Multi-scale modeling of malaria

organized by
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Workshop Summary

Overview.
This workshop was the result of two combined SQuaRE proposals, both related to multi-scale modeling of malaria. The overall aim of the workshop was to discuss how to build upon previous work on malaria modeling at different scales (i.e. within human host, within mosquito host, and on population level) to develop a multi-scale model of malaria parasite transmission, incorporating the detailed stages of the parasite life cycle in the human and vector hosts. The workshop was intentionally designed to bring together both mathematical modelers and biological researchers to close the gap between both disciplines and allow for input in both directions.

Each morning, there were two talks. For Monday through Wednesday, the talks were aimed to close the gap between biologists and mathematicians, the talks on Thursday and Friday were shorter and covered ongoing research on multi-scale modeling of malaria to promote discussion between participants.

The speakers were:

- Monday: Silvie Huijben and Miranda Teboh-Ewungkem
- Tuesday: Nakul Chitnis and Melissa Conrad
- Wednesday: Lauren Childs and Hayriye Gulbudak
- Thursday: Group presentation (Christina Edholm, Zhuolin Qu, Denis Patterson, Joan Ponce, Lihong Zhao) and Megan Greischar
- Friday: Isaac Stopard and Olivia Prosper

Problem list and initial progress.

On Monday afternoon, we had a problem session moderated by Denis Patterson. The discussion focused predominantly on the evolution of drug-resistance in malaria parasites and insecticide resistance in mosquitoes and the various factors that could impact their evolutionary trajectories. Overall, a total of over 25 problems were identified. The organizers narrowed down and condensed the problems to a list of the following 8 problems:

(1) What is the role of transmission intensity in emergence and spread of drug resistance?
(2) How do we manage drug (and/or insecticide) resistance?
(3) How do we combine various (realistic and pragmatic) definitions of resistance?
(4) How do we incorporate multiple aspects of fitness (e.g., in context, in different stages)?
(5) What is the influence of vector traits on malaria transmission?
(6) What are the features that promote drug resistance in southeast Asia?
(7) What is the impact of insecticide resistance on malaria epidemiology?

(8) How do we model immunity to capture key features of parasite dynamics?

While there was widespread interest in all the questions, the participants worked in groups on problems related to questions 2, 5, 6 and 8 from Wednesday afternoon through Friday afternoon with the exception of Thursday and Friday early morning talks.

Progress on problem sets.

Which resistance management strategies are most effective in reducing the spread of insecticide resistance?. Various insecticide resistance management strategies have been proposed to reduce the emergence or spread of insecticide resistance. The project aims to compare the efficacy of these different insecticide control strategies for minimizing insecticide resistance by 1) developing a model to track the emergence of resistant alleles that can flexibly account for a wide range of control strategies, and 2) apply principles from optimal experimental design/control theory to find strategies minimizing resistance under a range of viable conditions. During the workshop, we formulated a discrete time Markov model motivated from classical models of population genetics, which allows us to track the evolution of resistant traits of a mosquito population encoded from three haplotypes. In each generation, adult mosquitoes produce gametes proportional to a fitness matrix W describing the viability of each genotype, followed by insecticide spray reducing the proportion of egg-laying females according to a resistance matrix R. Finally, the proportion of eggs is adjusted according to a maturation matrix M to give the proportion of adults of each genotype in the next generation. The model therefore can recreate a key fitness tradeoff through the matrices W and M penalizing the recessive resistant genotypes, and the resistance matrix R. The next steps for the project are to fit the model to experimental data from Vera-Maloof et al 2020 [PLoS Negl Trop Dis 14(3): e0007753] and Grossman et al 2018 [Biol. Lett. 14: 20180022], which will provide information on the parameterization of fitness costs, and to extend the model to include patch dynamics and to encode resistance for multiple insecticides.

What is the role of vector traits on malaria transmission?. Foundational malaria modeling work of Sir Ronald Ross and George Macdonald in the early to mid 1900s demonstrated the importance of key vectorial traits such as longevity and biting rate in a simple, yet elegant, model of malaria transmission dynamics. With more realistic representation of traits of the malaria mosquito (Anopheles), as well as the incorporation of multiple malaria-transmitting species, it remains an open question how each trait impacts malaria epidemiology, particularly in the light of Anopheles resistance to the chemical agents embedded in indoor residual spraying (IRS) currently used in vector control. During the workshop, this group discussed the role of multiple Anopheles species and their mobility on the transmission dynamics and control of malaria in two adjacent regions (or patches) in Uganda (where IRS was implemented in one region and not in the other).The plan is to start with developing a modeling framework for one of the two regions (taking into account the variability in the coverage of the IRS intervention and the evolution of insecticide resistance), and later extend to a metapopulation framework for both regions. Focusing on a particular region will allow for a detailed incorporation of data-derived features. In addition to adding some pertinent features often ignored in malaria transmission modeling (such as the reinfection of infected and recovered individuals, and gametocyte load-dependent transmission dynamics), the group

plan to carry detailed rigorous qualitative analysis, as well as uncertainty quantification, of the resulting non-autonomous, deterministic systems of nonlinear differential equations.

What is the optimal conversion strategy in the face of immunity? . Within a human host the malaria parasite chooses between two developmental pathways: the asexual and sexual. Asexual parasites continue to proliferate at a high rate, leading to persistence in the human host, while sexual parasites are terminally differentiated in the human host, but essential for transmission to the mosquito vector. The fraction of parasites that commit to become sexual parasites is known as the conversion rate, and is thought to be impacted by processes such as the level of immunity in the human host. During the workshop we discussed how to model within-host immunity to a level of granularity sufficient to represent the process but without all the detailed biology. We revisited a delay differential equation model in Greischar et al. 2019 [Evolution 73(11): 2175-2188] and formulated a partial differential equation adaptation to this model incorporating immunity. The PDE model has multiple time scales to include system time, time since infection of the human host, and time since infection of the red blood cell. Future work aims to derive a numerical scheme to simulate this model and assess optimal control strategies.

Why is Southeast Asia an epicenter of drug resistance emergence?. This group created a list of hypotheses for why drug resistance tends to emerge in SE Asia. Out of this list, the group selected one hypothesis to test: does mixing of populations with different levels of malaria immunity create conditions that promote the emergence of drug-resistant parasites? To tackle this problem, the group identified a within-host differential equation model of malaria parasite dynamics with dynamic host immunity on which to build. The group then discussed how to embed this model within a stochastic individual-based model framework, composed of individual humans, each with their own infection and immunity dynamics, and mosquitoes modeled at the population level using difference equations. The model would track parasite populations that can be broadly categorized as drug-sensitive or drug-resistant. The goal is to determine what degree of mixing between mature-immunity and naive-immunity individuals, if any, promotes the emergence of resistant parasites.