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Using mathematical models to study the invasion of malarial parasites into red blood cells

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The symptoms of malarial infection are associated with a replication cycle which takes place within the red blood cells (RBCs) of the infected host. It begins when a parasite injected into the host's bloodstream by an infected female mosquito infects a susceptible RBC. During the following 48 hours the parasite develops and multiplies within these now infected RBCs and eventually causes them to rupture, releasing 8 to 32 daughter parasites into the bloodstream. These new parasites are then free to diffuse and subsequently infect other susceptible RBCs and begin a new replication cycle.

It is known from experimental studies that susceptible RBCs may be infected by more than one parasite. While the occurrence of these so-called multiply-infected RBCs is recognised, their inclusion in mathematical modelling exercises is sorely lacking. The cause of these multiply-infected RBCs is not fully understood, but is thought to be a combination of several factors including the age and overall health of the susceptible RBC, the inherent infectiousness of the parasites (which may depend on the species), the absolute number of RBCs as well as how well mixed together the parasites and RBCs are in the experimental culture. The lack of usable data combined with complex interplay of the factors just mentioned restricted the analysis in this work to consider only the number of RBCs and how well they were mixed with parasites, as the environmental variables.

The objective of my thesis was to develop two novel mathematical models which describe the dynamics of parasite invasion into RBCs during the initial stages of malarial infection. The variables in these models – those populations of cells whose numbers change as time progresses – were the parasites, uninfected RBCs, infected RBCs, multiply-infected RBCs and a complex consisting of a parasite and RBC. This complex may dissociate or break up thereby leaving the parasite and RBC once again as separate cells. This is extremely important in the current work, because it takes into account the fact that infection is not 100% guaranteed when a parasite bumps into a RBC. The evidence is very clear that a parasite may often need to make several attempts at infecting the same RBC before being successful. The inclusion of this complex is a new addition to the mathematical models describing the process of parasite infection.

One of the models was deterministic which simply means that if one starts with a certain amount of each type of cell (parasites, uninfected RBCs, etc.) one will always get the same number of cells out. The other model was a so-called random walk model which is a specific type of stochastic model. The basic principle behind this particular stochastic model is that the interactions between different cells are based on probabilities so that the outcome from one round of running the model (one simulation) is not guaranteed to be the same as the next. For example, any one parasite has a set number of steps it may take per simulation unless it dies or successfully infects a RBC. Instead of simply moving left, right, up or down, the direction in which it moves or "walks" is determined by picking an angle from an appropriate probability distribution. This simply means some angles have a bigger chance of being picked than others. A new angle is chosen for each step so that at the end of the simulation, every parasite has "walked" a unique path. The parameters responsible for the behaviour of the deterministic model were estimated from the available data. Some of these same parameters were then used in the random walk model in order to give predictions regarding the number of successful infections, the average number of attempts a parasite must make before being successful, the average distance travelled by a parasite before coming into contact with an uninfected RBC and how many of RBCs were infected by multiple parasites.

The most significant conclusion gained from this research was that while the mathematical models were constructed in a theoretically sound manner in which all interactions were based on observable reactions, the data required to robustly validate these models and acquire accurate estimates for the parameters was not available. An example of more useful data would be an experiment conducted in more physiologically realistic conditions in which parasites infect RBCs.

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Reference:

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