PhD in mathematical modelling of antigenic variation in malaria.

A phD position is available in the Laboratory of Parasite Host Interaction in Montpellier, France to start as soon as possible. The phD student will be directed by Prof. Ovidiu Radulescu and by Dr. Antoine Claessens.

We are seeking for highly motivated candidates with dual competence in mathematics and biology. The applicants should send a CV, a motivation letter and the names of three persons willing to recommend them to ovidiu.radulescu@umontpellier.fr

Summary:

Most of the half-million annual deaths from malaria are caused by Plasmodium falciparum. This unicellular eukaryote parasite is transmitted by female Anopheles mosquitoes. After developing in the liver, thousands of merozoites (invasive single cells) are released and quickly invade red blood cells. Within the erythrocyte, the parasite divides mitotically and over a dozen new merozoites burst out of the red blood cell every 48 hours, increasing the parasitaemia exponentially. The heavy burden of clinical malaria is only the tip of the iceberg. The vast majority of all P. falciparum infections worldwide are characterized by low parasitaemia and the absence of clinical symptoms. This reservoir of chronic malaria represents a substantial challenge to malaria eradication strategies. During the intra-erythrocytic phase of the parasite life cycle, P. falciparum presumably escapes the immune system with antigenic variation, mediated at least in part by var genes. Each parasite genome contains about 60 different var genes. At the transcriptomic and proteomic level, var genes undergo mutually exclusive expression, i.e. at any given time only a single type of VAR protein is exposed at the surface of the infected red blood cell. Several authors developed models for antigenic variation that successfully explain clinical malaria data. However, these models predict that all the 60 var gene variants will appear in the first 10 generations, which is enough to protect the parasite against immunity during development of exponential parasitaemia, but cannot offer long-term protection during chronic infection [1]. Recently, the team of Antoine Claessens in our lab showed that var genes undergo regular mitotic recombinations that generate novel “chimeric” sequences, and potentially encode new antigens [2]. The main goal of this thesis is to build a mathematical model of antigenic variation with recombination that explains long-term parasitaemia.

The mathematical modelling will be based on a novel approach developed in our lab. A mesoscopic model incorporating both single cell and population dynamics will be rigorously derived from first principles. The predictions of the model will be validated by a mRNA-seq experimental study of blood samples from a cohort of approximately 50 asymptomatic, chronic, P. falciparum carriers collected during the 2017 dry season in The Gambia, West Africa, by Antoine Claessens.

Keywords: stochastic processes, differential equations, antigenic variation, malaria

References

[1] Lauren M Childs and Caroline O Buckee. Dissecting the determinants of malaria chronicity: why withinhost models struggle to reproduce infection dynamics. Journal of The Royal Society Interface, 12(104): 20141379, 2015.
[2] Antoine Claessens, William L Hamilton, Mihir Kekre, Thomas D Otto, Adnan Faizullabhoy, Julian C Rayner, and Dominic Kwiatkowski. Generation of antigenic diversity in plasmodium falciparum by structured rearrangement of var genes during mitosis. PLoS genetics, 10(12):e1004812, 2014.