# Progress Report 6: Pyrimethamine Models and Differential Cues

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## Introduction

In the previous meeting, we spoke about exploring whether different cues would provide more information about drug action. For instance, malaria parasites that uses asexual iRBC density as a cue would not be able to differentiate between low parasite density due to initial invasion or drug/immune action.

We proposed the rate of change as an alternative. However, derivative does not take into account of density, which should bear an effect if we consider cue-gene expression interaction to exhibit typical receptor-ligand kinetics. The only case in which derivative-based cue can circumvent the issue of density is if the cue itself is a measurement of change. For instance, if bursting of iRBC releases the signal that triggers/suppresses gametocyte development, then the derivative would be an accurate representation of cue density in the environment (although we are assuming signal has very short half life here).

This week, I used the simple pyrimethemine drug model with single infection dynamics to further explore the effects of

- drug dosage
- drug administration timing
- different cues and their effects on drug action

## Progress

### 0.1 Pyrimethamine administration leads to slight transmission delay

To probe whether drug administration affects the optimal conversion rate strategy, I optimized the model for 10 mg/kg (concentration estimated to prevent recrudescent infection if drug is administered on day 11-12) of pyrimethamine administered on day 10, 12, 14, and 16 post-infection. Earlier infection cannot be simulated due to recurrent infection that occurs after drug wears off (strategy changes depending on length of simulation). I found that pyrimethamine administration resulted favours slightly delay transmission investment (Figure 1A), which results in higher gametocyte and iRBC density prior to drug administration (Figure 1B).

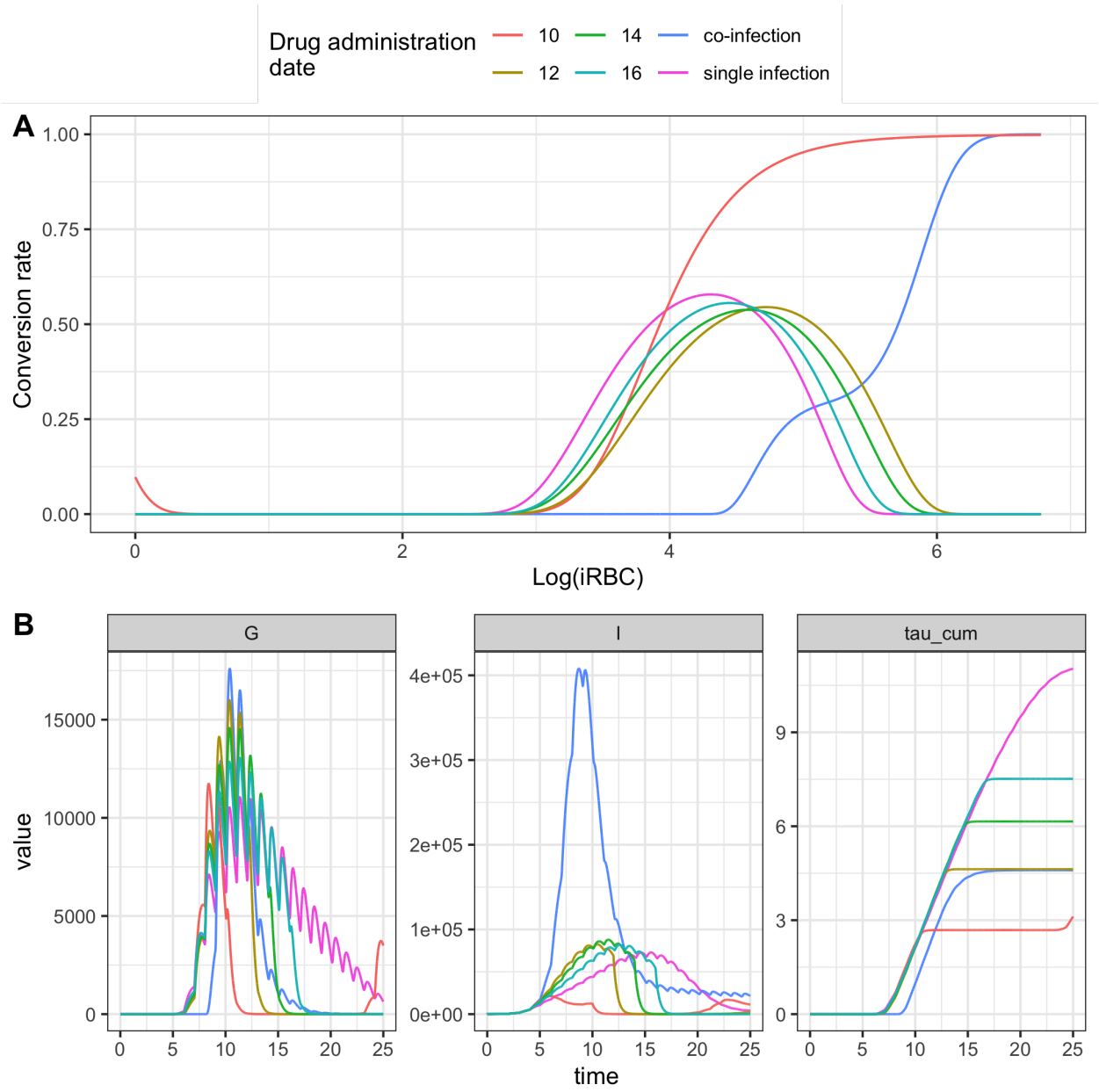


**Figure 1: Pyrimethamine administration leads favours transmission delay.** (A) Drug administration leads to transmission investment delay in reaction norm and in infection. (B) More acute infection in strains optimized against late-pyrimethamine administration.

## 0.2 Parasite-based derivative cues are unsuitable for cue

Before delving into the question: which cue should a parasite use to best respond to drugs, we have to consider the fact that a good cue should not oscillate wildly (unless the environment is also oscillating!). I plotted below the derivatives of different aspects of the model for the optimal single infection model. The model is simulated for 40 days with the Tsukushi model of immunity. I found that cue based on mature parasite density (G, M) exhibits large oscillation due to the wave-like nature of infection RBC burst patterns. In contrast, the derivative of iRBC and RBC are dampened but are nonetheless wavy. The instantaneous

death rate (ID; which can only be produced using derivatives)

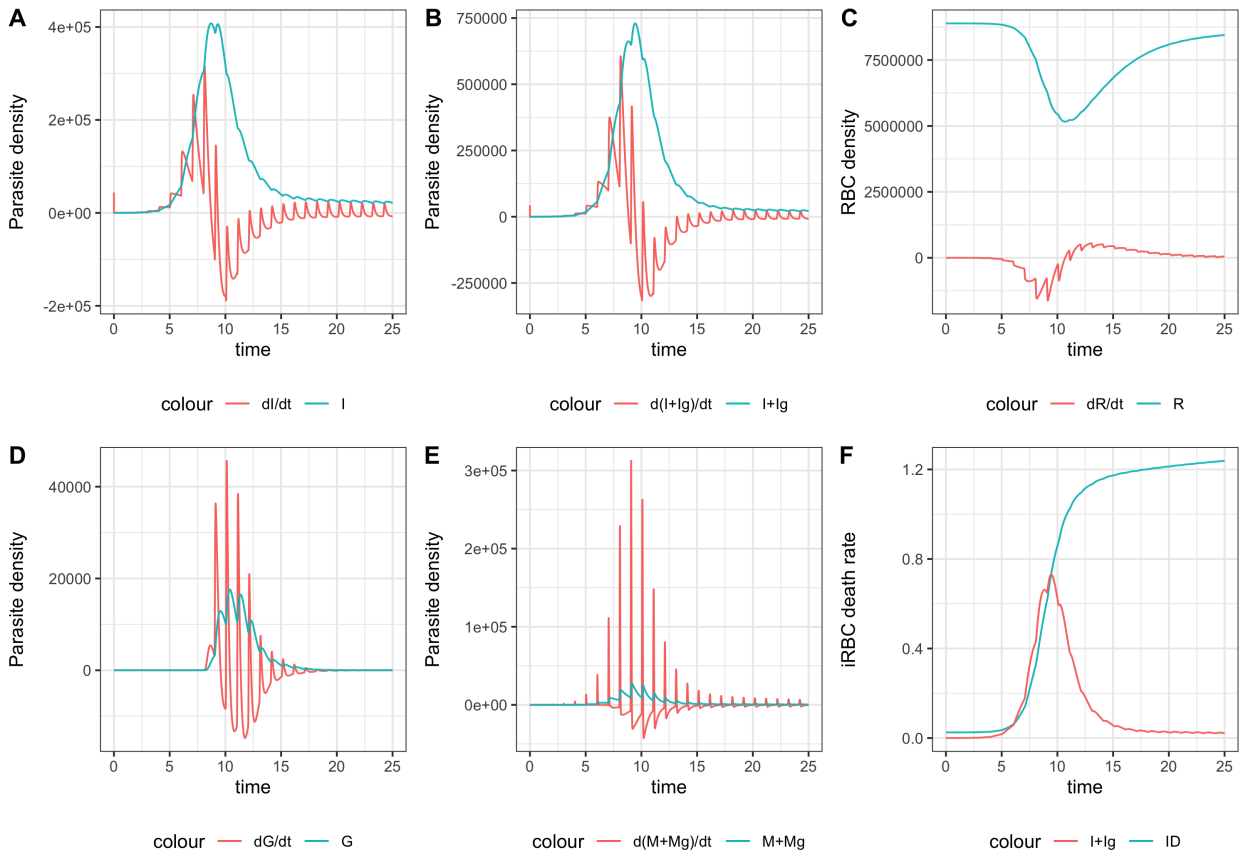


**Figure 2: Derivatives of parasite density oscillates wildly during infection**(A) Derivative of asexual iRBC density plotted against asexual iRBC density, (B) derivative of total iRBC density plotted against total iRBC density, (C) derivative of RBC density plotted against RBC density, (D) derivative of gametocyte density plotted against gametocyte density, (E) derivative of merozoite plotted against merozoite density, (F) iRBC death rate plotted against total iRBC density.

## 0.3 Troubleshooting derivative-based cue

For every new cue that I implement, it is an iterative process to find the optimal cue range to optimize for. Unfortunately, all of my derivative-based cue give constant conversion rate time series. Nonetheless, an interesting observation emerged out of these erroneous results. Most cues produced a peak in conversion rate before day 5 and the day of drug administration (Figure 3), suggesting that conversion rate declines with decreasing parasite population/recovery of RBC. Higher conversion rate also allows for recovery post drug-treatment (Figure 3C) whereas lower conversion rate does not.

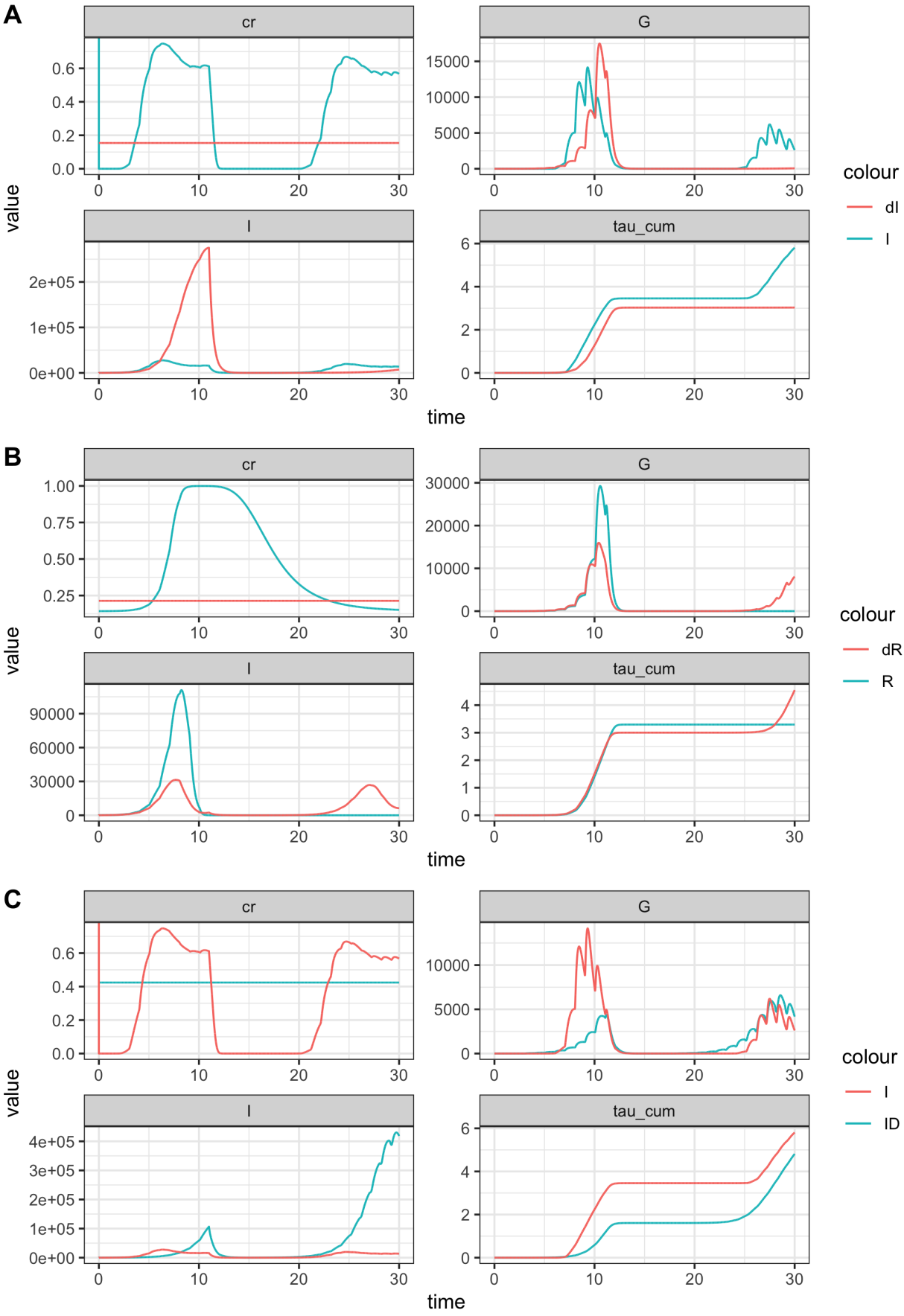




**Figure 3: Infection dynamics of parasite adapting frequency and derivative-based cues.** (A) Asxual iRBC-based cue, (B) RBC-based cue, (C) iRBC death rate-based cue with asexual iRBC as reference cue.

## Future tasks

In the coming weeks, I am hoping to:

- Debug derivative-based cue
- Find suitable cue range for derivative-based cue optimization
- Probe the effects of difference cue on parasite fitness with and without drug administration
- Explore "average" derivative cue to avoid the issue of oscillating cue (e.g. number of parasite burst in X time)