Progress Report 4: Co-Infection Modelling of Intra-Host Malaria Dynamics

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Introduction

Last week, I worked on creating a co-infection model to simulate more realistic intra-host malaria infection dynamics. This week, I hope to include more functionality to the existing to allow for different strains to adopt separate cue-based strategies (cue itself, whether cue is logged...). Doing so would allow more cue-based strategies to be directly compared in a competitive environment, offering insights into not only what the best conversion rate strategy is, but what kind of signals a malaria parasite should monitor in an infection. This is reminiscent of Dr. Greischar's attempt to correlate different cues to her optimal time-based conversion rate strategy. Here, instead, the benefit of one strategy over another is assessed directly and in a co-infection scenario.

This week is also mostly learning how to use the Compute Canada platform, which will take some time now but will drastically speed up future simulations. Using the newly created co-infection model, I performed a series of competition simulation, including

- optimal strategy obtained from natural log (from last report vs every strategy obtained from untransformed cue)
- co-infection strategy vs single infection strategy in a single infection scenario

Progress

0.1 Log10 cue transformation does not differ from natural log-transformation of cue for conversion rate optimization

Following our last discussion, I tested out whether natural log transformation of cue differ from log10 transformation of cue. Here, I performed optimization of single infection model with Kamiya's mode of immunity (Figure 1). Cue is set to dependent on either $I(t)$, $ln(I(t))$, or $log10(I(t))$.

Overall, for a single infection scenario, there is no difference in the optimal conversion rate between natural-log and log10 transformed cue. Hence, in the future, Log10 will be used in place of natural-log transformation.

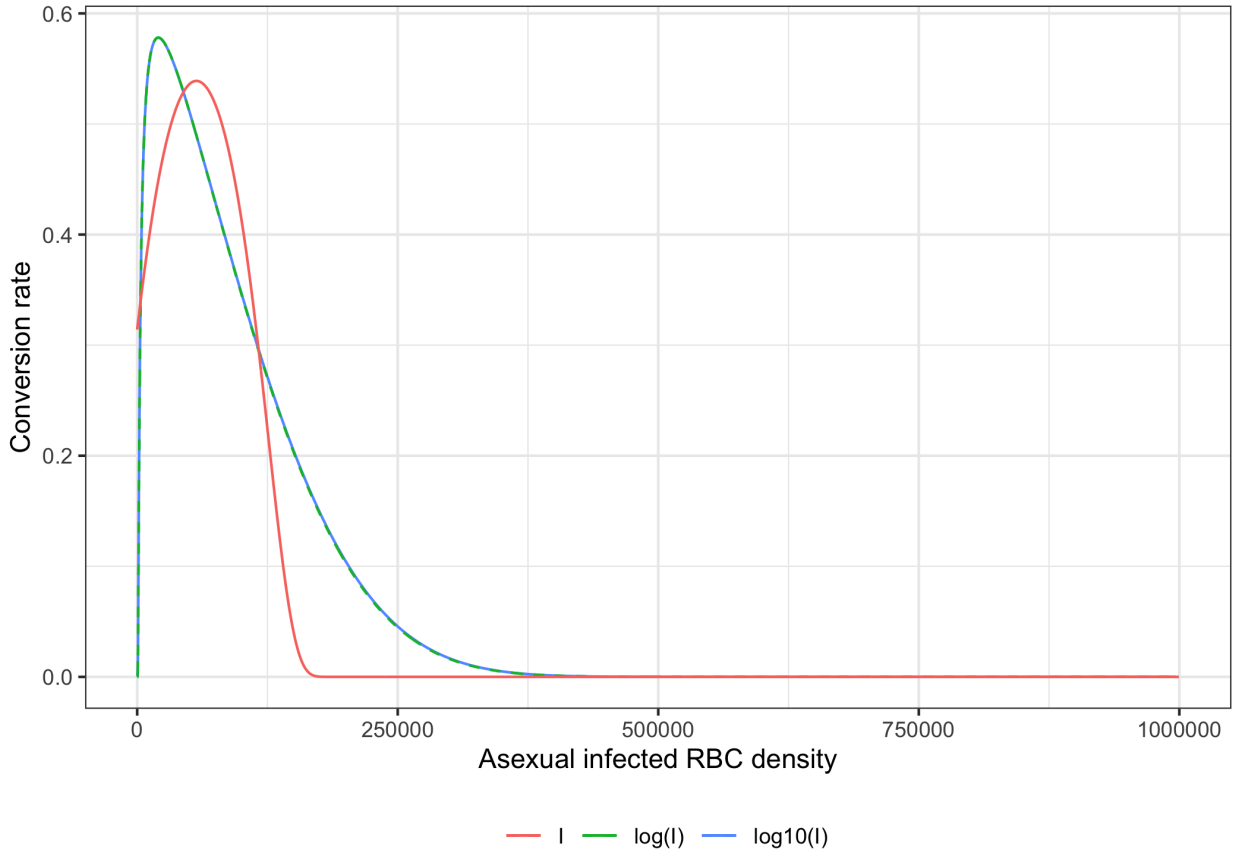

Figure 1: Natural-log transformation of cue is not significantly different from log10 transformation of cue. L-BFGS-B is used to optimize the lagged single infection model with Kamiya's mode for immunity, where cue is dependent on asexually infected RBC (maximum density of $6 * 10^6$).

0.2 Co-infection strategy is sub-optimal in single infection scenario

In the previous report, I found that in a co-infection environment, parasite adopting the optimal co-infection strategy has higher fitness than parasite adopting the optimal single-infection strategy. Here, I wanted to see how parasites adopting the co-infection strategy fare well in a single infection scenario. Lagged infection models were simulated using optimal single infection conversion rate strategy (natural log-transformed) and optimal co-infection conversion rate strategy (Figure 2).

In a single infection scenario, parasites adopting the best co-infection strategy scenario had lower fitness compared to parasites adopting the best single-infection strategy (Figure 2). Overall, the co-infection strategy advocates for both delayed transmission investment and lower overall conversion rate, leading to higher parasite density and immunity elicitation. The rapid removal of parasites by immunity results in swift decline in parasite density, which ultimately limits the fitness of parasites adopting a lower conversion rate strategy that is more suitable for co-infection.

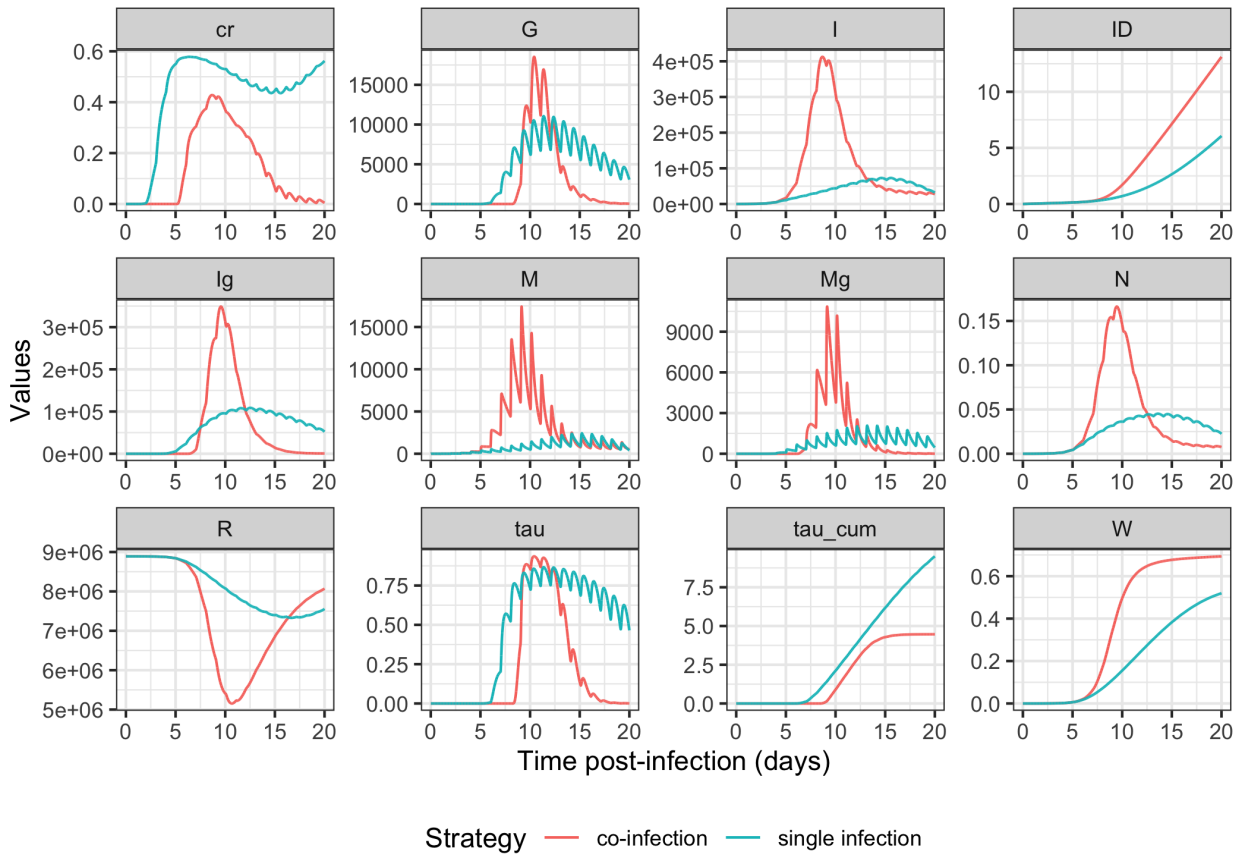

Figure 2: Adopting the best co-infection strategy leads to diminished fitness in single strain infection. L-BFGS-B is used to optimize the lagged single infection model with Kamiya's mode for immunity, where cue is dependent on asexually infected RBC (maximum density of $6 * 10^6$).

0.3 Log vs non-logged in co-infection

Last week, I found that co-infection model optimization using raw asexual iRBC density lead to negative-dependent selection of convergent strategy. The same oscillating property of optimal conversion strategy is not found when I natural-transformed the cue. I hypothesized that when parasites receive their signal in log-transformed terms, they can make better decisions (which is constrained by knot placement and computational power required to optimize spline with high df. If spline is flexible enough, I don't forsee any difference in conversion strategy between log-transformed and not transformed cue), which allows for one strategy to definitive "win out." Following that logic, then we expect a parasite adopting the optimal conversion rate strategy obtained via log-signal, they will have a higher co-infection fitness when competed with a parasite with an optimal conversion rate strategy obtained via non-transformed signal. Given that there is no definitive "best" strategy for my non-transformed co-infection model, I competed the optimal log-transformed strategy to every iteration of non-transformed strategy and compared their cumulative fitness (Figure 3). I also tried to maximize fitness difference between strains that receive non-transformed cue when competed against another strain that adopts the optimal log-transformed conversion rate strategy. Even after convergence, the optimal non-transformed conversion rate strategy had lower fitness (data not shown).

In a co-infection scenario, the optimal conversion rate strategy derived from natural log-transformed cue always obtains a higher fitness when competed against another conversion strategy derived using non-transformed cue (Figure 3), suggesting that parasites that receive their cue on the scales of logs may indeed

adopt better co-infection strategies.

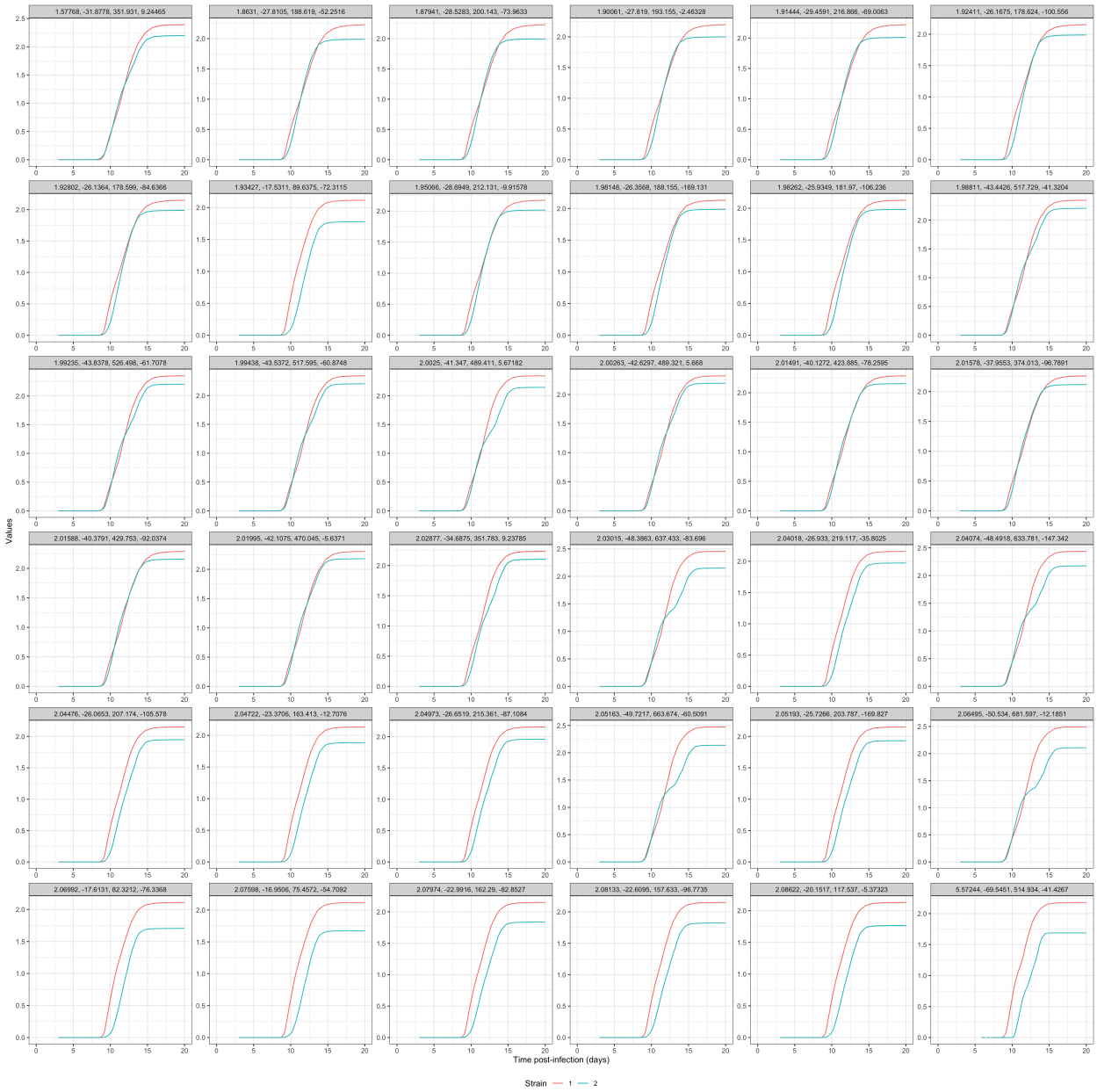

Figure 3: Optimal co-infection strategy derived from natural log-transformed cue out-competes every iteration of conversion rate strategy derived from non-transformed cue. Strain 1 always adopts the optimal conversion rate strategy obtained when cue is natural log-transformed. In every facet, strain 2 adopts a different iteration of co-infection strategy derived when cue is not transformed. Plotted is the fitness accumulation rate. L-BFGS-B is used to optimize the lagged co-infection model with Kamiya's mode for immunity, where cue is dependent on asexually infected RBC (maximum density of $6 * 10^6$).

Model reflection

Previously, my goal is to write a model that simulates a typical infection dynamic that are reasonably realistic, to which I defined as being able to capture experimental RBC and parasite dynamics within a 10-fold limit (taking into account, of course, of variations between mouse and parasite strains). Currently, in a single infection scenario, parasites adopting the optimal co-infection strategy has a peak asexual iRBC density of $4.1 * 10^5$ cells, a peak sexual iRBC density of $3.5 * 10^5$ cells, a peak mature gametocyte density of $1.85 * 10^4$ cells, and a minimum RBC density of $5.15 * 10^6$ cells. Overall, the peak asexual iRBC count looks good. However, the RBC density count is higher than expected. If we include only G as gametocyte, then the gametocyte looks good. If not, our model is over-predicting the gametocyte density but a lot. Overall, a more accurate model is predicting much lower conversion rate and I could not think of other processes (the only exception is adaptive immunity, but that is not my priority) to add.

Another area of model realism I am checking is conversion rate, which should be within reasonable limit. While our ability to accurately quantify conversion rate is limited [2], flow cytometry based assay does offer a sensitive estimation of conversion rate, albeit in an *in vitro* environment that does not capture the complexity of the intra-host environment. For *Plasmodium falciparum*, the upper limit of conversion is around 50% [1]. Currently, our co-infection model using asexually infected RBC-based cue suggests a maximum conversion rate of 40%, a characteristic that is surprisingly rigid given that sensitivity of cue-based model.

But perhaps more informative is the shape of the reaction norm. Based on how the *pfap2-g* locus is regulated, we could infer characteristics of what a realistic conversion rate strategy would look like. The current model of sexual commitment in *P. falciparum* suggests that even in the absence of environmental cues, the *pfap2-g* locus is stochastically activated in a small subpopulation of cells. The stochastic nature of baseline *pfap2-g* expression level meant that different parasites in a population would require varying levels of environmental cues to reach the threshold for sexual-commitment. This meant that when environmental signal is below the critical threshold needed to induce sexual commitment, increasing signal strength should lead to a gradual rise in conversion rate. The *pfap2-g* locus also exhibits positive autoregulation where free AP2-G proteins can bind to the cognate motif in its promoter and further increase gene transcription [3]. Positive autoregulation introduces an additional later "stage" in the reaction norm, where crossing the "activation threshold" for AP2-G promoter binding leads to further increase in *pfap2-g* transcription (thus conversion rate) [3]. Stochasticity and positive autoregulation are not the only regulatory motifs present in the *pfap2-g* locus but, together, they should lead to the formation of a two-humped reaction norm. The first hump is characterized by the slow increase in conversion rate due to varying level of baseline *pfap2-g* expression. The second, steeper hump is caused by the DNA binding activity of AP2-G that further increases its own transcription. Interestingly, the conversion rate strategy obtained for co-infection model with Kamiya's mode for immunity (asexual iRBC as cue) exhibits the so-called two-humped conformation (Figure 4).

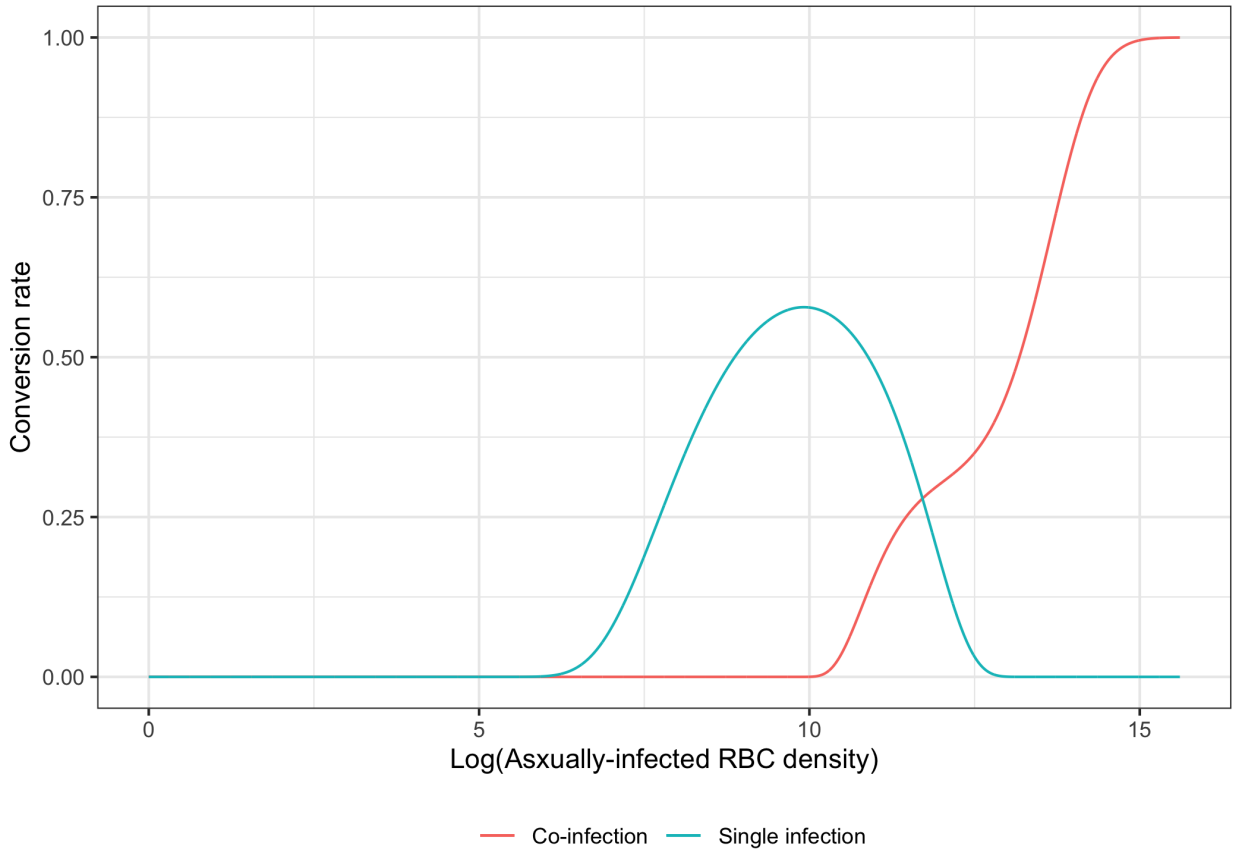

Figure 4: Two-humped conversion strategy of the co-infection model. Kamiya's mode for immunity is used and conversion rate is dependent on the density of asexual iRBC.

Future directions

In the next week, I am hoping to start experimenting with drug action, starting off with the well-studied pyrimethamine and slowly working towards artemisinin incorporation.

References

[1] Nicolas M.B. Brancucci et al. "Probing Plasmodium falciparum sexual commitment at the single-cell level". In: *Wellcome Open Research* 3.70 (Oct. 2018). DOI: 10.12688/WELLCOMEOPENRES.14645.4. URL: /pmc/articles/PMC6143928/%20/pmc/articles/PMC6143928/?report=abstract%20https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6143928/.

[2] Megan A. Greischar et al. "Quantifying Transmission Investment in Malaria Parasites". In: *PLOS Computational Biology* 12.2 (Feb. 2016), e1004718. ISSN: 1553-7358. DOI: 10.1371/JOURNAL.PCBI.1004718. URL: https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1004718.

[3] Asaf Poran et al. "Single-cell RNA sequencing reveals a signature of sexual commitment in malaria parasites". In: *Nature 2017 551:7678* 551.7678 (Sept. 2017), pp. 95–99. ISSN: 1476-4687. DOI: 10.1038/nature24280. URL: https://www.nature.com/articles/nature24280.