]:

$$\begin{aligned} \mathcal{R}(t) &= \sum_{k=1}^{k_N} \beta_k \alpha^{k+1} m_k(t), \\ m_k(t) &= \int_{-\infty}^{t} e^{-\alpha(t-s)} (t - s)^k c(X(s), s) ds \quad k = 0, \dots k_N. \end{aligned} \tag{3.5.2}$$

We have the following rules for the jumping terms:

$$\begin{aligned} \mathcal{Q}(\tau_{n+1}) &= 1 - \mathcal{Q}(\tau_{n+1}^-) \\ \theta(\tau_{n+1}) &= \theta(\tau_{n+1}^-) + Y_n \cdot \delta_0^{Q(t)} \\ \Lambda(\tau_{n+1}) &= 0. \end{aligned} \tag{3.5.3}$$

Remark 3.5.1. The variable $\mathcal{Q}$ describes in which phase the bacterium is: $\mathcal{Q} = 1$ represents the *running* phase, $\mathcal{Q} = 0$ the *tumbling* phase. We can identify the following features:

- at every discontinuity point the internal dynamics Λ is reset to the value 0;
- the process θ (the instantaneous direction) follows a Brownian motion on the sphere and jumps to a new location when there is a transition between *run* and *tumble*;
- the *tumbles* are exponentially distributed.

Remark 3.5.2. The expression for $\mathcal{R}$ can be rewritten as a system of ODE's [22]:
by taking time derivatives of m_k, it is easy to verify that the internal variables obey a set of closed equations. The equations have the common structure

$$\frac{d}{dt}m_k = -\alpha \cdot m_k + f_k, \tag{3.5.4}$$

featuring a relaxation term and a forcing term $f_k = k \cdot m_{k-1}$ for $k \geq 1$ and $f_0 = c$ for $k = 0$.

3.5.2 One dimensional Process

In this section we study the Fokker Plank equation of the process living on a line, by supposing that the duration of a *tumble* is negligible. In this case we can intensively use the setting of the *Stochastic Hybrid System* [63]. Thanks to the property of the memory kernel stated previously, we can simplify the general model and rewrite it in a cleaner way.

Suppose that a bacterium moves along the x-axis at a speed $\theta(t)$ that takes values in the set $\Theta = \{s, -s\}$ and let us consider now the following vector-valued process:

$$(X(t), m_0(t), m_1(t), m_2(t), \Lambda(t))_{t\in[0,T]},$$

whose components satisfy the following equations:

$$\begin{aligned} dX(t) &= \theta(t)dt \\ dm_j(t) &= f_j(t)dt + \sqrt{2\eta \cdot m_j}dW_j^m(t), \quad j = 0, 1, 2 \\ d\Lambda(t) &= \lambda(\mathcal{R}(t))dt + \sigma dW_\Lambda(t), \end{aligned}$$

where f_j and $\mathcal{R}(t)$ are as before.

We write now

$$\overline{\mathbb{M}} = \{-1\} \times \mathcal{X}_{-1} \cup \{1\} \times \mathcal{X}_1,$$

where $\mathcal{X}_\theta = \mathbb{R} \times \mathbb{R}^3 \times (-\infty, r_1)$ with $r_1 > 0$ the level for which the system switches direction for $\theta \in \Theta$. We consider the deterministic *reset map* $\Phi : \partial\mathbb{M} \to \mathbb{M}$ as follows:

$$\Phi(x, [m_j]_{j=0}^2, r_1, -1) = (x, [m_j]_{j=0}^2, 0, 1),$$

$$\Phi(x, [m_j]_{j=0}^2, r_1, 1) = (x, [m_j]_{j=0}^2, 0, -1),$$

which means that the *position* x and the *internal variables* m_j are not changed, the saturation process Λ is reset to the value 0 and the speed θ is reversed.

In this setting we can make use of Theorem 4 and Example 3.1 in [7], in particular by writing the system in matrix form:

$$d\begin{bmatrix} X(t) \\ m_0(t) \\ m_1(t) \\ m_2(t) \\ \Lambda(t) \end{bmatrix} = \begin{bmatrix} \theta(t) \\ c(t,x) - \nu m_0(t) \\ m_0 - \nu m_1(t) \\ 2 \cdot m_1 - \nu m_2(t) \\ \lambda(\mathcal{R}(t)) \end{bmatrix}$$

$$+ \begin{bmatrix} 0 & 0 & & 0 & 0 \\ 0 & \sqrt{2\eta \cdot m_0}(t) & 0 & 0 & 0 \\ 0 & 0 & \sqrt{2\eta \cdot m_0}(t) & 0 & 0 \\ 0 & 0 & 0 & \sqrt{2\eta \cdot m_0}(t) & 0 \\ 0 & 0 & & 0 & \sigma \end{bmatrix} \begin{bmatrix} dW_X(t) \\ dW_0^m(t) \\ dW_1^m(t) \\ dW_2^m(t) \\ dW_\Lambda(t) \end{bmatrix}.$$

The flux is given by

$$J_t = \begin{bmatrix} \theta(t) \\ c(t,x) - \nu m_0(t) \\ m_0 - \nu m_1(t) \\ 2 \cdot m_1 - \nu m_2(t) \\ \lambda(\mathcal{R}(t))) \end{bmatrix} p^\theta(t,x,m_j,\Lambda) - \frac{1}{2} \begin{bmatrix} 0 \\ 2\eta \cdot m_0(t) \\ 2\eta \cdot m_1(t) \\ 2\eta \cdot m_2(t) \\ \sigma^2 \end{bmatrix} \nabla p^\theta(t,x,m_j,\Lambda).$$

The application of Theorem 4 in [7] leads to the following parabolic differential equation with boundary values for $p^\theta(t,x,m_j,\Lambda)$:

$$\frac{\partial}{\partial t}p^\theta + \theta\frac{\partial}{\partial x}p^\theta + \sum_{j=0}^{2} \frac{\partial}{\partial m_j}\Big[\Big(f_j - \nu m_j - \eta m_j \frac{\partial}{\partial m_j}\Big)p^\theta\Big] + \Big(\lambda(\mathcal{R})\frac{\partial}{\partial \Lambda} - \frac{1}{2}\frac{\partial^2}{\partial^2 \Lambda}\Big)p^\theta = 0.$$

We have to impose continuity on $\mathcal{X}_\theta$ and the absorbing condition on the boundaries $\partial\mathcal{X}_\theta$.

3.5.3 General Case with Finite Tumble Time

In order to treat the general case (with special memory kernel $K(t)$ as before) it is convenient to extend the treatment to the case of finite time tumble. In this case some mathematical difficulties are avoided. As in the previous section we will try to fit the model in the framework of *Stochastic Hybrid Systems*. With the introduction of the *tumble* phase we can smooth the irregularities on the border and make use of a *stochastic* reset for the direction of the bacterium (in contrast with [7] where deterministic resets are allowed). The dynamics of the system is as in the introduction with the following specification:

- the *saturation process* is reset to the value 0 when a *tumble* starts (thanks to the properties of the kernel $K(t)$);
- the duration of a tumble is exponentially distributed with parameter given by $\frac{1}{\tau_t}$.

As before we consider the discrete set $\mathcal{R} = \{r, t\}$, where r stands for *run* and t for *tumble* and the domain for the continuous dynamics:

$$\mathcal{X}_\theta = \mathbb{R}^d \times \mathcal{S}^d \times \mathbb{R}^3 \times (-\infty, r_1),$$

where $\mathcal{S}^d$ is the d-dimensional sphere and r_1 is the threshold level.

By following [6] we can write down the Fokker-Planck equation for the density

$$p^r\Big(t, x, \theta, \Lambda, (m_k)_{k=1}^{k_M}\Big) \text{ and } p^t\Big(t, x, \theta, (m_k)_{k=1}^{k_M}\Big),$$

where $s \in \mathcal{R}$. We make a further hypothesis:

- we will assume that during a tumble the component Λ evolves as a diffusion with reflecting boundary in the domain $[-\epsilon_1, \epsilon_1]$, where ϵ_1 is a small parameter. This expedient is used to approximate the model: instead of driving the transition from tumble to run via the process Λ, we use standard techniques to write the Fokker-Plank equation for a markovian system. In this case we should have that in the domain of the tumble, the process Λ would have the constant value 0: this might lead p^r and p^t to become singular. We allow it to diffuse in the stripe $[-\epsilon_1, \epsilon_1]$, so that the boundary conditions of the flux of the probability density are easily writeable.

$$\frac{\partial}{\partial t}p^r + \nabla_x\Big(\theta \cdot p^r\Big) + \mathcal{M}[p^r] + \mathcal{A}^\Lambda[p^r] = D_\theta \Delta_{\mathbb{S}} p^r + \frac{1}{\tau_t}\int_{\mathbb{S}} p^t(\cdot, \eta)\mu_\theta(\eta),$$

$$\frac{\partial}{\partial t}p^t + \mathcal{M}p^r = -\frac{1}{\tau_t}p^r,$$

with boundary conditions given by

$$\partial_n p^t\Big|_{\Lambda=\pm\epsilon_1} = 0,$$

$$J^r = \Phi J^t,$$

where $\mathcal{M}[p^r]$ and $\mathcal{A}^\Lambda[p^r]$ are the generators of the SDE resp. for m and Λ.

3.5.4 Approximation

In this section we proceed in a first approximation of the general equation discussed previously. We can try to approximate the waiting time

$$\tau_\Lambda(\mathcal{R}(t)) = \sum_{k=1}^{N} Z(g_k(\mathcal{R})),$$

where Z are independent exponential random variables with parameter $g_k(\mathcal{R})$, such that

$$\mathbf{E}[\tau_\Lambda] = \sum_{k=1}^{N} \frac{1}{g_k(\mathcal{R})}.$$

We can follow the derivation of the hydrodynamic limit for the system with finite tumble times as in the Supplementary Information in [22]. We show the procedure in the case of $N = 2$ in the approximation of the time of the a run. The system is described by three states: *begin* of a run, *end* of a run and *tumble*; the probabilities for the system to be in one of the states are given respectively by p^a, p_e, p^t. We can write the Fokker-Planck equation for these quantities:

$$\frac{\partial}{\partial t}p^a + \nabla_x\Big(\theta \cdot p^a\Big) + \mathcal{M}[p^a] = D_\theta p^a + \frac{1}{\tau_t}\int_{\mathbb{S}} p^t(\cdot,\eta)\mu_\theta(eta) - g_1(\mathcal{R}(t))p^a,$$

$$\frac{\partial}{\partial t}p^e + \nabla_x\Big(\theta \cdot p^e\Big) + \mathcal{M}[p^e] = D_\theta p^e - g_1(\mathcal{R}(t))p^a + g_2(\mathcal{R}(t))p_e,$$

$$\frac{\partial}{\partial t}p^t + \mathcal{M}p^r = -\frac{1}{\tau_t}p^r + g_2(\mathcal{R}(t))p_e.$$

In case of a small value of $\mathcal{R}$ and asymptotic expansion of the functions $g_j(\mathcal{R}) \sim \frac{1-\alpha\cdot\mathcal{R}}{\tau_j}$, we conjecture that the form of the limit of the parabolically rescaled equation for the quantity

$$p(t,x) = \int_{\mathbb{S}}\int_{\mathbb{R}^{N_M}} \Big(p^a(t,x,\theta,m_j) + p_e(t,x,\theta,m_j) + p^t(t,x,\theta,m_j)\Big)d\theta \otimes_j dm_j,$$

is as follows

$$\frac{\partial}{\partial t}p(t,x) + \nabla(D_1(\tau_j,\tau_t)p(t,x)\nabla c(t,x)) = D_2(\tau_j,\tau_t)\Delta\Big(p(t,x)(1 + D_3c(t,x))\Big).$$

Remark 3.5.3. We would like to conclude this chapter with some remarks:

- the use of an underlying counting process for the *tumbles* that is not Poisson leads to extremely difficult mathematics which we were not able to overcome (only partially);
- the difference between the Poisson case and the non-Poisson case, in the field of chemotaxis for *E. coli*, is not so large to actually require such a complicate machinery;
- this chapter can be considered as a justification to keep using Poisson processes for the *tumble and run* events as a good approximation of the real distribution.

Remark 3.5.4. It could be possible to extend the model further and include an extra source of noise inside the coefficients of the SFDE for the process Λ. In fact we might consider the function $\lambda(\cdot)$ itself random, i.e. $\omega \mapsto \lambda(\omega,\cdot)$. In this setting we can obtain non diffusive behavior for the density of the population even using a standard Poisson process [87].

Chapter 4

SIMPLIFIED MODELS

The general model presented in Chapter 2 is very difficult to deal with in great generality, first of all because of the great freedom in the choice the the parameters. A careful choice of the form of the coefficient-functions for the different stochastic processes therein involved recasts us into well established models in the existing literature. In this sense the general model (HSHS) can be considered a generalization of the work that has been done in the study of random dynamic systems.

4.1 The Parameters-Game

If we look carefully at the system HSHS (2.2.2, 2.2.3), we recognize that the parameters that play a prominent work in the dynamics are the following:

- the sequence of random variables or deterministic numbers a_j that control the cádlág process $\mathcal{N}$;
- $\lambda(\cdot), \sigma(\cdot)$ the coefficients of the SFDE governing the random time change;
- D_θ the coefficient of the SDE on the sphere
- $F(\cdot)$ and $G(\cdot)$ the functions related to the internal dynamics.

In the following table we summarize some parameters: we use the notation

$$\lambda(K) = \frac{1}{\tau_r}\Big[1 - \int_{-\infty}^{s} K(s-r)c(X(r),r)ds,$$

with $K(t) = \lambda e^{-\lambda t}\sum_{k=1}^{k_M}\beta_k(\lambda t)^k \cdot \mathbf{1}_{\{t\geq 0\}}$ for the modek Vergassola and cellni.
For a better overview we refer to **picture 4.1**

Model in the Literature	a_j	$\lambda(\cdot)$	$\sigma(\cdot)$	D_θ	$F(\cdot), G(\cdot)$
Stroock [119]	$\sim \mathcal{E}(1)$	$\lambda(s,\theta,X)$	0	0	0
Othmer [102, 45, 128]	$\sim \mathcal{E}(1)$	$\lambda(s,\theta,X)$	0		Eq. 4.4.1
Orsingher [8]	$\sim \mathcal{E}(1)$	0	const	0	0
Vergassola and Celani [22, 21]	$\sim \mathcal{E}(1)$	$\lambda(K)$	0	0	Eq. 3.5.4
Lèvy Walk	$a_j = j$	0	const	0	

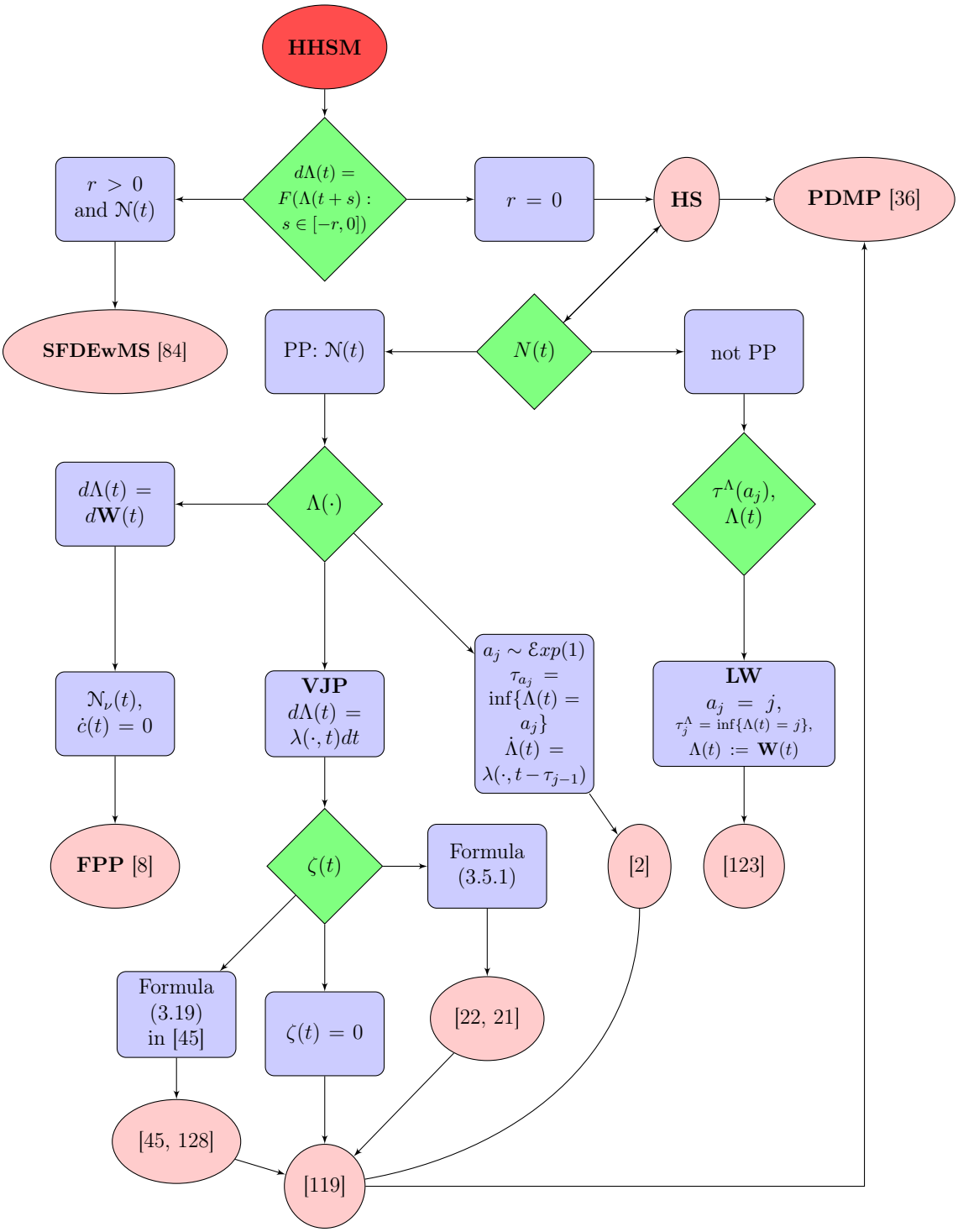


Figure 4.1: Branch-tree for the derivation from the HHSM to other models in the literature

In what follows we give a brief overview of different models and their connections with HSHS.

Time-changed Semimartingale

We can shrink the general idea behind the HSHS model to the one of random-time change, from this prospective we can better understand the connection between different models that HSHS realizes:
In [72] conditions are given on a semimartingale and a time-change, when a stochastic integral driven by the time-changed semimartingale is a time-changed stochastic integral driven by the original semimartingale. The central problem is to understand such integrals by rephrasing them in terms of integrals driven by the original semimartingale. Solving this problem is almost equivalent to providing a way to recognize SDEs driven by a time-changed semimartingale, which aids the analysis of problems that appear in applications.

The main point is that any stochastic integral driven by a time-changed semimartingale is a time-changed stochastic integral driven by the original semimartingale, as long as the semimartingale is in synchronization with the time-change.

Theorem 4.1.1. *(Time-changed Itô Formula) Let Z be an $(\mathcal{F}_t)$-semimartingale. Let D and E be a pair satisfying $[[D \to E]]$ or $[[E \to D]]$. Define a filtration $(\mathcal{G}_t)$ by $\mathcal{G}_t := \mathcal{F}_{E_t}$. Let X be a process defined by*

$$X_t = (A \bullet m)_t + (F \bullet E)_t + (G \bullet (Z \circ E))_t.$$

If $f : \mathbb{R} \to \mathbb{R}$ is a C^2 function, then $f(X)$ is a $(\mathcal{G}_t)$-semimartingale, and with probability one, for all $t \geq 0$,

$$\begin{aligned} f(X_t) - f(X_0) = &\int_0^t f'(X_{s^-})A_s ds + \int_0^{E_t} f'(X_{D(s)})F_{D(s)} ds \\ &+ \int_0^{E_t} f'(X_{D(s)})G_{D(s)} dZ_s + \frac{1}{2}\int_0^{E_t} f''(X_{D(s)})\{G_{D(s)}\}^2 d[Z,Z]^c_s \\ &+ \sum_{0<s\leq t} \{f(X_s)f(X_s)f'(X_s)\Delta X_s\}. \end{aligned}$$

Formally we can write the process HSHS as

$$\begin{bmatrix} X(t) \\ \theta(t) \end{bmatrix} = \int_0^t \begin{bmatrix} \theta(s) \\ 0 \end{bmatrix} ds + \begin{bmatrix} 0 \\ Y \end{bmatrix} \bullet \Big(\Psi \circ \beta(\int_0^t \lambda(s, \zeta(s), \zeta_s, \theta(s))(ds, dW(s))) \Big).$$

4.2 Brownian Time Change

In this section the time change is performed via some functionals of a Wiener process: the high irregularity of the simple path of the Wiener process leads to processes whose distributions solve fractional equations.

4.2.1 Fractional Poisson Process

Let us consider the following hypothesis:

- $\mathcal{N}$ is a Poisson process, i.e. a_j are i.i.d exponentially distributed RVs;
- $\lambda(\ldots) \equiv 0$;
- $\sigma(\ldots) \equiv \sigma$, constant;
- $D_\theta \equiv 0$.

We get the framework of the fractional Poisson process developed by Orsingher *et al.* in [99, 100, 8, 9], in this case we have: for $t \in [0, T]$

$$\begin{aligned} X(t) &= x_0(0) + c \cdot \int_0^t \theta(s) ds \\ \theta(t) &= \theta_0(0) + \overline{\sum}_{j=0}^{\Psi(t)} Y_j \\ \Psi(t) &= \mathcal{N}(\sup_{s \le t} \Lambda(s)), \\ \Lambda(t) &= \int_0^t \sigma \cdot dW(s). \end{aligned}$$

The process $\Psi(t)$ has the same distribution as the fractional Poisson process, $(\mathcal{N}_\nu(t))_{t \le 0}$, with $\nu = \frac{1}{2}$, whose distribution $p_k = \mathbb{P}(\mathcal{N}_\nu(t) = k)$, $k \ge 0$ solves the following equation

$$\frac{d^\nu}{dt^\nu} p_k(t) = -\lambda(p_k(t) - p_{k-1}(t));$$

$$p_k(0) = \delta_k^1,$$

where the fractional derivative is the one proposed by Dzerbayshan-Caputo [107]. It follows from the observation:

$$\Xi(t) = \sup_{s \le t} \Lambda(s) \stackrel{d}{=} \sigma \cdot |W(t)|.$$

We can make use of the theory developed in [8]. Let Y_j be uniformly distributed on the unit circle and, for simplicity, $\sigma \equiv 1$. From this we obtain the fractional process governing the changes of directions as $N_{1/2}(t) = N(|B(t)|)$, and derive that the conditional distribution of the random vector $(X(|W(t)|), Y(|W(t)|))$, $t > 0$ which may be written, for $k \ge 0$, $(x, y) \in \mathbb{R}^2$, as

$$\begin{aligned} &\mathbf{P}\Big(X(|W(t)|) \in dx, Y(|W(t)|) \in dy \Big| N_{1/2}(t) = k\Big) \\ &= \frac{dxdy}{B\left(\frac{1}{2}, \frac{k+1}{2}\right)} \int_0^1 w^{\frac{1}{2}} (1-w)^{\frac{k+1}{2}} \frac{1}{4\pi t w c^2} e^{-\frac{x^2+y^2}{4c^2 t w}} dw, \end{aligned}$$

where $B(\alpha, \beta)$ denotes a Beta function of parameters α and β, and $W(t)$, $t > 0$, is a standard Brownian motion, independent of $(X(t), Y(t))_{t \ge 0}$. This means that the planar motion with a Brownian time can be regarded as a planar Brownian motion, whose volatility is itself random and possesses a Beta distribution depending on the number of changes of directions.

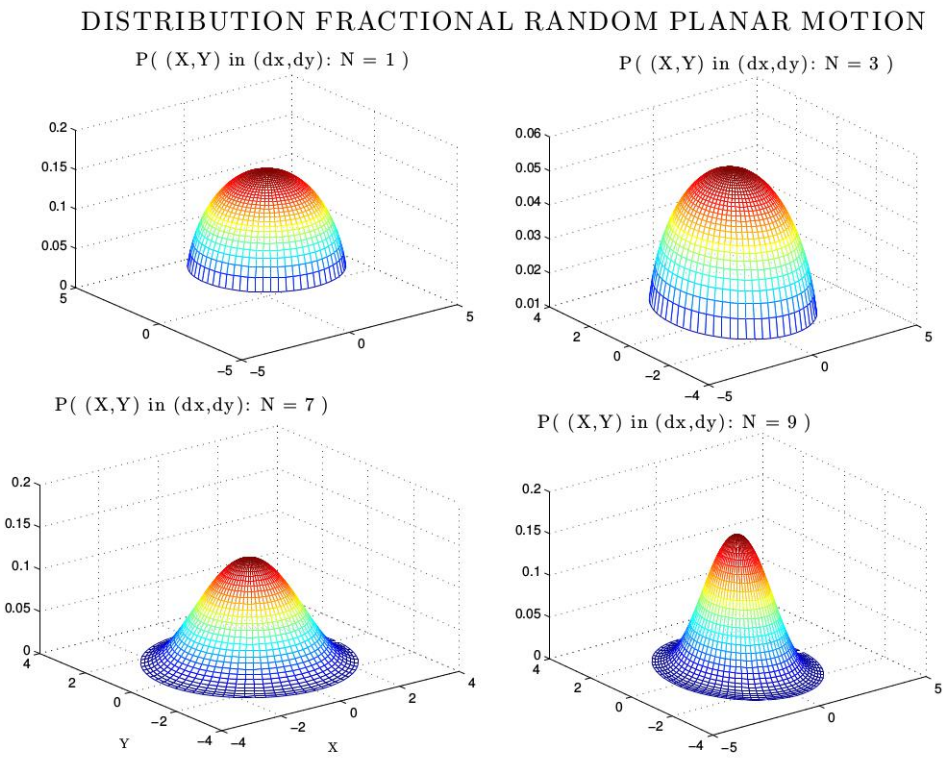


Figure 4.2: Distribution of the fractional planar random walk. The initial position is in the origin of the axis $(0,0)$ and the distribution of the new direction is assumed to be uniform over the unit circle.

4.2.2 Continuous Time Random Walk

CTRW - Deterministic Cádlág Process

Let us consider the system of HSHS in case $c(x,t)$ is constant. To be more precise, the general system becomes

$$X(t) = x_0 + \int_0^t \theta(s)ds, \quad \theta(t) = \theta_0 + \sum_{j=0}^{\mathcal{N}(t)} Y_j \quad 0 \le t \le T$$

$$\Lambda(t) = \eta_0 + \lambda \cdot t + \sigma \cdot W(t), \quad \mathcal{N}(t) = \sum_{k=1}^{\infty} \chi_{[\tau_k,\infty)}(s) \quad 0 \le t \le T$$

$$\tau_n = \inf\{s > \tau_{n-1} : \Lambda(s) = n \ge 1\} \quad \tau_0 = 0.$$

The vector $(\Lambda, \mathcal{N}, X, \theta)$ is Markovian and the distribution for the stopping times $\{\tau_n\}$ is well known: it is a sequence of random variables with inverse Gaussian distribution $\mathcal{IN}(\frac{1}{H}, \frac{1}{\sigma^2})$. We have already analyzed the problem when the parameter λ is positive and obtained that on the macroscale level the probability distribution of the random process $X(s)$ solves a diffusion equation. Briefly: for $\lambda > 0$ we have that the distributions of the waiting times and displacements are in L^2. From the central limit theorem it follows that the limiting

dynamics are given by the Wiener process.

From standard results on convergence of RV, we have that $\mathcal{IN}(\frac{1}{H}, \frac{1}{\sigma^2})$ converges in distribution as $\lambda \to 0$ towards a RV which follows a Lèvy distribution with parameters $\mathcal{L}(0, \frac{1}{\sigma^2})$. When we study the limit case $\lambda = 0$, it turns out that the limiting behavior of the distribution of the random variable $\frac{1}{n^\beta} X(\sum_j \tau_j)$ is more complicated.

CTRW - Poisson counting process

Similarly, if we let a_j in HSHS be exponentially distributed i.i.d RV's: the vector (Λ, N, X, θ) is Markovian and the distribution for the stopping times $\{\tau_n\}$ is well known: it is a sequence of random variables which have exponentially compound Inverse Gaussian distributions $\mathcal{IN}(\frac{\alpha}{H}, \frac{\alpha^2}{\sigma^2}), \alpha \sim Exp(\beta)$; a power law with exponent $\frac{1}{2}$.

Multidimensional Lévy walk and its scaling limits

The model HSHS, in this limiting case can be viewed as a multidimensional Lévy walk (LW), we briefly recollect it [123]:

Cádlág case: We start studying the CTRW which underlies our stochastic process: we will not follow the process along its trajectory, but only at the point when the process θ is discontinuous: more precisely we consider that $X(t)$ stays in a prescribed location and at τ_n it jumps outright to the new location given by $X(t) + \tau_n \theta_n$.
We will assume that

(I) waiting times T_i are i.i.d. random variables distributed according to some heavy-tailed power law with exponent $\alpha \in (0, 1)$, i.e.

$$\mathbf{P}(T_i > x) \sim C_0 x^{-\alpha} \text{ as } x \to \infty,$$

for some constant $C_0 > 0$

(II) jumps X_i are of the form

$$X_i = T_i V_i,$$

where $\{V_i\}_{i>0}$ is a sequence of i.i.d. random unit vectors in $\mathbb{S}^d$ with a distribution which is independent of the sequence $\{T_i\}_{i>1}$ and such that the distribution V_1 is not degenerated.

Unit vectors V_i govern the direction of jumps X_i, whereas T_i is the length of jump X_i.

In this case we have the following convergence results:

$$a_n \sum_{i=1}^{[nt]} X_i \Rightarrow \mathcal{L}_\alpha(t), \quad n \to \infty. \tag{4.2.1}$$

Here, $\mathcal{L}_\alpha(t)$ is the d-dimensional α-stable Lévy motion with Fourier transform

$$\log \phi_{\mathcal{L}_\alpha(t)}(k) = t \int_{\mathbb{S}^d} |\langle k, s \rangle|^\alpha \Big(i \cdot \text{sgn}(\langle k, s \rangle) \tan\Big(\frac{\pi\alpha}{2}\Big) - 1 \Big) \Lambda(ds).$$

For T_i, they belong to the domain of attraction of some one-sided α-stable law

$$a_n \sum_{i=1}^{[nt]} T_i \Rightarrow \mathcal{S}_\alpha(t), \quad n \to \infty,$$

where, $\mathcal{S}_\alpha(t)$ is the strictly increasing α-stable subordinator with Fourier transform

$$\log \phi_{\mathcal{S}_\alpha(t)}(k) = t|k|^\alpha \Big(i \cdot \mathrm{sgn}(k) \tan\Big(\frac{\pi\alpha}{2}\Big) - 1 \Big).$$

The normalizing constants in (4.2.1) is given explicitly by

$$a_n = \Big(C_0 \Gamma(1-\alpha) \cos\Big(\frac{\pi\alpha}{2}\Big) \cdot n \Big)^{-\frac{1}{\alpha}}.$$

It is important to note that as sequences X_i and T_i are strongly dependent, so are the processes $\mathcal{L}_\alpha(t)$ and $\mathcal{S}_\alpha(t)$. Particularly, $\mathcal{S}_\alpha(t)$ has jumps in the same instants of time and of the same length as $\mathcal{L}_\alpha(t)$. From [123] we have

Theorem 4.2.1. *Let $R(t)$ be a LW process generated by the sequence $\{(X_i, T_i)\}_{i\in\mathbf{N}}$ satisfying conditions (I) and (II). Then*

$$\frac{1}{n} R(nt) \Rightarrow \mathcal{Y}(t),$$

where $\mathcal{Y}(t)$ is the right-continuous version of the process $\mathcal{L}_\alpha^-(\mathcal{S}_\alpha^{-1}(t))$. The spectral measure Λ of $\mathcal{L}_\alpha(t)$ is equal to the distribution of the unit vector V_1. Moreover, the exact joint distribution of $\mathcal{L}_\alpha(t)$ and $\mathcal{S}_\alpha(t)$ is given by the formula

$$\nu_{(\mathcal{L}_\alpha, \mathcal{S}_\alpha)}(dx, ds) = \epsilon_{\|x\|}(ds) \nu_{\mathcal{L}_\alpha}(dx),$$

where

$$\nu_{\mathcal{L}_\alpha}(x \in \mathbb{R}^d : \|x\| > r) := \frac{\Lambda(\mathbb{S}^d)}{C_0 \Gamma(1-\alpha) \cos\left(\frac{\pi\alpha}{2}\right)} \cdot \frac{1}{r^\alpha}.$$

Continuous case: Let us consider in detail the situation: The structure reminds us of the one of *Continuous Time Random Walks* (CTRWs), but those are typically defined in the way that their trajectories are discontinuous step functions. In the present context the alternative definition of continuous time random walks with continuous trajectories (CP-CTRW) given in [132] fits better.

Following this article we have that

$$X(t) = S(N(t)) + \frac{S(N(t)+1) - S(N(t))}{T(N(t)+1) - T(N(t))} \cdot (t - T(N(t))),$$

where for $t \geq 0$ $S(t) = \sum_{j=1}^{[t]} Y_j$, $T(t) = \sum_{j=1}^{[t]} \tau_j$ and $N(t) = \max\{k \geq 0 : T(k) \leq t\}$. The idea is to apply the Theorem 2 in [132]. First it is necessary to clarify some notation: Let us consider the triangular array of random vectors $\{(Y_{n,k}, \tau_{n,k})\}$, where $Y_{n,k}$ are the random vectors in $\mathbb{R}^d$ and $\tau_{n,k}$ are positive random variables. For this array we define, for $t \geq 0$,

$$\Big(S_n(t), T_n(t) \Big) := \Big(\sum_{j=1}^{[t]} Y_{n,j}, \sum_{j=1}^{[t]} \tau_{n,j} \Big),$$

$$N_n(t) := \max\{k \geq 0 : T_n(k/n) \leq t\},$$

and the sequence of CTRW processes

$$R_n(t) := S_n\Big(\frac{N_n(t)}{n}\Big) = \sum_{j=1}^{N_n(t)} Y_{n,j}.$$

The last process may be written in the form $R_n = \Phi(S_n, T_n)$ where the mapping

$$\Phi : \mathcal{D}([0,), R^d \times [0,\infty)) \to \mathcal{D}([0,\infty), R^d)$$

is given by the formula

$$\Phi(x, y) := (x^- \circ (y^{-1})^-)^+.$$

The array $\{(Y_{n,k}, \tau_{n,k})\}$ generates also the sequence of CPCTRW, $\xi_n(t)$. Exploiting the mapping $f : \mathcal{D}([0,\infty), R^d \times [0,\infty)) \to \mathcal{D}([0,\infty), R^d)$, [132] Definition 2, defined as

$$f(x)(t) = x(\eta_x(t)) + \frac{x(\theta_x(t)) - x(\eta_x(t))}{\theta_x(t) - \eta_x(t)} \cdot (t - \eta_x(t)),$$

where, for $t \geq 0$, $\eta_x(t) = \sup\{s < t : x(s) \neq x(t)\}$, $\theta_x(t) = \inf\{s \geq t : x(s) \neq x(t-)\}$ the function $\xi(t)$ can be written as $\xi_n(t) := f(R_n(t))$.

Theorem 4.2.2. *Assume that $(S_n, T_n) \Rightarrow (A, D)$ in the space $\mathcal{D}([0,\infty), R^d \times [0,\infty))$ equipped with $\mathbb{J}_1$ topology, where almost surely the trajectories of process A are not constant on any interval $(a, b) \in [0,\infty)$ and D has strictly increasing realizations. Then*

$$\xi_n(t) \Rightarrow R(t) := f(R) = f(\Phi(A, D)),$$

in the space $\mathcal{D}([0,\infty), R^d)$ equipped with $\mathbb{SM}_1$ topology.

The application of this theorem is not directly possible with $\tau \sim \mathcal{IN}(0, 1/\sigma^2)$, and $Y \in \mathcal{L}^2$ since this leads to A given as an α-stable Y-Lévy motion -as in the previous section- and D an 1/2-stable Lévy process:

$$X_n(t) \Rightarrow \mathcal{L}_\alpha(D_{1/2}^{-1}),$$

since *there exists* (a, b) *such that almost surely the trajectories are constant on the interval* $(a, b) \in [0,\infty)$, but a little modification of the proof allows us to claim the same convergence stated in the theorem. In fact holds:

Theorem 4.2.3. *Assume that $(V_n \cdot T_n, T_n) \Rightarrow (A, D)$ in the space $\mathcal{D}([0, T), \mathbb{R}^d \times [0,\infty))$ equipped with $\mathbb{J}_1$ topology, D has strictly increasing realizations and A is a α-stable Lévy motion weighted on the sphere. Then*

$$\xi_n(t) \Rightarrow R(t) := f(R) = f(\Phi(A, D)),$$

in the space $\mathcal{D}([0,\infty), R^d)$ equipped with $\mathbb{SM}_1$ topology.

Proof. The part of the proof in [132] to be adapted is on page 14 line 6 where it is written "*Now we check that ...*":
Assume that R' is constant on $]\eta_{R'}(t), \theta_{R'}(t)[$ for some $t > 0$ and $\theta_{R'}(t) \in disc(R')$. Note that A' and D' jump at the same exact points, since the two process are coupled the way it is stated above: so it follows that the two processes $R' = \Phi(A', D')$ and $\Phi(D', D')$ are constant on the same intervals. Then all the analysis is done on $\Phi(D', D')$. □

4.3 Stochastic Hybrid Systems

If we eliminate the functional dependency in the driving equation we are recast in the standard theory of HSS [63, 19, 7, 6, 73].
If we assume that the jump to different states is driven by an independent Poisson process, then the same system with functional dependency in the coefficient is recast into the frame work of SFDE with Markovian switching [84].

4.4 Poisson Time Change

In this section we make the following assumptions:

- $F(\cdot)$ and $G(\cdot)$ are regular functions, in the sense that the equation for ζ is well defined and at least continuous;
- $\mathcal{N}(t)$ is a Poisson process $\mathcal{N}(t)$;
- $\lambda(\cdot)$ is a positive function which depends on $(\theta(t), X(t), \zeta(t))$;
- $\sigma \equiv 0$;

In this case HSHS can be viewed in the framework of the random-time changes proposed and intensively studied by Kurtz [47, 76]. Let $Y : \Omega \times [0,\infty) \to \mathcal{S}^2$ such that for all $t \in [0,\infty)$, $\mathbf{E}[Y(t)|\theta(t^-)] \sim \mu_{\theta(t^-)}$. For $0 \le t \le T$

$$\begin{aligned} X(t) =& x_0(0) + \int_0^t \theta(s)ds \\ \theta(t) =& \theta_0(0) + \int_0^t \mathbb{E}[Y(t)|\theta(t^-)] \cdot d\Psi(t) \\ \Psi(t) =& \mathcal{N}\Big(\int_0^t \lambda(s, \zeta(s), \zeta_s, \theta(s))ds \Big) \\ d\zeta(t) =& F(c(X(t),t), \zeta(t))dt + G(c(X(t),t), \zeta(t))dW(t). \end{aligned}$$

4.4.1 Stroock

As mention in Chapter 3, HSHS is a generalization of the model of Stroock [119]. Under the hypothesis stated above, if we eliminate the variable ζ, we are immediately recast into that model, in particular we can construct a temporally inhomogeneous Markov process $(x(t), \theta(t))$ on $\mathbb{R}^3 \times \mathbb{S}^2$ such that:

- $x(t) - x(s) = (t-s) \cdot \theta(s)$, if $\theta(\cdot)$ is constant during $[s,t)$;
- the conditional probability of $\theta(\cdot)$ being constant during $[t,s)$ given the past up to time s is

$$\mathbf{P}\Big(\theta(u) = \theta(s), u \in [s,t) \| \mathcal{F}_s\Big) = \exp\Big[- \int_s^t \lambda(u, x + (u-s)\theta, \theta)du \Big],$$

where λ is a given function

$$\lambda : [0,\infty) \times \mathbb{R}^3 \times \mathbb{S}^2 \to (0,\infty);$$

- the conditional distribution of the first place at which $\theta(\cdot)$ jumps after time s given the past up to time s is given by $\mu_{\theta(s)}$, a probability measure on $\mathbb{S}^2$.

4.4.2 Alt Model

In order to identify the model by Wolfgang Alt [2], we need some remarks:

- We may consider the model by Alt as a special case of the velocity-jump models (see for example [128]): we have that the *internal variable* (here τ) satisfies the differential equation $\dot{\tau} = -1$ and it is reset to the value 0 at every arrival time of a non-homogenous Poisson process: the process ζ is identified by the variable τ.

- We need to take care and proceed as in Section 3.5.1 to allow discontinuity and resetting of the processes: we can do it, since we are in a natural Markovian setting.

- Supposed that an individual at (t, x) has been running in direction θ for a time τ (counted from the beginning of the run): The hypothesis in [2], say that it will then stop at (t, x) to tumble with a probability rate given by $\beta(t, x, \tau, \theta)$: we identify β with our function λ.

4.4.3 Othmer at al.

A development of the model of Alt [2] and Stroock [119] is performed in [45, 128], in the sense the internal state variables were introduced to describe the time-dependent signal transduction and response. When this is done the transport equation becomes

$$\partial_t p + \epsilon v \cdot \nabla_x p + \mathrm{div}_y(F(y, S(x))p) = \lambda(S(x)y)(R(p) - p),$$

The entire signal transduction of bacteria is very complicated and detailed models involve many state variables [33], but the major processes consist of fast excitation in response to signal changes and slow adaptation that subtracts out the background signal. These processes can be captured by the cartoon description

$$\begin{aligned} \frac{d}{dt}y_1(t) &= \frac{G(c(t,x)) - (y_1 + y_2)}{\tau_a}, \\ \frac{d}{dt}y_2(t) &= \frac{G(c(t,x)) - y_2}{\tau_e}. \end{aligned} \tag{4.4.1}$$

By using this cartoon description for the internal dynamics, applying moment closure techniques and a regular perturbation method, the macroscopic equations are the classical Keller-Segel diffusion equation:

$$\frac{\partial}{\partial t}u(t,x) = \nabla_x\Big(\frac{\mu}{c}\nabla_x(c \cdot u(t,x)) - \chi u(t,x)\nabla_x\rho(t,x)\Big).$$

Particle-Based Models for Bacterial Chemotaxis

A special case of this model is developed in [111]. We write some detail of this model, since it will be used and adapted in Chapter 5. The evolution of the individual position of each bacterium, its internal state and jumps are given by

$$\frac{dX_t}{dt} = \epsilon V_t \quad V_t = \mathcal{V}_n \text{for} t \in [T_n, T_{n+1}[,$$

$$\frac{dY_t}{dt} = F(Y_t, S(X_t)), \quad \int_{T_n}^{T_{n+1}} \lambda(S(X_t) - Y_t)dt = \mathcal{E}_{n+1}^1.$$

The density of the probability distribution of the process with internal dynamics at time t with respect to the measure $dxM(dv)dy$ is denoted as $p(x, v, y, t)$, suppressing the dependence on ϵ for notational convenience, and evolves according to the Kolomogorov forward evolution equation (or master equation). A standard probabilistic diffusion approximation argument can be used to derive the pathwise diffusive limit of the process with internal state. We denote by

$$X_t^\epsilon = X_{t/\epsilon^2},$$

the process with internal state on diffusive time scales. With the assumption stated in [SR13], i.e.

$$\lambda(z) = \lambda_0 - b^T \cdot z + c_\lambda \mathcal{O}(|z|^k),$$
$$F_\epsilon(y, s) = \tau_\epsilon^{-1}(ys) + \epsilon^{1\delta} c_F \mathcal{O}(|sy|^2),$$

the following holds

Proposition 4.4.1. *Assume* $\lim_{\epsilon\to 0} \frac{\tau}{\lambda_{0\epsilon}+Id}$ *exists and that* $\delta > 1/k$. *Then, the process* X_{t/ϵ^2} *converges in distribution (for uniform convergence topology) towards the solution of the SDE*

$$dX_t^{c,0} = \Big(\frac{DA_0(X_t^{c,0})}{\lambda_0}dt + \sqrt{\frac{2D}{\lambda_0}}dW_t\Big),$$

where

$$D = \int_{S^{d-1}} v \otimes vM(dv)$$

and

$$A_0(x) = b^T \lim_{\epsilon\to 0} \frac{\tau_\epsilon}{\lambda_{0\epsilon} + Id} \nabla S(x).$$

4.4.4 Vergassola and Celani

The model of Vergassola and Celani [22] is a generalization in some sense of [45, 128], by allowing diffusion of the direction of the bacterium during a run, and a specialization of the cartoon model 4.4.1 to the special case of *E. coli*. We recover [22] when we select the following parameters:

- $r = \infty$
- $\sigma_X = 0$;

- $F(\cdot)$ follows Eq. 3.5.4 and $G(\cdot)$ is given by the relative formula in SI of [22].
- $\mathcal{N}(t)$ is a Poisson process with unit parameter;
- $\Lambda(t) = \int_0^t \frac{1}{\tau_r}\Big[1 - \int_{-\infty}^s K(s-r)c(X(r),r)dr\Big]ds$
- $K(t) = \lambda e^{-\lambda t}\sum_{k=1}^{k_M}\beta_k(\lambda t)^k \cdot \mathbf{1}_{\{t\geq 0\}}$

We refer to **Appendix B** for a review of this article.

Chapter 5

ONE POINT VARIABLE MEMORY

In this chapter a new model for the movement of *E. coli* is introduced and studied: it is a generalization of the PDMP where the current concentration of ligand is compared with the one at the beginning of the run.

5.1 PDMP - Countable numbers of directions

In 1984 M. H. A. Davis [36] proposed and studied intensively a special class of Markov processes, whose main characteristics may be used to analyze the problem of the movement of *E. coli*.

Let us construct the process: Let K be a countable (or a finite) subset of the unit sphere $\mathbb{S}^{d-1}$, and let $\mathcal{M}$ be $\mathbb{R}^d \times \mathbb{R} \times \mathbb{R}_+$. Consider then a given function $c : [0,T] \times \mathbb{R}^d \to \mathbb{R}$

Denote the state of the process as $\zeta(t) := (x(t), \eta(t), t, \theta(t)) \in \mathcal{M} \times K := E$, whose probability law is determined by the following objects.

- A measurable function $\lambda : E \to \mathbb{R}$;
- A transition measure $\mathbf{Q} : \mathcal{B}_{\mathcal{M}} \times E \to [0,1]$;
- A vector field $(\mathcal{H}_\theta)_{\theta \in K}$.

The motion of the process $(\zeta(t))_{t \in \mathbb{R}_+}$ starting from $\zeta_0 := (x_0, c(x_0,0), \theta_0)$ can be constructed as follows: Define a survivor function F by

$$F(t) = \exp\Big\{ - \int_0^t \lambda\Big(x_0 + \int_0^s \mathcal{H}_\theta\Big(c(x(u),u) - c(x_0,0)\Big)du, c(x_0,0), \theta_0\Big)ds\Big\}.$$

Select a random variable T_1 such that $\mathbf{P}\Big(T_1 > t\Big) = F(t)$ and independently an E-valued random variable (X, H, Θ) having distribution

$$\mathbf{Q}\Big(\ \cdot\ ,\ \Big[\int_0^{T_1} \mathcal{H}_\theta\Big(c(x(u),u) - c(x_0,0))\Big)du, c(x_0,0), T_1, \theta_0\Big]\Big),$$

where the structure of the measure is

$$\mathbf{Q}\Big(\mathcal{X} \times \mathcal{B} \times \mathcal{T} \times \mathcal{A}, [x, \eta, t, \theta]\Big) = \delta_x(\mathcal{X})\delta_{c(x,t)}(B)\delta_t(\mathcal{T})\mu_\theta(A).$$

Denote now

$$\Lambda_s^t(x,\eta,\theta) := x + \int_t^s \mathcal{H}_\theta\Big(c(x(u),u) - \eta\Big)du.$$

The trajectory of $\zeta(t))_{t\in\mathbb{R}_+}$ for $t \geq T_1$ is given by

$$\zeta(t) = \Big(X(t),\eta(t),t,\theta(t)\Big) = \begin{cases} \Big(\Lambda_0^t(x_0,c(x_0,0),\theta),t,\theta_0\Big) & t \leq T_1 \\ \Big(X,H,T_1,\Theta\Big) & t = T_1 \end{cases},$$

where

$$\Big(X,H,T_1,\Theta\Big) = \Big(\int_0^{T_1}\mathcal{H}_\theta\Big(c(x(u),u)-c(x_0,0)\Big)du, c\Big(\int_0^{T_1}\mathcal{H}_\theta\Big(c(x(u),u)-c(x_0,0)\Big)du,T_1\Big),T_1,\Theta\Big).$$

Starting from $\zeta(T_1)$ we now select the next inter-jump time $T_2 - T_1$ and post jump location $\zeta(T_2)$ in a similar way.

Let us consider now $t \in [T_k, T_{k+1}[$, then the distribution of the random variable $T_2 - T_1$ is given by

$$\mathbb{P}\Big(T_2-T_1 > s\Big) = \exp\Big\{-\int_0^s \lambda\Big(x_{T_k}+\int_{T_k}^{T_k+s}\mathcal{H}_\theta\Big(c(x(u),u)-c(x_{T_k},T_k)\Big)du, c(x_{T_k},T_k),\theta_{T_k}\Big)ds\Big\},$$

for $s > t$ one has for $\zeta(t) = (x_t,\eta_t,t,\theta_t)$

$$\begin{aligned}\mathbb{P}\Big(T_{k+1} > s \;\Big|\; T_k, T_{k+1} > t\Big) &= \mathbb{P}\Big(T_{k+1}-T_k > s - T_k \;\Big|\; T_k, T_{k+1}-T_k > t - T_k\Big) \\ &= \exp\Big\{-\int_{t-T_k}^{s-T_k}\lambda\Big(\Lambda_{T_k}^u(X(T_k)),\eta(T_k),\theta_{T_k}\Big)du\Big\} \\ &= \exp\Big\{-\int_0^{s-t}\lambda\Big(\leftarrow\!\Lambda_t^{t+u}(\leftarrow\!\Lambda_{t+u}^{T_k}X(T_k)),\eta_t,t+u,\theta_t\Big)du\Big\} \\ &= \exp\Big\{-\int_0^{s-t}\lambda\Big(\Lambda_t^{t+u}(X(t)),\eta_t,t+u,\theta_t\Big)du\Big\}.\end{aligned}$$

So the distribution of the next jump time depends only on $\zeta(t) = (x_t,\eta_t,t,\theta_t)$. Thus the Markov property is verified.

Since the process under investigation is an inhomogeneous Markov process the associated semigroup is a family of two index operators and the related infinitesimal generators is a family of operators:

The Extended Generator of the PDMP Process

Let us consider the following family of operators with two indices (t and s):

$$T_t^s f(x,\eta,t,\theta) := \mathbb{E}\Big[f(X(t+s),\eta(t+s),t+s,\theta(t+s))\Big|\; X(t)=x,\eta(t)=\eta,\theta(t)=\theta\Big].$$

The strong generator of this semigroup is given by

$$\mathcal{A}_s[f(x,\eta,s\theta)] := \lim_{t\to 0}\Big(\frac{T_s^{s+h}-\mathbb{I}}{h}\Big)[f(x,\eta,s\theta)].$$

Let us supposed that the vector field $\mathcal{H}_\theta$ in [36] works as follows:

$$\mathcal{H}_\theta := \theta g(c(x,t) - \eta) \cdot \nabla_x.$$

The family of generators is then given by

$$\begin{aligned}\mathcal{A}_s f(\zeta) :=& \frac{\partial}{\partial t} f(\zeta) + \theta \cdot g(c(x,t) - \eta) \cdot \nabla_x f(\zeta) \\ &+ \lambda(c(x,t) - \eta) \int_K [f(x, c(x,t), t, \mu) - f(x, \eta, t, \theta)] \mathbf{Q}(d\mu; x),\end{aligned}$$

where $\zeta := (x, \eta, s, \theta)$.

Remark 5.1.1. We underline that the construction of such a generator allows us to write down the Kolmogorov backward equation without effort. The question of the form of the forward equation is much more complicated, and it involves the use of Gauss's theorem and the identification of boundary conditions that come from the form of the domain of the generator [50, 51].

5.1.1 Related Models

In this section we give an overview of similar models that may be used to compare the performance of a strategy based on the simple modification of PDMP.

- A deterministic model where the direction is given by the gradient of the chemical substance, i.e.

$$\begin{aligned}\frac{d}{dt} X(t) &= g(\|\nabla c(X(t), t)\|^2) \cdot \nabla c(X(t), t), \\ X(0) &= x_0.\end{aligned}$$

- A perturbed deterministic model where the direction is given by the gradient of the chemical substance, i.e. for $0 < \epsilon << 1$

$$\begin{aligned}\frac{d}{dt} X(t) &= g(\|\nabla c(X(t), t)\|^2) \cdot \nabla c(X(t), t) + \epsilon \cdot \dot{W}(t), \\ X(0) &= x_0.\end{aligned}$$

- The model developed by E. Orsingher and N. E. Ratanov [101], i.e. two-dimensional telegraph process in an inhomogeneous plane.
  Consider the four continuous functions $c_{ij} = c_{ij}(x)$, $x = (x_1, x_2) \in \mathbb{R}^2, i, j = 1, 2$, and define a planar motion $X = X^x(t), t > 0$, by means of the following equations:

$$\begin{cases} dX_1^x(t) = c_{11}(X_1^x, X_2^x) dU_1(t) + c_{12}(X_1^x, X_2^x) dU_2(t), \\ dX_1^x(t) = c_{21}(X_1^x, X_2^x) dU_1(t) + c_{22}(X_1^x, X_2^x) dU_2(t) \end{cases}$$

  Here we denote by U_1 and U_2 the components of the standard telegraph process U in the plane, i.e.

$$U(t) = \xi \int_0^t (-1)^{N(s)} ds,$$

  with $\mathcal{L}(\xi) = \frac{1}{2}(\delta_{\{+1\}} + \delta_{\{-1\}})$ and $N(t)$ a Poisson process.

5.2 PDMP - Infinite Number of Directions

In the present section we adapt the general setup in [119] and generalize the model of the previous section to allow the bacterium to chose between an infinite number of directions: more precisely we will assume that the duration of a twiddle is negligible and therefore that it is possible to talk about the direction of the bacterium at a given instant. Let us consider that the direction of the bacterium is a Poisson-type process on the sphere $\mathbf{S}^2$, whose intensity λ depends on a number of additional parameters, i.e.

- the concentration of the chemical substance at the position of the bacterium;
- the concentration of the chemical substance at the position and time where the bacterium was located at the beginning of the run;

We supposed that

$$c : \mathbb{R}^3 \times [0, \infty) \to \mathbb{R}_+$$

is a given function, whose regularity is assumed to be enough to do all the analytical manipulation, that characterizes the chemical level of the attractant at the point $(x, t) \mapsto c(x, t)$. We assume that there is a function

$$\lambda : \mathbb{R} \times \mathbb{R} \to \mathbb{R}_+$$
$$(\xi, \gamma) \mapsto \lambda(\xi, \lambda) := \lambda(\xi - \lambda),$$

which is the intensity of the Poisson process. More precisely we assume that the conditional probability that a twiddle has not occurred between s and t given that at time s the bacterium was at x, oriented in the direction θ, with a recorded ligand concentration given by γ is given by the expression:

$$\exp\Big\{ - \int_s^t \lambda\Big(c(x + (\alpha - s)\theta), \alpha) - \gamma\Big) d\alpha\Big\}.$$

At a twiddle the càdlàg part of the process jumps in the following way:

- it is assumed that θ moves to a new point on $\mathbf{S}^2$ in such a way that the probability that the new direction is in a subset Θ of $\mathbf{S}^2$ given that the old direction was θ is $\mu_\theta(\Theta)$, where $\mu_\theta(\cdot)$ is a probability measure on $\mathbf{S}^2/\{\theta\}$;
- the process $(\gamma_t)_{t\in\mathbb{R}}$ moves from γ_{t^-} to $\gamma_t := c(x, t)$

  $$\gamma_t = \int_{\mathbb{R}_+} z \cdot \delta_{c(x(t),t)}(dz),$$

  where we make use of the following weak limit:

  $$\gamma_t := w - \lim_{\epsilon\to 0} \int_{\mathbb{R}} z \cdot \frac{1}{\sqrt{2\pi\epsilon}} e^{\frac{(z-c(x,t))^2}{2\epsilon}}.$$

These assumption give rise to a temporally inhomogeneous Lèvy-type diffusion on $\mathbb{R}^3 \times \mathbf{S}^2$. The backward equation associated with this diffusion is

$$\frac{\partial}{\partial t} u(t, x, \theta, \gamma) + \theta \cdot \nabla_x u(t, x, \theta, \gamma) + \lambda\Big(c(x, t) - \gamma\Big) \mathbf{K}_{c(x,t),\theta,\gamma}\Big[u(t, x, \theta, \gamma)\Big] = 0,$$

$$\mathbf{K}_{c(x,t),\theta,\gamma}\Big[u(t, x, \theta, \gamma)\Big] = \int_{\mathbf{S}^2\times\mathbb{R}_+} [u(t, x, \eta, z) - u(t, x, \theta, \gamma)] d\mu_\theta(d\eta) \otimes \delta_{c(x,s)}(dz)$$

The Model, its Construction and Basic Properties

What we want is a temporally inhomogeneous Markov process $(x(t), \theta(x), \gamma(t))$ on $\mathbb{R}^3 \times \mathbf{S}^2 \times \mathbb{R}_+$ with the property that

$$x(t) - x(s) = (t-s) \cdot \theta(s)$$
$$\gamma(t) = \gamma(s),$$

if $\theta(\cdot)$ is constant during $[s,t)$. Further we require that the conditional probability of $\theta(\cdot)$ being constant during $[s,t)$ given up to time s is

$$\exp\Big\{ - \int_s^t \lambda\Big(c(x + (\alpha - s)\theta), \alpha) - \gamma\Big) d\alpha \Big\}.$$

Finally, the conditional distribution of the first place to which $(\theta(\cdot), \gamma(\cdot))$ jumps after time s given the past up to time s is to be $\mu_{\theta(s)}(\cdot) \otimes \delta_{c(x(s),s)}(\cdot)$.
The idea is now to try to put all these things together and (*try to*) derive the Kolmogorov's equations. Let us consider the function

$$u(t,x,\theta,\gamma) = \mathbf{E}^s_{x,\theta,\gamma}\Big[f(x(T), \theta(T), \gamma(T)) \Big],$$

where $\mathbf{E}^s_{x,\theta,\gamma}[\cdot] = \mathbf{E}[\cdot \,\|(x(s);\theta(s);\gamma(s)) = (x,\theta,\gamma)]$. We can follow [119], an write

$$\mathbb{E}_{s,x,\theta}[f(x(T),\theta(T))] = \mathbb{E}_{s,x,\theta}[f(x(T),\theta(T)) : \tau > T] + \mathbb{E}_{s,x,\theta}[f(x(T),\theta(T)) : \tau \leq T],$$

where τ is the first jump time θ after time s. We can exploit the Markov property to obtain

$$\begin{aligned} u(s,x,\theta,\gamma) = {} & f(x + (T-s)\theta, \theta, \gamma) e^{-\int_s^T \lambda(c(x+(\alpha-s)\theta,\alpha)-\gamma)d\alpha} \\ & + \int_s^T \Big[\lambda(c(x+(\alpha-s)\theta,\alpha) - \gamma) e^{-\int_s^\alpha \lambda(c(x+(\beta-s)\theta,\beta)-\gamma)d\beta} \\ & \qquad \cdot \mathcal{A}u(\alpha, x+(\alpha-s)\theta, \theta, c(x+(\alpha-s)\theta,\alpha)) \Big] d\alpha, \end{aligned}$$

where

$$\mathcal{A}u(t,x,\theta,c(x,t)) = \int_{\mathbf{S}^2 \times \mathbb{R}_+} u(t,x,\eta,z) d\mu_\theta(d\eta) \otimes \delta_{c(x,s)}(dz).$$

5.2.1 Limit Behavior

In this section we will rescale the process parabolically, i.e. $x \mapsto \epsilon x$ and $t \mapsto \frac{t}{\epsilon^2}$ and study the following limit in distribution:

$$\lim_{\epsilon \to 0} \epsilon X(\frac{t}{\epsilon^2}).$$

We adapt the proofs and results in [111] that we have summarized in **Subsection 4.4.3**. For the rescaled process holds the following approximation:

$$\begin{aligned} \lambda(c(X(t),t) - c(X(T_n),T_n)) \sim \lambda(0) & - \epsilon\lambda'(0)\nabla c(X(T_n),T_n)\theta(T_n) \\ & - \epsilon\lambda'(0)\partial_t c(X(T_n),T_n) + \mathcal{O}(\epsilon^2). \end{aligned}$$

Then, for small ϵ the time between to jumps can be approximated as follows:

$$\Delta T_{n+1} \sim \mathcal{E}_{n+1}\frac{1}{\lambda(0)}\Big(1+\epsilon\frac{\lambda'(0)}{\lambda(0)}\nabla c(X(T_n,T_n)\theta(T_{n+1})+\lambda'(0)\partial_t c(X(T_n),T_n)\Big)+\mathcal{O}(\epsilon^2).$$

Comparing this process with a time inhomogeneous random walk, one obtains that the limiting process is a diffusion with coefficients given by

$$\sigma := \lambda(0)\mathbf{E}\big[\frac{\mathcal{E}_{n+1}\theta\otimes\theta}{\lambda(0)^2}\big] = \mathbf{E}\big[\frac{\theta\otimes\theta}{\lambda(0)}\big],$$

$$a_1(x,t) := \lambda(0)\mathbf{E}\big[\frac{\mathcal{E}_{n+1}\theta\lambda'(0)\nabla c(x,t)\otimes\theta}{\lambda(0)^2}\big] = \mathbf{E}\big[\frac{\lambda'(0)\nabla c(x,t)\theta(t)\otimes\theta(t)}{\lambda(0)}\big] \sim \lambda'(0)\nabla c(x,t)\cdot\sigma,$$

$$a_2(x,t) := \lambda(0)\mathbf{E}\big[\frac{\mathcal{E}_{n+1}\lambda'(0)\partial_t c(X(t),t)}{\lambda(0)^2}\big] = \mathbf{E}\big[\frac{\lambda'(0)\partial_t c(X(t),t)\theta(t)}{\lambda(0)}\big] \sim \lambda'(0)\partial_t c(x,t)\in o(\epsilon^2),$$

hence, it satisfies the following SDE

$$dX(t) = \sqrt{\sigma}dW + \lambda'(0)\nabla c(x,t)\cdot\sigma dt.$$

If we denote with $u(t,x)$ the density of bacterial positions, then the function u is the solution of the following PDE:

$$\partial_t u(x,t) = \frac{\sigma}{\lambda(0)}\nabla_x\Big(\nabla_x u(x,t) - \lambda'(0)\nabla c(x,t)\cdot u(x,t)\Big).$$

Part II

Simulation & Software

Chapter 6

SIMULATIONS

In this chapter we discuss the results of the simulations that we perform with the help of the software `EColi_Simulator`, a program we developed and which is described in detailed in the next chapter.

6.1 Results of the Simulations

In order to estimate the density function $p(t,x)dx$, representing the probability to find a bacterium at position x at time t, we use the kernel density estimation technique in its simplified version, i.e. via binning in a histogram. The kernel density estimation technique is the most widely used method when estimating complex density functions, owing to its flexibility and the plethora of theoretical results establishing its consistency for various rates of convergence.

The simulations agree with the theoretical results of the previous chapters, in particular with Chapter 3, and are not particular surprising or reviling of some strange or unexpected phenomenon. In this sense we are going to give a short summary of few significant simulations, underlying the difference of the models involved. This is also an example of the output and sort of analysis done by the program `EColi_Simulator`. We are not going in the direction of the stability analysis of the results with respect to the parameters, but we have used parameters from the literature. This might be a further branch of research, which can be easily performed with the help of `EColi_Simulator`.

We will briefly summarize here the main features and results of the simulations.

- **SIMULATIONS AND ANALYSIS**
  - We perform the simulations of stochastic particles in a given environment:
    - we chose to model the environment by a deterministic function $c(t,x)$, which describes the concentration of chemoattractant;
    - each particle performs a *run* and *tumble* random walk: the duration of the time spent in a given phase depends of the internal dynamics;
    - the internal dynamics, as well as the rules that govern the transition of phase (i.e. from *run* to *tumble* and vice versa) are specific of each model. We refer

to the next chapter for the details; we briefly say that the internal variable is the solution of a characteristic ODE (see for example equations (4.4.1) and (3.5.4)), while the transition is performed when the *generalized subordinator* crosses a specific threshold (see equation (3.2.1)).

– We estimate the density function $p(t,x)dx$ via binning in a histogram, i.e. let us divide the area of the experiment into a grid: we call the rectangle in position i along the x-axis and j along the y-axis $\Delta x_{i,j}$. We denote with N the number of particles in the simulation and with $x_k(t)$ the position of the particle k at time t. We compute the histogram of the density function as follows

$$\mathcal{H}(t,x) := \sum_{i,j}\sum_{k=1}^{N} \mathbf{1}_{\{x_k(t)\in\Delta x_{i,j}\}} \cdot \mathbf{1}_{\{x\in\Delta x_{i,j}\}};$$

We do not use a more sophisticated estimation since we perform no comparison with a continuous model. In case such a comparison should be performed, we should employ the kernel density estimation technique with more appropriate kernel functions.

– We perform the analysis of the barycenter of the population, i.e.

$$\mathcal{B}(t) := \frac{1}{N}\sum_{k=1}^{N} x_k(t);$$

its speed in direction $\vec{e_j}$, i.e.

$$\mathcal{V}_j(t) := \frac{1}{N}\sum_{k=1}^{N} \frac{\langle x_k(t+\delta t) - x_k(t), \vec{e_j}\rangle}{\delta t};$$

as well as the calculation of the mean square displacement

$$\langle r^2(\tau)\rangle = \lim_{N\to\infty} \frac{1}{N}\cdot\sum_{n=1}^{N}\left(x_n(\tau) - x_n(0)\right)^2,$$

and the simple linear regression (least-squares approach). In the present case it is appropriate to force the regression line to pass through the origin, i.e $\langle r^2(\tau)\rangle = \beta\cdot t$.

– We will display the results of the simulation of two models in different environments: these models are called `CV_rExp_tExp` and `CV_rIG_tExp`. The model of the internal dynamics that we used in these simulation is the one described in [22]. We report it here:

$$\begin{aligned}
\mathcal{Q}(t) &= \sum_{k=1}^{k_N} \beta_k \nu^{k+1} m_k(t) \\
m_k(t) &= \int_{-\infty}^{t} e^{-\nu(t-s)}(t-s)^k c(X(s),s)ds \quad k = 0,\dots k_N \\
\frac{d}{dt}m_k &= -\nu\cdot m_k + f_k,
\end{aligned}$$

where $f_k = k \cdot m_{k-1}$ for $k \geq 1$ and $f_0 = c$ for $k = 0$. In order to calculate the update of the internal dynamics we use a simple Euler's method. We report the (virtual) function that performs the calculation.

```
//**************************
void CV_rExp_tExp::agg_dyint(double dt, double t){
    int n_iteration=5;
    dt=dt/n_iteration;
    for (int i=0; i<n_iteration; ++i) {
        m[2]=m[2]+dt*(2*m[1]-nu_*m[2]);
        m[1]=m[1]+dt*(m[0]-nu_*m[1]);
        m[0]=m[0]+dt*(c-nu_*m[0]);
        Q=pow(nu_,2)*beta_2*m[1]+pow(nu_,3)*beta_3*m[2];
    }
}
```

The parameters that we used are listed below:

* `t` is the current time, which is not used in this model;
* `dt` is the time step, i.e. $dt = 0.01$ seconds;
* `nu_` is the exponent of the cut-off function for the memory term:
  `nu_=4*(1+3*D_theta*tau_r)/(3*tau_r)`$=2.\bar{6}$,
  where `D_theta = 0.25` and `tau_r = 0.8`;
* `beta_2=1`;
* `beta_3=-beta_2/2`.

$\mathcal{Q}(t)$ is the memory term that influence the mean distribution of a *run* ($m_r(\mathcal{Q})$) in the following sense:

$$m_r(\mathcal{Q}) = \frac{g(\mathcal{Q}(t))}{\tau_r},$$

where $g(x)$ is a function such that for $x \sim 0$, $g(x) \sim (1 - x)$. For both models the duration of tumble phase is exponentially distributed $\mathcal{E}(\lambda)$, with mean given by the value 0.1 seconds. The two models are different in what follows

* `CV_rExp_tExp`: the duration of a run τ is given by the solution of the following equation:
  $$\int_0^\tau m_r(Q(s))ds = \mathcal{E}(1).$$
* `CV_rIG_tExp`: the duration of a run τ is given by the solution of the following equation:
  $$\int_0^\tau \Big[m_r(Q(s))ds + \sigma dW(s)\Big] = 1,$$
  where σ is a constant and $W(t)$ is a Wiener process.
  Consider the SDE $d\Lambda_r(t) = m_r(Q(s))ds + \sigma dW(s)$, then we have that the process crosses a threshold b in the interval $[t, t+dt)$ if the following condition

is satisfied:

$$exp\Big\{ -2\frac{\Big(b-\Lambda(t)\Big)\cdot\Big(b-\Lambda(t+dt)\Big)}{dt\cdot\sigma^2}\Big\} \geq \mathcal{U}(0,1), \tag{6.1.1}$$

where $\mathcal{U}(0,1)$ is a uniform random variable on the interval $[0,1)$.

– We summarize the statistics relative to the duration of *runs* and *tumbles*. We divide the runs according to the sign of the *temporal gradient*, that is, if during a run the ligand concentration measured by the bacterium increases, decreases, remains constant, or it has a mixed behavior. We call this quantity $\langle\theta,\nabla c\rangle$. We give here the formal definition of this quantity. Let $[\tau_{k-1},\tau_k)$ be the duration of a *run* and $\{\Delta_k t\}_k$ a non-overlapping discretization of this interval. We define

* $\langle\theta,\nabla c\rangle = 0$, if for all $\Delta_n t \in [\tau_{k-1},\tau_k]$

$$\text{sign}\Big\{c\Big(t+\Delta t, x(t+\Delta t)\Big) - c(t,x(t))\Big\} = 0;$$

* $\langle\theta,\nabla c\rangle > 0$, if for all $\Delta_n t \in [\tau_{k-1},\tau_k]$

$$\text{sign}\Big\{c\Big(t+\Delta t, x(t+\Delta t)\Big) - c(t,x(t))\Big\} > 0;$$

* $\langle\theta,\nabla c\rangle < 0$, if for all $\Delta_n t \in [\tau_{k-1},\tau_k]$

$$\text{sign}\Big\{c\Big(t+\Delta t, x(t+\Delta)\Big) - c(t,x(t))\Big\} < 0;$$

* $\langle\theta,\nabla c\rangle mix$, if exists $\Delta_n t, \Delta_m t \in [\tau_{k-1},\tau_k]$

$$\prod_{i=n,m} \text{sign}\Big\{c\Big(t+\Delta_i t, x(t+\Delta_i t)\Big) - c(t,x(t))\Big\} < 0.$$

- **RESULTS:**
The qualitative behavior of the density distribution of the population $p(t,x)$ is the one of a reaction diffusion equation:

$$\frac{\partial}{\partial t}p(t,x) = \Delta_{xx}\Big((D+\gamma c(t,x))p(t,x)\Big) + \nabla\cdot\Big(\chi p(t,x)\nabla_x c(t,x)\Big).$$

In case of an environment constant in space and time we can obtain the value of the diffusive component, i.e. let $c(t,x) = c^*$

$$\frac{\partial}{\partial t}p(t,x) = \Delta_{xx}\Big((D+\gamma c^*)p(t,x)\Big).$$

We can infer the parameters thanks to the relation between the diffusion coefficient and the simple linear regression for the mean square displacement, i.e.

$$\langle r^2(\tau)\rangle = 2d(D+\gamma c^*)\cdot t.$$

If the environment grows enough, that is, if the component $\nabla \cdot \Big(\chi p(t,x)\nabla_x c(t,x)\Big)$ is strong enough we are able to identify the contribution of this component thanks to the relation that links a diffusion with drift to the mean square displacement:

$$\langle r^2(\tau)\rangle = \alpha \cdot t + \beta \cdot t^2.$$

In the case of `CV_rExp_tExp` it is possible to identify the parameters thanks to the explicit formula for the diffusion-scale limit of the density distribution. In the case `CV_rIG_tExp` we were not able to find such a limiting equation, so that only conjectures are possible.

The rest of this chapter is organized as follows:

i) Every subsection refers to a specific type of ligand concentration. We will give general informations on all the simulations which we performed in this specific scenario.

ii) Every subsection is organized in different sub subsections:

   a) every subsubsection is identified with the name of the model simulated. We present some specific comment and/or results of a particular model.

   b) in the last subsubsection, **Comments**, we compare the models with each other.

6.1.1 Constant Environment

We performed the following simulation: the population has 10 000 bacteria. The duration of the experiment is 1200 seconds, using a time step of 0.01 seconds. The population initially concentrates in the point $(x_0, y_0) = (0, 0)$, i.e

$$\mathbb{P}(X_n(0) \in dx) = \delta_{(x_0,y_0)}(dx).$$

At steady state:

- the mean time of a run is $\tau_r^0 = 0.8sec.$
- the mean time of a tumble is $\tau_t^0 = 0.1sec.$

The response type to the ligand concentration is given by $\phi(c) = c(t,x)$, while the diffusion coefficient for the angle θ is $D_\theta = 0.25$. The population does not interact with the ligand concentration, which remains constant for the duration of the experiment at the level

$$c(t,x) = 1.$$

The bacteria are adapted to a level of ligand equal to 1: this is performed in the initialization of the simulation, simulating the bacteria in an environment with level equal to 1, till they reach a steady state. We notice that the simulation was carried out in an area much bigger then the possible distance covered by a bacterium following a straight line. In this way we are able to study the behavior of a population of bacteria which is not subject to confinement

inside a bounded area. The simulations confirm the theoretical results, that is, the density of the distribution of the population follows the heat equation:

$$\frac{\partial}{\partial t}p(t,x) = D_d \Delta_{xx} p(t,x).$$

We are able to correctly identify the constant D_d and confirm with high precision the theoretical results. In the following we report the results for two specific simulations.

CV-rExp-tExp Model

We used the parameters reported above. We find that for exponentially distributed random variables the standard deviation equals the mean. As predicted from the theory we have a confirmation that the evolution of the density follows the heat equation. The population spreads uniformly in all spatial directions (Figure 6.2) and the mean square displacement grows linearly with time (see 6.1).

- The evolution of the barycenter

$$\mathcal{B}(t) := \frac{1}{N}\sum_{k=1}^{N} x_k(t)$$

  follows a 2D diffusion center around the initial value $(0,0)$. A confirmation of this is given by the plot of the trajectory of the barycenter and the one of its velocity. A calculation of the mean of the velocity shows that its value is approximately 0.

- At the bottom of Figure 6.1 we displayed the mean square displacement and its simple linear regression. We see that the two lines overlap exactly. We can exploit the relation that connects the mean square displacement and the constant of the heat equation, i.e.

$$\frac{\partial}{\partial t}p(t,x) = \Delta_{xx}\Big((D+\gamma c^*)p(t,x)\Big), \qquad \langle r^2(\tau)\rangle = 2dD_d \cdot t.$$

  If we substitute the parameters, we have that $\gamma = \beta_1 + 2\beta_2 = 0$ and $D_d = 1.2136 \cdot 10^{-4}$ and so

$$\langle r^2(\tau)\rangle = 4.8545 \cdot t \cdot 10^{-4},$$

  which is confirmed by the value of the coefficient of the linear regression, i.e.

$$\langle r^2(\tau)\rangle = 4.38 \cdot 10^{-4} \cdot t.$$

run/tumble	$\mathbf{E}[\tau_i]$	$\mathrm{var}[\tau_i]$	$\sqrt{\mathrm{var}[\tau_i]}$
τ_r: $\langle\theta, \nabla c\rangle = 0$	0.809631	0.639319	0.799574
τ_t	0.107593	0.00999627	0.0999814

Table 6.1: **CV-rExp-tExp** constant environment: there are 13 183 128 runs and 13 181 992 tumbles: τ_r refers to the duration of a *run* and τ_t stands for the duration of a *tumble*. We write $\langle\theta, \nabla c\rangle$ to indicate the sign of the measured gradient of $c(x,t)$ during a run.

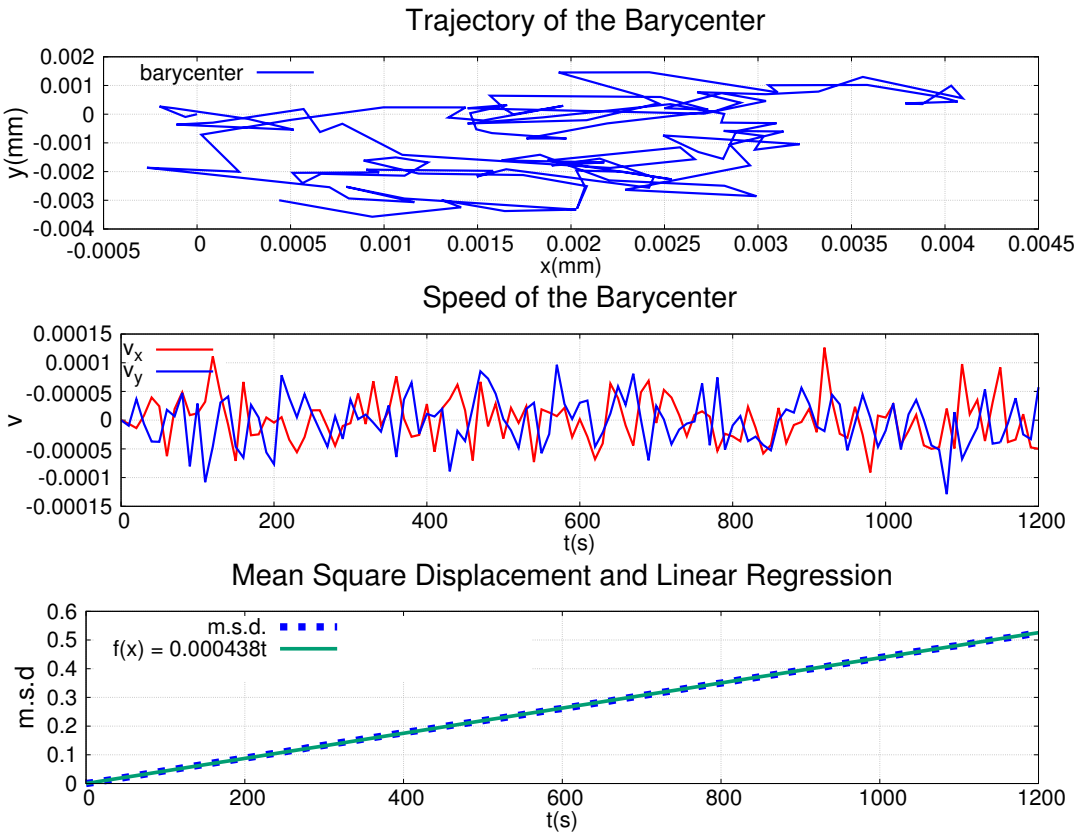


Figure 6.1: **CV-rExp-tExp Model** - constant environment. Plot of the barycenter of the population (**top**), x and y component of the speed of the center of mass (**middle**), mean square displacement of the population (**bottom**). We notice from the first plot, that the barycenter does not migrate and the mean square displacement (m.s.d) grows linearly with time: $m.s.q. = D \cdot t$, with $D = 4.38 \cdot 10^{-4}$.

CV-rIG-tExp Model

The simulation of the `CV-rIG-tExp` model is done using the same common parameters as in `CV-rExp-tExp`. We have only to specify which is the value of the diffusion coefficient for the SDE which models the generalised subordinator, i.e. σ in the expression

$$\int_0^\tau \Big[m_r(Q(s))ds + \sigma dW(s) \Big] = 1. \tag{6.1.2}$$

In order to obtain a good approximation of the experimental values, we used $\sigma = 1.6$. As we noticed in Section 3.3, for an inverse Gaussian distribution $X \sim \mathcal{IG}(\mu, \lambda)$ it holds:

$$\mathbf{E}[X] = \mu \quad \mathbf{Var}[X] = \frac{\mu^3}{\lambda}.$$

We can now solve the relation to find stationary λ^* and σ^*: this will give a theoretical result for the mean square of the duration of a run (Σ) close to the value reported in [12], i.e.

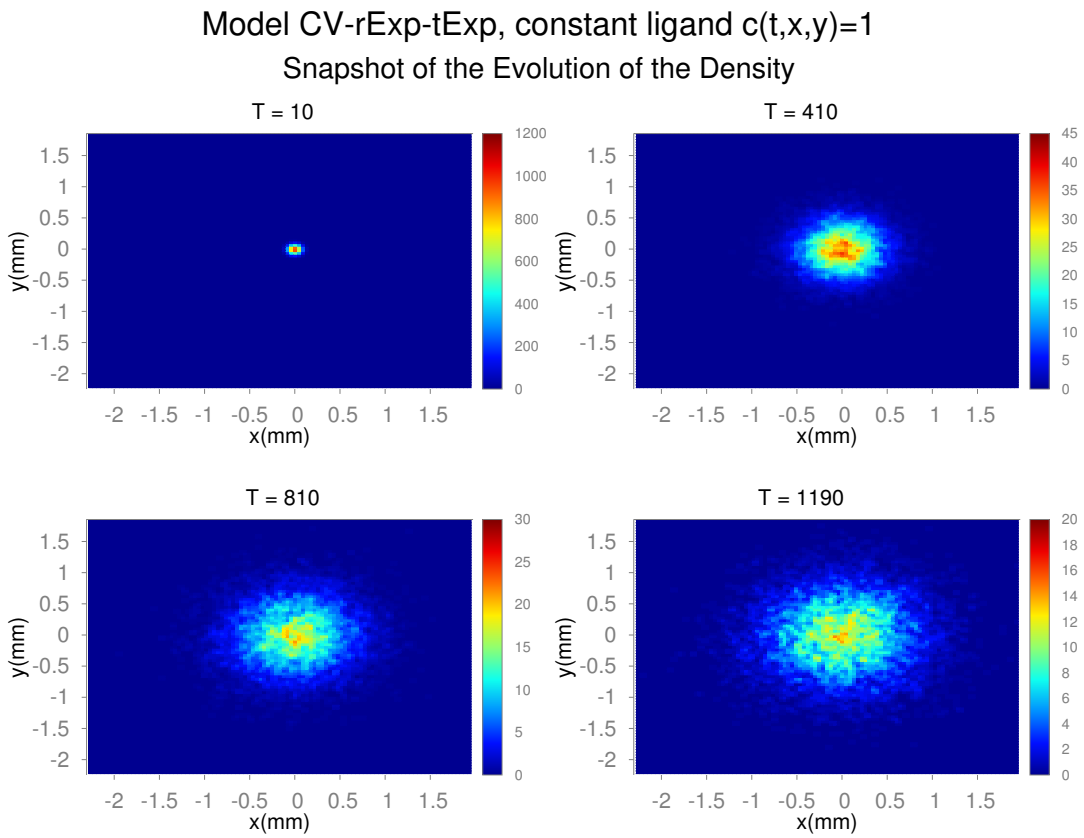


Figure 6.2: **CV-rExp-tExp Model** - constant environment: snapshots of the evolution of the density of the population at different time point. The unit of measure is mm. We notice that the dynamic looks similar to the classical diffusion, in accordance with the theory [22].

$\Sigma = 1.18$.

We perform the simulations and calculate the first two moments of the distribution of runs and tumbles as explained in the introduction. The relations between the moments of the random variable X with inverse Gaussian distribution $\mathcal{IG}(\mu, \lambda)$ and its parameters are confirmed by Table 6.2. This gives us confidence on the method used in order to solve equation (6.1.2), i.e. formula (6.1.1).

We carried out the same analysis as for the model `CV-rExp-tExp` and obtained the same qualitative behaviors (see Figure 6.4 and 6.3), i.e. the evolution of the barycenter

$$\mathcal{B}(t) := \frac{1}{N} \sum_{k=1}^{N} x_k(t)$$

follows a 2D diffusion around the in the initial value $(0, 0)$. At the bottom of Figure 6.3 we displayed the mean square displacement and its simple linear fit. We see that the two lines overlap exactly. If we substitute the parameters in the equation (3.4.2), which gives the diffusion coefficient D_d of the `CV-rIG-tExp` model in a constant environment, i.e.

$$\frac{\partial}{\partial t} p(t, x) = D_d \Delta_{xx} p(t, x).$$

we have

$$4dD_d = 0.000612792,$$

confirming the value of coefficient of the linear regression calculated from the output of the simulation, i.e.

$$\langle r^2(\tau)\rangle = 0.000617 \cdot t.$$

run/tumble	$\mathbf{E}[\tau_i]$	$\mathrm{var}[\tau_i]$	$\sqrt{\mathrm{var}[\tau_i]}$
τ_r: $\langle\theta, \nabla c\rangle = 0$	0.809396	1.39094	1.17938
τ_t	0.107562	0.00999049	0.0999524

Table 6.2: **CV-rIG-tExp** constant environment: there are 13 182 424 runs and 13 181 282 tumbles. τ_r refers to the duration of a *run* and τ_r stands for the duration of a *tumble*. We write $\langle\theta, \nabla c\rangle$ to indicate the sign of the measured gradient of $c(x,t)$ during a run.

Comments:

We notice that the evolution of the two populations for both setups (`CV-rExp-tExp` and `CV-rIG-tExp`) is qualitatively similar: both evolve following a diffusion equation ($\partial_t u = D\Delta_x u$). We underline that quantitatively we have a difference in the coefficients of the diffusion equation (see Figure 6.1 and 6.3): in particular the value for the `CV-rIG-tExp` is bigger than the one of the `CV-rExp-tExp` and this confirms the prediction in Section 3.4 of Chapter 3.
In the `CV-rIG-tExp` model the duration of a *run* is more persistent in the sense that the probability to have an extremely small swimming phase is very low: this leads to larger diffusion coefficients. This is the main difference using an Inverse Gaussian distribution instead of a exponential one for the duration of a *run*. We assume that in both cases we are facing a classical random walk, and the reason of the disappearance of the *persistence* is due to its small value. If we have a look at the theoretical derivation of the diffusion coefficient for the `CV-rIG-tExp` model (see equation 3.4.2) we can clearly observe this phenomenon. We underline also that the statistics of the `CV-rIG-tExp` model fits the data in [12] better.

6.1.2 Spatially exponential ligand profile

The population has 10 000 bacteria. The duration of the experiment is 1200 seconds, using a time step of 0.01 seconds. The population is initially concentrated at the point $(x_0, y_0) = (2, 2)$. The parameters for the steady state are the same as in the the previous section. In this simulation the ligand concentration is given as a space-dependent exponential function:

$$c(t, x) := C_{06} * exp(x/C_{16}) = 18.2 * e^{10*x}.$$

We underline that the internal dynamics at the beginning of the simulation is the steady state, i.e. the bacteria are kept at the prescribed concentration for sufficient time such that runs and tumbles assumes their steady state distribution. We notice also that the boundaries

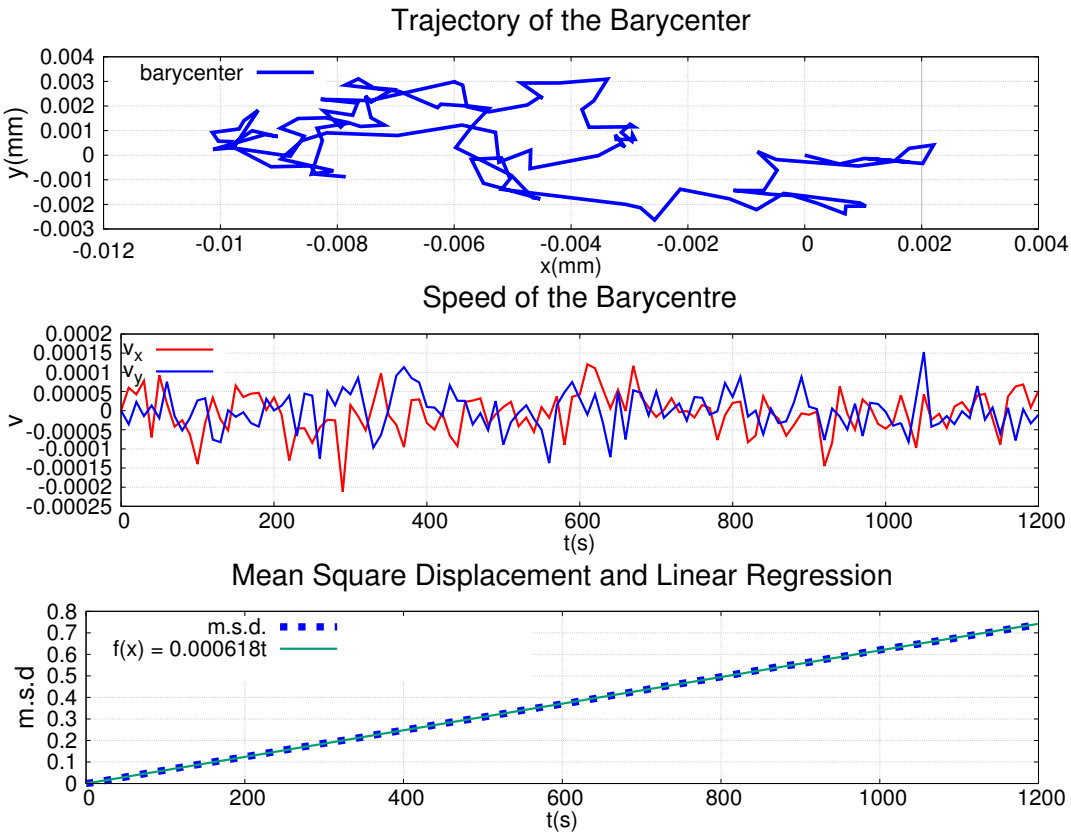


Figure 6.3: **CV-rIG-tExp Model** - constant environment. Plot of the barycenter of the population (**top**), x and y component of the speed of the barycenter (**middle**), mean square displacement of the position (**bottom**). The center of mass does not migrate and the mean square displacement (m.s.d) grows linearly with time: $m.s.q. = D \cdot t$, with $D = 0.000617$.

of the domain where the bacteria swim are so distant from the initial position that it is not possible for the bacteria to reach them during the time of a simulation.

In the present case the ligand concentration is not constant, we have therefore much freedom in the choice of the form of how the memory kernel Q modulates the mean distribution of a run, $m_r(Q)$. By following [128] we choose an arctangent-like function. Since the experiments [12] show that the response in terms of the duration of a run to positive gradients is not equal to the one for negative gradient we introduced some weights in order to take this feature into account, i.e.

$$m_r(Q) = \frac{1 - \frac{2}{\pi} \cdot atan\left[\frac{\pi}{2}\left(\mathbf{1}_{(-A_1,A_0)} \cdot Q + \mathbf{1}_{(Q \leq -A_1)} \cdot \beta Q + \mathbf{1}_{(Q \geq A_0)} \alpha Q\right)\right]}{\tau_r}.$$

We use the following parameters: $A_0 = 0.2$, $A_1 = 0.2$, $\alpha = 5$, $\beta = 0.7$.

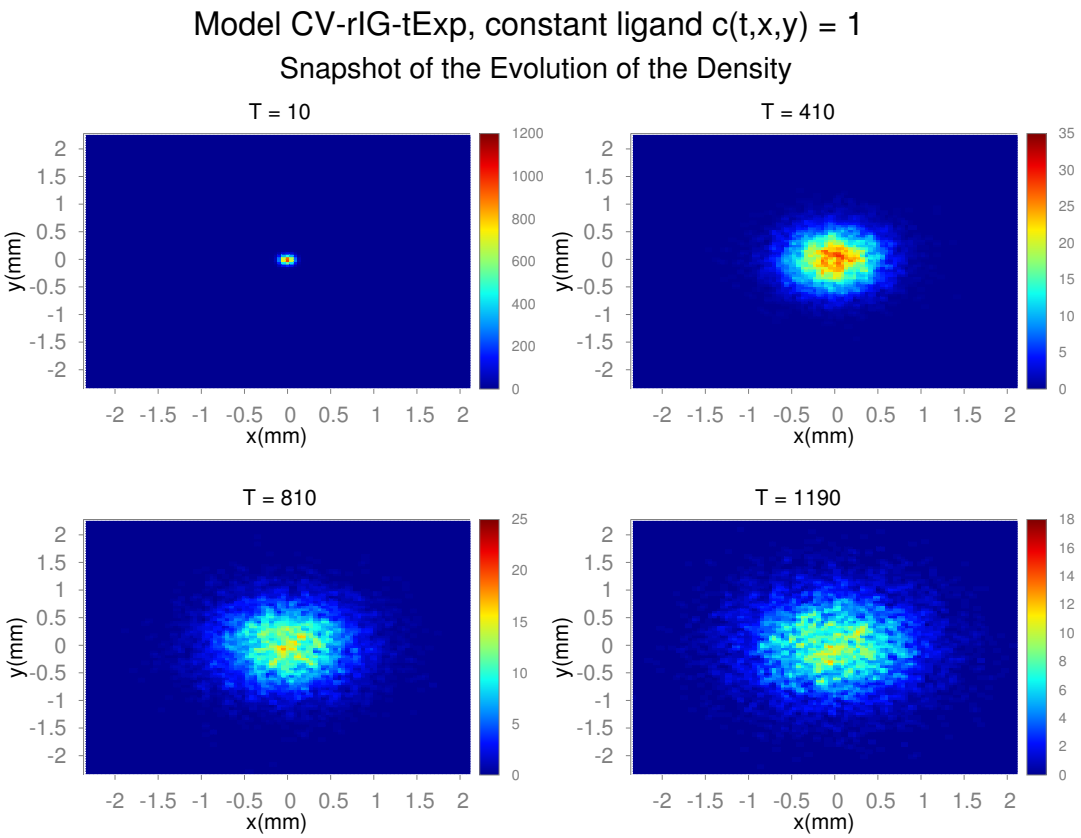


Figure 6.4: **CV-rIG-tExp Model** - constant environment: snapshot of the evolution of the density of the population. We notice that the dynamic looks similar to the classical diffusion, in accordance with the theory - see Section 3.4 of Chapter 3.

We notice, finally, that if $Q \sim 0$, then

$$m_r(Q) \sim \frac{1-Q}{\tau_r}.$$

CV-rExp-tExp Model:

We used the same parameters as in the constant environment scenario. In Figure 6.7 we display the function $m_r(Q)$, which controls the probability rate to start a new *run*. In Table 6.3 we report the statistics of the distribution of *run* and *tumble* lengths. With the help of Table 6.3 and Figure 6.6 (where we display on a logarithmic scale the fraction of runs (resp. tumble) bigger than a given value) we can notice that the particular choice of the function $m_r(Q)$ has the effect to shorten the length of a run downwards the gradient. The duration of a run upwards the gradient is significatly long (as compare to the steady state) and is the reason of the migration of the center of mass of the population.

run/tumble	$\mathbf{E}[\tau_i]$	$\mathrm{var}[\tau_i]$	$\sqrt{\mathrm{var}[\tau_i]}$
all τ_r	1.5606	11.3085	3.36281
τ_r: $\langle\theta, \nabla c\rangle > 0$	2.00557	15.9237	3.99045
τ_r: $\langle\theta, \nabla c\rangle < 0$	0.554272	0.310107	0.556872
τ_r: $\langle\theta, \nabla c\rangle mix$	4.06993	28.3447	5.32398
τ_t	0.107563	0.00999189	0.0999594

Table 6.3: **CV-rExp-tExp** spatially exponential ligand profile: there are 7 201 052 runs: 3 091 203 runs up the gradient, 3 324 677 runs down the gradient and 785 172 runs, during which the bacterium swam along a trajectory with different signs of the gradient. There are 7 200 433 tumbles. τ_r means duration of a *run* and τ_r stands for the duration of a *tumble*. We write $\langle\theta, \nabla c\rangle$ to indicate the sign of the measured gradient of $c(x,t)$ during a run.

If we have a look at Figure 6.8 and 6.9 we can clearly see what happens:

- the barycenter strongly migrates towards higher ligand concentrations along the x component. The y component stays around the initial position. We have a confirmation, both from the snapshot in Figure 6.9 and the plot of the speed of the barycenter in Figure 6.8.

- If we look at the theoretical result derived in [22] we have that the density of the population $p(t,x)dx$ solves

$$\frac{\partial}{\partial t}p(t,x) + \chi\nabla\cdot\Big(p(t,x)\nabla_x c(t,x)\Big) = \Delta_{xx}\Big((D+\gamma\phi(c(t,x)))p(t,x)\Big) \tag{6.1.3}$$

  We underline that from the choice of the parameters we have $\gamma = 0$.

- **Analysis of the mean square displacement**: we will now discuss the behaviour of the mean square displacement and the implication it has on the parameters of equation (6.1.3). The general formula that connects a diffusion with drift and its mean square displacement is given by

$$\langle r^2(\tau)\rangle = 2d\cdot D\cdot t + (V\cdot t)^2. \tag{6.1.4}$$

  – **Long times:** The mean square displacement does not grow linearly with time, and the appropriate approximation is given by a parabola. This is a diffusion with the presence of a drift term. If we approximate the data for the mean square displacement we find that the curve $y = 0.000046\cdot t^2 + 0.000001\cdot t$ overlaps the graph of $\langle r^2(\tau)\rangle$. The graph of the speed of the center of mass might lead to conclude that $\chi\nabla_x\phi(e^{\beta x})$ is a constant, in particular the simulated value of 0.0065 is consistent with the parabolic approximation of the m.s.d. (0.0000375). We underline that equation (6.1.3) is derived for value of the memory term $\mathcal{Q}$ close to 0, but in the present simulation the recorded values for $\mathcal{Q}$ do not satisfy this assumption (see Figure 6.5). For a steep profile of the ligand concentration like

the one in the present simulation and long times ($\sim$ 20 minutes), we have that the diffusive coefficient is really small. We cannot, however, argue that the density follows a simple transport equation, since a small diffusion is always present.

– **Short times:** If we have a closer look at the first 25 seconds of the simulation, we have a clear understanding of what is going on. We refer to Figure 6.10 for the plot of the trajectory of the barycenter, its speed and the mean square displacement as well as its linear and quadratic least square approximation. In Figure 6.11 we present 4 snapshots of the evolution of the density of the population. First of all we notice that the barycenter migrates towards higher ligand concentrations (right) at a speed that, after 10 seconds, reaches a steady state of circa $0.006\frac{mm}{s}$. The linear regression of the mean square displacement gives a not satisfactory approximation, while when we use the least-squares parabola $y = at^2 + bt$, we have an almost perfect overlapping of the curves. Because of the characteristic of the models and the other measured quantity we can conclude that the equation that the density of the population follows is an advection-diffusion equation with constant parameters, i.e.

$$\frac{\partial}{\partial t}p(t,x) + \chi\nabla\cdot\nabla_x = D\Delta_{xx}p(t,x).$$

We can clearly see the action of the diffusion and advection term in Figure 6.11. With the help of the above relation (6.1.4) these parameters can be identified. We have that

$$\langle r^2(\tau)\rangle = 0.000415\cdot t + 0.000043\cdot t^2.$$

Hence $D = 0.000103$ and $\chi = 0.0065$. The value of χ agrees with the expected value of the speed of the barycenter. The diffusion coefficient is similar to the one in the constant environment, which is predicted by the the general formula in [22].

– **Nonlinear diffusion coefficient:** The above discussion lead us to infer that in the presence of steep ligand concentration of the type $c(t,\vec{x}) = \beta e^{\alpha x_1}$, we have that the density of the population follows an advection-diffusion equation with nonlinear diffusion coefficient which goes to zero with time. We are in the presence of a ligand concentration which is constant in space. Even if we use the generalised equation developed in [21], i.e.

$$\begin{aligned}\frac{\partial}{\partial t}p(t,x) + \chi\nabla\cdot\Big(p(t,x)\int_{\infty}^{t} e^{\sigma(t-s)}K(t-s)\nabla_x c(s,x)ds\Big)\\ = \Delta_{xx}\Big((1+D_0\int_{-\infty}^{0}K(t-s)c(s,x)ds)p(t,x)\Big),\end{aligned}$$

we will not be able to explain the results of the simulation with this equation.

CV-rIG-tExp model:

For the model `CV-rIG-tExp` we cannot be as precise as in the `CV-rExp-tExp` model, since we were not be able to derive a general equation for the diffusion-scale. We could only give

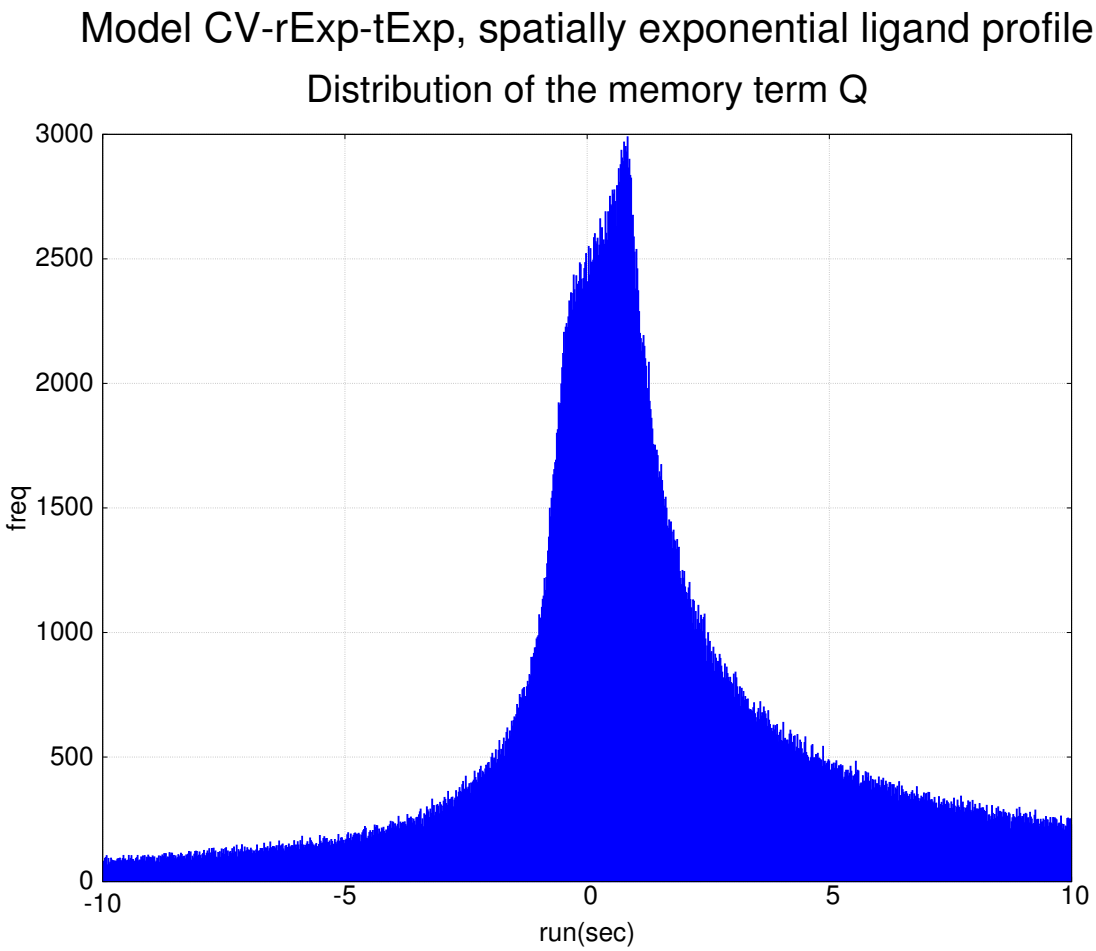


Figure 6.5: **CV-rExp-tExp Model** - distribution of the memory variable $\mathcal{Q}$ for the simulation in a spatially exponential ligand profile. The histogram represents the distribution of all the measured $\mathcal{Q}$, i.e. if $\mathcal{Q}_k(t_i)$ is the recorded value for the bacterium k at time t_i, the histogram is build from the values $\{\mathcal{Q}_k(t_i)\}_{i=1,k=1}^{n_t,n_c}$, where n_t is the number of recoded time points for bacterium and n_c is the number of bacteria simulated.

heuristic and approximate results. We can however say that the simulation confirms our conjectures in Chapter 3.

If we have a look at Figure 6.13 and 6.14, we can see that the qualitative behaviour is the same as in the `CV-rExp-tExp` case:

- the barycenter strongly migrates towards higher ligand concentrations along the x component. The y component stays around the initial position. We have a confirmation, both from the snapshot in Figure 6.14 and the plot of the speed of the barycenter in Figure 6.13.

- **Analysis of the mean square displacement**: We have a similar behavior as in the

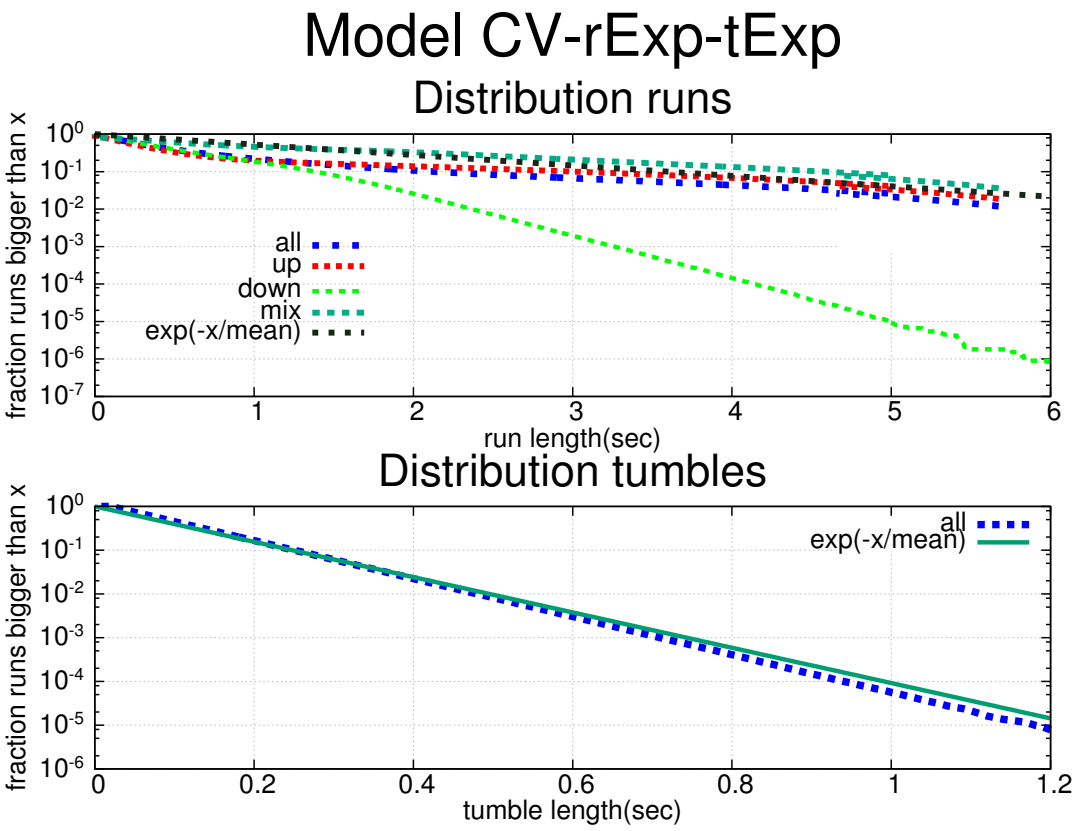


Figure 6.6: CV-rExp-tExp Model - distribution of the runs and tumble plotted in logarithmic scale. We notice the big difference of the distribution of runs upwards (red) and downwards (green) the gradients.

`CV-rExp-tExp` case, more precisely

– **Long times:** the mean square displacement does not grow linearly with time, and the appropriate approximation is given by a parabola. This is a diffusion with the presence of a drift term. If we approximate the data for the mean square displacement for long times we find that the curve

$$y = 0.00003x^2 + 0.00000002x$$

overlaps the graph of $\langle r^2(\tau)\rangle$. As in the `CV-rExp-tExp` model, we have a diffusive coefficient that is really small.

– **Short times:** As in the `CV-rExp-tExp`, if we have a closer look at the first 25 seconds of the simulation, we have a clear understanding of what is going on. We do not report the plots, since they are very similar to the ones of the `CV-rExp-tExp` model. Only the parameters change. When we performed the

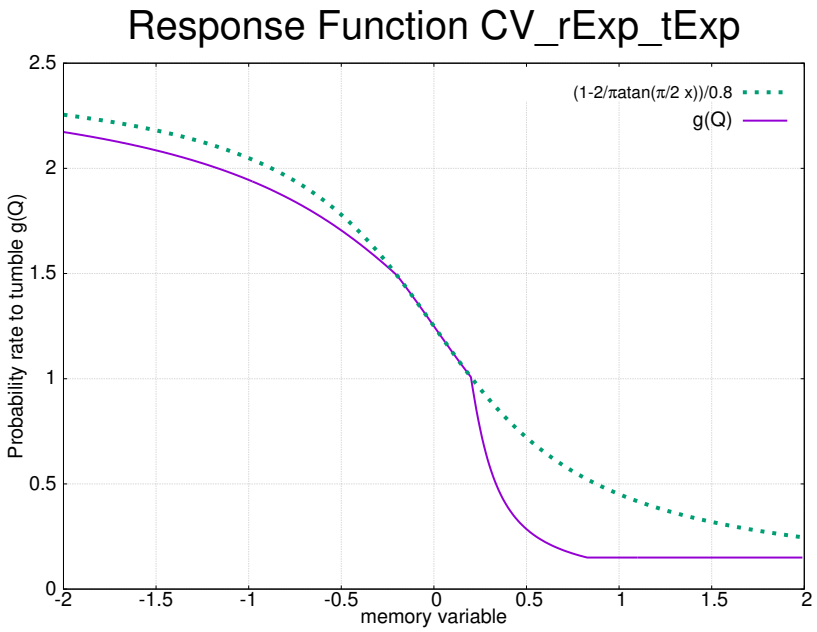


Figure 6.7: non-symmetric response function $m_r(Q)$ for the CV-rExp-tExp model as a function of the memory term (Q), taken from [22] and the relative symmetric one. In the simulations we used the non-symmetric one.

least-squares parabola $y = at^2 + bt$, we have a almost perfect overlapping of the curves with the following parameters:

$$\langle r^2(\tau)\rangle = 0.000327 \cdot t + 0.000038 \cdot t^2.$$

The density of the population follows is an advection-diffusion equation with constant parameters, i.e.

$$\frac{\partial}{\partial t}p(t,x) + \chi\nabla \cdot \nabla_x = D\Delta_{xx}p(t,x).$$

With the help of the above relation (6.1.4) these parameters can be identified. We have that

$$\langle r^2(\tau)\rangle = 0.000327 \cdot t + 0.000038 \cdot t^2.$$

Hence $D = 0.00008175$ and $\chi = 0.0061$. We can say that the conjecture in Chapter 3, i.e. that the density of the population $p(t,x)dx$ solves an advection-diffusion equation of the following type

$$\frac{\partial}{\partial t}p(t,x) + \chi\nabla \cdot \Big(p(t,x)\nabla_x c(t,x)\Big) = \Delta_{xx}\Big((D + \gamma c(t,x))p(t,x)\Big)$$

is confirmed by these simulations. About the parameters of this equation, too many possibilities are open and only a clean analytical derivation might lighten them up.

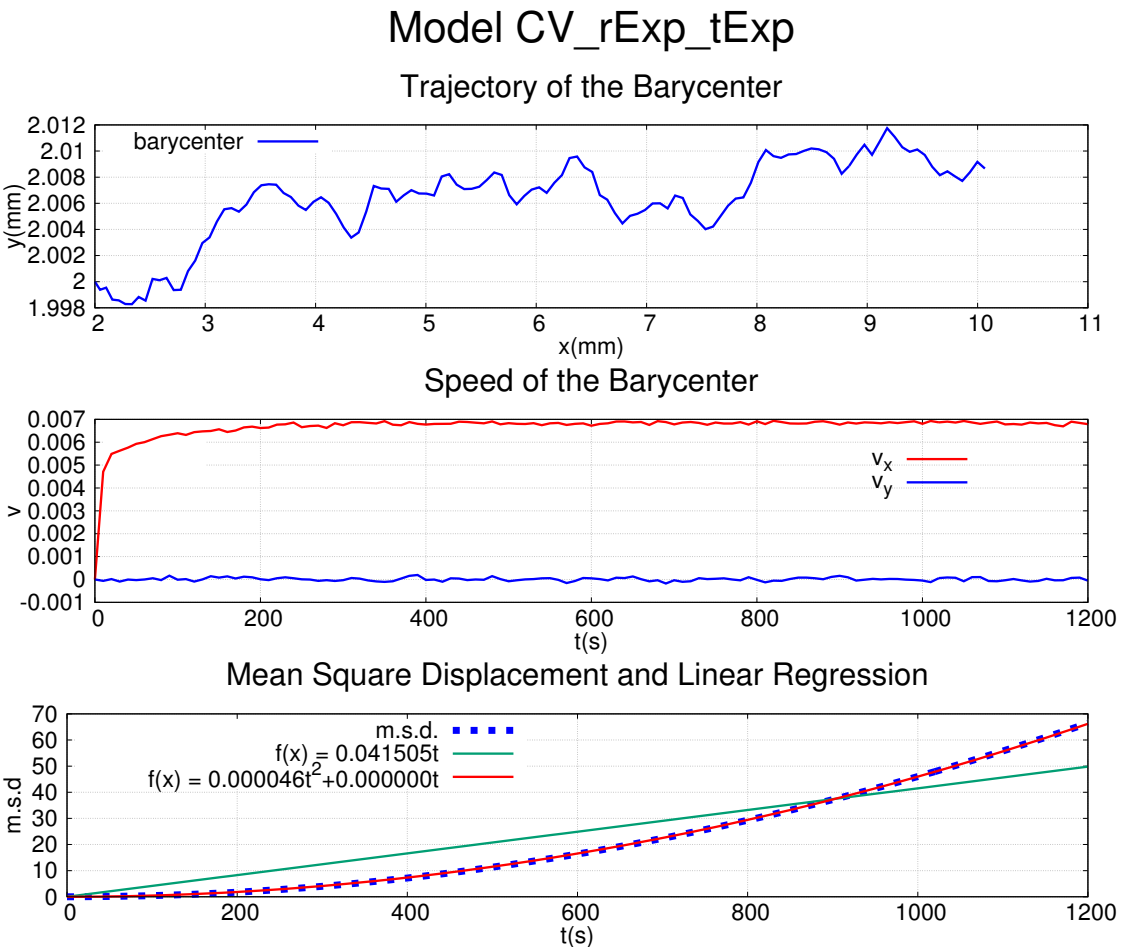


Figure 6.8: **CV-rExp-tExp Model** - Exponential grow in Space: Plot of the barycenter of the population (**top**), speed of the x and y component of the speed of the barycenter (**middle**), mean square displacement of the population (**bottom**). The center of mass strongly migrates towards the higher ligand concentration (right). The mean square displacement does not grow linearly with time.

  - **Nonlinear diffusion coefficient:** The above discussion lead us to infer that in the presence of a steep ligand concentration of the type $c(t, \vec{x}) = \beta e^{\alpha x_1}$, we have that the density of the population follows an advection-diffusion equation with nonlinear diffusion coefficient, exactly as in the `CV-rExp-tExp` model.

- When we have a closer look at Table 6.4 and Figure 6.12 we notice that the distribution of the length of runs has the following characteristic:

  - the runs downwards the gradient are significantly shorter then the others.
  - the distribution of runs upwards the gradient is not so high as in the `CV-rExp-tExp` case. This is due to the nature of the general subordinator. This contributes to a smaller drift in the advection-diffusion equation reported above as compare to

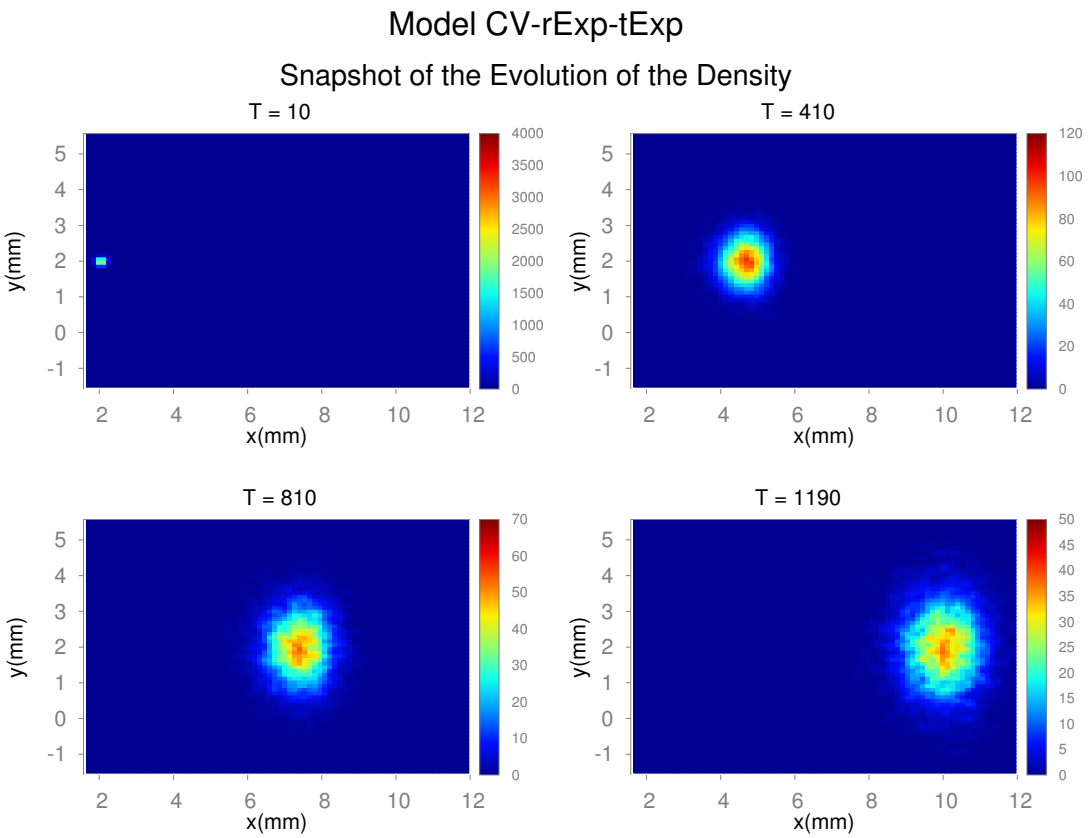


Figure 6.9: CV-rExp-tExp Model - spatially exponential ligand profile: snapshots of the evolution of the density of the population. We notice that the population migrate strongly towards higher ligand concentrationd (right).

the `CV-rExp-tExp` model.

run/tumble	$\mathbf{E}[\tau_i]$	$\mathrm{var}[\tau_i]$	$\sqrt{\mathrm{var}[\tau_i]}$
all τ_r	1.28113	27.1503	5.2106
τ_r: $\langle\theta, \nabla c\rangle > 0$	1.13139	13.7218	3.70429
τ_r: $\langle\theta, \nabla c\rangle < 0$	0.538537	0.372852	0.610616
τ_r: $\langle\theta, \nabla c\rangle mix$	5.67682	201.675	14.2012
τ_t	0.107613	0.0100115	0.100057

Table 6.4: **CV-rExp-tExp Exponential grow in Space**: there are 8608649 runs: 3820377 up the gradient, 3984930 down the gradient and 803342 having different signs of the gradients. There are 8607935 tumbles. τ_r refers to the duration of a *run* and τ_t stands for the duration of a *tumble*. We write $\langle\theta, \nabla c\rangle$ to indicate the sign of the measured gradient of $c(x,t)$ during a run.

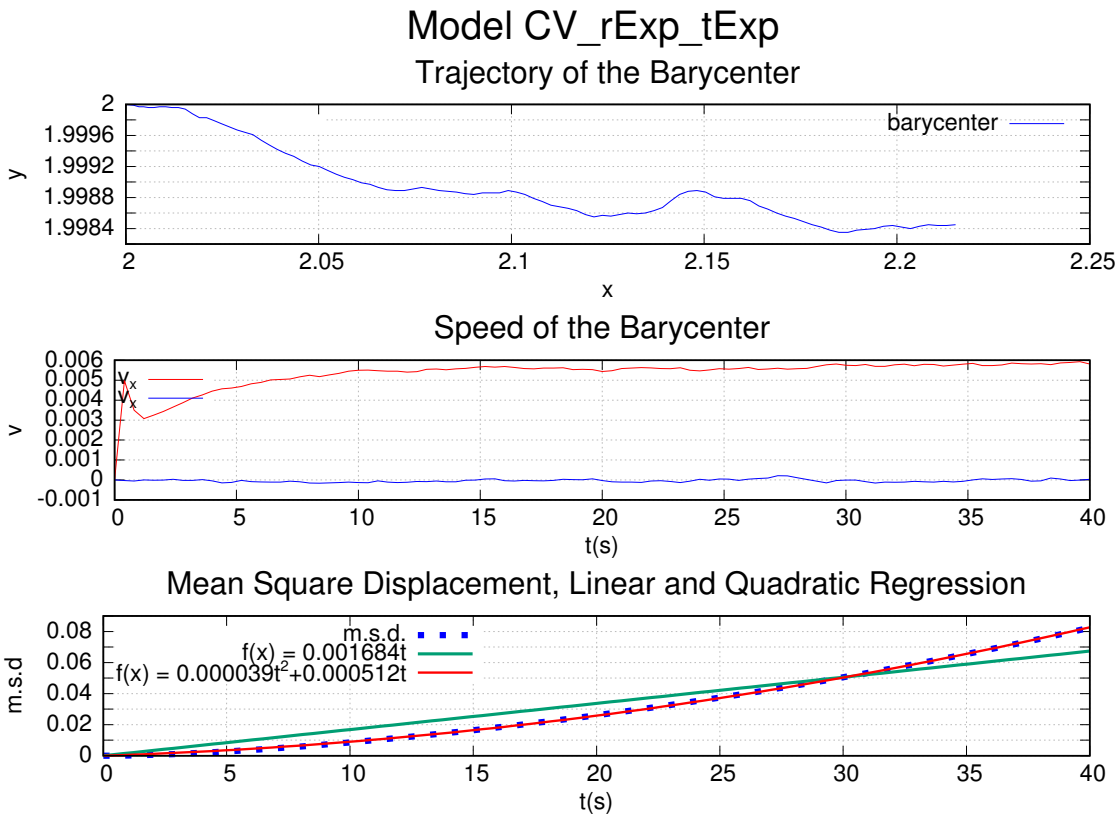


Figure 6.10: **CV-rExp-tExp Model** - Exponential grow in Space: short times. Plot of the barycenter of the population (**top**), speed of the x and y component of the speed of the barycenter (**middle**), mean square displacement of the population (**bottom**). The center of mass strongly migrates towards the higher ligand concentration (right). The mean square displacement does not grow linearly with time.

Comments:

In the case when the environment is very steep, we have a clear change in the collective behavior of the population. The population dynamics follow an advection-diffusion equation (see Chapter 3). The qualitative dynamics of the two models under examination are quite similar: both are characterised by a translating barycenter (which moves towards higher concentrations of ligand (right)) at an almost constant speed. The reason of this constant speed might be found in the initial position of the population. It starts, in fact, at a point where the gradient is quite steep. If we consider a reference axis which migrates along with the barycenter, we notice that the relative dynamics of the population is that of a diffusion: the diffusion coefficient, however, becomes smaller with time. We have the clear picture of this, if we investigate the behaviour of the population on different durations.

- The speed of the barycenter in `CV-rExp-tExp` is higher then the one of `CV-rIG-tExp` ($\sim 0.06\frac{mm}{s}$ against $\sim 0.05\frac{mm}{s}$). We notice that while in the `CV-rExp-tExp` model the speed of the barycenter almost immediately reaches the steady state, in `CV-rIG-tExp`

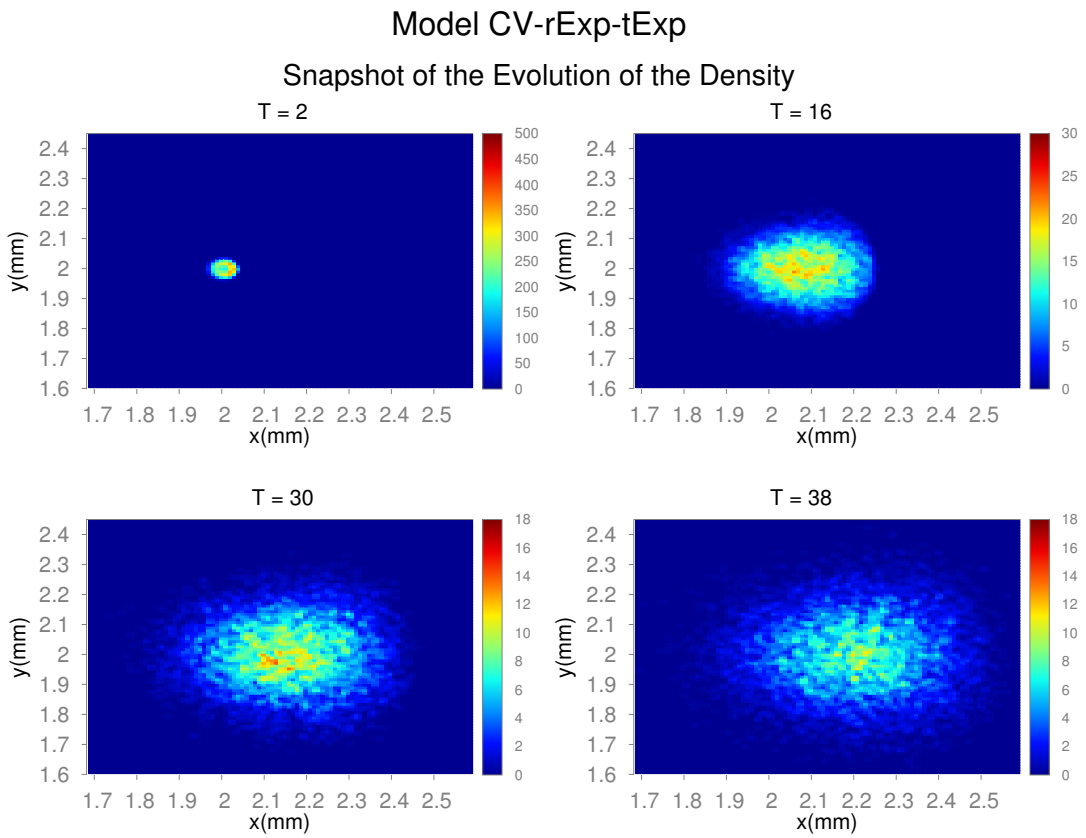


Figure 6.11: CV-rExp-tExp Model - spatially exponential ligand profile: short times. Snapshots of the evolution of the density of the population. We notice that the dynamic migrate strongly towards higher concentration of ligand (right).

the time needed to reach its steady state is much longer (~ 50 *sec.*). It is influenced for persistency in the Inverse Gaussian model: starting from the same initial condition a `CV-rIG-tExp`-bacterium running in a certain direction will keep swimming straight for a longer period (on average) than the corresponding `CV-rExp-tExp` counterpart.

- from the analysis of the mean square displacement we can conjecture that the diffusion coefficient can depend on the history of the ligand concentration in some functional way, as suggested in [21]. For short times we obtain for the Inverse Gaussian model

$$\langle r^2(\tau)_{IG} \rangle = 3.27 \cdot 10^{-4} \cdot t + 3.8 \cdot 10^{-5} \cdot t^2,$$

while for the exponential one

$$\langle r^2(\tau)_{Exp} \rangle = 5.12 \cdot 10^{-4} \cdot t + 3.9 \cdot 10^{-5} \cdot t^2.$$

Suppose now that the two populations follow an advection-diffusion equation with constant parameters, we can then conclude that the diffusivity of the `CV-rExp-tExp` diffuses faster than for the `CV-rIG-tExp` model and also the chemosensitivity of the `CV-rExp-tExp` population is slightly higher, i.e. the chemotactic drift is faster.

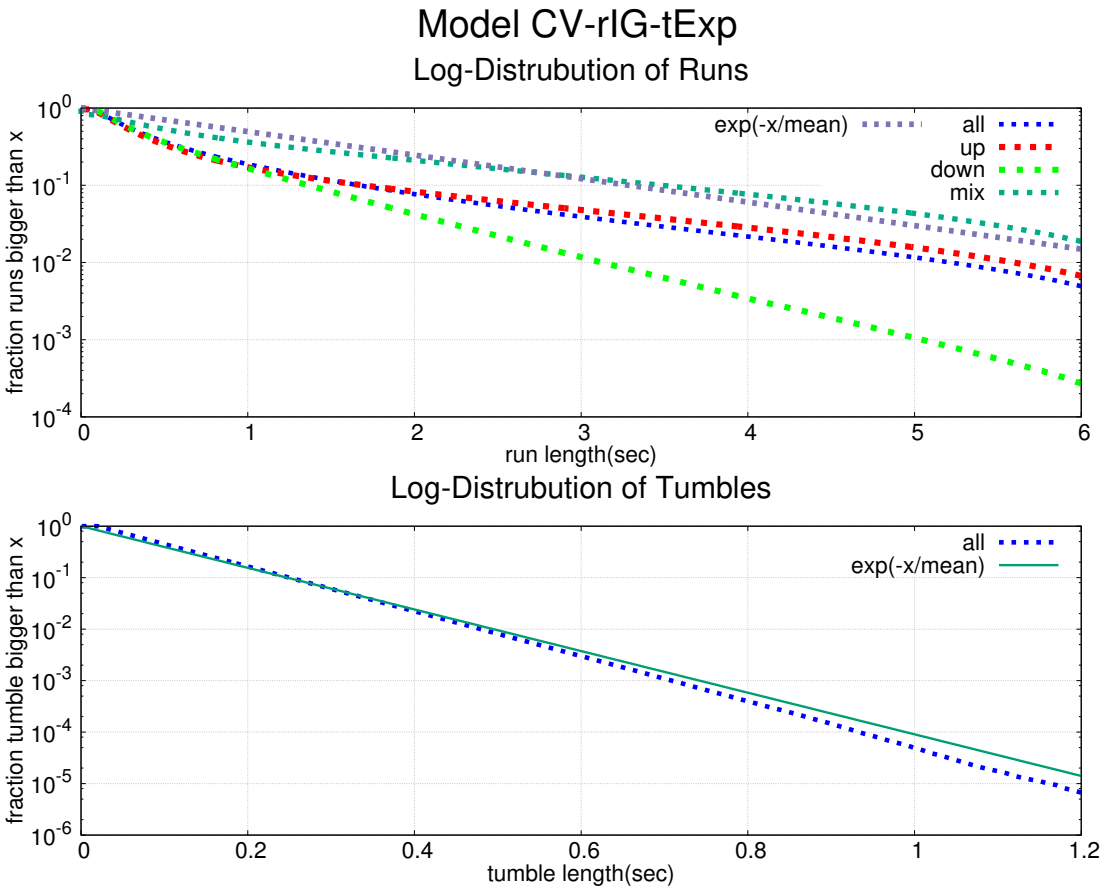


Figure 6.12: **CV-rIG-tExp Model** - spatially exponential ligand profile. Distribution of the runs and tumbles plotted on a logarithmic scale. We notice the big difference of the distribution of runs upwards (red) and downwards (green) the gradients. The distributions are clearly different from the relative distribution in the CV-rExp-tExp Model and the probability of really small runs is going towards zero.

6.1.3 Spatially homogeneous ligand profile growing exponentially with time

The population has 10 000 bacteria. The duration of the experiment is 100 seconds, using a time step of 0.01 seconds. The population is initially concentrated in the point $(x_0, y_0) = (0, 0)$ $(\delta_{(x_0,y_0)})$. The mean duration of a run is $\tau_r^0 = 0.8sec$ and the mean time of a tumble is $\tau_t^0 = 0.1sec$. The ligand is spatially homogeneous growing exponentially with time and its dynamics is independent of the population of bacteria:

$$c(t, x) := C_07 * exp(C_27 * t) = 18.2 * exp(0.2 * t).$$

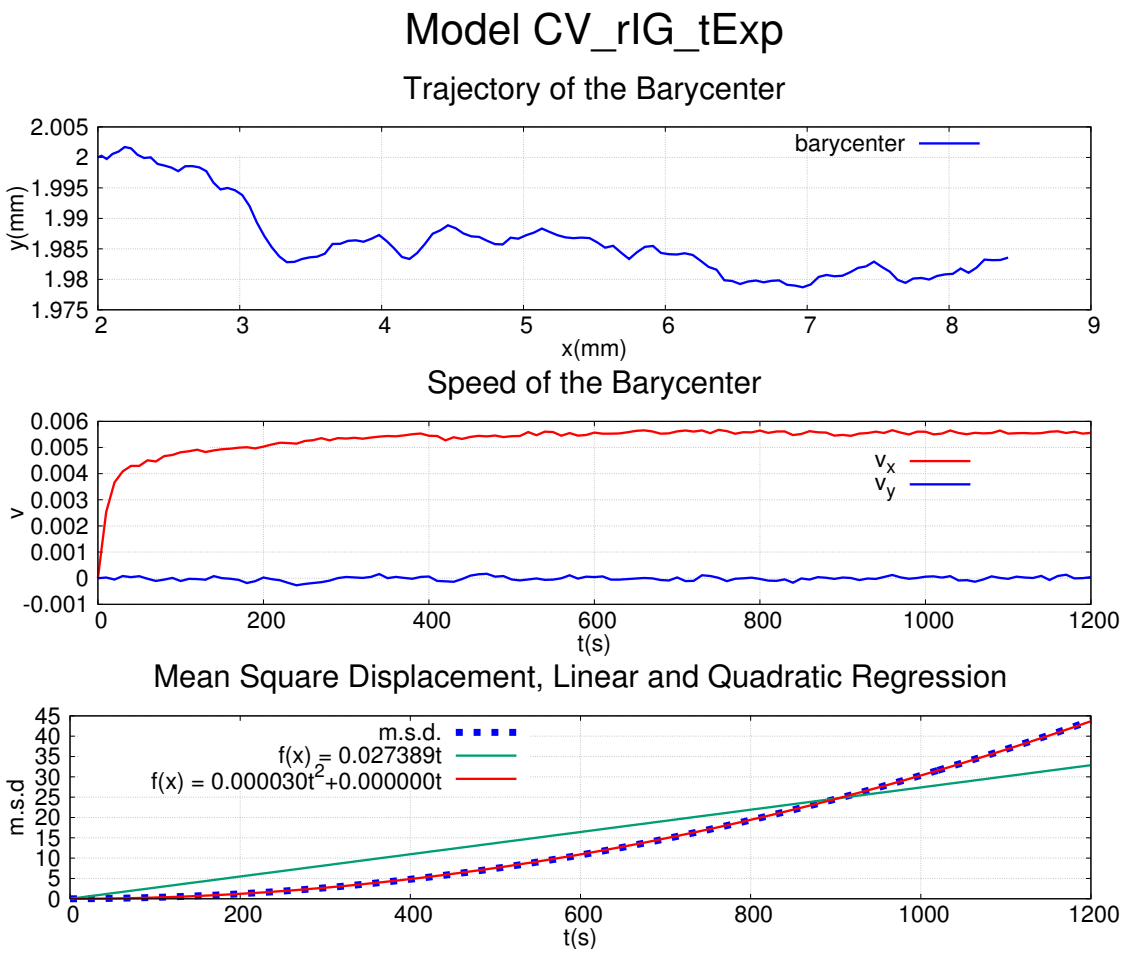


Figure 6.13: **CV-rIG-tExp Model** - spatially exponential ligand profile. Plot of the barycenter of the population (**top**), x and y component of the speed of the barycenter (**middle**), mean square displacement of the population (**bottom**). The barycenter strongly migrates towards the higher ligand concentration (right). The mean square displacement grows non-linear with time. This is clear because it is not a diffusion, but diffusion plus chemotactic drift, hence, there is a ballistic component.

CV-rExp-tExp model:

As we can see from the example of a trajectory of one bacterium (Figure 6.15), the length of the runs is very long (up to 20 seconds). We might be lead lo think that the density of the population follows a super-diffusion, but this conjecture is not supported by the simulations.

Comments:

We notice that the bacterial distribution initially takes the form of a circular traveling wave. With time this ring smoothes out and the bacteria are almost homogeneously distributed behind the front (see Figure 6.16). We can explain it by saying that every bacterium, inde-

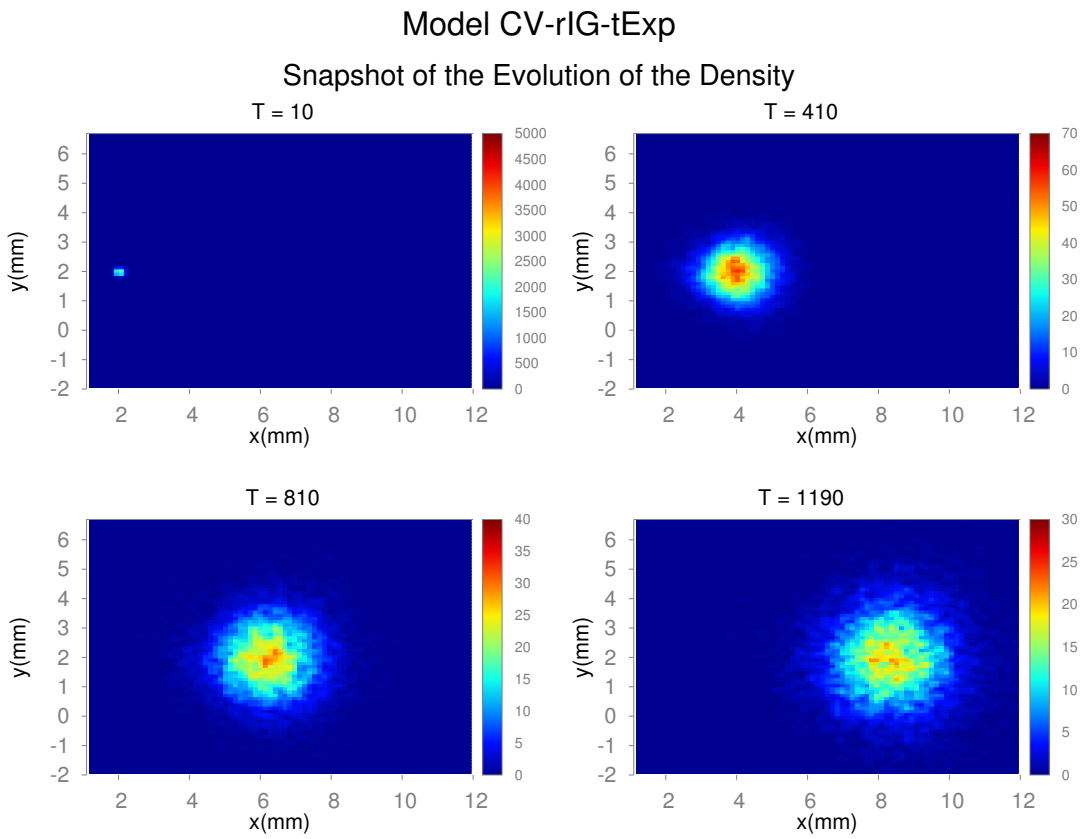


Figure 6.14: CV-rIG-tExp Model - Spatially exponential ligand profile: snapshots of the evolution of the density of the population. We notice that the population migrate strongly towards higher ligand concentrations (right).

pendent of its direction feels that the concentration of the attractant is strongly increasing along the current direction: since the initial distribution of the bacterial directions is uniform, it is clear that the ring shape front will be created. The ring shape dissolves because the probability rate to perform a tumble is bounded away from zero, yielding, even in highly favourable environments tumble events with non-zero probability. When we have a closer look at Figure 6.17 we can find different possible equations that explain the results of the simulation:

- on one side, if we do not want to move too far away from the limiting equation derived in [22], might argue that what we have is still an advection-diffusion equation, where the coefficients are time dependent in a way that the drift term goes to zero with time, while the diffusion coefficient, initially small, grows with the time and smooths out the density. We might invoke the generalized equation developed in [21], i.e.

$$\frac{\partial}{\partial t}p(t,x) + \chi\nabla\cdot\Big(p(t,x)\int_{\infty}^{t} e^{\sigma(t-s)}K(t-s)\nabla_x c(s,x)ds\Big) = D_0\Delta_{xx}\Big((1+\int_{-\infty}^{0} K(t-s)c(s,x)ds)p(t,x)\Big),$$

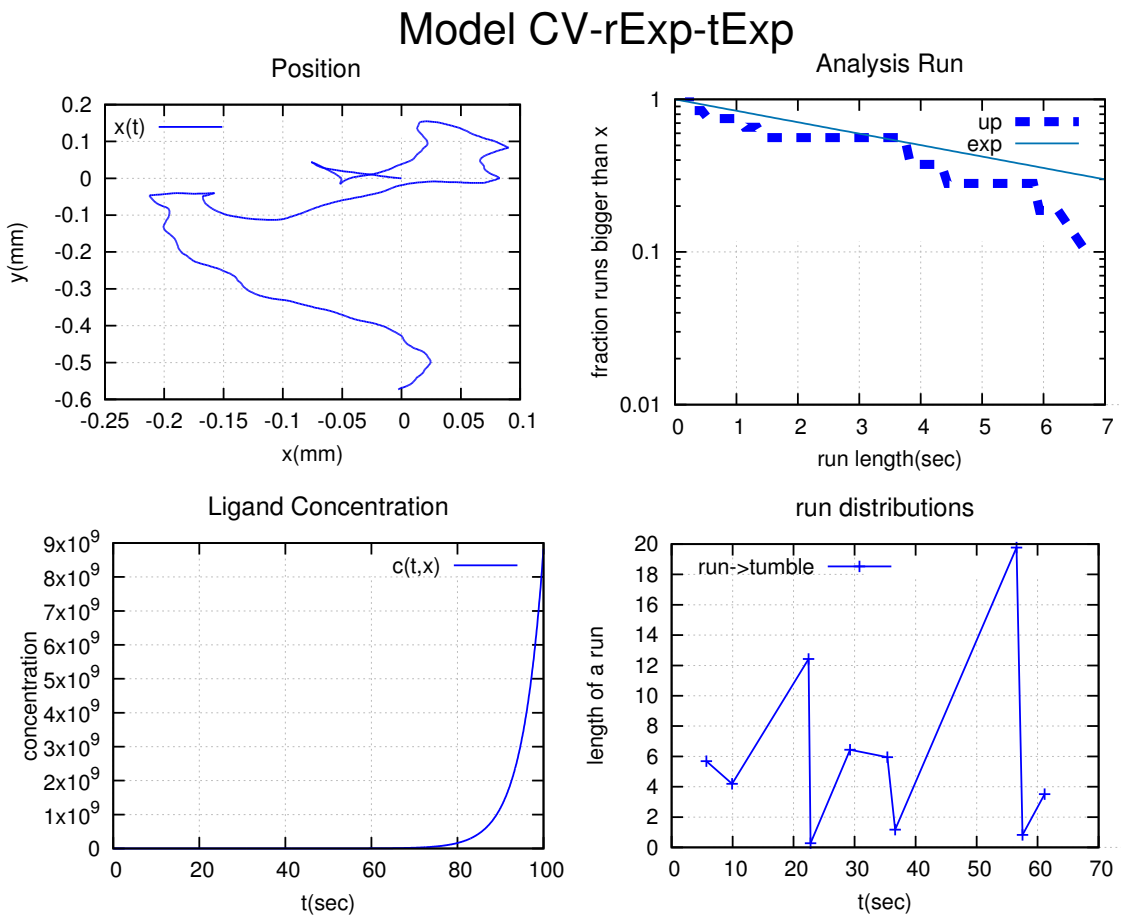


Figure 6.15: CV-rIG-tExp Model - spatially homogeneous ligand profile growing exponentially with time. Top left: an example of the trajectory of one of the 10 000 bacteria. Top right: distribution on a logarithmic scale of the duration of runs. Bottom right: the length of the runs We see that the bacterium performs very long runs, up to 20 seconds. Bottom left: evolution of the ligand concentration along the trajectory.

which partially describes this phenomena. In this case we will have that $c(t,x) = \zeta e^{\mu t}$ and $K(t) := \lambda e^{-\lambda t} \sum_{k=1}^{2} \left(\beta_k \lambda^k t^k\right)$. When we perform the integral, we find

$$\int_{-\infty}^{t} K(t-s)c(t,x)ds = \frac{\lambda^2 e^{\mu t}}{(\lambda+\mu)^3}\Big(\lambda(2\beta_2+\beta_1)+\beta_1\lambda\Big).$$

We have in fact a time-dependent diffusion equation. The explanation of the ring might just be due to the initial condition. We have in fact a singular initial distribution $(p(0,x,y) = \delta_{(0,0)}(x,y)$, while the direction of the bacteria at the beginning is uniformly distributed over the interval $[0, 2\pi)$. We have also to take into account that the equation presented in [21] is valid under two conditions, i.e. the quantity $Q(t) := \int_{-\infty}^{t} K(t-s)c(t,x)ds$ should be small, and it is a macroscopic equation for the dynamics of the

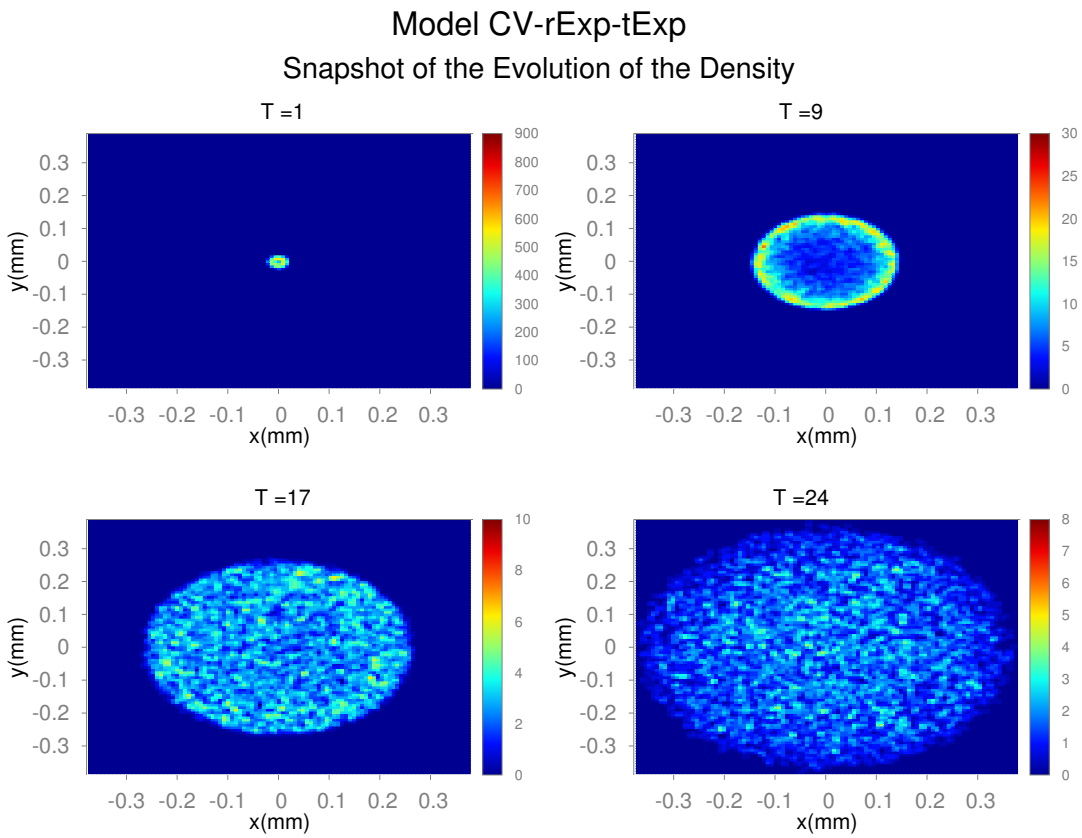


Figure 6.16: CV-rExp-tExp Model - spatially homogeneous ligand profile growing exponentially with time: snapshots of the first 24 seconds of the evolution of the density of the population. We notice that at the beginning of the simulation we have a wave front that smooths out at the end of the simulation.

bacterial density at scales larger than the length of a single run, so we cannot directly use it for the beginning of the simulation.

- on the other hand we might consider the following heuristic generalization:
  we might want to follow [45, 128] and see if a hyperbolic modification of the equation is obtainable with the right rescaling, i.e.

$$H(t,c,p)\frac{\partial^2}{\partial^2 t}p(t,x)+\frac{\partial}{\partial t}p(t,x)+\chi\nabla\cdot\Big(p(t,x)\int_{\infty}^{t}e^{\sigma(t-s)}K(t-s)\nabla_x c(s,x)ds\Big)$$
$$=D_0\Delta_{xx}\Big((1+\int_{-\infty}^{0}K(t-s)c(s,x)ds)p(t,x)\Big),$$

  for some coefficient $H(t,c,p)$.

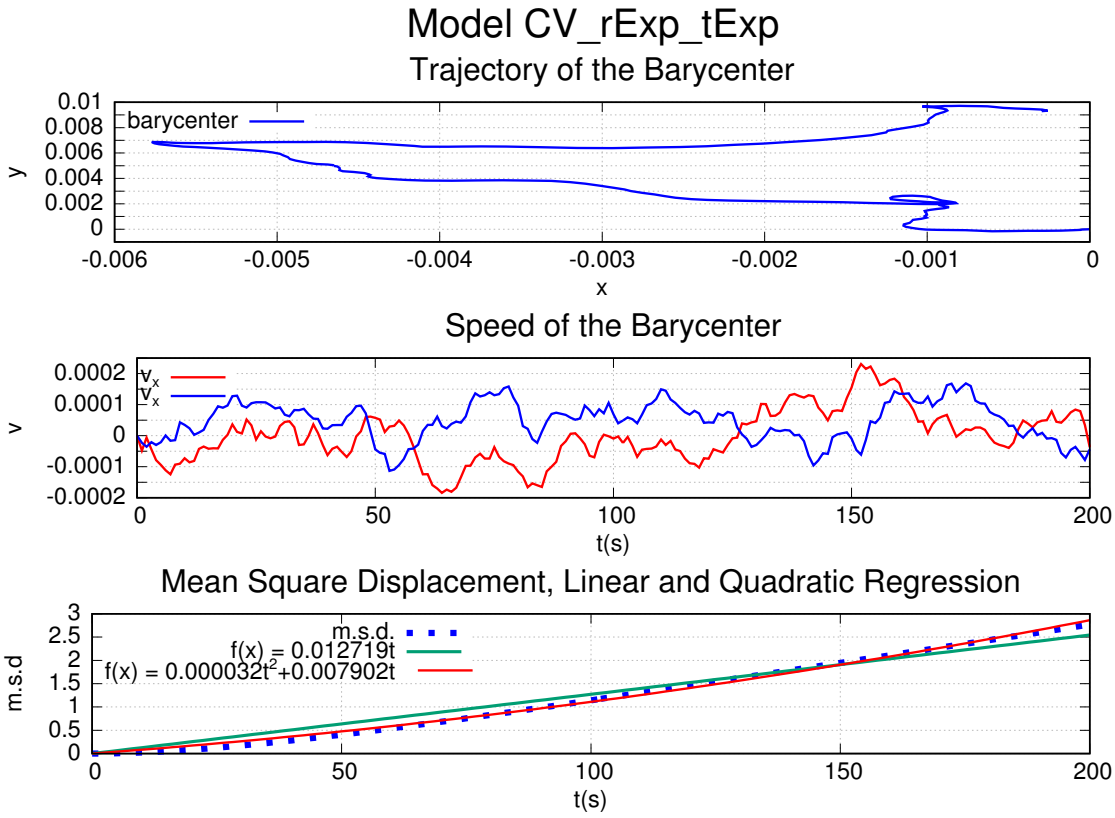


Figure 6.17: CV-rExp-tExp Model - spatially homogeneous ligand profile growing exponentially with time: Plot of the barycenter of the population (**top**), x and y component of the speed of the barycenter (**middle**), mean square displacement of the population (**bottom**). Notice that the plot of the density in Figure 6.16 corresponds to the first 24 seconds of this simulation.

Chapter 7

THE PROGRAM *EcoliSimulator*

In this chapter we describe the structure of the software `EcoliSimulator` that we developed to perform, analyze and compare simulations of different models for the *E. coli* movement.

7.1 Introduction

The program *EcoliSimulator* is a command-line based simulator of different models for *E. coli*, which produces graphical, numerical and statistical analysis of the simulations.
The program is completely written in C++ and uses `gnuplot` and/or `Matlab` as a graphical toolbox.
The different models are implemented to give the maximal freedom to the user to modify parameters and and to analyze the output.
It is designed to be usable in a step-by-step (the duration of the simulations are estimated) or a pre-set mode and produces a `.tex` file where all the information about the simulations and output is collected in a systematic, an hopefully, coherent and readable way. We save along with the summary all data and all scripts generated and used to produce the pictures and the analysis with `gnuplot`.

It is possible to choose between three different options:

- **Simulation**: to perform the simulation of the viable models;
- **Statistical Analysis**: to produce the statistical analysis of data given to the program;
- **Simulation and Statistical Analysis**: to perform first the simulation of the chosen models and afterwords analysis them, without *a priori* knowing the model simulated.

7.1.1 Type of Simulations

The program simulates 2D bacterial motion, we can perform simulations of the motion of a single bacterium, or of large populations. We can select between:

- **Simulation of an independent population**: this simulates a single bacterium or a population of bacteria swimming in a solution of ligand concentration, which evolves

according to a function (that the user chooses) without being influenced by the population of bacteria.

- **Simulation of a population interacting with the ligand**: produces the simulation of a single bacterium or a population of bacteria swimming in a solution of ligand concentration. The evolution of the ligand concentration follows a diffusion function with sinks and sources influenced by the bacteria population.

Remark 7.1.1. The program allows the simulation to be done in parallel. The default option is to use half of the cores of the computer. The user can communicate to the program the number of cores are to be used.
The program produces a log file (`Ecoli.LogEcoli`), where all the important information, possible errors and timing of the simulation are saved (appending new tasks). The user can use this file to analyze the performance of the program. In order to have an idea of the increase of performance that the parallelization provides we report the time to needed complete the simulation of the examples reported in the previous chapter. On a MacBook Pro (end 2011), processor 2,2 GHz Intel Core i7 memory 8 GB DDR3 a 1333 MHz the single thread program performed the task in circa 2 hours and 30 minutes, while the same task, with the help of 3 extra cores was performed in 45 minutes, even faster if the output of the video is save as multilayer .gif instead of the .png version.

Available Models

For the options *Simulation of an independent population* and *Simulation of a population interacting with the ligand* it is possible to choose among 9 different models for the dynamics of the bacteria.

a *Celani Vergassola Memory Kernel* [22];

b *Molecular Level Implementation*: Implementation of the signaling pathway in [21].

c *Othmer et al. Model* [45].

For every model it is possible to choose between three steady state run length distribution, i.e. exponential, inverse-gaussian or exponential-inverse gaussian. The user has the possibility to select and modify a great variety of parameters (Figure 7.2).
We have not yet developed the GUI version of this program completely, but to give a better understanding of its characteristics, we refer to the Main Window of the GUI version and the dialog to change the parameters for the function `lambda`.

7.1.2 Ecoli Classes

The program structures the different models in classes that are hierarchically organized. The base class is **E_coli**, which defines the common variables and implements (as **virtual** when needed) the basic functions to produce the simulation of the movement of an *E. coli* (see Figure 7.3).
The program is versatile and easy adaptable to include new models: it is only needed to implement the interface of the *E. coli* concerning the internal dynamic and visualization (9

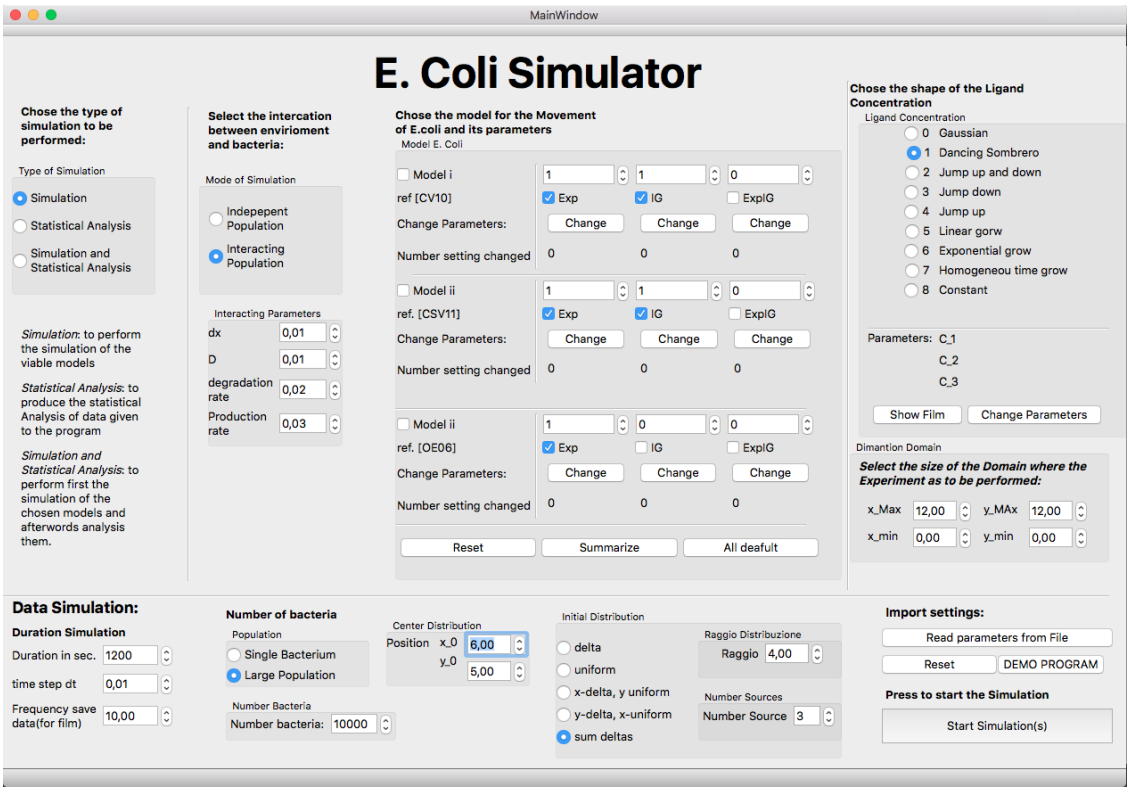


Figure 7.1: Main windows of the GUI version of the program: it summaries the main feature of the Software. [CV10]: model which uses the memory kernel in [22], [CSV11]: simulates the internal dynamics according to the model presented in [21], [EO06] uses the internal cartoon dynamic developed in [102, 45, 128]

.

functions).
The names of the derived classes have the following feature:

`name_rNameDistribution_tNameDistribution`,

where name is the *identification name*, *rNameDistribution* means that the *run* distribution follows, in the stationary case the distribution *DistributionName*. Similar for t which refers to the distribution of the tumble, for example `r_IG` means the *run* distribution in the steady state follows an Inverse Gaussian distribution.

- `Exp`: Exponential distribution
- `IG`: Inverse Gaussian distribution
- `ExpIG`: Compound exponential-inverse Gaussian distribution

CV_rExp_tExp Class

The first model is taken from [22], whose identification name is `CV_rExp_tExp`. The main feature is the variable $Q(t)$ which takes the memory of the bacterium into account to build

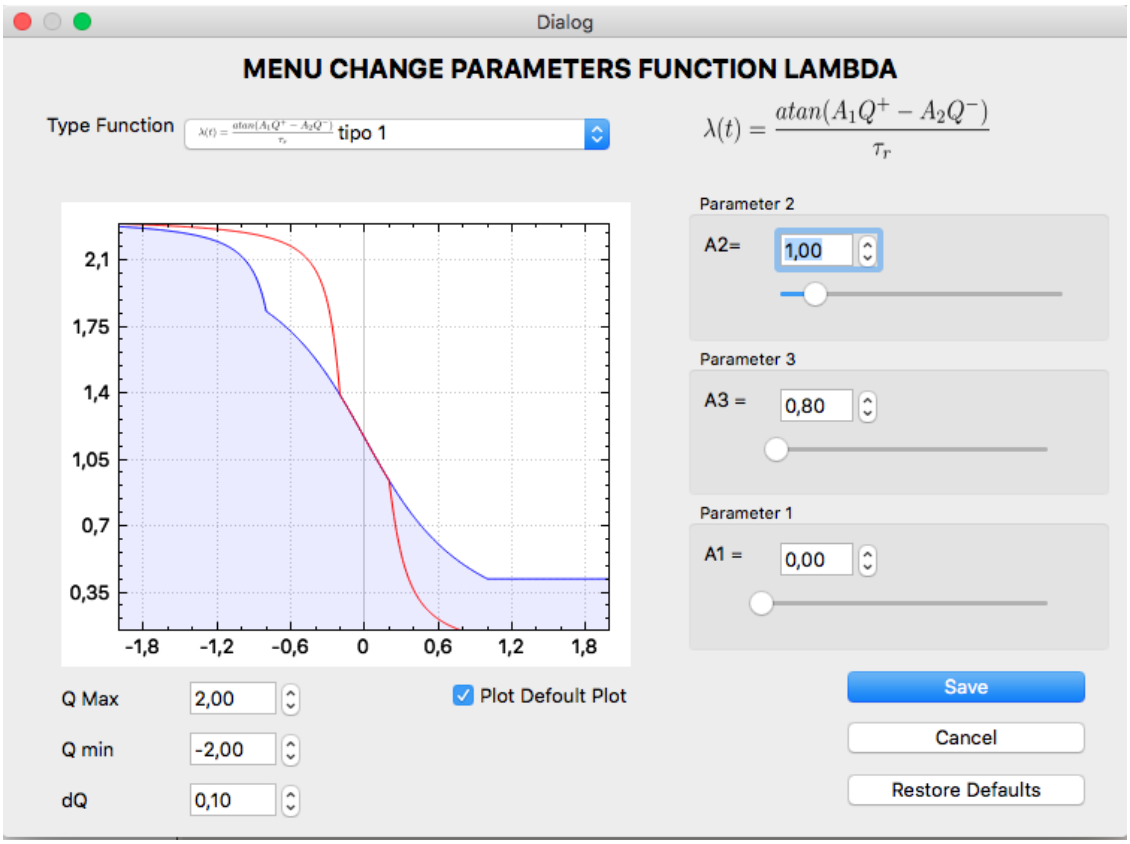


Figure 7.2: Dialog GUI version to select and save the parameters for the function lambda, which controls the probability rate of a tumble-event.

the *rate function* of the jump process associated to the *runs*. The threshold for the *runs* follows an exponentially distributed random variable, with mean equal to 1.

CV_rExpIG_tExp Class

This class extends the class `CV_rExp_tExp` (`CV_rExpIG_tExp : public CV_rExp_tExp`). Its main feature is that the evolution of the *rate function*, which depends also on $Q(t)$, is not a deterministic process, but a *diffusion process* , i.e.

$$d\Lambda(t) = \lambda(Q(t))dt + \sigma(Q(t))dW(t).$$

CV_rIG_tExp Class

This class is similar to `CV_rExpIG-tExp` with the only difference that here the barrier for the runs is deterministic.

Molecular_rx_ty

This model is taken from [21], and implements the *mean field* approximation for the molecular-based model of the internal dynamics of the bacterium. For the detailed expressions we refer

to Chapter 1, Equations (1.2.1). The generalisation to the inverse Gaussian and exponential-inverse Gaussian is straightforward as explained for the previous model.

$$d\Lambda(t) = \lambda(m, a, c)dt$$

$$\lambda(t) = \frac{h}{1-h} \cdot \frac{1}{\tau_0^t}$$

EO_rx_ty

This model is taken from [45]: the function for the internal dynamics are those reported in 4.4.1 in **Chapter 4**. As in the previous case the generalization to the inverse Gaussian and exponential-inverse Gaussian is straightforward.

7.2 Ligand evolution

In case the program mode selected is *Simulation of a population interacting with the ligand* the ligand concentration follows the equation:

$$\frac{\partial}{\partial t}c(t,x,y) = D_c\Delta_{(x,y)}c(t,x,y) - K_c c(t,x,y) + K_p \sum_{i=1}^{n_c} \delta_{(t,x,y)}(p_b^i(t,x,y)) \tag{7.2.1}$$

where p_b^i is the position of the bacterium number i. We discretize this PDE on a uniform mesh.
We first simulate the bacteria, one by one: the update of the position, direction is exactly as in the case of a population that does not interact with the environment: the ligand concentration recorded by the bacteria is calculated as a linear interpolation of the concentration of the closest nodes of the mesh of the ligand. In case the bacteria produce some chemoattractant: at the end of a time-step (usually 0.01 seconds) the bacterium produces some ligand according to the rate K_p. This is equally distributed on the closest mesh point for the ligand concentration.

The simulation of the evolution of the ligand is performed using an Alternate Direction Implicit method (ADI) [105] with Neumann's boundary conditions. The method is as follows: Let $U = (q_{i,j})_{i=1\ldots n_x, j=1\ldots n_y}$ be the matrix of the mesh for the rectangular domain and Q the matrix of the source and sinks. Let $L_x^{n_x}$ be the Laplacian-matrix in the x direction, i.e. a $n_x \times n_x$ matrix (similar for y), then using the Thompson's Algorithm for the resulting tridiagonal system we solve the PDE in two steps:

$$L_x^{n_x} \otimes U = (U \otimes L_y^{n_y})^T + \frac{dt \cdot Q}{2}$$

$$L_y^{n_y} \otimes U^T = (U^T \otimes L_x^{n_x})^T + \frac{dt \cdot Q^T}{2}$$

where with $\otimes$ we indicate the *matrix* product, and with Q^T the transpose of Q.

Remark 7.2.1. Although the ADI method is very powerful and fast, the simulation of this scenario is very demanding: the main problem is due to the difficulties to parallelize the simulations. We think that a better implementation of a population interacting with the ligand should use Finite Element Methods: the PDE is quite simple. We are currently developing this with the help of DUNE, the Distributed and Unified Numerics Environment is a modular toolbox for solving partial differential equations (PDEs) with grid-based methods [41, 14].

7.3 Statistical Analysis

The program allows the user to fit the data to the models called `CV_x_y`. We have to pass to the program the following data:

t_j	c_{τ^r}	c_{τ^t}	τ^r	τ^t

where t_j is the time of the beginning of the j-th run, c_{τ^r} is the concentration recorded at the time of the end of the run j, c_{τ^t} is the concentration recorded at the beginning of the tumble j and τ^r are (resp. τ^t) the duration of the j-th run (resp. tumble).

Format 1:

Once the program identifies which kind of data are to be analyzed it proceeds to find the best model fitting the data, extrapolating from the data the memory kernel $Q(t)$ presented in [22]. The algorithm is as follows:

step 0 Construct a vector of classes `Q_tau_stat` whose dimension depends on the maximum value of the index Q and the discretization of the interval $[\min Q : dQ : \max Q]$ with step size dQ.

step 1 Read all entries from the file.

step 2 Calculate the Q-index from [22] and all the corresponding statistics.

step 3 Plot the calculated data.

step 4 Calculate the empirical rate-function using a piecewise linear model in Q.

step 5 Calculate the weighted-mean square approximation (one for positive Q, and one for negative values of Q).

step 6 Produce a Kolmogorov-Smirnov test using the idea in [18] for the goodness of fit of point processes.

step 7 Iterate the steps [0] - [6] adapting the discretization of the variable Q and the maximum and minimum value that it can assume.

At the end of the iteration the discretization which produces the best Kolmogorov-Smirnov test is used to build a discrete response function (`lambda`) and, if the model allows it, the diffusion coefficient of the diffusion driving the *generalized subordinator*. These functions are then used to perform a new simulation of the bacteria and to compare the statistics of

the estimated model and the data recorded from the experiment or a previous simulation to validate the statistical analysis.

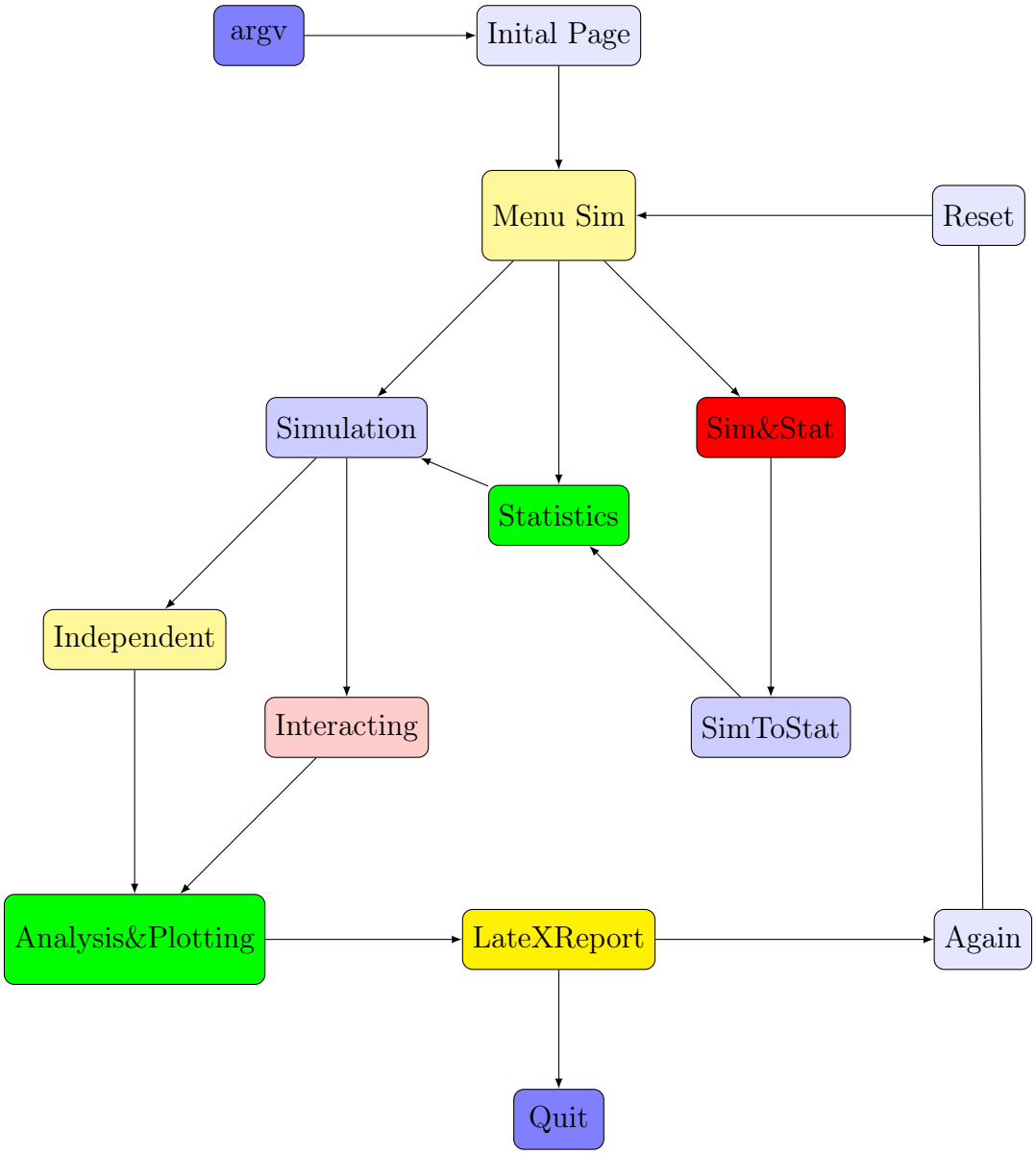


Figure 7.3: General scheme of the main branches of the program Ecoli_Simulator

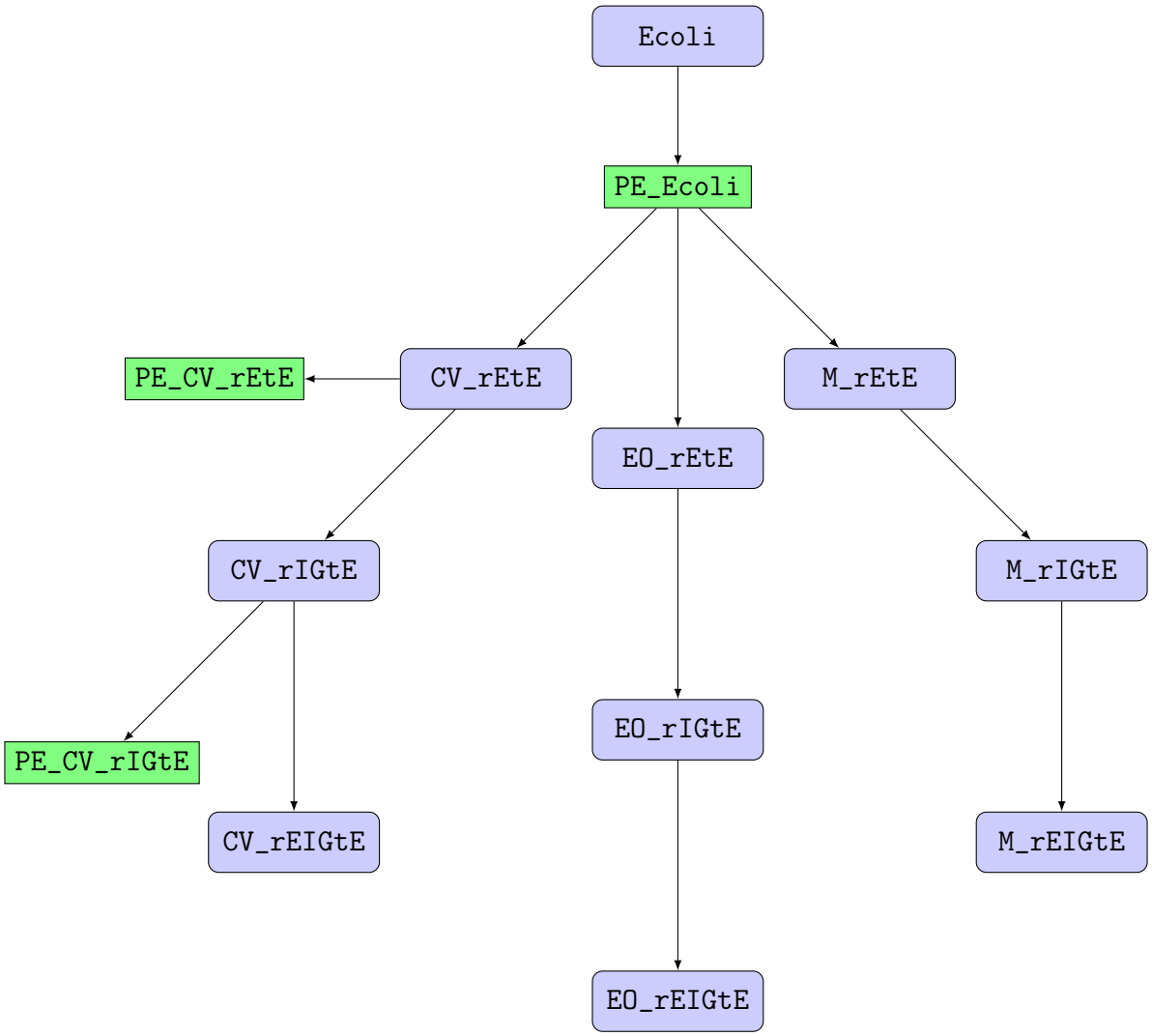


Figure 7.4: Main bacteria classes dependency for the program Ecoli_Simulator: the classes used in the statistical analysis are displayed in green, the one for the simulations are in blue. **Note:** *PE* stands for *Parameter Extimation*, *M* for *Molecular* and *E* for *Exp*.

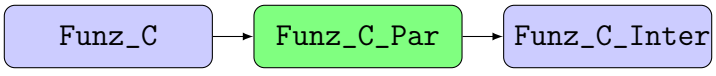


Figure 7.5: Function C classes dependency for the program Ecoli_Simulator

Chapter 8

CONCLUSIONS AND OUTLOOK

8.1 Final Remarks

Starting from the study of bacterial movement and chemotaxis we have developed a new stochastic mathematical model that applies to general hybrid systems. We identified this model as a generalization of Stochastic Hybrid Systems [19, 63] where we allow functional dependency in the coefficients of the leading equations [91]. Because of this feature we call this model *hereditary stochastic hybrid system* [23, 26]. It can be shortly described as an interleaving between a finite or countable family of diffusion processes and jump processes, where a particular process (called *generalized subordinator*) forces the system to change its state. We analyzed the basic analytical and probabilistic properties and gave sufficient conditions for the well-posedness, continuity of the generalized subordinator with respect to the initial conditions and Markovian properties. We studied then the problem of the distribution of the duration of time that the system spends in a determined state, say τ_q. We connect the distribution of this random variable τ_q with the solution of a functional Kolmogorov equation with boundary conditions, by using representation formulae of Feynman-Kac type [130]. We applied this general framework to the study of *E. coli* movement, which performs a *run* and *tumble* random walk to search for nutrients. We studied in detailed the case of an environment constant in space and time, analyzed hydrodynamic limits with parabolic rescaling and generalized the results in [122], by inserting a diffusion term that controls the evolution of the direction of the bacterium during a run. By using the framework in [7, 6] we wrote the Fokker-Planck-Kolmogorov equation for the hereditary stochastic hybrid system for *E. coli*, where the dynamics of the processes happening inside the cell are taken from [22, 21]: we used the feature that the tumble time is exponentially distributed to allow more general resets then in [7]. We identified many models in the existing literature as a special case of our model (see Figure 4.1).
We developed an additional model for *E. coli*, where the bacterium compares the current level of the ligand concentration with the one measured at the beginning of a *run*: we studied the limit of the parabolic rescaled process adapting the proofs in [110, 111]. We finally developed a software to simulate and compares different models of *E. coli* movement.

8.1.1 Gain and Loss

As we have said, the HSHS model is quite general and might be applied with success to other fields other then the study of *E. coli* movement: for example the Feynmann-Kac formulae developed in **Chapter 2** and the calculation of the first exit time probability for SFDE (see **Subsection 2.4.7**) might present an application in finance.

The price of options in the continuous time (B, S)-market has been a subject of extended research in recent years. Let us consider a slight modification of the model proposed in [26]. The idealized Black-Scholes (B, S)-market often consists of an account $(B(t))_{t\in[0,T]}$ and the stock $(S(t))_{t\in[0,T]}$. The equations for the evolution of the prices of these two financial products are given by the following system of SFDE's: Let us suppose that the solution process $B(\phi)$ satisfies the following equality

$$B(t) = \phi(0)e^{\int_0^t r(s)ds}$$

where $(\phi(t))_{t\in[-r,0]}$ is the initial condition. Let $T > 0$ be the expiration time for the European options considered in this example. Assume that the stock price $(S(t))_{t\in[-r,T]}$ satisfies the following nonlinear stochastic functional differential equation:

$$\frac{dS(t)}{S(t)} = f(S_t)dt + g(S_t)dW(t), \quad t \in [0, T]$$

with initial price function ψ. Using classical arguments for Trading Strategy and Equivalent Martingale Measure, the pricing formula $V : [0, T] \times C[-r, 0] \to \mathbb{R}$ satisfies the following expression:

$$V(t, \psi) = \mathbb{E}^t_\psi\Big[e^{-\int_t^T r(s)ds}\lambda(S_T)\Big]$$

Theorem 8.1.1. *Assume that* $V(t, \psi) \in \mathbf{C}^{1,2}_{Lip}([0, T] \times \mathbf{C}) \cup \mathcal{D}(S)$ *and that the market is* self-financial*, then* $V(t, \psi)$ *satisfies the following equation:*

$$\begin{aligned} r(t)V(t,\psi) =& \frac{\partial}{\partial t}V(t,\psi) + S(V)(t,\psi) + \overline{DV(t,\psi)}(r(t)\psi(0)\mathbf{1}_0) \\ &+ \overline{D^2V(t,\psi)}(\psi(0)g(\psi)\mathbf{1}_0, \psi(0)g(\psi)\mathbf{1}_0) \quad (t,\psi) \in [0,T)\times\mathbf{C} \\ V(T,\psi) =& \lambda(\psi) \qquad \psi \in \mathbf{C} \end{aligned}$$

The reverse holds in the sense of a viscosity solution.

If we, instead, confine ourself to the investigation of the *E. coli* movement, the analysis of the benefits and disadvantages that the use of the HSHS model brings need some more words. When we have a look at the existing literature about *E. coli* models, we immediately notice that the hypothesis that in the steady state the distribution of the duration of a *run* is exponentially distributed. In our model we include this possibility as a special case, and allow for more general distributions. What we have to pay back for this generalization is the loss of the analytical tractability (at least for us), if not in special cases: this leads us to the question of the necessity and rationality of such a complicated model for the problem under investigation. As is always suitable for models of the reality, the answer is cannot be

a simple *yes* or *no*.
As we explained in **Chapter 3 Subsection 3.3** the HSHS model specialized for the inverse Gaussian distribution is able to fit the experimental data [12] better than an exponential distribution. **Subsection 3.4** gives a clear insight what happens to the distribution of the population when we performed the limit of the parabolically rescaled equation for large time: we have that the variance of the run distribution plays a role in the value of the diffusion coefficient in the heat equation that governs this limit distribution. The magnitude of the difference of the coefficients for the two models is not so big, and we might conclude that for large time the exponential distribution is able to capture most of the features of the *E. coli*, with the advantage to be able to derive analytically formulae and relations also for the case where the environment is not constant. We are pushed to investigate further the theory behind the HSHS model as well as the generalized jump processes. This new model might stimulate new experiments in oder to establish the shape of the distribution of the duration of runs.

If we look at the microscopic level, we might want to see what is the relationship between the different models, in the sense how the inverse Gaussian, the Compound-Exponential-Inverse Gaussian (see **Subsection 2.4.1**) or the exponential distribution reflects what happens inside the bacterium.
If we have a sequence of Bernullian experiments, the if we properly rescale it, we obtain an exponential distribution. Similarly a properly rescaled random walk leads to a Brownian motion, and the hitting time of this Brownian motion with a barrier leads to an inverse Gaussian distribution. We have the Compound-Exponential-Inverse Gaussian distribution when the barrier is not a deterministic threshold but exponentially distributed.
Let us focus for simplicity on the case when the ligand concentration is constant during an experiment and the bacteria start from a steady state. Let us consider that the bacterium, at each time step, with some probability rate decides to switch from run to tumble (or *vice versa*): this is a Bernoulli process. If we rescale properly the involved parameters we obtain the exponential distribution.
If we now think that the bacterium does not take a decision to run or tumble at every time step, but only if a certain process (depending on the kinase, CheY-P concentration etc.) crosses a threshold. We might want to impose the oscillation of this process with normal noise around a mean value: as in the case of the Bernoulli process, rescaling the parameters leads us to the HSHS model.

8.1.2 Further Work

We would like, shortly, explain how the results, models and assumptions in the present thesis might be extended.
We start by looking at the microscopic level: if we focus on the exponential setting, the simplified model of the chemotactic pathway might not be enough. Interesting might be to follow [21] for a more detailed description of what happens inside the cell [86] and derive more accurate equations. The same might be applied to the corresponding HSHS model with fading memory.
If we look at any of the models, we might want to add stochasticity inside the parameters:

something similar can be found in [87]. Let us consider one of the parameters of the model, for example λ. We can consider that λ is itself a random variable, i.e.

$$\omega \in \Omega \mapsto \lambda(\omega, \cdot).$$

In this case every bacterium (independently of the time) has it characteristic parameter.
Another possibility is to subordinate the parameter to a random process, i.e. let $W(t)$ a random process, then we consider the composition

$$\lambda(W(t), \cdot).$$

Both these approaches lead to more realistic models. Clearly not all bacteria behave the same, but behave similarly to each other and the introduction of a family of parameters governed by some randomness achieves the description of this situation.
These are somehow general considerations, which apply to the HSHS as well as many articles about *E. coli* movement and velocity-jump process or hybrid system in general.
generalised velocity-jump process [122] suffer from the limitation that the distribution of the different phases is stationary: this make it possible to export this theory (in the general setting) only to the stationary environment. The analysis of such non-stationary processes is very interesting, but also very challenging.

8.2 Moderately Interacting Stochastic Many Particle Systems

In the remaining part of this chapter, we will heuristically present a new mathematical model that combines functional calculus and moderately interacting stochastic many particle systems. In oder to formulate the problem we to use the formalism of functional derivatives developed by Dupire, Cont und Fournie. A mathematical rigorous derivation of the model is under investigation.

In this section we present a heuristic analysis of a generalization of the model present in [115], i.e. using the theory developed by Oelschläger of moderately interacting diffusion processes [97, 98]. *E. coli* are unable to sense any spatial gradient and so the SDE [115] on page 186 for the bacteria must be changed and the dynamics are influenced by the window process of the recorded level of chemical substance.

8.2.1 Notation

The notation used is adapted to the one in [115].

Let N be the number of particles in the system. In the following, the subscript E marks terms related to the *E. coli* and c marks terms related to the chemical substance.
Let

$$S(N,t) = S_E(N,t) + S_c(N,t)$$

denote the set of all particles in the N-particle system. Let

$$X_N^k(t) \in \mathbb{R}^d,$$

be the position of the bacteria (resp. chemical substance) k at time t. We have that $d = 2, 3$ when $k \in S_E(N,t)$ (resp. $Z_N^k(t) \in \mathbb{R}^d$, with $d = 2, 3$ when $k \in S_c(N,t)$). For $k \in S_E(t,N)$ the average concentration level at time t, i.e. $\zeta_N^k(t)$ and the direction of the bacteria k at time t, i.e. $\theta_N^k(t)$. Let us introduce the measure valued empirical processes

$$t \mapsto \mu_E^N(t) = \frac{1}{N} \sum_{k \in S_E(N,t)} \epsilon_{X_N^k(t)} \epsilon_{\zeta_N^k(t)} \epsilon_{\theta_N^k(t)}, \quad t \mapsto \mu_c^N(t) = \frac{1}{N} \sum_{k \in S_c(N,t)} \epsilon_{Z_N^k(t)}.$$

The dynamics are influenced by the configuration of the other particles via a smoothed version of the empirical process

$$\hat{\mu}_r^N(t,x) = (\mu_r^N * W_N * \hat{W}_N)(x) \quad r = E, c,$$

where W and $\hat{W}$ (similarly V_{Nr}, h_{Nr} and s_{Nr}) are like in [115].

8.2.2 Dynamics of the Many Particle System

For each particle in the many-particle system, the motion through space is described by a (path-dependent) stochastic differential equation where the function g is continuous.

$$\begin{array}{lcl} dX_N^k(t) & = & \chi_N(\hat{\mu}_c^N(t, X_N^k(t)), \zeta_N^k(t)) \theta_N^k(t) + \sigma dW^k(t) \\ \zeta_N^k(t) & = & \int_{t-r}^t \hat{\mu}_c^N(t, X_N^k(s)) g(s-t) ds \\ d\theta_N^k(t) & = & \frac{\theta_N^k(t)' \theta_N^k(t)}{\theta_N^k(t)' \theta_N^k(t)} dt + \left(\mathbf{I} - \frac{\theta_N^k(t)' \theta_N^k(t)}{\theta_N^k(t)' \theta_N^k(t)} \right) dW_\theta^k \\ dZ_N^k(t) & = & \eta dW^k(t) \end{array}$$

Each bacterium is characterized by the position X, which follows an Itô process with diffusion coefficient σ and drift given by the quantity $a(t)$:

$$a(t) := \chi_N(\hat{\mu}_c^N(t, X_N^k(t)), \zeta_N^k(t)) \theta_N^k(t).$$

We notice that the direction is given by the vector θ, which follows a Brownian motion on the sphere ([118], page 5 (344)), while its speed in modulus is a function of the memory term ζ and the measured environment. The term ζ, as anticipated, is the *memory* term: it is a weighted average (with weigh $g(t)$) over the interval $[t-r, t]$ of the ligand concentration along the trajectory.
The process Z describes the position of the particles that form the ligand: they follow a Brownian motion without any drift.

Remark 8.2.1. Discontinuities for $\mu_c^N(t)$ as explained in [115] (from page 186 till the end of the section on page 187) are allowed. In fact the bacteria, with a certain rate, produce or consume ligand.

8.2.3 Heuristic Analysis of the Model

In order to deal with systems of interacting stochastic many particle systems, one uses Itô's formula to project the measure-valued empirical process onto the space of continuous functions. In the present framework, however, we cannot apply the usual Itô's formula, because of the presence of the path dependent process $\zeta_N^k(t)$. In order to deal with these features we use the Functional Stochastic Calculus developed by Dupire [42, 30, 31, 32].

A Brief Primer on Functional Itô Calculus

In this part we will present a short review for the functional Itô calculus introduced in [112]. The goal is to familiarize the reader with the notation, main definitions and theorems needed for the results that follow. The space of cádlág paths in $[0,t]$ will be denoted by Λ_t. For a fixed time horizon $T>0$, we define the space of paths as

$$\Lambda = \bigcup_{t\in[0,T]} \Lambda_t.$$

We will denote elements of Λ by upper case letters and often the final time of their domain will be subscripted, e.g. $Y \in \Lambda_t \subset \Lambda$ will be denoted by Y_t. The value of Y_t at a specific time will be denoted by lower case letters: $y_s = Y_t(s)$, for any $s \le t$. Moreover, if a path Y_t is fixed, the path Y_s, for $s \le t$, will denote the restriction of the path Y_t to the interval $[0,s]$. The following important path deformations are always defined in Λ.

Definition 8.2.2. For $Y_t \in \Lambda$ and $t \le s \le T$ the *flat extension* of Y_t up to time $s \ge t$ is defined as

$$Y_{t,s-t}(u) = \begin{cases} y_u & 0 \le u \le t \\ y_t & t \le u \le s \end{cases}.$$

For $h \in \mathbb{R}$ and $Y_t \in \Lambda$, the *bumped path* of Y_t is defined as

$$Y_t^h(u) = \begin{cases} y_u & 0 \le u \le t \\ y_t + h & u = t \end{cases}.$$

We define now a metric on Λ.

Definition 8.2.3. For any Y_t, Z_s in Λ, where it is assumed without loss of generality that $s \ge t$, we define the following metric in Λ:

$$d_\Lambda(Z_s, Y_t) := \|Y_{t,t-s} - Z_s\|_\infty + |t-s|.$$

Remark 8.2.4. One could show that (Λ, d_Λ) is a complete metric space.

Additionally, a *functional* is any function $f : \Lambda \to \mathbb{R}$. Continuity with respect to d_λ is defined as the usual definition of continuity in a metric space and is denominated Λ-continuity.

Definition 8.2.5. For a functional f and a path Y_t with $t < T$, the *time functional derivative* of f at Y_t is defined as

$$\mathcal{D}_t f(Y_t) = \lim_{\delta t \to 0^+} \frac{f(Y_{t,\delta t}) - f(Y_t)}{\delta t},$$

whenever this limit exists.
The *space functional derivative* of f at Y_t is defined as

$$\nabla_x^{\mathcal{D}} f(Y_t) = \lim_{h \to 0} \frac{f(Y_t^h) - f(Y_t)}{h},$$

whenever this limit exists. We define

$$\Delta_{xx}^{\mathcal{D}} f(Y_t) := \nabla_x^{\mathcal{D}} \Big(\nabla_x^{\mathcal{D}} f(Y_t) \Big).$$

We state now the functional Itô formula.

Theorem 8.2.6 (Functional Itô Formula)**.** *Let X be a continuous semimartingale and $f \in \mathscr{C}^{1,2}$. Then for any $t \in [0,T]$,*

$$f(X_t) = f(X_0) + \int_0^t \mathcal{D}_t f(X_s) ds + \int_0^t \nabla_x^{\mathcal{D}} f(X_s) dX_s + \frac{1}{2} \int_0^t \Delta_{xx}^{\mathcal{D}} f(X_s) d\langle X_s \rangle.$$

Let us apply these derivatives to our process: We set

$$\mathcal{K}^{j,l}(u) := W_N(u) \hat{W}_N \Big(u - [Z_N^j(s) + X_N^k(s)] \mathbf{1}_{[t-r,r]}(s) - [Z_N^j(t) + X_N^k(t)] \mathbf{1}_{[t,t+h]}(s) \Big) du.$$

Hence

$$\begin{aligned}
\mathcal{D}_t \zeta_N^k(t) &= \lim_{h \to 0} \frac{1}{h} \Big\{ \int_{t+h-r}^{t+h} \sum_{j \in S_c(N,t)} \int_{\mathbb{R}^d} \mathcal{H}^{j,k}(u) g(s-t-h) ds - \zeta_N^k(t) \Big\} \\
&= \lim_{h \to 0} \frac{1}{h} \Big\{ \int_t^{t+h} \sum_{j \in S_c(N,t)} \int_{\mathbb{R}^d} W_N(u) \hat{W}_N(u - Z_N^j(s) - X_N^k(s) \mathbf{1}_{[t,t+h]}(s)) du g(s-t-h) ds \Big\} \\
&\quad - \lim_{h \to 0} \frac{1}{h} \Big\{ \int_{t-r}^{t+h-r} \sum_{j \in S_c(N,t)} \int_{\mathbb{R}^d} W_N(u) \hat{W}_N(u - Z_N^j(s) - X_N^k(s) \mathbf{1}_{[t,t+h]}(s)) du g(s-t) ds \Big\} \\
&= \hat{\mu}_c^N(t, X_N^k(t)) g(0) - \int_{t-r}^t \Big(\hat{\mu}_c^N(s, X_N^k(s)) \Big) \frac{d}{ds} g(s-t) ds - \hat{\mu}_c^N(t-r, X_N^k(t-r)) g(-r)
\end{aligned}$$

where $g(\cdot)$ is continuous in $[-r, 0]$ in the convergence of the first integral.

$$\begin{aligned}
&\frac{1}{h} \Big| \int_t^{t+h} h(\zeta(t)) g(s-t+h) ds - h(\zeta(t)) g(0) \Big| = \\
&= \frac{1}{h} \Big| \int_t^{t+h} \Big[W(\zeta(t)) g(s-t+h) ds - W(\zeta(t)) g(0) \Big] ds \Big| \leq \\
&\leq |W(\zeta(t))| \cdot \sup_{s \in [t,t+h]} |g(t-s) - g(0)| \to 0.
\end{aligned}$$

From this relation, we can rewrite the system under investigation in the differential form as

$$\begin{aligned}
dX_N^k(t) &= \chi_N(\hat{\mu}_c^N(t, X_N^k(t)), \zeta_N^k(t))\theta_N^k(t) + \sigma dW^k(t) \\
d\zeta_N^k(t) &= \hat{\mu}_c^N(t, X_N^k(t))g(0) - \int_{t-r}^t \Big(\hat{\mu}_c^N(s, X_N^k(s))\Big)\frac{d}{ds}g(s-t)ds - \hat{\mu}_c^N(t-r, X_N^k(t-r))g(-r) \\
d\theta_N^k(t) &= \frac{\theta_N^k(t)'\theta_N^k(t)}{\theta_N^k(t)'\theta_N^k(t)}dt + \Big(\mathbf{I} - \frac{\theta_N^k(t)'\theta_N^k(t)}{\theta_N^k(t)'\theta_N^k(t)}\Big)dW_\theta^k \\
dZ_N^k(t) &= \eta dW^k(t)
\end{aligned}$$

Since $F \in \mathscr{C}^1(\mathbb{R})$, we can use the chain rule, and conclude that

$$\mathcal{D}_t F\Big(\zeta_N^k(t)\Big) = \frac{dF}{dx}\Big(\zeta_N^k(t)\Big) \cdot \mathcal{D}_t \zeta_N^k(t)$$

More precisely, this equality follows by an application of the mean-value theorem

$$\frac{1}{h}\Big[F(\zeta_N^k(t;h)) - F(\zeta_N^k(t))\Big] = \int_0^1 \frac{dF}{dx}\Big(\zeta_N^k(t;u)\Big)\frac{1}{h}[\zeta_N^k(t;h) - \zeta_N^k(t)]du$$

with $\zeta_N^k(t;u) = (1-u)\zeta_N^k(t) + u\zeta_N^k(t;h)$, $0 < u < 1$.

As in the case [32] page 9, formula (23), $\nabla_x \zeta_N^k(t) = 0$ and $\nabla_x^2 \zeta_N^k(t) = 0$:

$$\begin{aligned}
\nabla_x \zeta_N^k(t) &= \lim_{h\to 0}\frac{1}{h}\Big\{\int_{t-r}^t \sum_{j\in S_c(N,t)} \int_{\mathbb{R}^d} W_N(u)\hat{W}_N\Big(u - Z_N^j(s) - X_N^k(s) + h\mathbf{1}_{\{t\}}(s)\Big)dug(s-t)ds - \zeta_N^k(t)\Big\} \\
&= \lim_{h\to 0}\frac{1}{h}\Big\{\int_{t-r}^t dsg(s-t)\sum_{j\in S_c(N,t)}\int_{\mathbb{R}^d} duW_N(u)\cdot \\
&\qquad \cdot\Big[\hat{W}_N\Big(u - Z_N^j(s) - X_N^k(s) + h\mathbf{1}_{\{t\}}(s)\Big) - \hat{W}_N\Big(u - Z_N^j(s) - X_N^k(s)\Big)\Big]\Big\} \equiv 0
\end{aligned}$$

$[\hat{W}_N(u - Z_N^j(s) - X_N^k(s) + h\mathbf{1}_{\{t\}}(s)\Big) - \hat{W}_N\Big(u - Z_N^j(s) - X_N^k(s))]$ is identically zero since the Lebesgue measure of the singleton $\{t\}$ is zero.
Let $A(t)$ be defined as

$$A(t) := \langle \mu_E^N(t), f(t, \cdot_X, \cdot_\zeta, \cdot_\theta)\rangle$$

According to [32] Theorem 4.1 on page 10 we have

$$
\begin{aligned}
A(t) &= \frac{1}{N}\sum_{k\in S_E(t,N)} f(t, X_N^k(t), \zeta_N^k(t), \theta_N^k(t)) \\
&= \langle \mu_E^N(0), f(0,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle + \int_0^t \langle \mu_E^N(s), \frac{\partial}{\partial s} f(s,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle ds \\
&+ \int_0^t \langle \mu_E^N(s), \chi_N(\hat{\mu}_c^N(t,\cdot_X),\cdot_\zeta)\cdot_\theta \nabla_x f(s,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle ds \\
&+ \int_0^t \langle \mu_E^N(s), \frac{1}{2}\sigma^2 \Delta_x f(s,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle ds \\
&+ \int_0^t \langle \mu_E^N(s), a_\theta(\cdot_\theta)\nabla_\theta f(s,\cdot_X,\cdot_\zeta,\cdot_\theta) + \sigma_\theta(\cdot_\theta)\Delta_\theta f(s,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle ds \\
&\quad + \int_0^t \langle \mu_E^N(s), \nabla_\zeta f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\cdot \hat{\mu}_c^N(s,\cdot_x) g(0)\rangle ds \\
&\quad - N\int_0^t \langle \mu_E^N(s-r), \hat{\mu}_c^N(s-r,\cdot_x) g(-r)\rangle \langle \mu_E^N(s), \delta_i^j \nabla_\zeta f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle ds \\
&\quad - N\int_0^t \langle \mu_E^N(s), \nabla_\zeta f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle \delta_i^j \cdot \int_{s-r}^s \langle \mu_E^N(u), \hat{\mu}_c^N(u,\cdot)\frac{d}{ds} g(u-s)\rangle du ds \\
&\quad + M^N(t).
\end{aligned}
$$

The equation for $\langle \mu_c^N(t), f(t,\cdot_Z)\rangle$ is the same as (3) in [115].

Heuristically: assuming that the quadratic variation of the martingale $M_r^N(t)$ tends to 0 for $N\to\infty$ - and that the processes are *asymptotically independent*[1] - one obtains, at least formally

$$
\begin{aligned}
\langle \mu_E^N(t), f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle &\to \langle \mu_E^\infty(t), f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle \\
\langle \mu_c^N(t), f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle &\to \langle \mu_c^\infty(t), f(t,\cdot_X)\rangle
\end{aligned}
$$

where it is assumed that the density exists at least for $\mu_c^\infty(t) = c(t,x)dx$

$$
\begin{aligned}
\langle \mu_E^\infty(t), f(t,\cdot_X,\cdot_\zeta,\cdot_\theta)\rangle &= \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(0) f(0,x,\zeta,\theta) dx d\zeta d\theta \\
&\quad + \int_0^t ds \Big\{ \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx,d\zeta,d\theta)\frac{\partial}{\partial s} f(s,x,\zeta,\theta)
\end{aligned}
$$

[1] to be understood as, at least formally and abusing of notation, $N\delta_j^i p(x_k) \to p(x_1,\cdot,p_N)$: there might be a problem in this consideration trying to make it rigorous

$$
\begin{aligned}
&+ \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx,d\zeta,d\theta)\chi_\infty(c(t,x),\zeta)\theta\nabla_x f(s,x,\zeta,\theta)\\
&+ \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx,d\zeta,d\theta)\frac{1}{2}\sigma^2\Delta_x f(s,x,\zeta,\theta)\\
&+ \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx,d\zeta,d\theta)a_\theta(\theta)\nabla_\theta f(s,x,\zeta,\theta)\\
&+ \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx,d\zeta,d\theta)\sigma_\theta(\theta)\Delta_\theta f(s,x,\zeta,\theta)\\
&+ \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx,d\zeta,d\theta)\nabla_\zeta f(t,x,\zeta,\theta)\cdot c(s,x)g(0)\\
&- \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s-r)(dx,d\zeta,d\theta)c(s-r,x)g(-r)\cdot\\
&\qquad\qquad \cdot\int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s)(dx',d\zeta',d\theta')\nabla_\zeta f(t,x',\zeta',\theta')\\
&- \int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(s-r)(dx,d\zeta,d\theta)\nabla_\zeta f(s,x,\zeta,\theta)\cdot\\
&\qquad\qquad \cdot\int_{s-r}^{s}\int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}} \mu_E^\infty(u)(dx',d\zeta',d\theta')c(u,x')\frac{d}{ds}g(u-s)du\Big\}.
\end{aligned}
$$

Integration by parts gives the weak version: in the case in which $\mathcal{L}_{(X(t),\zeta(t),\theta(t))}$ admits a density, i.e.

$$\Phi(t,x,\zeta,\theta)dxd\zeta d\theta = \mathcal{L}_{(X(t),\zeta(t),\theta(t))}$$

we can write the following system of equations:

$$
\begin{aligned}
\frac{\partial}{\partial t}\Phi(t,x,\zeta,\theta) =&\nabla_x\Big(\frac{\sigma^2}{2}\nabla_x\Phi(t,x,\zeta,\theta) - \Phi(t,x,\zeta,\theta)\chi_\infty(c(t,x),\zeta)\cdot\theta\Big)\\
&+\nabla_\theta\Big(\nabla_\theta[\sigma_\theta(\theta)\Phi(t,x,\zeta,\theta)] - a_\theta(\theta)\Phi(t,x,\zeta,\theta)\Big)\\
&-c(t,x)g(0)\nabla_\zeta\Phi(t,x,\zeta,\theta)\\
&+c(s-r,x)g(-r)\nabla_\zeta\Phi(t,x,\zeta,\theta)\int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}}\Phi(t-r,x',\zeta',\theta')dx'd\zeta'd\theta\\
&+\nabla_\zeta\Big(\int_{\mathbb{R}^d}\int_{\mathbb{R}^d}\int_{S^{d-1}}\Big[\Phi(t,x,\zeta,\theta)\int_{s-r}^{s}\Phi(u,x',\zeta',\theta')c(u,x')\frac{d}{dt}g(u-s)du\Big]dx'd\zeta'd\theta'\Big)
\end{aligned}
$$

and

$$
\begin{aligned}
\frac{\partial}{\partial t}c(t,x) =&\frac{\eta^2}{2}\Delta_x c(t,x) + \beta\Big(c(t,x),\Phi(t,x,\zeta,\theta)\Big)\Phi(t,x,\zeta,\theta)\\
&-c(t,x)\gamma\Big(c(t,x),\Phi(t,x,\zeta,\theta)\Big)
\end{aligned}
$$

Remark 8.2.7. Concentrating on the structure of the equation for $\Phi(t,x,\zeta,\theta)$ one can see that

- **first line** with an improper language "The equation in the variable x is the same as the chemotaxis equation, where the direction θ is given by an additional variable;

- **second line** the additional variable θ, being a Brownian motion evolves like a diffusion on the sphere;
- **third $\rightarrow$ fifth lines** involve how the past influences the present state in a non-linear way not to easy too identify clearly.

Remark 8.2.8. If the idea of a Brownian motion as leading direction of the SFDE for $X_N^k(t)$ might be considered to be too irregular and unrealistic, then - given the structure of the equations and the independence of the process - one can substitute it with a Poisson process on the sphere with a specific jump measure $d\xi(\eta)$ and rate λ, in the limiting *weak version* equation one has to substitute

$$\nabla_\theta\Big(\nabla_\theta[\sigma_\theta(\theta)\Phi(t,x,\zeta,\theta)] - a_\theta(\theta)\Phi(t,x,\zeta,\theta)\Big) \mapsto \lambda\cdot\int_{S^{d-1}}[\Phi(t,x,\zeta,\eta)-\Phi(t,x,\zeta,\theta)]d\xi(\eta),$$

or maybe more generally, with

$$\lambda(x,\zeta)\cdot\int_{S^{d-1}}[\Phi(t,x,\zeta,\eta)-\Phi(t,x,\zeta,\theta)]d\xi(\eta).$$

Part III

Appendix

Appendix A

PROBABILISTIC "ZIBALDONE"

A.1 Notations and Definitions

Let $(\Omega, \mathcal{F}, \mathcal{F}_t, \mathbf{P})$ be a complete filtered probability space where $\mathcal{F}_t$ is a filtration of sub-σ-algebras of $\mathcal{F}$ that satisfies the following *usual conditions:*

(i) $\mathcal{F}_t$ is complete, i.e. $\mathcal{F}_{t_0}$ contains all $\mathbf{P}$-null sets

(ii) $\mathcal{F}_t$ is nondecreasing, i.e. if $t_1 \leq t_2$, then $\mathcal{F}_{t_1} \subseteq \mathcal{F}_{t_2}$,

(iii) $\mathcal{F}_t$ is right-continuous, i.e.

$$\mathcal{F}_t = \mathcal{F}_{t+} := \bigcap_{s>t} \mathcal{F}_s,$$

for all times t.

For a generic Banach (or Hilbert) space $(B, \|\cdot\|_B)$, whose Borel σ-algebra we indicate with $\mathcal{B}(B)$, and a sub-σ-algebra $\mathcal{G}$ of $\mathcal{F}$, let $L^2(\Omega, B; \mathcal{G})$ be the collection of all B-valued random variables $X : (\Omega, \mathcal{G}, \mathbf{P}) \to (B, \mathcal{B}(B))$ that are $\mathcal{G}$-measurable and satisfy

$$\|X\|^2_{L^2(\Omega,B)} := \mathbb{E}[\|X\|^2_B] := \int_\Omega \|X(\omega\|^2_B \, d\mathbf{P}(\omega) < \infty,$$

where $\mathcal{B}(B)$ is the Borel σ-algebra induced by $\|\cdot\|_B$.

If $\mathcal{F} = \mathcal{G}$, we simply write $L^2(\Omega, B)$ for $L^2(\Omega, B; \mathcal{F})$.

For $0 < T \leq \infty$, let $\mathscr{C}([0,T]; L^2(\Omega, B))$ be the space of all square integrable continuous B-valued processes $X(\cdot) := \{X(s) : s \in [0,T]\}$.

A.2 Stochastic Functional Differential Equations

In many applications, one assumes that the system under consideration is governed by a principle of Markovianity; that is, the future state of the system is independent of the past states and is determined solely by the present. However, under closer investigation, it becomes apparent that this principle is often only a first approximation to the true situation and that a more realistic model would include some of the past states of the system. Simple

motivating examples include the noisy feedback loop, the logistic time-lag model with Gaussian noise, and the classical heat-bath model of R. Kubo [75], modeling the motion of a large molecule in a viscous fluid. Stochastic functional differential equations give a mathematical formulation for such systems [66, 77, 34, 91, 85]. For a complete review we refer to [67].

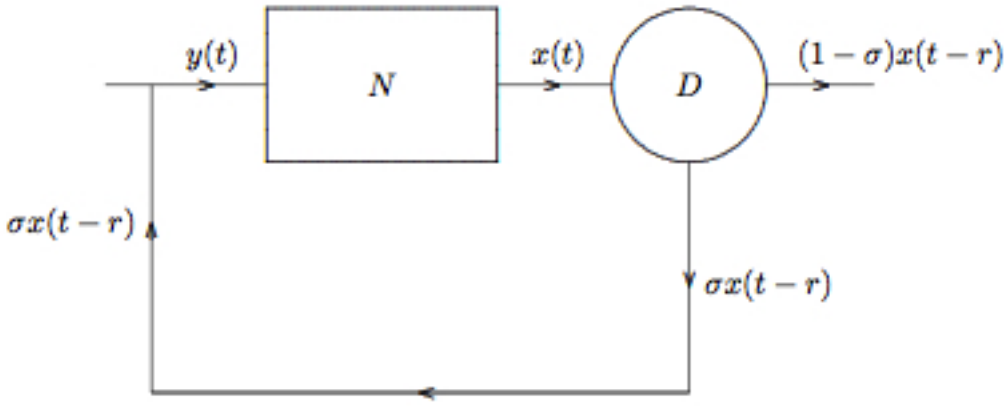


Figure A.1: Noisy Feedback Loop

Example A.2.1 ([91])**.** Consider the above noisy feedback loop. In the box N, the input $y(t)$ and the output $x(t)$ at time $t > 0$ are related through the stochastic integral:

$$x(t) = x(0) + \int_0^t y(s)dW(s)$$

where $W(s)$ is a Brownian motion and $a(s)$ and $b(s)$ are measurable functions. Unit D delays the signal $x(t)$ by r units of time, where r is a positive number. A proportion σ of the signal is transmitted through the link D and the rest $(1 - \sigma)$ is used for other purposes; therefore $y(t) = \sigma x(t - r)$. By substituting in the above equation, it gives the Itô integral equation:

$$x(t) = x(0) + \int_0^t \sigma x(s - r)dW(s).$$

In the non-delay case, $r = 0$, and it becomes a linear stochastic ODE with the closed-form solution

$$x(t) = x(0)e^{\sigma W(t) - \sigma^2 t/2}.$$

Suppose the delay r is positive. To solve it in this case, we need an initial process $\eta(t)$, with $t \in [-r, 0]$, i.e.

$$x(t) = \eta(t) \ a.s., \quad t \in [-r, 0].$$

We solve it by successive Itô integrations over steps of length r, which gives

$$x(t) = \theta(0) + \int_0^t \theta(u - r)dW(s) \quad t \in [0, r].$$

By substituting the next r-interval we get:

$$x(t) = x(r) + \sigma \int_r^t \Big[\theta(0) + \sigma \int_0^{(v-r)} \theta(u-r)dW(u)\Big]dW(v) \quad t \in [r, 2r].$$

and so on. We remark that no closed form solution is known (even in the deterministic case).

A.2.1 Basic Setting and Assumptions

Let $(\Omega, \mathcal{F}, \mathcal{F}_t, \mathbb{P})$ be a complete filtered probability space that satisfies the following *usual conditions* and let $W(t)$ be an n-dimensional Wiener process. In this sections we will summarize the basic theory of SFDE's [91, 23]. Consider the following d-dimensional SFDE with bounded memory $r \in [0, \infty)$:

$$dx(s) = f(s, x_s)ds + g(s, x_s)dW(s), \quad s \in [0, T] \tag{A.2.1}$$

with initial condition

$$(t, x_t) = (t, \eta_t) \in [0, T] \times L^2(\Omega, \mathscr{C}; \mathcal{F}(f));$$

x_t is the segment process defined by

$$x_t(s) := x(t + s) \quad s \in [-r, 0],$$

and the coefficients

$$\begin{aligned} f :&[0, T] \times L^2(\Omega, \mathscr{C}) \to \mathbb{R}^d \\ g :&[0, T] \times L^2(\Omega, \mathscr{C}) \to \mathbb{R}^{d\times n}. \end{aligned}$$

are continuous functions that are to be specified later.

Memory Maps:

a natural map associated with the SFDE (A.2.1) with bounded memory $r \in [0, \infty)$ is the *memory map*:

$$: [0, T] \times \mathscr{C}([-r, T], \mathbb{R}^d) \to \mathscr{C}$$

defined by

$$(t, \phi) = \phi_t, \quad (t, \phi) \in [0, T] \times \mathscr{C}([-r, T], \mathbb{R}^d).$$

We have the following

Lemma A.2.2. *For each $T \in (0, \infty)$, the memory map is jointly continuous.*

Corollary A.2.3. *The stochastic memory map*

$$^* : [0, T] \times L^2(\Omega, \mathscr{C}([-r, T], \mathbb{R}^d)) \to L^2(\Omega, \mathscr{C})$$

defined by $(t, x(\cdot)) \mapsto x_t$ is a continuous map.

The Assumptions:

In (A.2.1), the functions f and g are continuous functions that satisfy the following Lipschitz continuity and either the linear growth condition or the monotonicity one.
Assumption 1 (*Lipschitz Continuity*) There exists a constant $K_L > 0$ such that, for all (s, ϕ) and (t, ψ), elements in $[0, T] \times L^2(\Omega, \mathscr{C})$

$$\mathbb{E}\Big[|f(s,\phi) - f(t,\psi)| + |g(s,\phi) - g(t,\psi)|\Big] \leq K_L\Big(|t-s| + \|\phi - \psi\|_{L^2(\Omega,\mathscr{C})}\Big).$$

Assumption 2 There exists a constant $K_G > 0$ such that

$$\mathbb{E}\Big[|f(s,\phi)| + |g(s,\phi)|\Big] \leq K_G\Big(1 + \mathbb{E}[\|\phi\|]\Big).$$

Assumption 3 For each compact subset $C \subset \mathscr{C}$, there exists a number K_C and some $r_C \in (0, r)$ such that for all $x, y \in \mathscr{C}$ with $x(s) = y(s)$ for all $s \in [r, r_C]$

$$2\langle f(x) - f(y), x(0) - y(0)\rangle + \|g(x) - g(y)\|^2 \leq K_C \|x - y\|^2 .$$

Theorem A.2.4. *Suppose that **Assumption 1** and **Assumption 2** hold. Then the SFDE (A.2.1) has a unique strong solution* $\{x(s; t, \psi_t), s \in [t - r, T]\}$.

Proof. See [91, 23]. □

In [127] the authors relax the conditions on the coefficients of a SFDE with bounded memory driven by Brownian motion which guarantee existence and uniqueness of a maximal local and global strong solution for each initial condition.

Theorem A.2.5. *Assume that the coefficients f and g are time independent and satisfy **Assumption 3**, then (A.2.1) admits a unique maximal strong solution (x, σ).*

Proof. See [127]. □

A.2.2 Markovian Properties

Let $x(\cdot)$ be the strong solution of (A.2.1).

Theorem A.2.6. *Assume that the functions f and g satisfy **Assumption 1** and **Assumption 2**. Then the $\mathscr{C}$-valued process $\{x_s, s \in [0, T]\}$ of (A.2.1) describes a $\mathscr{C}$-valued Markov process with probability transition function*

$$p : [0, T] \times \mathscr{C} \times [0, T] \times \mathcal{B}(\mathscr{C}) \to [0, 1],$$

where $p(t, x_t, s, B)$, for $s \in [t, T]$ and $B \in \mathcal{B}(\mathscr{C})$, is given by

$$p(t, x_t, s, B) := \mathbf{P}\Big(x_s \in B \Big\| x_t\Big) := \mathbf{P}^{t,x_t}\Big(x_s \in B\Big).$$

This function has the following properties:

(a) For any $s \geq t$, $B \in \mathcal{B}(\mathscr{C})$, the function $(t, x_t) \mapsto p(t, x_t, s, B)$ is $\mathcal{B}([0,T]) \times \mathcal{B}(\mathscr{C})$-measurable.

(b) For any $t \leq s \leq u$, $B \in \mathcal{B}(\mathscr{C})$

$$\mathbf{P}\Big(x_u \in B \Big\| \mathcal{F}(s)\Big) = \mathbf{P}^{s,x_s}\Big(x_s \in B\Big) = p(s, x_s, u, B)$$

Under **Assumption 1** and **Assumption 2** we can also show that the $\mathscr{C}$-valued strong solution of (A.2.1) satisfies the following strong Markov property too [77, 23].

Theorem A.2.7. *Under **Assumption 1** and **Assumption 2** the $\mathscr{C}$-valued process $\{x_s, s \in [0,T]\}$ of (A.2.1) satisfies the following strong Markov property: for all $\mathcal{F}_t$-stopping times τ such that $t \leq \tau \leq u$*

$$\mathbf{P}\Big(x_u \in B \Big\| \mathcal{F}(\tau)\Big) = \mathbf{P}\Big(x_u \in B \Big\| x_\tau\Big) = \mathbf{P}^{s,x_\tau}\Big(x_s \in B\Big)$$

A.3 Stochastic Calculus for Systems with Memory

A.3.1 Weak Infinitesimal Generator for SFDE

We start with a theorem about the properties of the infinitesimal generator of a semigroup.

Theorem A.3.1 ([43])**.** *Given the weak infinitesimal generator $A_w : \mathcal{D} \subset \mathscr{C}_b \to \mathscr{C}_b$ of a one parameter semigroup $(P_t)_{t\geq 0}$*

$$A_w(\phi) := w - \lim_{t\to 0^+} \frac{P_t(\phi) - \phi}{t},$$

then

- *$\mathcal{D}(A_w) \subset \mathcal{C}_b^0$ is weakly dense in $\mathcal{C}_b$ and $P(t)(\mathcal{D}(A)) \subset \mathcal{D}(A)$*
- *If $\phi \in \mathcal{D}$, the following weak derivative exists*

$$\frac{d}{dt}P_t(\phi) = w - \lim_{h\to 0} \frac{P_{t+h}(\phi) - P_t(\phi)}{h}, \quad t > 0$$

and the following holds

$$\frac{d}{dt}P_t(\phi) = A_w(P_t(\phi)) = P_t(A_w(\phi)),$$

$$P_t(\phi) - \phi = \int_0^t P_u(A_w(\phi))du, \quad \forall t > 0.$$

In order to deal with the infinitesimal generator of a SFDE it is necessary to *augment* the state space $\mathscr{C}$ by adjoining a canonical d-dimensional direction [91].
Let $\mathcal{L}(C)$ and $\mathcal{B}(C)$ be the space of bounded linear functionals $\Phi : C \to \mathbb{R}$ and bounded bilinear functionals $\tilde{\Phi} : C \times C \to \mathbb{R}$, of the space C, respectively. They are equipped with

the operator norms which will be, respectively, denoted by $\|\cdot\|_{\mathcal{L}}$ and $\|\cdot\|_{\mathcal{B}}$. With $\mathbf{1}_{[a,b]}(t) := \mathbf{1}_{[-r,0]\cap[a,b]}(t)$

$$F_n := \{v\mathbf{1}_{\{0\}} : v \in \mathbb{R}^n\}.$$

We form the direct sum

$$C \oplus F_n := \{\phi + v\mathbf{1}_{\{0\}} | \phi \in C, v \in \mathbb{R}^n\},$$

and equip it with the norm $\|\cdot\|$ defined by

$$\left\|\phi + v\mathbf{1}_{\{0\}}\right\| := \sup_{t\in[-r,0]} \phi(t) + |v| \quad \phi \in C, v \in \mathbb{R}^n.$$

Note that for each sufficiently smooth function $\Phi : C \to \mathbb{R}$, its first order Frèchet derivative $D\Phi(\phi) \in \mathcal{L}(C)$ has a unique and continuous linear extension $\overline{D\Phi(\phi)} \in \mathcal{L}(C \oplus F_n)$. Similarly, its second order Fréchet derivative $D^2\Phi(\phi) \in \mathcal{B}(C)$ has a unique and continuous linear extension $\overline{D^2\Phi(\phi)} \in \mathcal{B}(C \oplus F_n)$. For a Borel measurable function $\Phi : C \to \mathbb{R}$, we also define the Shift Operator

$$\Gamma_t(\Phi)(\phi) := \Phi(\tilde{\phi}_t)$$

where, for each $\phi \in C$ and $t \geq 0$, $\tilde{\phi} : [-r, \infty) \to \mathbb{R}^n$ is defined by

$$\tilde{\phi}(t) := \begin{cases} \phi(0) & t > 0 \\ \phi(t) & t \in [-r, 0]. \end{cases}$$

We define the operator

$$S(\Phi)(\phi) := \lim_{t\to 0} \frac{1}{t}\Big[\Gamma_t(\Phi)(\phi) - \Phi(\phi)\Big]$$

whose domain $\mathcal{D}(S)$ is the set of functions for which the limit exists.

It is possible to state the following Theorem due to Mohammed [91]:

Theorem A.3.2. *Suppose that $\Phi \in \mathscr{C}([0,T] \times \mathscr{C})$ satisfies the smoothness condition $\Phi \in \mathscr{C}^{1,2}_{Lip}([0,T] \times \mathscr{C})$ with $\Phi \in \mathcal{D}(S)$. Let $\{X_s, s \in [t,T]\}$ be the C-valued Markov solution defined above subject to the initial condition $(t, \phi_t) \in [0,T] \times C$. Then*

$$\begin{aligned}\widetilde{\mathcal{A}}_w\Phi(t,\phi) =& \lim_{\epsilon\to 0} \frac{\mathbb{E}[\Phi(t+\epsilon, X_{t+\epsilon})] - \Phi(t,\phi_t)}{\epsilon} \\ =& \frac{\partial}{\partial t}\Phi(t,\phi_t) + S(\Phi)(t,\phi_t) + \overline{D\Phi(t,\phi_t}(H(t,\phi_t)\mathbf{1}_{\{0\}}) \\ &+ \frac{1}{2}\sum_{j=1}^{m} \overline{D^2\Phi(t,\phi_t}(G(t,\phi_t)(\mathbf{e}_j)\mathbf{1}_{\{0\}}, G(t,\phi_t)(\mathbf{e}_j)\mathbf{1}_{\{0\}}),\end{aligned}$$

where $\mathbf{e}_j$, $j = 1 \ldots n$ is the $j-$th vector of the standard basis in $\mathbb{R}^m$.

The following proposition links the concept of infinitesimal generators and Markov processes to the one of Martingales.

Proposition A.3.3 ([47] Chapter 4 - Proposition 1.7)**.** *Let X be an E-valued Markov process with transition function $P(t,x,\Gamma)$ and let $\{T(t)\}_{t\in\mathbb{R}}$ and $\hat{A}$ the corresponding semigroup and full generator, i.e. $\hat{A} := \{(f,g) \in L \times L : T(t)f - f = \int_0^t T(s)gds,\, t \geq 0\}$. If $(f,g) \in \hat{A}$ then*

$$M(t) \equiv f(X(t)) - \int_0^t g(X(s))ds$$

is a $\mathcal{F}_t^X$-martingale.

A.3.2 Martingale problem

Without loss of generality for formulating the martingale problem, we can consider the autonomous SFDE:

$$dx(s) = f(x_s)ds + g(x_s)dW(s), \quad s \in [0,T] \tag{A.3.1}$$

with the initial condition $\eta \in L^2(\Omega, \mathscr{C}; \mathcal{F}(0))$, at time $t = 0$. Let us assume that **Assumption 1** holds.
Let us consider an operator $\mathbf{\Gamma} : \mathcal{D}(\mathbf{\Gamma}) \to \mathscr{C}_b([0,T], \mathscr{C})$ and let μ be a probability measure on $(\mathscr{C}, \mathcal{B}(\mathscr{C}))$. We list the conditions that might be applicable to the operator $\mathbf{\Gamma}$:

C1. There exists $\Phi \in \mathscr{C}_b([0,T], \mathscr{C})$ such that, for $\Psi \in \mathcal{D}(\mathbf{\Gamma})$ and $\phi \in \mathscr{C}$

$$|\mathbf{\Gamma}\Psi(\phi)| \leq K_\Psi \Phi(\phi)$$

where K_Ψ is a constant depending on Ψ.

C2. There exists a countable subset $\Psi_k \subset \mathcal{D}(\mathbf{\Gamma})$ such that

$$\{(\Psi, \Phi^{-1}\gamma\Psi) | \Psi \in \mathcal{D}(\mathbf{\Gamma})\} \subset \overline{\{(\Psi_k, \Phi^{-1}\gamma\Psi_k) | k \geq 1\}}$$

where the closure $\overline{\{\ldots\}}$ is in the bounded point-wise (bp) convergence topology.

C3. $\mathcal{D}(\mathbf{\Gamma})$ is an algebra that separates points in $\mathscr{C}$ and contains the constant functions.

We define a solution to the martingale problem as follows [23].

Definition A.3.4. A $\mathscr{C}$-valued process $X(\cdot) := \{X(s), s \in [0,T]\}$ defined on some complete filtered probability space $(\Omega, \mathcal{F}_t, \mathbf{P})$ is said to be a solution to the martingale problem for $(\mathbf{\Gamma}, \mu)$ if:

(i) $\mathbf{P} \circ X^{-1}(0) = \mu$

(ii) $\int_0^s \mathbf{E}[\Phi(X(s))]dt < \infty$ for all $s \in [0,T]$

(iii) for all $\Psi \in \mathcal{D}(\mathbf{\Gamma})$,

$$\mathbf{M}^\Psi(s) := \Psi(X(s)) - \Psi(X(0)) - \int_0^t \mathbf{\Gamma}(X(t))dt$$

is an $\mathcal{F}$-martingale.

Definition A.3.5. The martingale is said to be well posed in the class of $\mathscr{C}$-valued processes $\mathcal{C}$ if $X^{(i)}(\cdot)$, $i = 1, 2$, are two solutions to the martingale problem for $(\mathbf{\Gamma}, \mu)$, then $X^1(\cdot)$ and $X^2(\cdot)$ have the same probability laws.

The following results state that the uniqueness of the solution of a martingale problem for an operator $\mathbf{\Gamma}$, sufficiently regular, always implies the Markovian property.

Lemma A.3.6. *Suppose that the operator $\mathbf{\Gamma}$ satisfies the Conditions **C1** and **C2**. Furthermore, assume that the martingale problem for $(\mathbf{\Gamma}, \epsilon_\psi)$ is well posed in the class of right continuous with left limits processes for every $\psi \in \mathscr{C}$. Then the solution $X(\cdot)$ to the martingale problem is a $\mathcal{F}$-Markov process. Furthermore, if $\mathcal{A}$ is the infinitesimal generator of $X(\cdot)$, then $\mathcal{D}(\mathbf{\Gamma}) \subset \mathcal{D}(\mathcal{A})$ and $\mathbf{\Gamma}$ and $\mathcal{A}$ coincide on $\mathcal{D}(\mathbf{\Gamma})$.*

Below we establish the $\mathscr{C}$-valued segment process $\{x_s, s \in [0, T]\}$ as the unique solution to the martingale problem.

Theorem A.3.7. *Suppose $\psi \in L^2(\Omega, \mathscr{C})$ and the operator $\mathcal{A}_q$ defined in Theorem A.3.2. Then the martingale problem for $(\mathcal{A}_q, \psi)$ is well posed when restricted to the class of quasi-tame functions.*

A.3.3 Malliavin Calculus

Malliavin calculus was conceived in the years 1970's and in the years 1980's and 1990's a huge amount of work has been done in this field. It is interpreted as functional analysis on the Wiener space and several monographs on this subject are available nowadays (see e.g Nualart [95], Øksendal and Di Nunno [40]). The main application of Malliavin calculus was to give sufficient conditions in order that the law of a random variable has a smooth density with respect to Lebegue's measure and to give bounds for this density and its derivatives. In his initial papers Malliavin used the absolute continuity criterion in order to prove that under Hörmander's condition the law of a diffusion process has a smooth density and in this way he gave a probabilistic proof of Hörmander's theorem. Afterwards people used this calculus in various situations related with stochastic PDE's. These last years Malliavin calculus found new applications in probabilistic numerical methods, essentially in the field of mathematical finance. These applications are quite different from the previous ones, because the integration by parts formula in Malliavin calculus is employed in order to produce some explicit weights which come on in nonlinear algorithms. [5]

We denote by D the Malliavin differentiation operator. Let F be a random variable which belongs to the domain of D and $T = [0, T]$. Its derivative DF is a stochastic process $\{D_t F : t \in T\}$. The derivative DF may be considered as a random variable taking values in the Hilbert space $H = L^2(T, \mathbb{R}^n)$. More generally the N-th derivative of F, $D^N F := D^{j_1}_{s_1} \cdots D^{j_N}_{s_N}$ is an $H^{\hat{\otimes}_2 N}$ random variable. For any positive integer N and real number $p > 1$ we denote by $\mathbb{D}^{N,p}$ the Banach space of all random variables having all the i-th derivatives belonging to $L^p(\Omega, H^{\hat{\otimes}_2 N})$ with the norm defined by

$$\|F\|_{N,p} = \|F\| + \left\| \left\| D^N F \right\|_{(2)} \right\|_p ,$$

where $\|\cdot\|_{(2)}$ is the Hilbert-Schmidt norm in $H^{\hat{\otimes}_2 N}$

$$\left\|D^N F\right\|_{(2)}^2 = \sum_{j_1,\cdot j_N=1}^{n} \int_{T^N} \mathbb{E}[(D^N F)_{s_1,\ldots,s_N}^{j_1,\ldots,j_N}]^2 ds_1 \ldots ds_N.$$

We denote by δ the divergence operator, and by $\delta(u)$ the Skorohod stochastic integral of the process u; δ is the adjoint operator of D. We denote by $\mathbb{L}^{1,2}$ the class of all processes $u \in L^2(T \times \Omega)$ such that $u(t) \in \mathbb{D}^{1,2}$ for almost all t and there exists a measurable version of the two parameter process $D_s u(t)$ satisfying $E \int_T \int_T (D_s u(t))^2 ds dt < \infty$. $\mathbb{L}^{1,2}$ is a Hilbert space with the norm

$$\|u\|_{1,2}^2 = \|u\|_{L^2(T\times\Omega)}^2 + \|Du\|_{L^2(T^2\times\Omega)}^2 .$$

Note that $\mathbb{L}^{1,2}$ is isomorphic to $L^2(\Omega, \mathbb{D}^{1,2})$. For every $p > 1$ and any positive integer k we denote by $\mathbb{L}^{k,p}$ the space $L^2(\Omega, \mathbb{D}^{k,p})$.

A.3.4 Anticipating Calculus and Itô Formula for SFDE

The Itô formula derived by Mohammed and Yan for solutions of SFDE is proved via anticipating calculus methods. To understand the need for anticipating calculus in such an intrinsically adapted setting, it is instructive to look at the following simple one-dimensional SFDE, where g is a regular function:

$$dX(t) = g(X(t-1), X(t))dW(t), t \leq 0$$

$$X(t) = W(t), t \in [-1, 0].$$

Formally, for $t \in (0, 1]$

$$\begin{aligned} dg(X(t-1), X(t)) =& dg(W(t-1), X(t)) \\ =& \frac{\partial g}{\partial x}(W(t-1), X(t))dW(t-1) \\ &+ \frac{\partial g}{\partial y}(W(t-1), X(t))g(X(t-1), X(t))dW(t) \\ &+ \text{ second order terms} \end{aligned}$$

Note that, although the coefficient $g(X(t-1), X(t))$ is $\mathcal{F}_t$ -measurable, the first term

$$\frac{\partial g}{\partial x}(W(t-1), X(t))dW(t-1),$$

on the right-hand side of the last equality is an anticipating differential.
Now let us define the *segment operator* $\mathcal{O} : H \oplus V \to H\hat{\otimes}_2 V$

$$\mathcal{O}\phi(t, s) := \phi(t + s), \quad t \in [-r, 0], s \in [0, T] \quad \phi \in H \oplus V.$$

Let $\mathcal{O}_t\phi = \phi_t$ and $\mathcal{O}^* : H\hat{\otimes}_2 V \to H \oplus V$ be its adjoint. Denote by P_H (resp P_V) the projection from $H \oplus V$ on H (resp. V), and define $\mathcal{O}_H^* = P_H \circ \mathcal{O}^*$.

Definition A.3.8. Suppose $W = (W(t))_{t\in[0,T]}$ is a m-dimensional standard Brownian motion. Denote by δ the divergence operator and $Dom(\delta)$ its domain, for a two parameter process $X \in (\mathcal{O}_H^*)^{-1}(Dom(\delta))$; the Skorohod segment integral of X with respect to the Brownian segment $(W_t)_{t\in[0,T]}$ is defined as

$$\int_0^T \langle X_t, W_t\rangle = \delta(\mathcal{O}_H^* X).$$

Consider the SFDE:

$$X(t) = \tilde{\eta}_0(t) + \int_0^{t\vee 0} v(s)ds + \int_0^{t\vee 0} u(s)dW(s), \quad t \geq -r$$

with coefficients $u : T \times \Omega \to L(\mathbb{R}^n, \mathbb{R}^m)$ and $v : T \times \Omega \to \mathbb{R}^m$ that may not be adapted to the Brownian filtration $(\mathcal{F}_t)_{t\geq 0}$.

Theorem A.3.9 (Itô formula for SFDE [130] Theorem 8.6)**.** *Let $f = f(t, \eta, x) \in \mathscr{C}_b^1(T \times V \times \mathbb{R}^m)$ with second bounded derivative, $u \in \mathbb{L}^{1,2}$ and $v \in \mathbb{L}^{1,2}$ then the following Itô formula holds:*

$$\begin{aligned} f(t, X_t, X(t)) - f(0, X_0, X(0)) &= \int_0^t \frac{\partial f}{\partial s}(s, X_s, X(s))ds + \int_0^t \langle \frac{\partial f}{\partial \eta}(s, X_s, X(s), dX_s\rangle_V \\ &+ \int_0^t \frac{\partial f}{\partial x}(s, X_s, S(s))dX(s) + \int_0^t \frac{\partial^2 f}{\partial \eta^2}(s, X_s, X(s))(\Theta_s)ds \\ &+ \int_0^t \frac{\partial^2 f}{\partial \eta \partial x}(s, X_s, X(s))[(u\Lambda)_s X(s)]ds \\ &+ \int_0^t \frac{\partial^2}{\partial x \partial \eta}(s, X_s, X(s))[u(s)D_s X_s]ds \\ &+ \frac{1}{2}\sum_{i=1}^d \int_0^t \frac{\partial^2 f}{\partial x^2}(s, X_s, X(s))[(\nabla_+^i X)(s) \otimes \dot{u^i}(s)]ds, \end{aligned} \tag{A.3.2}$$

where

$$\begin{aligned} \Theta_s(\alpha, \beta) &= \frac{1}{2}((u\Lambda)_s X_s(\alpha, \beta) + (u\Lambda)_s X_s(\beta, \alpha)), \\ (u\Lambda)_s X_s(\alpha, \beta) &= \mathbf{I}_{\{0\leq s+\alpha\wedge\beta\}} u(s+\alpha) D_{s+\alpha} X(s+\beta), \\ (\nabla_+^i X)(s) &= \lim_{\epsilon\to 0}(D_t^i X(t+\epsilon) + D_t^i X(t-\epsilon)), \\ (u\Lambda)_s X(s)(\alpha) &:= u(s+\alpha) D_{s+\alpha} X(s) \mathbf{I}_{\{s+\alpha\geq 0\}}. \end{aligned}$$

A.4 Piecewise Deterministic Markov Processes

A.4.1 General introduction

The piecewise deterministic Markov processes (denoted PDMPs) were first introduced in the literature by Davis [36]. Already at this time, the theory of diffusions had such powerful tools

as the theory of Itô calculus and stochastic differential equations at its disposal. Davis's goal was to endow the PDMP with rather general tools. The main reason for that was to provide a general framework, since up to then only very particular cases had been dealt with, which turned out not to be easily generalizable.

PDMPs form a family of càdlàg Markov processes involving a deterministic motion punctuated by random jumps. The motion of the PDMP $\{X(t)\}_{t\geq 0}$ depends on three local characteristics, namely the jump rate λ, the flow ϕ and the transition measure Q according to which the location of the process at the jump time is chosen. The process starts from x and follows the flow $\phi(x,t)$ until the first jump time T_1 which occurs either spontaneously in a Poisson-like fashion with rate $\lambda(\phi(x,t))$ or when the flow $\phi(x,t)$ hits the boundary of the state-space. In both cases, the location of the process at the jump time T_1, denoted by $Z_1 = X(T_1)$, is selected by the transition measure $Q(\phi(x,T_1),\cdot)$ and the motion restarts from this new point as before. This fully describes a piecewise continuous trajectory for $\{X(t)\}$ with jump times $\{T_k\}$ and post jump locations $\{Z_k\}$, and which evolves according to the flow ϕ between two jumps.

A.4.2 Definition and some properties of PDMPs

Let M be an open subset of $\mathbb{R}^n$, ∂M its boundary, $\overline{M}$ its closure and $\mathcal{B}(M)$ the set of real-valued, bounded, measurable functions defined on M. A PDMP is determined by its local characteristics (ϕ, λ, Q) where:

- The flow $\phi : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ is a one-parameter group of homeomorphisms: ϕ is continuous, $\phi(\cdot,t)$ is an homeomorphism for each $t \in \mathbb{R}$, satisfying the semigroup property: $\phi(\cdot, t+s) = \phi(\phi(\cdot,s),t)$.

  For each x in M, we introduce the hitting time of the boundary that forces a transition in the discrete component

  $$t^\star(x) := \inf\{t > 0 : \phi(x,t) \in \partial M\}, \tag{A.4.1}$$

  with the convention $\inf \emptyset = \infty$.

- The jump rate $\lambda : \overline{M} \to \mathbb{R}_+$ is assumed to be a measurable function satisfying: for all $x \in M$, there exists $\epsilon > 0$ such that

  $$\int_0^\epsilon \lambda(\phi(x,s))ds < \infty.$$

- Q is a Markov kernel on $(\overline{M}, \mathcal{B}(\overline{M}))$ satisfying the following property: for all $x \in \overline{M}$,

  $$Q(x, M - \{x\}) = 1.$$

From these characteristics, it can be shown [36] that there exists a filtered probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}, \{\mathbb{P}_x\})$ such that the motion of the process $\{X(t)\}$ starting from a point $x \in M$ may be constructed as follows. Consider a random variable T_1 such that

$$\mathbb{P}_x\{T_1 > t\} = \begin{cases} e^{-\Lambda(x,t)} & \text{for } t < t^\star(x), \\ 0 & \text{for } t \geq t^\star(x), \end{cases}$$

where for $x \in M$ and $t \in [0, t^\star(x)]$

$$\Lambda(x,t) = \int_0^t \lambda(\phi(x,s))ds.$$

If T_1 is equal to infinity, then the process X follows the flow, i.e. $t \in \mathbb{R}_+$, $X(t) = \phi(x,t)$. Otherwise select independently a M-valued random variable (labelled Z_1) having distribution $Q(\phi(x,T_1),\cdot)$, namely $\mathbb{P}_x(Z_1 \in A) = Q(\phi(x,T_1),A)$ for any $A \in \mathcal{B}(M)$. The trajectory of $\{X(t)\}$ starting at x, for $t \in [0,T_1]$, is given by

$$X(t) = \begin{cases} \phi(x,t) & \text{for } t < T_1, \\ Z_1 & \text{for } t = T_1. \end{cases}$$

Starting from $X(T_1) = Z_1$, we now select the next inter-jump time $T_2 - T_1$ and post-jump location $X(T_2) = Z_2$ in a similar way.

This construction properly defines a Markov process $\{X(t)\}$ which satisfies the strong Markov property with jump times $\{T_k\}_{k\in\mathbb{N}}$ (where $T_0 = 0$). A very natural Markov chain is linked to $\{X(t)\}$, namely the chain $(\Theta_n)_{n\in\mathbb{N}}$ defined by $\Theta_n = (Z_n, S_n)$ with $Z_n = X(T_n)$ and $S_n = T_n - T_{n-1}$ for $n \geq 1$ and $S_0 = 0$. Clearly, the process $(\Theta_n)_{n\in\mathbb{N}}$ is a Markov chain.

Appendix B

NOTE ON THE PAPER CELANI & VERGASSOLA 2010

In this chapter of the Appendix we explicitly perform the calculations in the fundamental paper [22]. We report first the abstract of the paper: *regular environmental conditions allow for the evolution of specifically adapted responses, whereas complex environments usually lead to conflicting requirements upon the organism's response. A relevant instance of these issues is bacterial chemotaxis, where the evolutionary and functional reasons for the experimentally observed response to chemoattractants remain a riddle. Sensing and motility requirements are in fact optimized by different responses, which strongly depend on the chemoattractant environmental profiles. It is not clear then how those conflicting requirements quantitatively combine and compromise in shaping the chemotaxis response.* In [22] the authors *show that the experimental bacterial response corresponds to the maximin strategy that ensures the highest minimum uptake of chemoattractants for any profile of concentration.* the authors *show that the maximin response is the unique one that always outcompetes motile but nonchemotactic bacteria. [They] results are generally relevant to biological optimization principles and provide a systematic possibility to get around the need to know precisely the statistics of environmental fluctuations.*

In [22] the authors considered a quite complete model which can be considered a generalization of the *velocity-jump model* [45]: bacteria are supposed to run at (fixed) velocity u in the direction θ, and the transition rate from the running to the tumbling phase at time t depends on the detection history experienced by the bacterium via the quantity $Q(t) = \int_{-\infty}^{t} K(t-s)c(X(s),s)ds$. Here the convolution kernel is the one presented in the first chapter;

- $X(t)$ is the trajectory followed by the bacterium;
- $c(x,t)$ is the chemoattractant concentration field;
- τ_r is the running time in the absence of chemoattractants.

They use homogenization methods to analyze the hydrodynamic limit of the distribution of the population. They rescale $x \mapsto \epsilon x$ and $t \mapsto \epsilon^2 t$, and obtain the final form of the effective

diffusion equation:

$$\frac{\partial}{\partial t}n(x,t) + \nabla \cdot \Big(\chi \cdot n(x,t)\nabla c(x,t)\Big) = D_0 \Delta\Big[\Big(1+\gamma c(x,t)\Big)n(x,t)\Big]$$

where

$$\gamma := \frac{\alpha}{\sigma}\int_0^\infty K(t)dt \text{ and } \chi := D_0\frac{\alpha}{\sigma}\int_0^\infty e^{-\sigma t}K(t)dt$$

In what follows we explicitly perform the calculations, since they might be useful in a further generalization of their model.

B.1 Projection of the Equation

The continuity equation and the one for the (average) flux $\langle \overline{J}\rangle := u\langle\theta\overline{J}\rangle$ are given by the equations [S4] and [S5]

$$\frac{\partial}{\partial t}\langle\overline{P}\rangle + \nabla\cdot\langle\overline{J}\rangle = 0, \tag{S4}$$

$$\frac{\partial}{\partial t}\langle\overline{J}\rangle + \frac{u^2}{d}\nabla\langle\overline{P}\rangle = -D(d-1)\langle\overline{J}\rangle - \frac{1-\omega d^{-1}}{\tau_r}\overline{g(Q)\langle J\rangle}, \tag{S5}$$

while the lowest-order moments satisfy the equation [S6] and [S7]

$$\frac{\partial}{\partial t}\langle\overline{J}\rangle + \frac{u^2}{d}\nabla\langle\overline{P}\rangle = -D(d-1)\langle\overline{J}\rangle - \frac{1-\omega d^{-1}}{\tau_r}\overline{g(Q)\langle J\rangle}; \tag{S7}$$

$$\frac{\partial}{\partial t}\overline{m_k\langle P\rangle} + \nabla\cdot\overline{m_k\langle J\rangle} - \delta_0^k c\langle P\rangle + k\overline{m_{k-1}P} - \lambda\overline{m_k\langle P\rangle} = 0. \tag{S6}$$

B.1.1 Derivation of the Equation for the Average Flux

Let us consider [S3]:

$$\begin{aligned}\frac{\partial}{\partial t}P(t,x,\theta,m) =& -u\nabla_x\Big(\theta\cdot P(t,x,\theta,m)\Big) - \nabla_m\Big((km_{j-1}(t)-\lambda m_j(t))_{j\in\mathbb{N}}\cdot P(t,x,\theta,m)\Big)\\ &+ D\Delta_\theta P(t,x,\theta,m) + \frac{1}{\tau_r}[1-Q(t)]\int_S\Big[P(t,x,\eta,m)-P(t,x,\theta,m)\Big]\mu_\theta(d\eta).\end{aligned}$$

Multiplying this equation by $u\theta$ and integrating with respect to m and θ we obtain that

- The first term, using the fact that θ doesn't depend on t

$$\int_{\mathbb{R}}\int_S[u\theta\frac{\partial}{\partial t}P(t,x,\theta,m)]dmd\theta = \frac{\partial}{\partial t}\int_{\mathbb{R}}\int_S[u\theta P(t,x,\theta,m)]dmd\theta = \frac{\partial}{\partial t}\langle\overline{J}\rangle.$$

- Using the identity $\Delta_\theta\theta = (1-d)\theta$, and in the last equality integrating by parts, the following holds:

$$D(1-d)\langle\overline{J}\rangle = \langle D(1-d)\overline{J}\rangle = \langle D(1-d)\theta\overline{P}\rangle = \langle D\Delta_\theta\theta\overline{P}\rangle = \langle D\theta\overline{\Delta_\theta P}\rangle.$$

- as in the derivation of the continuity equation, the mean of the term that accounts for the change in the variable m is zero, so that

$$\overline{\langle u\theta\nabla_m\Big((km_{j-1}(t)-\lambda m_j(t))_{j\in\mathbb{N}}\cdot P(t,x,\theta,m)\Big)\rangle}=0;$$

- the proof of the second term on the left hand side comes from the following considerations[1]: from $\int_S\theta_i\theta_j d\theta=\frac{1}{d}\Omega_d\delta^i_j$, one deduces that $(\pi_i)_{i=1\dots d}$, where $\pi_i(\theta)=\sqrt{\frac{d}{\Omega_d}}\theta_i$, is an orthonormal set[2] for the space $(S,\langle\cdot,\cdot\rangle)$ with $\langle f(\theta),g(\theta)\rangle:=\int_S f(\theta)g(\theta)d\theta$; in particular one obtains that

$$\theta\nabla\cdot(\theta P)=\Big(\sum_{j=1}^d\theta_i\theta_j\frac{\partial}{\partial x_j}P\Big)_{i=1\dots d},$$

and so from $f(\theta):=\sum_{j=1}^d\theta_j\frac{\partial}{\partial x_j}P(t,x,\theta,m)$ and $g(\theta)=\theta_i$ it follows that

$$\int_S f(\theta)g(\theta)d\theta=\frac{1}{d}\int_S\frac{\partial}{\partial x_i}P(t,x,\theta,m)d\theta;$$

and so

$$\int_S\int_{\mathbb{R}}\Big[u\theta u\nabla_x\Big(\theta\cdot P(t,x,\theta,m)\Big)\Big]d\theta dm=\frac{u^2}{d}\nabla\langle\overline{P}\rangle;$$

- the last term on the right hand side comes from a similar consideration[3] as above: Using the expression $\mu_\theta(\eta)=\frac{1}{\Omega_d}(1+\omega\theta\cdot\eta)d\eta$, multiplying by $u\theta$ and integrating with respect to θ one obtains for

$$\int_S u\theta\frac{g(Q)}{\tau_r}\int_S\Big[P(t,x,\eta,m)-P(t,x,\theta,m)\Big]\mu_\theta(d\eta)d\theta:=K(t,x,m),$$

$$K(t,x,m)=\frac{g(Q)}{\tau_r}\Big\{\frac{u\omega}{\Omega_d}\int_{S\times S}\theta(\theta\cdot\eta)P(t,x,\eta,m)d\eta d\theta+\frac{u\omega}{\Omega_d}\underbrace{\int_S\theta d\theta}_{=0}\int_S P(t,x,\eta,m)d\eta-\langle J\rangle\Big\},$$

for the first integral one has

$$\begin{aligned}\int_{S\times S}\theta(\theta\cdot\eta)P(t,x,\eta,m)d\eta d\theta&=\Big(\int_{S\times S}\theta_i\sum_{j=1}^d\theta_j\eta_jP(t,x,\eta,m)d\theta d\eta\Big)_{i=1\dots d}\\&=\Big(\sum_{j=1}^d\int_S\eta_jP(t,x,\eta,m)\Big[\int_S\theta_i\theta_jd\theta\Big]d\eta\Big)_{i=1\dots d}\\&=\Big(\frac{\Omega_d}{d}\delta^j_i\int_S\eta_jP(t,x,\eta,m)d\eta\Big)_{i=1\dots d}=\langle J\rangle.\end{aligned}$$

[1] This seems to be somehow similar to *Spherical Harmonics*

[2] to obtain a base it is necessary to consider all the spherical harmonics

[3] $\int_S\theta_i\theta_jd\theta=\frac{1}{d}\Omega_d\delta^i_j$

B.1.2 Equation for the lowest-order moments

To obtain [S7], similarly as in the derivation of the flux one has to multiply equation [S3] by m_k and perform the integration with respect to dm and $d\theta$.

If we simply interchange integral and temporal derivative we have the first term, i.e. $\frac{\partial}{\partial t}\langle\overline{J}\rangle$. In a similar fashion the second term is obtained. Here the interchange is done between the spatial derivative and the integral. In the last term one uses integration by parts:

$$\overline{\langle m_k, \mathcal{M}P\rangle} = \overline{\langle \mathcal{M}^* m_k, P\rangle},$$

where one use the adjoint of $\mathcal{M}$, i.e.

$$\mathcal{M}^* u(t,x,\theta,m) = -\sum_{k=0}^{k_M}(\delta_0^k c + k m_{k-1} - \lambda m_k)\frac{\partial}{\partial m_k}u(t,x,\theta,m).$$

If we substitute $u(t,x,\theta,m) = m_k$, we obtain the equation [S7].

Exactly as in the derivation of [S5] one obtains [S6] by multiplying equation [S3] by $u\theta m_k$ and performing integration with respect to m and θ. By using the integration by parts formula for $\mathcal{M}$ stated above we have the result.

B.1.3 Hydrodynamic Limit

The effective diffusion equation obtained via a *homogenization method* reads as

$$\frac{\partial}{\partial t}n(x,t) + \nabla\cdot\Big(\chi\cdot n(x,t)\nabla c(x,t)\Big) = D_0\Delta\Big[\Big(1+\gamma c(x,t)\Big)n(x,t)\Big], \tag{S14}$$

where the parameters are given by

$$\alpha := \frac{1}{\tau_r}\Big(1-\frac{\omega}{d}\Big), \quad \sigma := D(d-1)+\alpha, \quad D_0 = \frac{u^2}{d\sigma}, \quad \gamma := \frac{\alpha}{\sigma}(2\beta_2+\beta_1),$$

$$\chi = D_0\frac{\alpha}{\sigma}\Big[2\beta_2\frac{\lambda^3}{(\lambda+\sigma)^3} + \beta_1\frac{\lambda^2}{(\lambda+\sigma)^2}\Big].$$

B.1.4 Homogenization Limit

Starting from the equation

$$\partial_t a + \mathbf{M}a = 0, \quad a^T = \Big(\langle\overline{P}\rangle, \langle\overline{J}\rangle; \overline{m_k\langle P\rangle}, \overline{m_k\langle J\rangle} : j = 0\dots k_M\Big),$$

with $k_M = 2$, from the equation for the lowest-moment one obtains that

$$\mathbf{M} = \begin{pmatrix}
0 & \nabla\cdot & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{u^2}{d}\nabla\cdot & \sigma & 0 & 0 & 0 & -\beta_1\lambda^2\alpha & 0 & \beta_2\lambda^3\alpha \\
-c & 0 & \lambda & \nabla\cdot & 0 & 0 & 0 & 0 \\
0 & -c & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma & 0 & 0 & 0 & 0 \\
0 & 0 & -1 & 0 & \lambda & \nabla\cdot & 0 & 0 \\
0 & 0 & 0 & -1 & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma & 0 & 0 \\
0 & 0 & 0 & 0 & -2 & 0 & \lambda & \nabla\cdot \\
0 & 0 & 0 & 0 & 0 & -2 & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma
\end{pmatrix}.$$

Now the rescaling is done with $\nabla \mapsto \epsilon\nabla$ and $\partial_t \mapsto \epsilon^2\partial_t$: developing a and $\mathbf{M}$ in powers of ϵ one has the following equation:

$$\partial_t \sum_{m\geq 0} a^{(m)}\epsilon^{2+m} + \sum_{m\geq 0}\sum_{n\geq 0} M^{(m)}a^{(n)}\epsilon^{m+n} = 0,$$

where the superscript (m) denotes the coefficient of ϵ^m. Now, since there are no terms in $\mathbf{M}$ of the form ∇^m, with $m \geq 1$, it follows that $M^{(j)} = 0$ for $j \geq 2$ and so

$$M^{(0)} = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma & 0 & 0 & 0 & -\beta_1\lambda^2\alpha & 0 & -\beta_2\lambda^3\alpha \\ -c & 0 & \lambda & 0 & 0 & 0 & 0 & 0 \\ 0 & -c & 0 & \lambda+\sigma & 0 & 0 & 0 & 0 \\ 0 & 0 & -1 & 0 & \lambda & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & \lambda+\sigma & 0 & 0 \\ 0 & 0 & 0 & 0 & -2 & 0 & \lambda & 0 \\ 0 & 0 & 0 & 0 & 0 & -2 & 0 & \lambda+\sigma \end{pmatrix},$$

$$M^{(1)} = \begin{pmatrix} 0 & \nabla\cdot & 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{u^2}{d}\nabla\cdot & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \nabla\cdot & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{u^2}{d}\nabla\cdot & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \nabla\cdot & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{u^2}{d}\nabla\cdot & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \nabla\cdot \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{u^2}{d}\nabla\cdot & 0 \end{pmatrix}.$$

Comparing terms of equal order in ϵ, one obtains

$$\begin{aligned} \epsilon^0 &: \quad M^{(0)}a^{(0)} = 0 \\ \epsilon^1 &: \quad M^{(0)}a^{(1)} + M^{(1)}a^{(0)} = 0 \Rightarrow M^{(0)}a^{(1)} = -M^{(1)}a^{(0)} \\ \epsilon^2 &: \quad \partial_t a^{(0)} + M^{(0)}a^{(2)} + M^{(1)}a^{(1)} + \underbrace{M^{(2)}}_{\equiv 0}a^{(0)} = 0 \Rightarrow M^{(0)}a^{(2)} = -M^{(1)}a^{(1)} - \partial_t a^{(0)} \\ &\cdots \\ \epsilon^m &: \quad \partial_t a^{(m-2)} + \sum_{i=0,1}\sum_{n:n+i=m} M^{(i)}a^{(n)} = 0. \end{aligned}$$

To solve this sequence of equations, one uses the Fredholm alternative condition. Let us search for the Kern$((M^{(0)})^T)$. From the form of $(M^{(0)})^T$, its first column is entirely composed of zeros. The immediate consequence is that its kernel contains any vector ν with its first component nonzero and all the others vanishing. Solving the system $(M^{(0)})^T\nu = 0$ one is lead to the following set of conditions for the components of ν:

$$\nu_{2k+1} = 0;$$

$$\begin{pmatrix} \sigma & 0 & 0 & -c \\ 0 & 1 & 0 & \lambda+\sigma \\ 0 & 0 & 2 & \frac{-\beta_1 c\lambda^2\alpha}{\sigma}+(\lambda+\sigma)^2 \\ 0 & 0 & 0 & \Big(-2\beta_2 c-\beta_1 c\Big)-\beta_1 c\frac{\sigma}{\lambda}+\frac{\sigma}{\lambda^3\alpha}(\lambda+\sigma)^3 \end{pmatrix} \begin{pmatrix} \nu_2 \\ \nu_6 \\ \nu_8 \\ \nu_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}.$$

Now since $|k!\beta_k c| \ll 1$ it follows that $\nu_4 = 0$ and then all $\nu_k = 0$. So $\langle (n, \underline{0}) \rangle = Kern((M^{(0)})^T)$. By using the above structures of $a^{(0)}$[4] and $M^{(0)}$ in the second equation in ϵ^1 , a straightforward calculation gives the expression:

$$\overline{\langle J^{(1)} \rangle} = -D_0 \nabla n - D_0 \gamma \nabla(cn) + \chi n \nabla c.$$

Solving the system for $\epsilon^0 : M^{(0)} a^{(1)} = -M^{(1)} a^{(0)}$,
one obtains that

$$\begin{aligned} \Big(1 - \frac{\beta_1\lambda^2\alpha c}{\sigma(\lambda+\sigma)^2} - \frac{2c\beta_2\lambda^3\alpha}{(\lambda+\sigma)^3\sigma}\Big) a_2 = &-\frac{\beta_1\lambda\alpha}{(\lambda+\sigma)^2}\frac{u^2}{d\sigma}\nabla(cn) - \frac{\beta_1\alpha}{(\lambda+\sigma)}\frac{u^2}{d\sigma}\nabla(cn) \\ &- \frac{2\beta_2\lambda^2\alpha}{(\lambda+\sigma)^3}\frac{u^2}{d\sigma}\nabla(cn) - \frac{2\beta_2\lambda\alpha}{(\lambda+\sigma)^2}\frac{u^2}{d\sigma}\nabla(cn) \\ &- \frac{2\beta_2\alpha}{(\lambda+\sigma)}\frac{u^2}{d\sigma}\nabla(cn) - \frac{u^2}{d\sigma}\nabla n, \end{aligned}$$

since $|\beta_k k! c| \ll 1$, one can develop the term $(1 - \frac{\beta_1\lambda^2\alpha c}{\sigma(\lambda+\sigma)^2} - \frac{2c\beta_2\lambda^3\alpha}{(\lambda+\sigma)^3\sigma})^{-1}$ in a Taylor Series and we obtain:

$$\Big(1 - \frac{\beta_1\lambda^2\alpha c}{\sigma(\lambda+\sigma)^2} - \frac{2c\beta_2\lambda^3\alpha}{(\lambda+\sigma)^3\sigma}\Big)^{-1} = 1 + \frac{\beta_1\lambda^2\alpha c}{\sigma(\lambda+\sigma)^2} + \frac{2c\beta_2\lambda^3\alpha}{\sigma(\lambda+\sigma)^3} + o(\beta_1 c + 2\beta_2 c).$$

By solving for a_2 one obtains that on the right hand side one can ignore all the terms of the form $(\chi \cdot c) \cdot \phi c \nabla n$ since they are of order $\mathcal{O}\Big((\beta_1 c + 2\beta_2 c)^2\Big)$

$$\begin{aligned} a_2 = &-\frac{\beta_1\lambda\alpha}{(\lambda+\sigma)^2}\frac{u^2}{d\sigma}\nabla(cn) - \frac{\beta_1\alpha}{(\lambda+\sigma)}\frac{u^2}{d\sigma}\nabla(cn) - \frac{2\beta_2\lambda^2\alpha}{(\lambda+\sigma)^3}\frac{u^2}{d\sigma}\nabla(cn) - \frac{2\beta_2\lambda\alpha}{(\lambda+\sigma)^2}\frac{u^2}{d\sigma}\nabla(cn) \\ &- \frac{u^2}{d\sigma}\nabla n - \frac{u^2}{d\sigma}\frac{\alpha}{\sigma}\Big(\frac{\beta_1\lambda^2}{(\lambda+\sigma)^2} + \frac{2\beta_2\lambda^3}{(\lambda+\sigma)^3}\Big) c\nabla n + o(\beta_1 c + 2\beta_2 c). \end{aligned}$$

Now we make use of the following identity:

$$\begin{aligned} -\beta_1\Big(\frac{\lambda}{(\lambda+\sigma)^2} + \frac{1}{(\lambda+\sigma)}\Big) - \beta_2\Big(\frac{\lambda^2}{(\lambda+\sigma)^3} + \frac{\lambda}{(\lambda+\sigma)^2} + \frac{1}{(\lambda+\sigma)}\Big) \\ -\frac{1}{\sigma}\Big(\frac{\beta_1\,\lambda^2}{(\lambda+\sigma)^2} + \frac{2\,\beta_2\,\lambda^3}{(\lambda+\sigma)^3}\Big) = -\frac{\beta_1 + 2\,\beta_2}{\sigma}. \end{aligned}$$

The following relation holds:

$$a_2 := \overline{\langle J^{(1)} \rangle} = -\frac{u^2}{d\sigma}\nabla n - \frac{u^2}{d\sigma}\frac{\alpha}{\sigma}(2\beta_2+\beta_1) n\nabla c + \frac{u^2}{d\sigma}\frac{\alpha}{\sigma}\Big[2\beta_2\frac{\lambda^3}{(\lambda+\sigma)^3} + \beta_1\frac{\lambda^2}{(\lambda+\sigma)^2}\Big]\nabla(nc) + o(\beta_1 c + 2\beta_2 c),$$

[4] solution $a^{(0)}$ to the equation in ϵ^0 has only odd components with the following ratios $a^{(0)} = (n, 0, nc/\lambda, 0, nc/\lambda^2, 0, 2nc/\lambda^3)$

which coincides with

$$\overline{\langle J^{(1)}\rangle} = -D_0\nabla n - D_0\gamma\nabla(cn) + \chi n\nabla c.$$

By using the equation

$$\partial_t a_1^{(0)} + M_{12}^{(1)} a_2^{(1)} = \partial_t a_1^{(0)} + \nabla\cdot a_2^{(1)},$$

one gets the final form [S14]

$$\frac{\partial}{\partial t}n(x,t) + \nabla\cdot\Big(\chi\cdot n(x,t)\nabla c(x,t)\Big) = D_0\Delta\Big[\Big(1+\gamma c(x,t)\Big)n(x,t)\Big]. \tag{S14}$$

B.1.5 Hydrodynamic limit for general $K(t)$

Exactly as in the case with $k_M = 2$ we start from the equation

$$\partial_t a + \mathbf{M}a = 0, \quad a^T = \Big(\langle\overline{P}\rangle, \langle\overline{J}\rangle; \overline{m_k\langle P\rangle}, \overline{m_k\langle J\rangle} : j = 0\dots k_M\Big).$$

From the equation for the lowest moments we obtain that

$$\mathbf{M} = \begin{pmatrix}
0 & \nabla\cdot & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\frac{u^2}{d}\nabla\cdot & \sigma & 0 & 0 & 0 & -\beta_1\lambda^2\alpha & 0 & \beta_2\lambda^3\alpha & 0 & -\beta_3\lambda^4\alpha \\
-c & 0 & \lambda & \nabla\cdot & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -c & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & -1 & 0 & \lambda & \nabla\cdot & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -1 & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & -2 & 0 & \lambda & \nabla\cdot & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -2 & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & -3 & 0 & \lambda & \nabla\cdot \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -3 & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma
\end{pmatrix}$$

with the matrix having the following form: for $i = 2k+3, 2k+4; k > 3$

- for $j = 2k+1, \dots, 2k+4$

$$\mathbf{M}_{i,j} = \begin{pmatrix} -k & 0 & \lambda & \nabla\cdot \\ 0 & -k & \frac{u^2}{d}\nabla\cdot & \lambda+\sigma \end{pmatrix};$$

- for $j \geq 1$

$$\mathbf{M}_{2,4+2j} = -\beta_j\lambda^{j+1}\alpha;$$

- otherwise $\mathbf{M}_{i,j} = 0$.

Following exactly the same procedure as before we solve the same system for this matrix, expanding $\mathbf{M}$ and a in powers of ϵ. We have that $M^{(k)} = 0$ for $k > 1$. $M^{(1)}$ contains only the differential operator, while $M^{(0)}$ is built with the only *real* parameters of M. The Fredholm alternative leads to the equation

$$\Big(\partial_t a^{(0)} + M^{(1)}a^{(1)} = 0\Big)_1 := \partial_t a_1^{(0)} + \nabla\cdot a_2^{(1)} = 0.$$

By solving the equation for ϵ^0, we have that $a^{(0)}$ has the following form:
for $k = -1, \dots, k_M$:

$$a^{(0)}_{2k+3} = \frac{k!}{\lambda^{k+1}} nc,$$

where we used the convention $k! := 1, k \leq 1$. By solving the system for $a^{(1)}$, i.e. $M^{(0)}a^{(1)} = -M^{(1)}a^{(0)}$ with the above structure of $M^{(i)}$ and $a^{(0)}$ we have:

- the odd and even components of the vector $a^{(1)}$ are independent, i.e. to solve with respect to $a^{(1)}_2$ one has only a relation with $a^{(1)}_{2k}$. The general relation for $a^{(1)}_2$ is given by:

$$\begin{aligned} a_2 = &- \frac{u^2}{d\sigma}\nabla n + \frac{u^2}{d\sigma}\frac{\alpha}{\sigma}\Big(\sum_{j=1}^{k_M} \frac{j!\beta_j\lambda^{j+1}}{(\lambda+\sigma)^{j+1}}\Big)\nabla(nc) \\ &- \sum_{j=1}^{k_M} \frac{u^2}{d\sigma}\alpha j!\beta_j\Big(\sum_{i=1}^{j} \frac{\lambda^{i-1}}{(\lambda+\sigma)^i}\Big)\nabla c \cdot n \\ &- \frac{u^2}{d\sigma}\frac{\alpha}{\sigma}\Big(\sum_{j=1}^{k_M} \frac{j!\beta_j\lambda^{j+1}}{(\lambda+\sigma)^{j+1}}\Big) n\nabla c + o(\sum_{j=1}^{k_M} k_M!\beta_j c), \end{aligned}$$

  where we have to remember that

$$\Big[1 - \frac{\alpha}{\sigma}\Big(\sum_{j=1}^{k_M} \frac{j!\beta_j\lambda^{j+1}}{(\lambda+\sigma)^{j+1}}\Big)c\Big]a_2 = -\frac{u^2}{d\sigma}\nabla n - \sum_{j=1}^{k_M} \frac{u^2}{d\sigma}\alpha j!\beta_j\Big(\sum_{i=1}^{j} \frac{\lambda^{i-1}}{(\lambda+\sigma)^i}\Big)\nabla c \cdot n.$$

- from the relations:

$$\int_0^\infty K(t)dt = \sum_{j=1}^{k_M} \Gamma(j+1)\cdot\beta_j = \sum_{j=1}^{k_M} j!\beta_j,$$

$$\sum_{j=1}^{k_M} \frac{j!\beta_j\lambda^{j+1}}{(\lambda+\sigma)^{j+1}} = \int_0^\infty e^{-\sigma t}K(t)dt,$$

$$-\sum_{j=1}^{k_M} \alpha j!\beta_j\Big(\sum_{i=1}^{j} \frac{\lambda^{i-1}}{(\lambda+\sigma)^i}\Big) - \Big(\sum_{j=1}^{k_M} \frac{j!\beta_j\lambda^{j+1}}{(\lambda+\sigma)^{j+1}}\Big) = \frac{\alpha}{\sigma}\Big(\sum_{j=1}^{k_M} j!\beta_j\Big) = \frac{\alpha}{\sigma}\int_0^\infty K(t)dt,$$

  follows the general relation for [S14] with

$$\gamma := \frac{\alpha}{\sigma}\int_0^\infty K(t)dt \text{ and } \chi := D_0\frac{\alpha}{\sigma}\int_0^\infty e^{-\sigma t}K(t)dt.$$

To prove this one can use mathematical induction.

B.2 Effective Diffusion Equation and Bacterial Uptake

Based on the fact that the leading equation has a term which is $o(\sum_{j=1}^{k_M} k_M!\beta_j c)$ and from [S14] with $n = n_0 + \eta$, with $(\partial_t n_0 - D_0\Delta n_0 = 0)$ and $\eta = \mathcal{O}(\beta c)n_0$, substituting directly

$$\begin{aligned}\underbrace{\frac{\partial}{\partial t}n_0(x,t) - D_0\Delta n_0(x,t)}_{\equiv 0} = &-\Big(\frac{\partial}{\partial t} - D_0\Delta\Big)\eta(x,t) + \\ &- \underbrace{\nabla\cdot\Big(\chi\cdot\eta(x,t)\nabla c(x,t)\Big)}_{o(\beta c)} - \nabla\cdot\Big(\chi\cdot n(x,t)\nabla c(x,t)\Big) \\ &+ \underbrace{D_0\Delta\Big(\gamma c(x,t)n_0(x,t)\Big)}_{o(\beta c)} + D_0\Delta\Big(\gamma c(x,t)\eta_0(x,t)\Big) + o(\beta c).\end{aligned}$$

B.2.1 Bacterial Uptake of Chemoattractants

The trick to solve the integral in $S'(t)$ is the following: one can rewrite it in the following form:

$$S'(t) = \int_0^t ds\int_0^s du\int_{\mathbb{R}^d}\Big(c(x,u)\cdot[G*\nabla(G\nabla c)](x,u)\Big)dx.$$

using the property of the convolution that $[G*\nabla(G\nabla c)](x,u) = \nabla[G*(G\nabla c)]$ and integrating by parts (once for S and twice for S') one has:

$$\begin{aligned}a[c](t) &= \int_{\mathbb{R}^d}dx\int_0^t ds\int_0^s \nabla c(x,s)\cdot[G*(G\cdot\nabla c)](x,u) \\ &= \int_{\mathbb{R}^{2d}}dxdy\int_0^t ds\int_0^s \nabla c(x,s)\cdot\nabla c(y,u)G(y,u)G(x-y,s-u),\end{aligned} \tag{S19.a}$$

$$\begin{aligned}b[c](t) &= \int_{\mathbb{R}^d}dx\int_0^t ds\int_0^s \Delta c(x,s)\cdot[G*(G\cdot c)](x,u) \\ &= \int_{\mathbb{R}^{2d}}dxdy\int_0^t ds\int_0^s \Delta c(x,s)\cdot c(y,u)G(y,u)G(x-y,s-u).\end{aligned} \tag{S19.b}$$

B.2.2 General Maxmin Analysis

From equation [S17] with the new variables

$$z = \frac{|x|^2}{4D_0t},\quad \eta(z,t) = G(z(x,t),t)\cdot\phi(z(x,t),t),\quad G(z,t) = \frac{e^{-z}}{(4\pi D_0t)^{d/2}},$$

follows equation [S28] with the following rules and functional relations:

$$\nabla_x f(z,t) = \partial_z f\cdot\nabla_x z(x,t);$$

$$\Delta_x f(z,t) = \partial^2_{zz}f(z,t)\cdot|\nabla_x z(x,t)|^2 + \partial_z f(z,t)\cdot\Delta_x z(x,t);$$

$$\partial_t f(z,t) = \partial_z f(z,t)\partial_t z(x,t) + \partial_t f(z,t);$$

$$\nabla_x z(x,t) = \frac{2x}{4D_0 t} = \sqrt{\frac{z}{t}} \Rightarrow |\nabla_x z(x,t)|^2 = \frac{z}{t};$$

$$\Delta_x z(x,t) = \frac{2d}{4D_0 t}, \quad \partial_t z(x,t) = -\frac{x^2}{4D_0 t^2} = -\frac{z}{t};$$

$$\partial_z G(z,t) = -G, \quad \partial^2_{zz} G(z,t) = G,$$

and so one can rewrite the l.h.s. of [S17] as

$$\underbrace{\Big(\partial_t G - D_0 \Delta G\Big)}_{=0} + G \cdot \Big(-\frac{z}{t}\partial_z \phi + \partial_t \phi\Big) + 2D_0 G \cdot \frac{z}{D_0 t}\partial_z \phi - D_0 G\Big(\frac{z}{D_0 t}\partial^2_{zz}\phi + \frac{2d}{4D_0 t}\partial_z \phi\Big).$$

By simplifying we obtain

$$\frac{G(z,t)}{t}\Big\{t\partial_t - \Big[z\partial^2_{zz} + \Big(\frac{d}{2} - z\Big)\partial_z\Big]\Big\}\phi(z,t).$$

For the r.h.s:

$$\chi G\cdot\Big[-\frac{z}{D_0 t}\partial_z c + \Big(\frac{z}{D_0 t}\partial^2_{zz} c + \frac{d}{2D_0 t}\partial_z c\Big)\Big] + \gamma D_0 G\cdot\Big[\frac{z}{D_0 t}\partial^2_{zz} c + \frac{2d}{4D_0 t}\partial_z c + \frac{z}{D_0 t}c - \frac{2d}{4D_0 t}c - 2\frac{z}{D_0 t}, \partial_z c\Big]$$

which leads to

$$\frac{G(z,t)}{t}\Big[-\frac{\chi}{D_0}\Big(z\partial^2_{zz} + \Big(\frac{d}{2} - z\Big)\partial_z + \gamma\Big(z\partial^2_{zz} - 2z\partial_z + \frac{d}{2}\partial_z - \frac{d}{2} + z\Big)\Big]c(z,t),$$

and then [S28].

$$\Big\{t\partial_t - \Big[z\partial^2_{zz} + \Big(\frac{d}{2} - z\Big)\partial_z\Big]\Big\}\phi(z,t) = \Big[-\frac{\chi}{D_0}\Big(z\partial^2_{zz} + \Big(\frac{d}{2} - z\Big)\partial_z + \gamma\Big(z\partial^2_{zz} - 2z\partial_z + \frac{d}{2}\partial_z - \frac{d}{2} + z\Big)\Big]c(z,t). \tag{S28}$$

In oder to solve this equation the Mellin transform is introduced: As long as $t^s\phi(t,z) \to 0$ as $t \to \infty$ one has the following relation

$$\int_0^\infty t^s \partial_t \phi(t,z)dt = t^s \phi(t,z)\Big|_{t=0}^{t=\infty} - s\int_0^\infty t^{s-1}\phi(t,z)dt = -s\hat{\phi}(s,z),$$

$$\int_0^\infty t^{s-1}\alpha z^n \partial^m_{z\dots z}\phi(t,z)dt = \alpha z^n \partial^m_{z\dots z}\hat{\phi}(s,z).$$

In particular in the previous equation one has that for $\{\mathcal{M}\phi\}(s) = \hat{\phi}(z,s)$ and $\{\mathcal{M}c\}(s) = \hat{c}(z,s)$, multiplying both sides by t^{s-1} and integrating with respect to dt one obtains

$$\Big\{-s - \Big[z\partial^2_{zz} + \Big(\frac{d}{2} - z\Big)\partial_z\Big]\Big\}\hat{\phi}(z,s) = \Big[-\frac{\chi}{D_0}\Big(z\partial^2_{zz} + \Big(\frac{d}{2} - z\Big)\partial_z + \gamma\Big(z\partial^2_{zz} - 2z\partial_z + \frac{d}{2}\partial_z - \frac{d}{2} + z\Big)\Big]\hat{c}(z,s). \tag{S29}$$

It is suggested to use the expansion in Laguerre polynomials[5]:

For the l.h.s. with $\hat{\phi}(z,s) := \sum_{k\in\mathbf{N}} \hat{\phi}_k(s) L_k^{d/2-1}(z)$ follows

$$\Big\{ -s - \Big[z\partial_{zz}^2 + \Big(\frac{d}{2} - z\Big)\partial_z \Big] \Big\} \hat{\phi}(s) = \sum_{k\in\mathbf{N}} \hat{\phi}_k(s) \Big(-s - \underbrace{\Big[z\partial_{zz}^2 + \Big(\frac{d}{2} - z\Big)\partial_z \Big]}_{=-kL_k^{d/2-1}(z)} \Big) L_k^{d/2-1}(z)$$
$$= \sum_{k\in\mathbf{N}} (-s+k)\hat{\phi}_k(s) L_k^{d/2-1}(z)..$$

the same applies with $\hat{c}(z,s) := \sum_{k\in\mathbf{N}} \hat{c}_k(s) L_k^{d/2-1}(z)$ to the first term on the r.h.s. which gives

$$\sum_{k\in\mathbf{N}} \frac{k\cdot\chi}{D_0} \hat{c}_k(s) L_k^{d/2-1}(z).$$

Using now (8.971.3)[6] for the second term:

$$\Big(z\partial_{zz}^2 - 2z\partial_z + \frac{d}{2}\partial_z - \frac{d}{2} + z \Big)\hat{c}(s) = \sum_{k\in\mathbf{N}} \hat{c}_k(s) \Big[\underbrace{\Big(z\partial_{zz}^2 - (\frac{d}{2} - z)\partial_z \Big) L_k^{d/2-1}(z)}_{=-k\cdot L_k^{d/2-1}(z)} +$$
$$- \Big(z\partial_z + \frac{d}{2} - z \Big) L_k^{d/2-1}(z) \Big]$$
$$= -\sum_{k\in\mathbf{N}} \hat{c}_k(s) \Big(z\partial_z + (k + \frac{d}{2} - 1 + 1 - z) \Big) L_k^{d/2-1}(z)$$
$$= -\sum_{k\in\mathbf{N}} \hat{c}_k(s)(k+1) L_{k+1}^{d/2-1}(z) = -\sum_{k\in\mathbf{N}} \hat{c}_{k-1}(s) k L_k^{d/2-1}(z).$$

By setting the coefficients of the same Laguerre polynomials to equal each other, follows that

$$\hat{\phi}_k(s) = \frac{k}{k-s} \Big(\frac{\chi}{D_0} \hat{c}_k(s) - \gamma \hat{c}_{k-1}(s) \Big).$$

One reads *In addition to the poles possibly inherited from the field c, poles are present at* $s = 1, 2, \ldots$ *because of the existence of homogeneous solutions* $\phi_{hom} = t^{-k} L_k(z)$: in fact the equation is linear in ϕ and so the poles are those for the homogenous solution and those for the special integrals; using the differential equation defining $L_k^{\alpha}(t)$ and $t\partial_t t^{-k} = -kt^{-k}$

$$\Big\{ t\partial_t - \Big[z\partial_{zz}^2 + \Big(\frac{d}{2} - z\Big)\partial_z \Big] \Big\} t^{-k} L_k^{d/2-1}(z) = \Big\{ -kt^{-k} - t^{-k} \Big[z\partial_{zz}^2 + \Big(\frac{d}{2} - z\Big)\partial_z \Big] \Big\} L_k^{(d/2-1)}(z) = 0.$$

It is said that: *The constant term* $k = 0$ *in the series expansion for* ϕ *is ruled out because the right-hand side of [S17] contains only space derivative terms. The integral of the right-hand side over the whole volume is therefore equal to zero. Because the diffusion operator*

[5]For arbitrary real polynomial solutions of the differential equation

$$x L_n^{(\alpha)\prime\prime}(x) + (\alpha + 1 - x) L_n^{(\alpha)\prime}(x) + n L_n^{(\alpha)}(x) = 0$$

are called *generalized Laguerre polynomials.*

[6]$x L_n^{(\alpha)\prime}(x) + (n + \alpha + 1 - x) L_n^{(\alpha)}(x) = (n+1) L_{n+1}^{(\alpha)}(x)$ and not formula (8.971.2)

conserves the normalization, we conclude that the integral of η in space vanishes at any time t and that the term $k = 0$ in the expansion of ϕ is absent. $L_0^{d/2-1}(z) := 1$ and then

$$s\hat{\phi}_0(z,s) = 0 \Rightarrow \phi_0 = 0$$

The calculation of the uptake is done as follows: By using the spherical coordinate for the d-sphere and the hypothesis on the functions c and η

$$\begin{aligned} S' &= \int_0^\infty dt \int_{\mathbb{R}^d} dx \Big(c(x,t)\eta(x,t) \Big) \\ &= \int_0^\infty dt \int_{\mathbb{R}_+} dr r^{d-1} \Big(c\Big(\frac{r^2}{4D_0 t}, t\Big) \eta\Big(\frac{r^2}{4D_0 t}, t\Big)\Big) \int_{[0,2\pi)\times[0,\pi)^{d-2}} \mathcal{H}(\phi_j) d\phi_{d-1} \otimes_{j=1}^{d-2} d\phi_j \end{aligned}$$

The last integral is the surface of the d-sphere $\int_{[0,2\pi)\times[0,\pi)^{d-2}} \mathcal{H}(\phi_j) d\phi_{d-1} \otimes_{j=1}^{d-2} d\phi_j = \frac{2\pi^{d/2}}{\Gamma(d/2)}$. By changing the variable $\frac{r^2}{4D_0 t} = z$ one gets that $r^{d-1}dr = \frac{1}{2}(4D_0 t)^{d/2} z^{d/2-1}$, using the explicit form of $G(z)$ and expanding c and ϕ in Laguerre polynomials one has

$$\begin{aligned} S' &= \frac{\pi^{d/2}}{\Gamma(d/2)} \int_0^\infty dt \int_{\mathbb{R}} \Big((4D_0 t)^{d/2} c(z,t)\phi(z,t) G(z,t) \Big) z^{d/2-1} dz \\ &= \frac{1}{\Gamma(d/2)} \int_0^\infty dt \int_{\mathbb{R}} \Big(c(z,t)\phi(z,t) e^{-z} \Big) z^{d/2-1} dz \\ &= \frac{1}{\Gamma(d/2)} \int_0^\infty dt \int_{\mathbb{R}} \Big(\sum_{k=1}^\infty c_k(z,t) L_k^{d/2-1}(z) \sum_{n=1}^\infty \phi_n(z,t) L^{d/2-1}(z) e^{-z} \Big) z^{d/2-1} dz \\ &= \frac{\Gamma(k+d/2)}{\Gamma(k+1)\Gamma(d/2)} \int_0^\infty \Big(\sum_{k=1}^\infty c_k(t)\phi_k(t) \Big) dt \end{aligned}$$

where the equation [G.R. 8.980][7] about the orthonormality of L_k^α has been used in the last equality. To compute the last integral we notice that:

$$\begin{aligned} \int_0^\infty \Big(\sum_{k=1}^\infty c_k(t)\phi_k(t) \Big) dt &= \sum_{k=1}^\infty \int_0^\infty \Big(\frac{1}{2\pi i} \int_{\nu-i\infty}^{\nu+i\infty} c_k(z,t)\hat{\phi}_k(z,s) t^{-s} ds \Big) dt \\ &= \sum_{k=1}^\infty \frac{1}{2\pi i} \int_{\nu-i\infty}^{\nu+i\infty} \hat{\phi}_k(z,s) \Big(\int_0^\infty c_k(z,t) t^{-s} dt \Big) ds \\ &= \sum_{k=1}^\infty \frac{1}{2\pi i} \int_{\nu-i\infty}^{\nu+i\infty} \Big(\hat{\phi}_k(z,s)\hat{c}_k(z,1-s) \Big) ds \end{aligned}$$

since $\hat{c}_k(1-s) = \int_0^\infty c_k(t) t^{-s} dt$.
In conclusion we obtain [S31]:

$$S' = \frac{\Gamma(k+d/2)}{\Gamma(k+1)\Gamma(d/2)} \frac{1}{2\pi i} \int_{\nu-i\infty}^{\nu+i\infty} \sum_{k=1}^\infty \Big(\hat{\phi}_k(z,s)\hat{c}_k(z,1-s) \Big) ds \tag{S31}$$

[7] $\int_0^\infty x^\alpha e^{-x} L_n^{(\alpha)}(x) L_m^{(\alpha)}(x) dx = \frac{\Gamma(n+\alpha+1)}{\Gamma(n+1)} \delta_{n,m}$

The relation for $\nu = \frac{1}{2}$, $\hat{c}_k(s) = c_k(1-s)^\star$ follows from:

$$\hat{c}_k\Big(\frac{1}{2}+i\nu\Big) = \int_0^\infty c_k(t)t^{i\nu-\frac{1}{2}}, \quad \hat{c}_k\Big(1-(\frac{1}{2}+i\nu)\Big) = \int_0^\infty c_k(t)t^{-i\nu-\frac{1}{2}}$$

and so one is the complex conjugate of the other. Integrating parallel to the imaginary axis one has the following: since $s = \frac{1}{2}+i\nu \Rightarrow ds = id\nu$

$$\frac{1}{2\pi i}\int_{\nu-i\infty}^{\nu+i\infty} c(s)ds = \frac{1}{2\pi}\int_{-\infty}^{\infty} c\Big(\frac{1}{2}+i\nu\Big)d\nu$$

One has to notice now that the following holds:

$$\begin{aligned}\int_{-\infty}^{\infty} \frac{1}{k-\frac{1}{2}-i\nu}c_k(\nu)c_k^\star(\nu)d\nu &= \int_{-\infty}^{\infty} \frac{k-\frac{1}{2}+i\nu}{\Big(k-\frac{1}{2}\Big)^2-\nu^2}c_k(\nu)c_k(-\nu)d\nu \\ &= \int_{-\infty}^{\infty} \Re\Big(\frac{1}{k-\frac{1}{2}-i\nu}\Big)c_k(\nu)c_k^\star(\nu)d\nu\end{aligned}$$

By using the relation [S30], the expression [S32] in the text follows. To evaluate the eigenvalues of the matrix defined in [S33] one has the following:

Let $D := (\lambda_i)_i$ be a diagonal matrix with $\lambda_i \neq \lambda_j$ and let H be a Hermitian tridiagonal perturbation with null diagonal, then one has that if μ_i are the eigenvalues of $D+H$ then

$$|\lambda_1 - \mu_1| \leq \frac{H_{11}\cdot H_{11}^\star}{\min_{i,j}\{|\lambda_i-\lambda_j|\}}$$

In the present case we have that $\lambda_1 = 0$, hence

$$|\mu_1| \leq \frac{H_{11}\cdot H_{11}^\star}{\min_{i,j}\{|\lambda_i-\lambda_j|\}} \leq \zeta$$

where $\zeta := \frac{\frac{\gamma^2\mu_1^\star(\nu)\cdot\mu_1(\nu)}{4}}{S_{11}} = \frac{D_0\gamma^2}{4\chi}\frac{\mu_1^\star(\nu)\cdot\mu_1(\nu)}{\Re(\mu_1(\nu))}$ and $\mu_1(\nu) = \frac{\Gamma(1+d/2)}{\Gamma(d/2)}\frac{1/2-i\nu}{1/4-\nu^2} = \frac{d}{2}\frac{1/2-i\nu}{1/4-\nu^2}$

$$\frac{\mu_1^\star(\nu)\cdot\mu_1(\nu)}{\Re(\mu_1(\nu))} = \frac{d}{2}\frac{1/2-i\nu}{1/4-\nu^2}\frac{1/2+i\nu}{1/4-\nu^2}\frac{1/4-i\nu}{1/2} = d$$

and it follows then that for small γ, for the smallest eigenvalues one has $\mu_1 \simeq -\frac{dD_0\gamma^2}{4\chi}$.

Bibliography

[1] Julius Adler. Chemotaxis in bacteria. In *Surface Membrane Receptors*, pages 419–435. Springer, 1976.

[2] Wolgang Alt. Biased random walk models for chemotaxis and related diffusion approximations. *Journal of Mathematical Biology*, 9(2):147–177, 1980.

[3] David Applebaum. Brownian motion and Lévy processes on locally compact groups. *Methods of Functional Analysis and Topology*, 12(2):101–112, 2006.

[4] Sho Asakura and Hajime Honda. Two-state model for bacterial chemoreceptor proteins: The role of multiple methylation. *Journal of Molecular Biology*, 176(3):349–367, 1984.

[5] Vlad Bally. An elementary introduction to Malliavin Calculus. 2003.

[6] Julien Bect. A unifying formulation of the Fokker-Planck-Kolmogorov equation for general stochastic hybrid systems. *Nonlinear Analysis: Hybrid Systems*, 4(2):357–370, 2010.

[7] Julien Bect, Hana Baili, and Gilles Fleury. Generalized Fokker-Planck equation for piecewise-diffusion processes with boundary hitting resets. In *MTNS 2006*, pages 1360–1367, 2006.

[8] Luisa Beghin and Enzo Orsingher. Fractional Poisson processes and related planar random motions. *Electron. J. Probab*, 14(61):1790–1826, 2009.

[9] Luisa Beghin and Enzo Orsingher. Poisson-type processes governed by fractional and higher-order recursive differential equations. *Electron. J. Probab*, 15(22):684–709, 2010.

[10] Denis R Bell and Salah-Eldin A Mohammed. The Malliavin calculus and stochastic delay equations. *Journal of Functional Analysis*, 99(1):75–99, 1991.

[11] Howard C Berg. *E. coli in Motion*. Springer Science & Business Media, 2008.

[12] Howard C Berg, Douglas A Brown, et al. Chemotaxis in Escherichia coli analysed by three-dimensional tracking. *Nature*, 239(5374):500–504, 1972.

[13] William Bialek and Sima Setayeshgar. Physical limits to biochemical signaling. *Proceedings of the National Academy of Sciences of the United States of America*, 102(29):10040–10045, 2005.

[14] Markus Blatt, Ansgar Burchardt, Andreas Dedner, Christian Engwer, Jorrit Fahlke, Bernd Flemisch, Christoph Gersbacher, Carsten Gräser, Felix Gruber, Christoph Grüninger, et al. The distributed and unified numerics environment, version 2.4. *Archive of Numerical Software*, 4(100):13–29, 2016.

[15] Benzion Boukai. An explicit expression for the distribution of the supremum of Brownian motion with a change point. *Communications in Statistics-Theory and Methods*, 19(1):31–40, 1990.

[16] David R Brillinger. A particle migrating randomly on a sphere. In *Selected Works of David Brillinger*, pages 73–87. Springer, 2012.

[17] Douglas A Brown and Howard C Berg. Temporal stimulation of chemotaxis in *Escherichia coli*. *Proceedings of the National Academy of Sciences*, 71(4):1388–1392, 1974.

[18] Emery N Brown, Riccardo Barbieri, Valérie Ventura, Robert E Kass, and Loren M Frank. The time-rescaling theorem and its application to neural spike train data analysis. *Neural Computation*, 14(2):325–346, 2002.

[19] Manuela L Bujorianu and John Lygeros. Towards a general theory of stochastic hybrid systems. In *Stochastic Hybrid Systems*, pages 3–30. Springer, 2006.

[20] Vincenzo Capasso and David Bakstein. An introduction to continuous-time stochastic processes. *Theory, models*, 2005.

[21] Antonio Celani, Thomas S Shimizu, and Massimo Vergassola. Molecular and functional aspects of bacterial chemotaxis. *Journal of Statistical Physics*, 144(2):219–240, 2011.

[22] Antonio Celani and Massimo Vergassola. Bacterial strategies for chemotaxis response. *Proceedings of the National Academy of Sciences*, 107(4):1391–1396, 2010.

[23] Mou-Hsiung Chang. *Stochastic Control of Hereditary Systems and Applications*, volume 59. Springer Science & Business Media, 2008.

[24] Mou-Hsiung Chang, Tao Pang, and Moustapha Pemy. Viscosity solutions of infinite dimensional Black-Scholes equation and numerical approximations. *preprint*, 2006.

[25] Mou-Hsiung Chang, Tao Pang, and Moustapha Pemy. Optimal control of stochastic functional differential equations with a bounded memory. *Stochastics An International Journal of Probability and Stochastic Processes*, 80(1):69–96, 2008.

[26] Mou-Hsiung Chang and Roger K Youree. Infinite-dimensional Black-Scholes equation with hereditary structure. *Applied Mathematics and Optimization*, 56(3):395–424, 2007.

[27] Gregory S Chirikjian. Stochastic Processes on Lie Groups. In *Stochastic Models, Information Theory, and Lie Groups, Volume 2*, pages 361–388. Springer, 2012.

[28] Damon A Clark and Lars C Grant. The bacterial chemotactic response reflects a compromise between transient and steady-state behavior. *Proceedings of the National Academy of Sciences of the United States of America*, 102(26):9150–9155, 2005.

[29] Philippe Cluzel, Michael Surette, and Stanislas Leibler. An ultrasensitive bacterial motor revealed by monitoring signaling proteins in single cells. *Science*, 287(5458):1652–1655, 2000.

[30] Rama Cont and David-Antoine Fournie. A functional extension of the Itô formula. *Comptes Rendus Mathematique*, 348(1):57–61, 2010.

[31] Rama Cont and David-Antoine Fournié. Change of variable formulas for non-anticipative functionals on path space. *Journal of Functional Analysis*, 259(4):1043–1072, 2010.

[32] Rama Cont, David-Antoine Fournié, et al. Functional Itô calculus and stochastic integral representation of martingales. *The Annals of Probability*, 41(1):109–133, 2013.

[33] Giuseppe Da Prato and Jerzy Zabczyk. *Ergodicity for infinite dimensional systems*, volume 229. Cambridge University Press, 1996.

[34] Giuseppe Da Prato and Jerzy Zabczyk. *Stochastic equations in infinite dimensions*, volume 152. Cambridge University Press, 2014.

[35] Mary E Davey and George A O'Toole. Microbial biofilms: from ecology to molecular genetics. *Microbiology and Molecular Biology Reviews*, 64(4):847–867, 2000.

[36] Mark HA Davis. Piecewise-deterministic Markov processes: A general class of non-diffusion stochastic models. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 353–388, 1984.

[37] Mark HA Davis. *Markov Models & Optimization*, volume 49. CRC Press, 1993.

[38] Donald Dawson. *Measure-valued Markov processes*. Springer, 1993.

[39] P-G De Gennes. Chemotaxis: the role of internal delays. *European Biophysics Journal*, 33(8):691–693, 2004.

[40] Giulia Di Nunno, Bernt Karsten Øksendal, and Frank Proske. *Malliavin calculus for Lévy processes with applications to finance*. Springer, 2009.

[41] DUNE. Distributed and unified numerics environment (https://www.dune-project.org/).

[42] Bruno Dupire. Functional Itô calculus. *Bloomberg Portfolio Research Paper*, (2009-04), 2009.

[43] Evgeni B Dynkin. *Markov processes*. Springer, 1965.

[44] John E Eisenstein and Dori F Zaleznik. Enterobacteriaceae. *Principles and Practice of Infectious Diseases*, 2:1972–1973, 2000.

[45] Radek Erban and Hans G Othmer. From signal transduction to spatial pattern formation in *E. coli*: a paradigm for multiscale modeling in biology. *Multiscale Modeling & Simulation*, 3(2):362–394, 2005.

[46] Theodor Escherich. Die Darmbakterien des Neugeborenen und Säuglings. *Fortschr Med*, 3:515–522, 1885.

[47] Stewart N Ethier and Thomas G Kurtz. *Markov processes: characterization and convergence*, volume 282. John Wiley & Sons, 2009.

[48] Sven Eule, Rudolf Friedrich, Frank Jenko, and Igor M Sokolov. Continuous-time random walks with internal dynamics and subdiffusive reaction-diffusion equations. *Physical Review E*, 78(6):060102, 2008.

[49] William H Ewing et al. *Edwards and Ewing's identification of Enterobacteriaceae*. Elsevier Science Publishing Co. Inc., 1986.

[50] William Feller. The parabolic differential equations and the associated semi-groups of transformations. *Annals of Mathematics*, pages 468–519, 1952.

[51] William Feller. Diffusion processes in one dimension. *Transactions of the American Mathematical Society*, 77(1):1–31, 1954.

[52] Peter Feng, Stephen D Weagant, Michael A Grant, and William Burkhardt. BAM: Enumeration of *Escherichia coli* and the Coliform Bacteria. *Bacteriological Analytical Manual [Monograph on the internet]. US Food and Drugs Administration*, 2002.

[53] Roseanne M Ford and Peter T Cummings. On the relationship between cell balance equations for chemotactic cell populations. *SIAM Journal on Applied Mathematics*, 52(5):1426–1441, 1992.

[54] Roseanne M Ford and Peter T Cummings. Errata: On the Relationship Between Cell Balance Equations for Chemotactic Cell Populations. *SIAM Journal on Applied Mathematics*, 53(5):1505–1505, 1993.

[55] Mark I Freuidlin. *Functional integration and partial differential equations*. Number 109. Princeton University Press, 1985.

[56] Rudolf Friedrich, Frank Jenko, Adrian Baule, and Sven Eule. Exact solution of a generalized Kramers-Fokker-Planck equation retaining retardation effects. *Physical Review E*, 74(4):041103, 2006.

[57] Felipe Gerhard, Robert Haslinger, and Gordon Pipa. Applying the multivariate time-rescaling theorem to neural population models. *Neural Computation*, 23(6):1452–1483, 2011.

[58] Izrael S Gradshteyn and Iosif M Ryzhik. Table of Integrals, Series, and Products, 2000.

[59] Nili E.Z.C.E. Grossman, Eliora Z Ron, and Conrad L Woldringh. Changes in cell dimensions during amino acid starvation of *Escherichia coli*. *Journal of Bacteriology*, 152(1):35–41, 1982.

[60] Vincenzo Guerriero. Power law distribution: Method of multi-scale inferential statistics. *Journal of Modern Mathematics Frontier*, 1(1):21–28, 2012.

[61] Jack K Hale. *Functional differential equations*. Springer, 1971.

[62] Robert Haslinger, Gordon Pipa, and Emery Brown. Discrete time rescaling theorem: determining goodness of fit for discrete time statistical models of neural spiking. *Neural computation*, 22(10):2477–2506, 2010.

[63] Jianghai Hu, John Lygeros, and Shankar Sastry. Towards a theory of stochastic hybrid systems. In *Hybrid Systems: Computation and Control*, pages 160–173. Springer, 2000.

[64] Yaozhong Hu, Salah-Eldin A Mohammed, Feng Yan, et al. Discrete-time approximations of stochastic delay equations: the Milstein scheme. *Annals of Probability*, 32(1A):265–314, 2004.

[65] Nail K Ibragimov. *Elementary Lie group analysis and ordinary differential equations*, volume 197. Wiley New York, 1999.

[66] Kiyosi Itô and Makkiko Nisio. On stationary solutions of a stochastic differential equation. *Math. Kyoto Univ*, pages 4–1, 1964.

[67] AF Ivanov, YI Kazmerchuk, and AV Swishchuk. Theory, stochastic stability and applications of stochastic delay differential equations: a survey of results. *Differential Equations Dynam. Systems*, 11(1-2):55–115, 2003.

[68] Jean Jacod and Albert Shiryaev. *Limit theorems for stochastic processes*, volume 288. Springer Science & Business Media, 2013.

[69] Jean Jacod and Albert N Shiryaev. Skorokhod topology and convergence of processes. *Limit theorems for stochastic processes*, pages 324–388, 2003.

[70] Evelyn F Keller and Lee A Segel. Initiation of slime mold aggregation viewed as an instability. *Journal of Theoretical Biology*, 26(3):399–415, 1970.

[71] Evelyn F Keller and Lee A Segel. Model for chemotaxis. *Journal of theoretical biology*, 30(2):225–234, 1971.

[72] Kei Kobayashi. Stochastic calculus for a time-changed semimartingale and the associated stochastic differential equations. *Journal of Theoretical Probability*, 24(3):789–820, 2011.

[73] Jaroslav Krystul, Henk AP Blom, and Arunabha Bagchi. Stochastic differential equations on hybrid state spaces. *Stochastic Hybrid Systems*, 24:15–45, 2006.

[74] HE Kubitschek and JA Friske. Determination of bacterial cell volume with the Coulter Counter. *Journal of Bacteriology*, 168(3):1466–1467, 1986.

[75] Rep Kubo. The fluctuation-dissipation theorem. *Reports on Progress in Physics*, 29(1):255, 1966.

[76] Thomas G Kurtz. Representations of Markov processes as multiparameter time changes. *The Annals of Probability*, pages 682–715, 1980.

[77] Harold J Kushner. On the stability of processes defined by stochastic difference-differential equations. *Journal of Differential Equations*, 4(3):424–443, 1968.

[78] Shigeo Kusuoka and Daniel Stroock. Applications of the Malliavin calculus, part I. *North-Holland Mathematical Library*, 32:271–306, 1984.

[79] Utah University Parkinson Lab. An overview of *E. coli* chemotaxis (http://chemotaxis.biology.utah.edu/parkinson_lab).

[80] Paul Legassé. The Columbia Electronic Encyclopedia, 2007.

[81] Ming Liao. Lévy processes and Fourier analysis on compact Lie groups. *Annals of Probability*, pages 1553–1573, 2004.

[82] Robert M Macnab and DE Koshland. The gradient-sensing mechanism in bacterial chemotaxis. *Proceedings of the National Academy of Sciences*, 69(9):2509–2512, 1972.

[83] Robert M Macnab and May K Ornston. Normal-to-curly flagellar transitions and their role in bacterial tumbling. Stabilization of an alternative quaternary structure by mechanical force. *Journal of Molecular Biology*, 112(1):1–30, 1977.

[84] Xuerong Mao. Stability of stochastic differential equations with Markovian switching. *Stochastic Processes and their Applications*, 79(1):45–67, 1999.

[85] Xuerong Mao. *Stochastic differential equations and applications*. Elsevier, 2007.

[86] Franziska Matthäus. *Managing Complexity, Reducing Perplexity: Modeling Biological Systems*, chapter A Hybrid Model for *E. coli* Chemotaxis: From Signaling Pathway to Pattern Formation, pages 37–44. Springer International Publishing, Cham, 2014.

[87] Franziska Matthäus, Marko Jagodič, and Jure Dobnikar. E. coli superdiffusion and chemotaxis search strategy, precision, and motility. *Biophysical Journal*, 97(4):946–957, 2009.

[88] Franziska Matthäus, Mario S. Mommer, Tine Curk, and Jure Dobnikar. On the origin and characteristics of noise-induced lèvy walks of *E. coli*. *PloS one*, page e18623, 2011.

[89] Patrick J Mears, Santosh Koirala, Chris V Rao, Ido Golding, and Yann R Chemla. *Escherichia coli* swimming is robust against variations in flagellar number. *Elife*, 3:e01916, 2014.

[90] Mark M Meerschaert, Erkan Nane, and P Vellaisamy. The fractional Poisson process and the inverse stable subordinator. *Electronic Journal of Probability*, 16(59):1600–1620, 2011.

[91] Salah-Eldin A Mohammed. *Stochastic functional differential equations*. Number 99. Pitman Advanced Publishing Program, 1984.

[92] Daniela Morale, Vincenzo Capasso, and Karl Oelschläger. An interacting particle system modelling aggregation behavior: from individuals to populations. *Journal of Mathematical Biology*, 50(1):49–66, 2005.

[93] Benno Müller-Hill. *The Lac Operon: a Short History Of A Genetic Paradigm*. Walter de Gruyter New York:, 1996.

[94] David E Nelson and Kevin D Young. Penicillin binding protein 5 affects cell diameter, contour, and morphology of *Escherichia coli*. *Journal of Bacteriology*, 182(6):1714–1721, 2000.

[95] David Nualart. *The Malliavin calculus and related topics*, volume 1995. Springer, 2006.

[96] David Nualart and Étienne Pardoux. Stochastic calculus with anticipating integrands. *Probability Theory and Related Fields*, 78(4):535–581, 1988.

[97] Karl Oelschläger. A law of large numbers for moderately interacting diffusion processes. *Zeitschrift für Wahrscheinlichkeitstheorie und verwandte Gebiete*, 69(2):279–322, 1985.

[98] Karl Oelschläger. On the derivation of reaction-diffusion equations as limit dynamics of systems of moderately interacting stochastic processes. *Probability Theory and Related Fields*, 82(4):565–586, 1989.

[99] Enzo Orsingher and Luisa Beghin. Time-fractional telegraph equations and telegraph processes with Brownian time. *Probability Theory and Related Fields*, 128(1):141–160, 2004.

[100] Enzo Orsingher and Federico Polito. The space-fractional Poisson process. *Statistics & Probability Letters*, 82(4):852–858, 2012.

[101] Enzo Orsingher and Nikita Ratanov. Random motions in inhomogeneous media. *Theory of Probability and Mathematical Statistics*, 76:141–153, 2008.

[102] Hans G Othmer and Thomas Hillen. The diffusion limit of transport equations derived from velocity-jump processes. *SIAM Journal on Applied Mathematics*, 61(3):751–775, 2000.

[103] George C Papanicolaou. Asymptotic analysis of transport processes. *Bulletin of the American Mathematical Society*, 81(2):330–392, 1975.

[104] Pierre Patie and Chantal Winter. First exit time probability for multidimensional diffusions: a PDE-based approach. *Journal of Computational and Applied Mathematics*, 222(1):42–53, 2008.

[105] Donald W Peaceman and Henry H Rachford, Jr. The numerical solution of parabolic and elliptic differential equations. *Journal of the Society for Industrial and Applied Mathematics*, 3(1):28–41, 1955.

[106] Theodore J Perkins, Andrea Y Weiße, and Peter S Swain. Chance and Memory. *Quantitative Biology: From Molecular to Cellular Systems*, page 51, 2012.

[107] Igor Podlubny. *Fractional differential equations: an introduction to fractional derivatives, fractional differential equations, to methods of their solution and some of their applications*, volume 198. Academic Press, 1998.

[108] Markus Reiß, Markus Riedle, and Onno Van Gaans. Delay differential equations driven by Lévy processes: Stationarity and Feller properties. *Stochastic Processes and their Applications*, 116(10):1409–1432, 2006.

[109] Sheldon M Ross. *Introduction to probability and statistics for engineers and scientists*. Academic Press, 2014.

[110] Mathias Rousset and Giovanni Samaey. Individual-based models for bacterial chemotaxis and variance reduced simulation. *preprint*, 2010.

[111] Mathias Rousset and Giovanni Samaey. Individual-based models for bacterial chemotaxis in the diffusion asymptotics. *Mathematical Models and Methods in Applied Sciences*, 23(11):2005–2037, 2013.

[112] Y. F. Saporito. Functional Meyer-Tanaka Formula. *ArXiv e-prints*, August 2014.

[113] S Setayeshgar, CW Gear, HG Othmer, and IG Kevrekidis. Application of coarse integration to bacterial chemotaxis. *Multiscale Modeling & Simulation*, 4(1):307–327, 2005.

[114] SE Shreve and I Karatzas. Brownian motion and stochastic calculus. *Graduate Texts in Mathematics*, 113, 1991.

[115] Angela Stevens. The derivation of chemotaxis equations as limit dynamics of moderately interacting stochastic many-particle systems. *SIAM Journal on Applied Mathematics*, 61(1):183–212, 2000.

[116] Angela Stevens. Erratum: The Derivation of Chemotaxis Equations as Limit Dynamics of Moderately Interacting Stochastic Many-Particle Systems. *SIAM Journal on Applied Mathematics*, 61(6):2200–2200, 2001.

[117] Angela Stevens and Hans G Othmer. Aggregation, blowup, and collapse: the ABC's of taxis in reinforced random walks. *SIAM Journal on Applied Mathematics*, 57(4):1044–1081, 1997.

[118] Daniel W Stroock. On the growth of stochastic integrals. *Zeitschrift für Wahrscheinlichkeitstheorie und Verwandte Gebiete*, 18(4):340–344, 1971.

[119] Daniel W Stroock. Some stochastic processes which arise from a model of the motion of a bacterium. *Probability Theory and Related Fields*, 28(4):305–315, 1974.

[120] Daniel W Stroock. The Malliavin calculus, a functional analytic approach. *Journal of Functional Analysis,*, 44(2):212–257, 1981.

[121] Daniel W Stroock. The Malliavin calculus and its application to second order parabolic differential equations: Part I. *Mathematical Systems Theory*, 14(1):25–65, 1981.

[122] Jake P Taylor-King, E Emiel van Loon, Gabriel Rosser, and S Jon Chapman. From birds to bacteria: generalised velocity jump processes with resting states. *Bulletin of Mathematical Biology*, 77(7):1213–1236, 2015.

[123] Marek Teuerle, Piotr Żebrowski, and Marcin Magdziarz. Multidimensional Lévy walk and its scaling limits. *Journal of Physics A: Mathematical and Theoretical*, 45(38):385002, 2012.

[124] Marcus J Tindall, Philip K Maini, Steven L Porter, and Judith P Armitage. Overview of mathematical approaches used to model bacterial chemotaxis II: bacterial populations. *Bulletin of mathematical biology*, 70(6):1570–1607, 2008.

[125] Marcus J Tindall, SL Porter, PK Maini, G Gaglia, and Judith P Armitage. Overview of mathematical approaches used to model bacterial chemotaxis I: the single cell. *Bulletin of Mathematical Biology*, 70(6):1525–1569, 2008.

[126] Yuhai Tu, Thomas S Shimizu, and Howard C Berg. Modeling the chemotactic response of *Escherichia coli* to time-varying stimuli. *Proceedings of the National Academy of Sciences*, 105(39):14855–14860, 2008.

[127] Max-K von Renesse and Michael Scheutzow. Existence and uniqueness of solutions of stochastic functional differential equations. *Random Operators and Stochastic Equations*, 18(3):267–284, 2010.

[128] Chuan Xue and Hans G Othmer. Multiscale models of taxis-driven patterning in bacterial populations. *SIAM Journal of Applied Mathematics*, 70(1):133–167, 2009.

[129] Feng Yan. *Topics on Stochastic Delay Equations*. PhD thesis, Southern Illinois University at Carbondale, 1999.

[130] Feng Yan and Salah Mohammed. A stochastic calculus for systems with memory. *Stochastic Analysis and Applications*, 23(3):613–657, 2005.

[131] Kôsaku Yosida. Brownian motion on the surface of the 3-sphere. *The Annals of Mathematical Statistics*, 20(2):292–296, 1949.

[132] Piotr Zebrowski and Marcin Magdziarz. Limit theorems for continuous time random walks with continuous paths. *arXiv preprint arXiv:1305.4058*, 2013.