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Implementation and parameter estimation of an intra-host model describing human immune responses in *falciparum* malaria

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Naturally acquired immunity against *falciparum* malaria is poorly understood. In the absence of clear biological evidence mathematical models provide a good tool to investigate different hypotheses. Malariology has a long history of modelling. The malariologist Ronald Ross, a pioneer in the field of malaria research, was among the first to apply a mathematical model in order to describe relationships in malaria epidemiology.

In this work we use a model from the literature as starting point. It describes the intra-host dynamics of *Plasmodium falciparum* infections in non-immune hosts. The model was subsequently adapted and relevant properties were changed for our purposes. The objectives of this thesis were 1) to implement the model and to further investigate the characteristics of three immune mechanisms represented by the model; 2) to identify model parameters which are relevant for the description of the three immune responses and to estimate these parameters by use of a systematic estimation approach; 3) to investigate how the information contained in a dataset on the natural course of 35 malaria infections can be extracted and combined best in order to be used as a quantitative evaluation criteria for model fit; 4) to explore alternatives on how the switching behavior between variants of the *Plasmodium falciparum* Erythrocyte Membrane Protein 1 (*PfEMP1*) could be regulated and to investigate the resulting dynamics in the appearance of different *PfEMP1* variants over time.

To address these objectives the mathematical model was implemented in Java using a modular object-oriented architecture. It was integrated into a simulation framework with graphical user interface.

For the purpose of parameter estimation an evolutionary algorithm (EA) was implemented and compared with a grid method (GM). An evaluation of the results showed that a modification of the EA was necessary to achieve more consistent estimation results. The estimates of the modified EA were comparable to the results obtained by the GM.

The target functions used to evaluate model fit are based on nine statistical descriptions of the simulated and observed parasitaemia curves. We applied three alternative combinations of these characteristics to quantify the fit between the simulations and the observed data. Of the three target functions considered, the option based on the Wilcoxon rank-sum test of the distribution of the nine characteristics was found to be the most appropriate one.

The original model was substantially modified in order to incorporate three candidate models for *var* gene switching: a random model assuming that parasites switch at a uniform rate, a sequential model where parasites switch in a strictly ordered manner and a hierarchical model assuming that variants have varying intrinsic on-switch probabilities. Several simulations were performed with each of the three switching models and the simulation outcome was compared to the patient data. The hierarchical switching model exhibited the best fit to patient data.

An analysis of the frequency and distribution of variants over time in 100 simulated infections showed that the number of concurrently active variants increased from one to a maximum of 29 variants at around day 25. However even at this high level of concurrently active variants, parasitaemia was dominated by only a small number of variants (median number between 1 and 3). After day 100 the number of active variants decreased substantially.

Our simulation results confirmed that an immediate innate immune mechanism is of eminent importance in the control of high parasitaemia levels at the beginning of the infection. At lower parasitaemia levels the influence of the innate immune response became negligible and the dynamics were dominated by the acquired immune responses which finally lead to the elimination of parasitaemia.

Different limits for the efficacy of the variant-transcending immunity were evaluated. An upper limit of approximately 80% was necessary to generate parasitaemia curves which fit the observed pattern.