Progress Report 8: Preliminary Thoughts on Malaria Cue Perception

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Introduction

In our last meeting, we spoke about planning out a set of analyses in hopes of generating a 'complete' story for a potential manuscript. In this last week, I have been doing too much analysis and mostly invested my time into reading broadly about phenotypic plasticity in general.

Before delving into possible cues we should explore, I want to bring up a question I never thought of before. The canonical pathway for malaria sexual commitment is the next cycle conversion (NCC) where the decision to enter gametogenesis is made in the generation before [1]. However, same cycle conversion (SCC) is also possible. The switch between NCC to SCC seems to be a threshold-dependent phenomenon that relies on the extent of *pfap2-g* expression during early ring stage [1]. The existence of SCC suggest that the dominance of NCC is not due to inherent implausibility of rapid cue-sensing and reaction. Hence, what puzzled me is why would malaria take-part in NCC when SCC seems to be, intuitively, a better option? In the phenotypic plasticity literature, NCC would be referred to as anticipatory parental effect (APE) [3]. APE is expected to evolve when parental environmental conditions can reliably predict offspring environmental conditions [3]. However, then the logic follows that the most reliable prediction of offspring environmental condition is the environmental condition sensed by the offspring. Hence, under what condition can APE (NCC) be a better strategy than irreversible developmental plasticity (SCC)? One of the reasons I thought of is biological noise. In NCC, the decision of whether to sexually commit is made based on malaria cue-perception from ring stage to early schizont stage [4, 2]. This period of time buffers potential biological noises in cue (think of our previous attempt to smooth derivative-based cues). In contrast, if malaria makes most of their decision via SCC, then the decision of sexual commitment must be made during early ring-stage, increasing the effect of biological noise on sexual commitment decision-making. Hence, the dominance of NCC over SCC suggest that malaria might be sacrificing cue-predictability (accuracy) for higher cue-reliability (precision). Hence, in our examination of cues, we must incorporate the effects of "cue-smoothing" on the viability of each environmental signal.

Progress

Cues exhibit a diverse range of noisiness and degree of state differentiation

As promised, here is a table of cues I am hoping to explore and some rationale behind each of them(LaTeX tables does not like me). `https://docs.google.com/document/d/1-TTn2lc3w0EwqyMShTMpPJatMhfjR99miKEBQogE4hA/edit?usp=sharing`

Before running the models, I performed preliminary quantification of cue noise and information load. As I mentioned in my previous report, a good cue should allow parasites to distinguish between different parts of infection course (initial infection, growth, peak, decline), otherwise referred to as state differentiation. A cue must also be reliable to minimize the extent of noise that parasite detects. In the following analysis, I quantified the extent of state differentiation as the difference between normalized average cue during parasite growth phase and the normalized average cue during parasite decline phase. Growth phase is defined as the time period from $t = 0$ to the time of maximum total iRBC density (best-strategy co-infection model). The noisiness of a cue is quantified using a typical signal-to-noise ratio (SNR) formula such that

$$SNR = \frac{\bar{x}}{\sigma}$$

over a 1-day neighbourhood.

The characteristic of each cue is plotted over a scatter plot with the degree of state differentiation as the x-axis and the average SNR over the 20-day infection period as the y-axis (Figure 1). As expected, cues with lower magnitudes (e.g. gametocyte density, merozoite density) have a lower SNR (Figure 1) whereas cues that exhibit a sigmoid time-series (data not shown; extent of targeted immunity, extent of iRBC burst) display a high SNR and a high degree of state differentiation. Interestingly, log-transformation of the cues resulted in both an increase in SNR and degree of differentiation (Figure 1), suggesting that the increase in fitness we previously observed with logged vs not logged cue may not be only due to spline-constraint. Interestingly, I found RBC density to exhibit high degree of state differentiation and high SNR. Hence, RBC density is a priority for future model simulation attempts, especially in regard to optimizing the range at which RBC is sensed by the parasite.
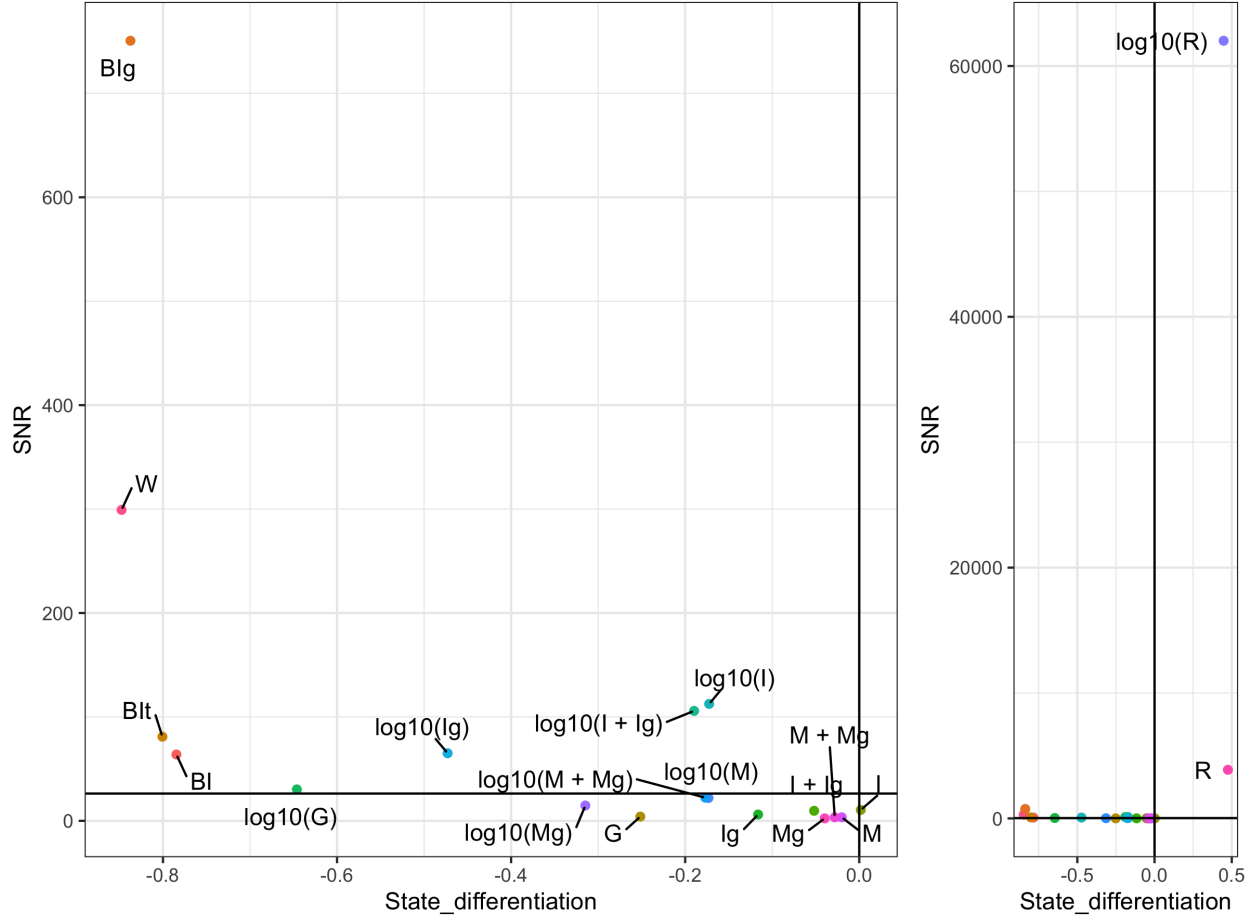
Figure 1: Extent of state differentiation and average signal-to-noise ratio (SNR) conferred by different cues. Cue characteristics were calculated based on the infection course of a 20-day co-infection model when the parasite employs the optimal strategy Abbreviations: BIg, sexual iRBC burst frequency; BIt, total iRBC burst frequency; BI, asexual iRBC burst frequency.

NCC disproportionately benefits certain cues

In the introduction, I brought up the conundrum of malaria's engagement in NCC as opposed to SCC. One of my hypothesis is that malaria engages in NCC to increase cue reliability (higher SNR) in exchange for lower cue accuracy (parental cue is less representative of offspring cue). To model the effects of engaging in NCC on cue characteristics, I calculated the difference between SNR of the smoothed cue (running mean with 1-day window to simulate the approximate period of asexual iRBC development) and the original SNR. To model the effects of 1-day delay on cue accuracy, I calculated the absolute mean difference between normalized cue and its value 1-day ago.

I found that engaging in NCC disproportionately benefit some cues over others (Figure 2). For instance, log-transformed iRBC and merozoite density experienced large increase in SNR in exchange for slight increase in cue inaccuracy. Whereas other cues, such as raw parasite density, experienced little increase in SNR, but large increase in cue inaccuracy (Figure 2). Strangely, cues that reflect parasite death (e.g. W, BIt, BI) experienced a decrease in SNR after smoothing. The decrease in SNR for these cues may be due to the monotonic nature and inherent smoothness of the original cue. Subsequent smoothing, thus, decreases the mean value of the original cue and decreases SNR.
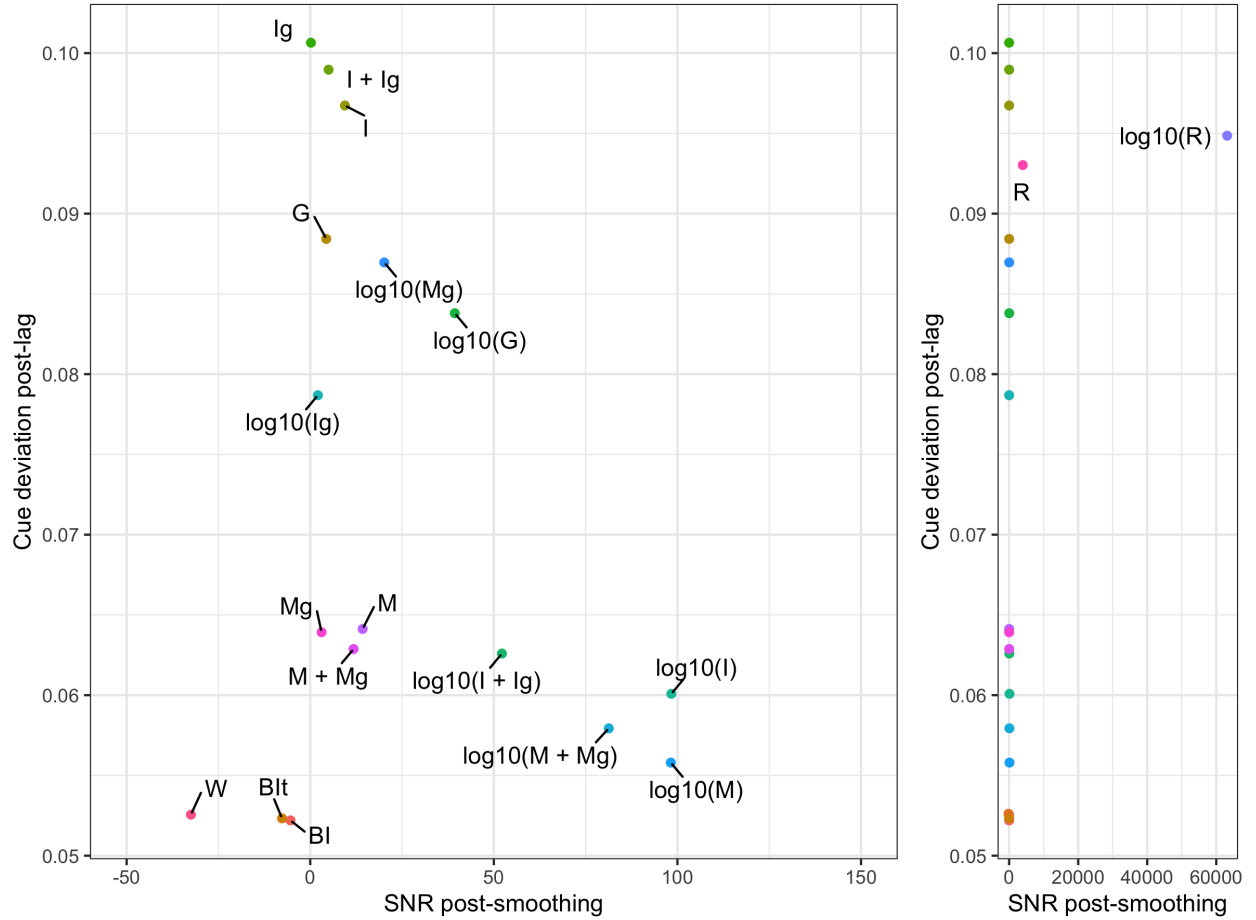
Figure 2: Next cycle conversion benefit some cues more than others. The x-axis represent the difference in SNR between smoothed cue (moving average over 1-day window) and the cue's original SNR. The y-axis represent the normalized difference between cue value and their value 1-day ago.

Future tasks

- Compare cue characteristics with simple drug action

- Start code-review of present model functions

- Work on optimizing dual cue performance

References

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