# Summary

Malaria kills nearly 1.5 million and affects more than 500 million people annually, mostly in sub-Saharan Africa. The malaria parasite has developed resistance against almost all of the known drugs used for treatment. This fact has resulted in a constant battle between developing new anti-malarials and the parasite evolving resistance. One of the main drug combinations, pyrimethamine/sulfadoxine, targets the dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) proteins in the folate synthesis pathway of human malaria parasite, *Plasmodium falciparum*. The folate synthesis pathway is absent from the human host and thus presents itself as an ideal target for parasite-specific drugs.

The three dimensional atomic coordinates of a target protein can help in designing new, more effective drugs. Malarial proteins are notoriously difficult to crystallize and thus homology modelling was chosen as an alternative method to obtain a protein structure. DHPS and PPPK occur as a bifunctional protein in the folate metabolism pathway. In this study, homology modelling was used to do *in silico* modelling of *P. falciparum* DHPS and hydroxymethyldihydropteridine pyrophosphokinase (PPPK). For the *P. falciparum* DHPS model the crystal structures of *M. tuberculosis* and *B. anthracis* DHPS were used as templates and for the *P. falciparum* PPPK model, the crystal structure of *E. coli* PPPK. Molecular dynamics was used to investigate loop movement in DHPS and PPPK as well as to reveal the effect of resistance-causing mutations on sulfadoxine binding in *P. falciparum* DHPS.

This study revealed that four of the five known sulfadoxine resistance-causing mutations in DHPS disrupt the interaction between sulfadoxine and DHPS. This translates to a reduced capacity for sulfadoxine to inhibit DHPS, and results in resistance. The simulations also showed that both DHPS and PPPK have extensive loop movements during catalysis. The loop movements in DHPS and PPPK may also play a role in determining the catalytic rate of the enzymes.

The work presented here provides researchers with models of *P. falciparum* DHPS and PPPK. These models can be used to design experiments to investigate resistance, design new drugs and probe the structure of the PPPK-DHPS bifunctional enzyme.

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