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Contribution ID: **363** Type: **Oral Presentation**

Modelling drug action on parasites during blood stage Plasmodium infection.

Thursday, 12 July 2018 10:30 (20 minutes)

The artemisinins are our most effective class of antimalarials, and are the internationally recommended drugs for treating malaria. This class of antimalarials has been an important factor in reducing mortality due to malaria globally. However, the emergence of resistance to this most effective and widely used class of antimalarials threatens this progress. Despite their high efficacy the artemisinins are known to have high treatment failure when used without a longer acting partner drug. It has been proposed that this may be due to a persisting population of parasites that goes dormant and emerge after drug pressure has waned. Further, artemisinin resistant parasites have been studied and it has been found that they have an altered development pathway, which protects parasites during treatment. More recently, we have observed that a non-drug based stress can cause parasites to mature more slowly, highlighting the possibility that altering the developmental cycle is a general survival strategy of the parasite. Hence, we are interested in studying the development of parasites through their life cycle with and without treatment and to quantify how drugs perturb normal development. Here, we used a novel experimental system to track the development of malaria parasites after being exposed to different antimalarials in mice. We do this by measuring the RNA and DNA content of parasites over time. Using a Gaussian mixture model (GMM) and partial differential equations we attempt to determine what fraction of parasites had their life-cycle perturbed and whether perturbed parasites matured more slowly or not at all.
By fitting the GMM to data and simulating the PDE model, our preliminary results suggest that in the case of antimalarial drug treatment, we have two distinct parasite populations. We observed a population with arrested maturation and a second population with slower maturation compared to the untreated parasites. This work is ongoing, but preliminary results indicate that antimalarial drugs completely arrest a proportion of the exposed parasites, and alter the maturation of the surviving population.

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Session Classification: Parasites & pathogens

Track Classification: Disease - infectious