

# Immune regulation of malaria infection: model calibration and Agent-Based Communities

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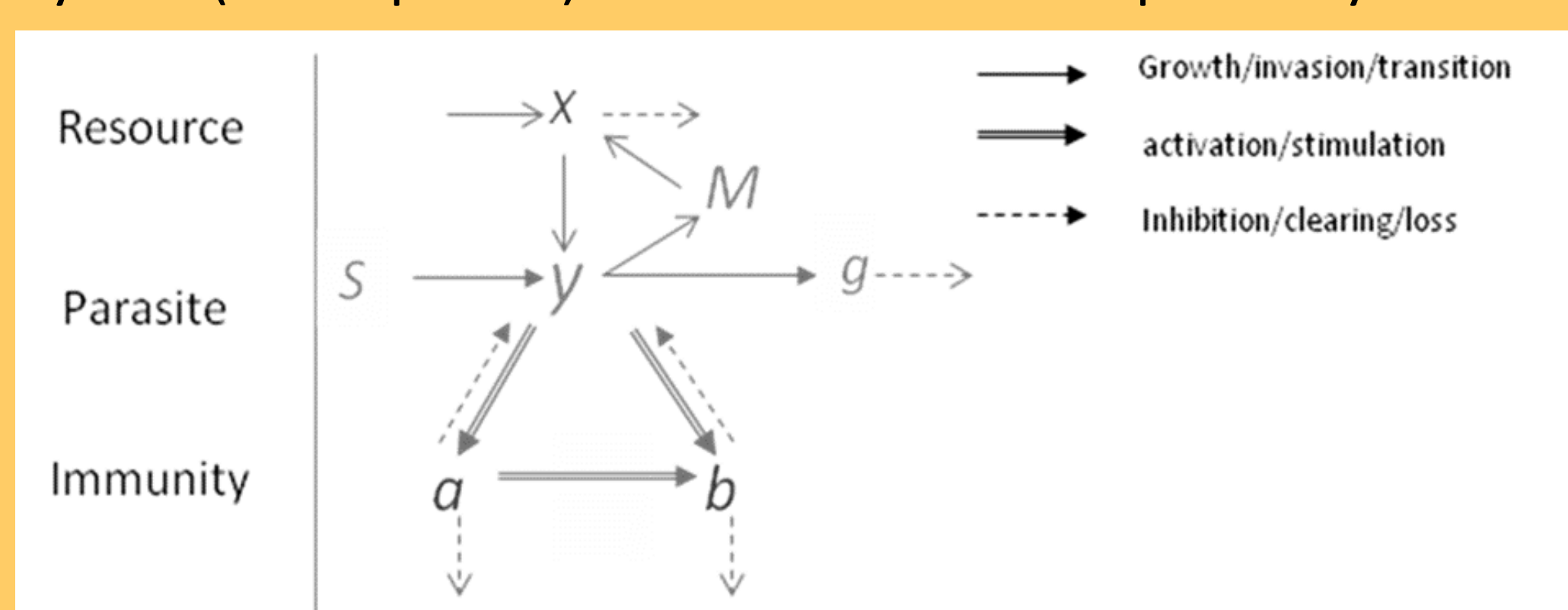
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## Introduction

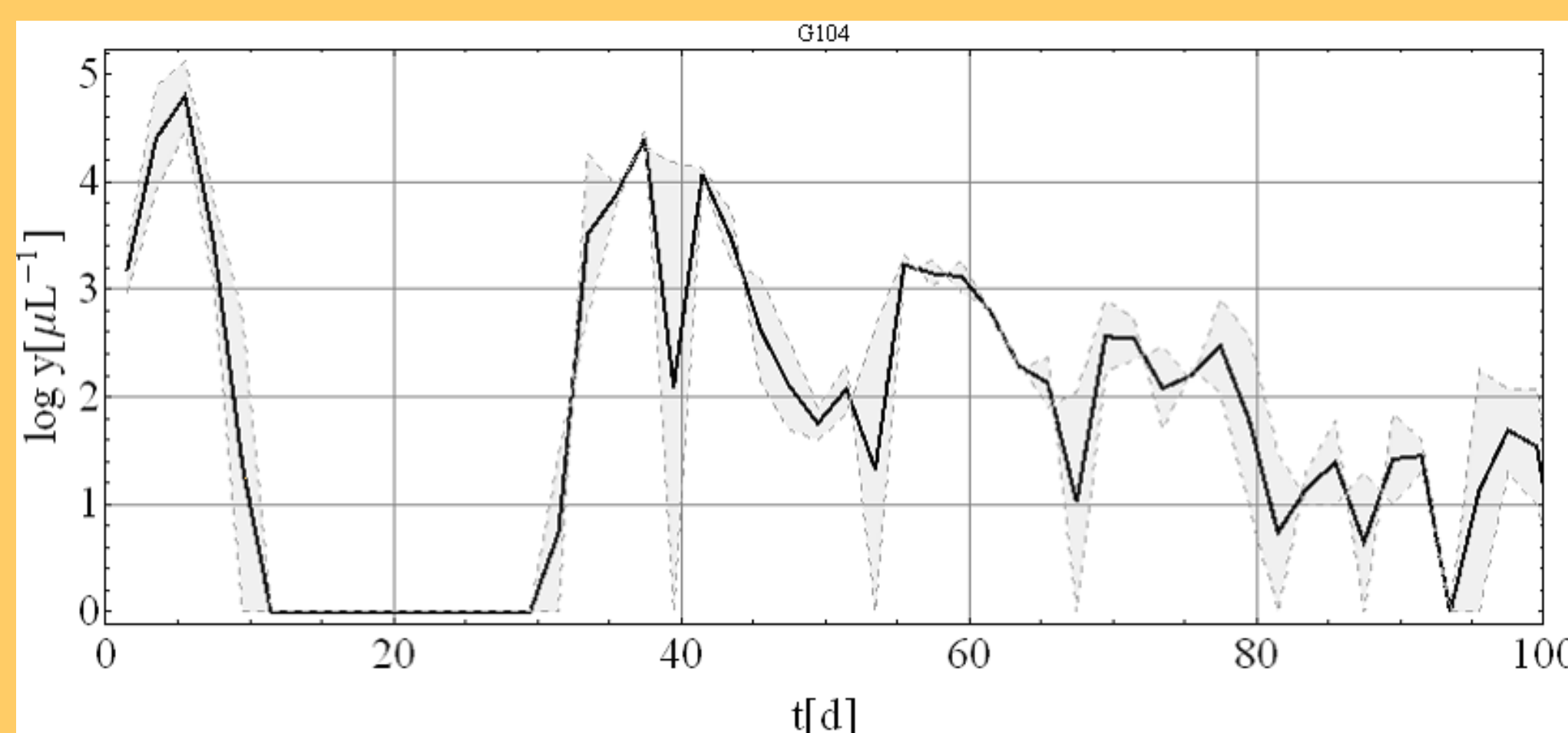
Individual- or *agent-based modeling* of malaria infection offers an attractive alternative to the conventional Ross-Macdonald (population-based) methodology. It allows to accommodate heterogeneous 'host/vector/parasite' populations and realistic transmission environment. To provide the basis for simulated communities of such hosts, a new within-host model of 'parasite – immune' interactions was developed and calibrated using patient data from *malaria-therapy* (MT) studies. Deterministic models alone cannot account for irregular parasitemia patterns found in MT data. Therefore a stochastic element based on antigenic variation of *Plasmodium falciparum* was incorporated into our system. A two step calibration procedure was used to account for the deterministic and stochastic components of MT patient histories. We applied this calibration procedure to 127 MT patients to select 'best-fit' in-host parameters (20 to 50, for each host). The resulting pool of best parameter choices can be used for creating Agent-Based Communities (ABC). The in-host model presented here, while simplified in many ways, can predict MT histories with sufficient accuracy similar to more detailed models proposed earlier. Then we used calibrated parameters to create agent-based communities (ABC) of MT-like hosts, and run numeric studies by subjecting them to various levels and patterns of inoculation (EIR). Our preliminary results are consistent with the available data (from Africa and Papua New Guinea) on infection prevalence and parasitemia distribution in host populations.

## Methods: Model Setup and Calibration

Our within-host model combines *resource-limited growth* of the parasite with *immune stimulation* and parasite *clearing*. Red blood cells ( $x$ ), and parasitized RBC ( $y$ ), are both measured by their densities per  $\mu\text{L}$  of blood. Innate and adaptive immunity are represented by two (host-specific) variables  $a$  and  $b$  respectively.

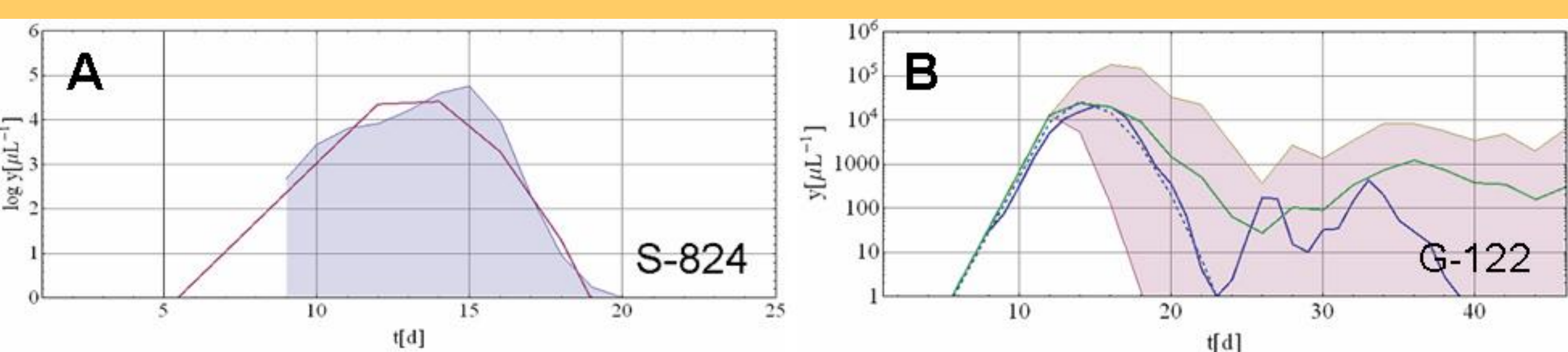


**Figure 1: Schematic representation of in-host model.** The population of uninfected red blood cells ( $x$ ) provides the source for infected population ( $y$ ), and merozoite release ( $M$ ). Innate immune effector ( $a$ ) is stimulated by  $y$ . Adaptive effector ( $b$ ) is stimulated by  $y$  interacting with  $a+b$ .



**Figure 2: Typical MT pattern with its 'odd-even' envelop (shaded) and geometric mean curve (black).** MT parasitemia curves are characterized by fluctuations between consecutive days (due to sequestration) and long-term recrudescence waves, due to immune evasion by parasite (antigenic variation). Fast (2-day) oscillations were filtered out by running their floating (geometric) mean over two-day intervals.

The model was calibrated MT data and a *two-step calibration* procedure. In the *first step* a deterministic fit was applied to the first-wave parasitemia (of each MT dataset). Then for multiple-wave datasets we implemented the *second step*, that involved a stochastic component, to account for *antigenic variation* (AV) of parasite. The resulting 'ensemble envelop' of random realizations of such process was fitted to the corresponding MT-history. Examples are shown in Figure 3.

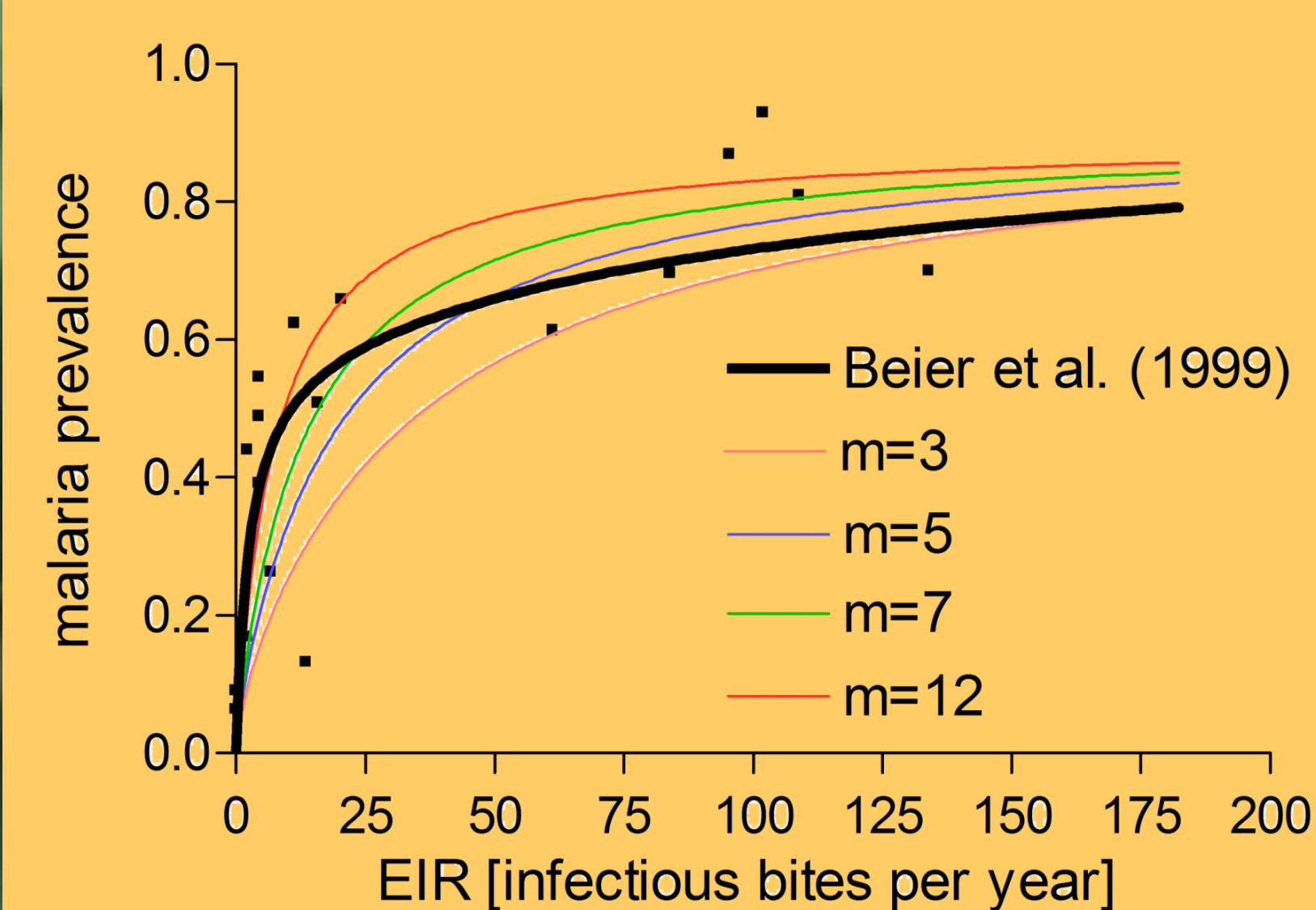


**Figure 3: Model fit to MT data:** (A) Single wave dataset (shaded blue) fitted with the deterministic calibrated curve of step #1 (purple). (B) multi-wave history (solid blue) fitted by 2-step procedure: deterministic fit of step #1 (dashed blue) shown alongside the AV-ensemble envelope (shaded purple) and its mean curve (green), resulting from step #2.

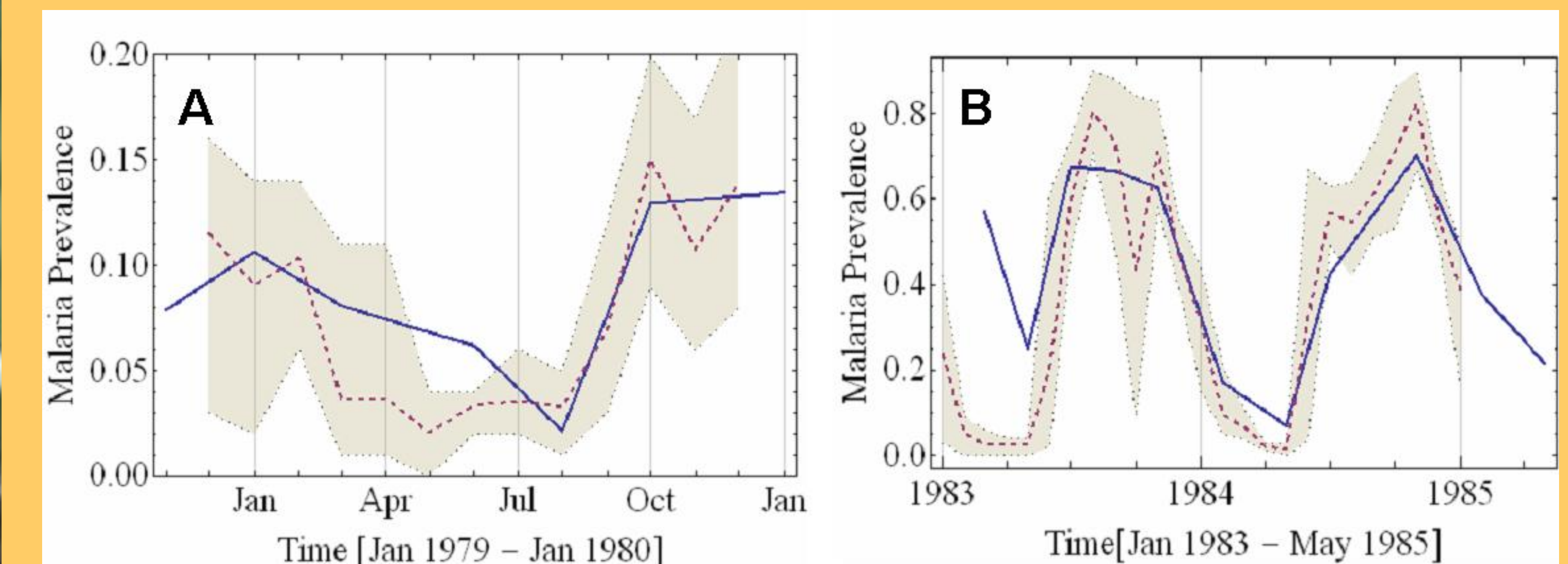
By screening 127 MT datasets we selected 3200 'best-fit' parameter choices, and used them as the basis for creating *agent-based communities* (ABC) of virtual MT-like hosts. Those ABC were exposed to different inoculation patterns ('stationary' or 'seasonal' EIR), and their predicted prevalence levels (based on various detection thresholds) were compared to the field data. In particular, we used data from African studies conducted in the 1980's, for seasonal EIR

## Results

The model was applied to reproduce malaria prevalence as at different stationary and seasonal inoculation regimes (EIR) as described in studies by Beier (1999, Figure 4), Vercruyse (1983, Figure 5) and Gazin (1988, Figure 5)



**Figure 6: Comparison of model predictions (colored curves) with malaria prevalence data from Africa (Beier et al., 1999):** colors (uncertain parameter  $m$ ) corresponds to different number of antigenically distinct parasite variants used in simulated ABC.



**Figure 5: Comparison of model predictions to field data from sites with seasonal malaria.** Panel A: Malaria prevalence as reported by Vercruyse et al. (1983) (solid blue) and model prediction as monthly average (dashed purple) and envelope of monthly minima and maxima (shaded olive) using as input the EIR pattern from the same study. Panel B: Malaria prevalence as reported by Gazin et al. (1988) (solid blue) and model prediction as monthly average (dashed purple) and envelope of monthly minima and maxima (shaded olive) using as input the EIR pattern from the same study.

## Conclusions

We introduce a new, computationally efficient in-host model in which parasite load triggers an innate and an adaptive immune responses, that control parasitemia. The model was calibrated using MT data and a 2-step calibration procedure, that combines deterministic fit for all datasets (step 1), and stochastic 'antigenic variation' fit (step 2), for longer, irregular MT histories. We applied this model to build agent-based communities (ABC), and study the effect of EIR on infection levels. Our ABC can reproduce some field observations from Africa with reasonable accuracy. The future model development and applications will include gametocyte production determined by the asexual parasitemia, and realistic 'human-mosquito environment as well as malaria control interventions.

The model was implemented and run in Wolfram Mathematica 7.

## References

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