Progress Report 5: Co-infection dynamics with delayed invasion strain

Avril Wang

October 7th, 2021

Introduction

In the previous meeting, I proposed that it is time to focus more on drugs. However, the idea of looking into the effects of delayed infection is intriguing. In regions with high transmission intensity, rare invading mutants have a higher probability of infecting a host that is already infected by the residence strain. Hence, the optimal co-infection strategy at the early stages of invasion may be different from the optimal strategy in later stages of invasion.

In the last two weeks, I focused most of my energy on creating delayed co-infection model. I also started thinking of incorporating drug actions into my model, which much more complicated than previously expected (as with all things in research!).

Progress

0.1 Delaying infection also delays transmission investment

To incorporate delayed infection dynamics, I made the following modifications. Initial value for strain 1 is set to 0 and the injection of strain 1 is modelled as an instantaneous event that occurs at $t = delay$. The death of initial infected RBC of strain 1 is modelled as a β distribution that is horizontally transformed by x days. In addition, all components of the piece-wise ODEs are shifted x days forward. I tested the modified function on the single-infection model and was able to confirm infection delay and no changes to other aspects of infection dynamics (data not shown).

I next explored the effects of increasing delays on optimal co-infection. Even small delays in infection date prevents invasion strain from having a higher fitness than the residence strain (data not shown). Hence, I altered my co-infection wrapper function `https://github.com/avril-microbes/Project-Plasmodium/blob/main/functions/co_infection_opt.R` to 1) repeat optimization once more if strain 1 fitness is less than strain 2 fitness (starting parameter set as final parameter set from last optimization attempt) 2) repeat algorithm if repetition improved results, and 3) exit loop if repetition did not improve strain fitness. To investigate the effects of delayed infection time on optimal conversion rate strategy, I set the residence strain to the optimal co-infection strategy (no delay) and delayed the invading strain infection time by $0.5, 1, 2$, and 3 days. When optimized using L-BFGS-B, I found that increasing delays in invading strain infection time increased the threshold for transmission investment (Figure 1A) but did not delay transmission investment in an actual infection (Figure 1B). Interestingly, increasing infection delays increased conversion rate amplitude and shortened the duration of heightened conversion rate (Figure 1B). When the length of delay reaches 2

days, further increase in delay duration did not significantly alter the optimal conversion rate strategy (Figure 1A). The changes in conversion rate strategy led to delayed asexual iRBC and gametocyte production in the delayed strain (Figure 1B). I next assessed whether adopting a delayed conversion rate strategy affected parasite fitness for earlier and later infection. Overall, there is a fitness cost for earlier infection when parasites adopt the optimal delayed conversion rate strategy and there seems to be little fitness gain for delayed infection (Figure 1C). The lack of fitness gain conferred by delayed conversion rate strategy could be due to the intrinsic low fitness of late-invading strains where a delay of more than 5 days always resulted in infection failure (Figure 1D). Interestingly, day 5 is also where both non-specific and targeted immunity starts to increase (Figure 1D), suggesting that immunity could be the main barrier towards delayed parasite invasion.

Overall, delaying infection seems to lower the optimal conversion rate strategy (shortened duration should trump increased amplitude). However, given that delayed infection strains have low fitness, there is little advantages in adopting the optimal delayed conversion rate strategy. This conclusion does not apply to scenarios in which the starting inoculum concentration is different. In the delayed infection scenario, not only does the residence strain have the advantage of earlier infection, it also has sufficient time to trigger an immune response which leads to the rapid elimination of the invasion strain, even during the period where the asexual population of the residence strain is declining (hence why even later infection at day 18 fails). When the difference is in the starting inoculum concentration, however, the invading strain is not burdened by the heightened immune response and would likely need to adopt alternative conversion rate strategies.

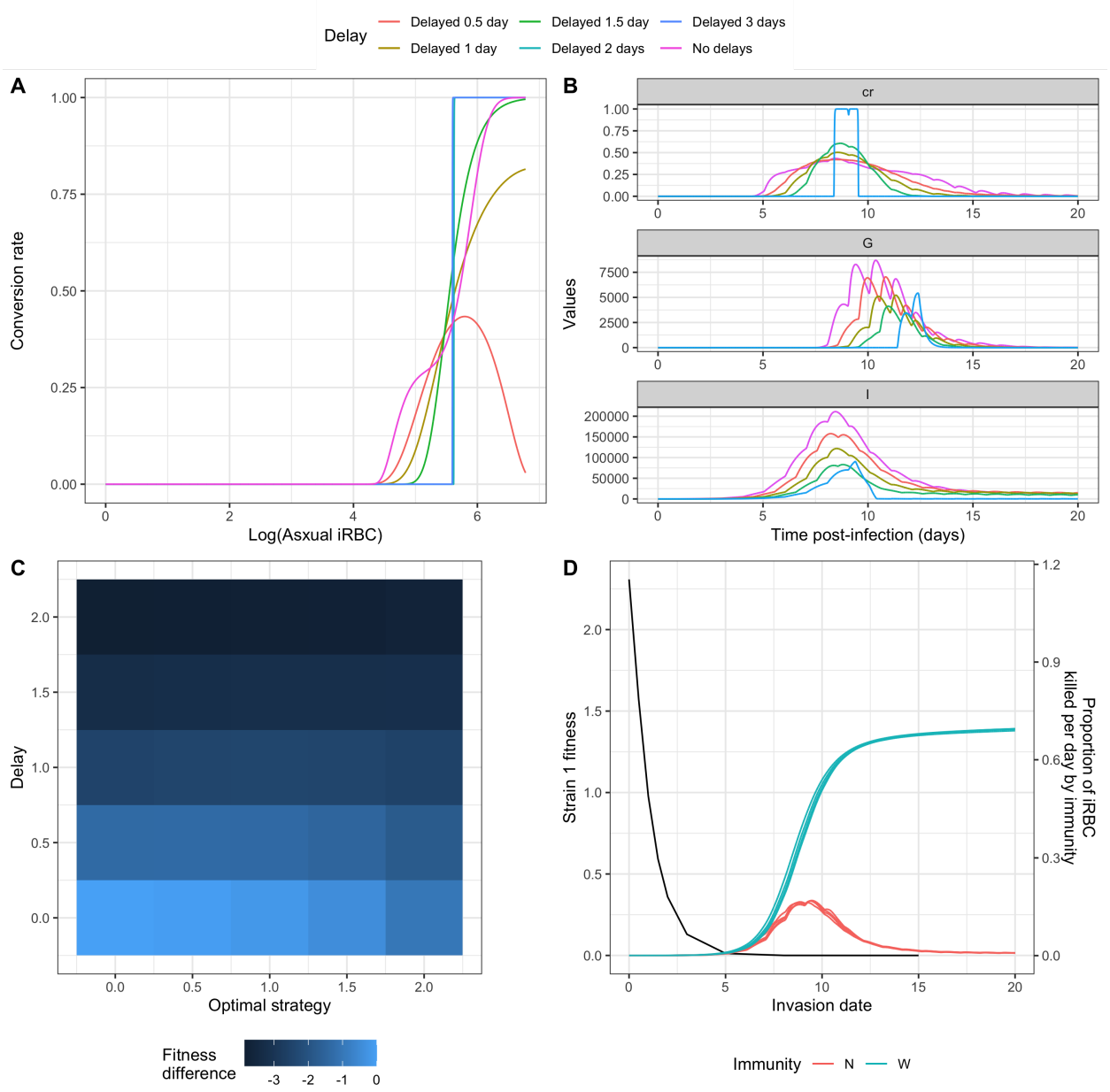

Figure 1: Optimal delayed conversion strategy has a higher threshold for transmission investment but did not significantly improve fitness. (A) Optimal conversion rate strategy for strains that invaded at various times after residence strain invasion. (B) Conversion rate dynamics for co-infection between delayed strain and residence strain adopting the optimal 0-day conversion rate strategy. (C) Fitness difference between invading strain and the residence strain. The invading strain adopts various strategy optimized for specific delays (x-axis) while invading at various days (y-axis). (D) Maximum invading strain fitness for varying days of infection delay plotted against time-series immunity action. Each line of immunity represent the simulation of co-infection with invasion date set to $0.5, 1, 1.5$, or 2 days. N = Non-specific removal of RBC, W = targeted parasite killing. 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 $6 * 10^6$).

0.2 Decreasing starting dose mimic effects of delayed infection

To investigate whether varying the inoculation size affected the optimal conversion rate strategy, I set the invading strain initial inoculum volume as 0.75, 0.5, 0.25, and 0.1 times the residence strain (10^4 parasites).

Overall, decreasing initial inoculum volume increased transmission delay (Figure 2A), increased time-series conversion rate amplitude (Figure 2B), and decreased heightened conversion rate period (Figure 2B). Parasites with smaller starting dosage also had delayed iRBC and gametocyte production (Figure 2C). Parasites seem to respond to decreasing initial dosage similarly to increasing infection delays. Interestingly, decreasing starting dosage exerts almost a linear relationship with parasite fitness, as opposed to the exponential relationship seen in delayed infection (Figure 2D). The decreased penalty of smaller starting dosage could be due to the fact that strains with smaller inoculum volume are not faced with high immunity at the start of infection, unlike delayed infection strains.

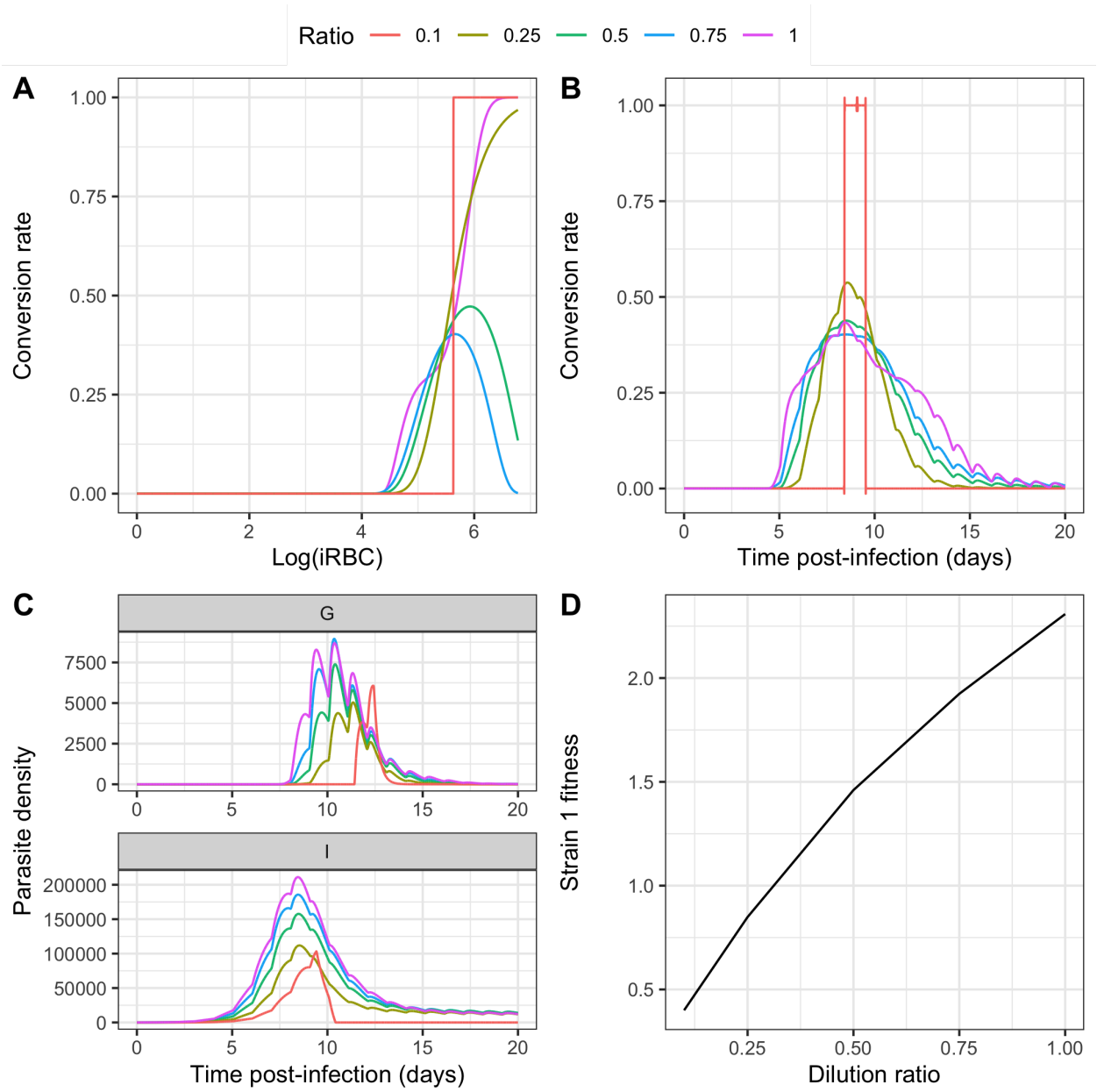

Figure 2: Decreasing starting dosage increased transmission investment delay. (A) Optimal conversion rate strategy for strains that invaded at various times after residence strain invasion. (B) Conversion rate dynamics for co-infection between delayed strain and residence strain adopting the optimal 0-day conversion rate strategy. (C) Gametocyte and asexual iRBC dynamics of invading strain with varying starting dose ratio. (D) Optimal strain 1 fitness for varying starting dosage dilution ratio.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 $6 * 10^6$).

0.3 Rigid pyrimethamine dosing increases optimal conversion rate

I implemented a simple model of pyrimethamine administration as used in Birget *et al.* [1]. Here, pyrimethamine is administered on day 11 and 12 and the length of drug action after day 12 is determined by the function:

$$length = 3.557 - \frac{2.586}{1 + e^{-8.821+d}}$$

where d is drug dosage in mg/kg. While the drug is present in the body at a sufficiently high concentration, it kills 94% parasites per day, giving us an instantaneous death rate of $\mu_d = -ln(1 - 0.94) = 2.81$.

I performed single infection optimization with pyrimethamine doses that varied from 0 mg/kg to 14 mg/kg (Birget *et al.* tested up to 15 mg/kg). NOTE: Need to reperform simulation with increase time range in case parasite can recover for lower drug dosage. Pyrimethamine administration led to increased transmission delay of the optimal conversion rate strategy (Figure 3A). Administration of even a small amount of drug lead to rapid gametocyte and iRBC density decline (Figure 3B). Here, the delay in transmission investment allows infection to peak earlier such that gametocyte density is maximized before drug treatment (Figure 3B), suggesting that transmission investment delay allows for more acute infection.

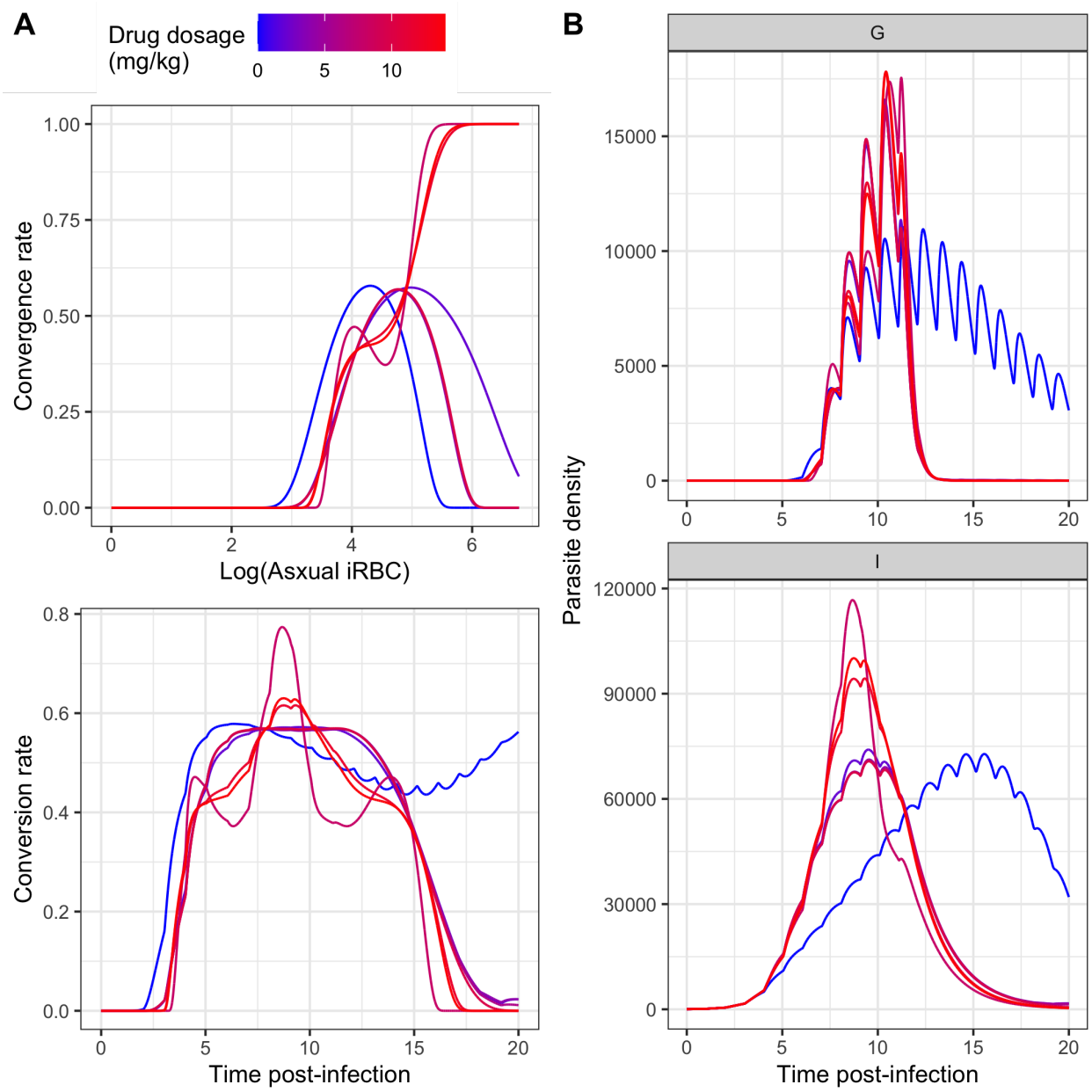

Figure 3: Pyrimethamine administration on day 11 leads to delays in transmission investment. (A) Drug administration leads to transmission investment delay in reaction norm and in infection. (B) Drastic decline in parasite density after drug administration. Delay in transmission investment results in earlier gametocyte peak that proceeds drug treatment.

Future tasks

I am hoping to analyze the simple drug model more, specifically exploring the effects of different drug administration day, the possibility of "triggered" drug administration (drug only administered when parasitemia reaches certain concentration, representing that sicker patients tend to seek medical treatment), and the effects varying cue usage on drug evasion.