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Using iterative methods to determine an antigenic switching network in *Plasmodium falciparum*

Background: The malaria parasite *Plasmodium falciparum* evades host protective antibody responses by transcriptional switching between members of the var gene family, which encode the immunodominant surface proteins and virulence factors PfEMP1. This process of antigenic variation must be coordinated across a whole population of parasites during infection to minimise exposure of the parasites limited antigenic repertoire. Analysis of in vitro transcription data has previously suggested that this process underlies a non-random pattern of transcriptional change in which activation and silencing not only differs significantly between individual var genes but may also be biased [1,2].

Methods: To elucidate whether switching between var genes is predominantly governed by local switch hierarchies, whereby activation of var genes is dominated by switch biases between different genes, or by a more global hierarchy in which the rate of activation is independent of the previously active gene, we analysed in vitro expression data from eleven clones of the HB3 isolate together with the parent culture. We used simulated annealing and a Markov Chain Monte Carlo method to determine the off-rates and switch biases that best fitted the data, enabling us to construct a global gene switching network of the var gene repertoire of HB3. Tests using artificial data confirmed that these algorithms can recover reliable estimates despite the large parameter space.

Principle findings: Our results suggest that the course of antigenic variation in *P. falciparum* can be described by a fixed network of transition rates. Consistent with previous studies we found that activated var genes switch off at fixed rates which range between 0.3% and 5.2% per generation. Our results further show that the likelihood of a particular var being activated depends on which var is switching off, with biases towards one dominant gene found to vary from less than 25% to more than 75%. This indicates that var gene switching in *P. falciparum* is a combination of local switch biases and global activation hierarchies.

REFERENCES

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