

Malaria parasite development is rhythmic and is synchronised with host feeding-fasting rhythms: How? Why? Huh?

Aidan J. O'Donnell¹, Kimberley F. Prior, & Sarah E. Reece^{1,2}

¹Institutes of Evolution, Immunology and Infection Research, University of Edinburgh, Edinburgh, UK

²Centre for Immunity, Infection and Evolution, University of Edinburgh, Edinburgh, UK.

Research into the role of daily rhythms in infections is gaining traction because explaining the regulatory mechanisms and fitness consequences of biological rhythms exhibited by parasites and hosts offers new avenues to treat infections. Malaria (*Plasmodium*) parasites exhibit ~24h developmental rhythms during replication in the mammalian host's blood and during transmission to insect vectors. The survival and transmission of malaria parasites is determined by whether these developmental rhythms are synchronised to the host's circadian rhythms, but how periodicity in these parasite traits is generated and maintained during infection is poorly understood. We address this using rodent malaria (*Plasmodium chabaudi*) infections of wild type (WT) and arrhythmic clock mutant (*Per1/2* double knock out) mice. We compare parasite and host rhythms in WT mice kept in LD and DD, with rhythms observed in mutant mice in DD. Second, we use the mutant mice and a restricted feeding regime to decouple host rhythms in feeding from body temperature and locomotor activity and examine the consequences for parasite rhythms. Finally, we apply a 'phase-shift' to parasites and track the parasite schedule for over ten cycles to determine how they resynchronise with host rhythms. We show that (i) parasite rhythms match the phase of the host's feeding-fasting rhythm and not the phase of rhythms in activity or body temperature; (ii) the timing of the parasite replication cycle is independent of the canonical 'core' host clock (i.e. transcription translation feedback loop); (iii) following perturbation, parasites reschedule to regain synchrony with the timing of the host's rhythm within 7 replication cycles and achieve this by speeding up the replication rhythm by 2-3 hours per cycle. We discuss how it is beneficial for parasites to be in synchronization with their host's feeding-fasting rhythms and plasticity in their development duration facilitates this synchrony by enabling parasites to make small daily changes to their schedule when necessary.