

## ABSTRACT

**Individual based modeling** offers many advantages compared to conventional SIR models (Ross-Macdonald) of malaria transmission. These include:

- Accurate account of host **infectious/immune status**
- Seamless accommodation of various **communal heterogeneities** (age, susceptibility, history of exposure, spatial distribution, contact patterns, etc.)
- Natural way to introduce **multiple parasite species and strains** (mixed infections).

However, its efficient implementation requires the in-host model to be *realistic* yet simple enough to allow efficient implementation to build and explore “large” communities within a complex (multi-parasite, multi-vector), spatially distributed environment.

We list a few sample in-host models of increased complexity: I. **Stochastic 3-state** “disease-state” model of [1]; II. **Continuous DE model** of single and mixed infections w. stimulated immunity ([2]-[3]) III. **Multi-strain (multi-variant) Pf model**, coupled to RBC

## Applications

We show several application on “individual” and “community” levels.

- **Model I** was used to study **severe malaria** in young age cohorts, in particular the effect of inoculation (EIR) and **early interventions** (treatment /vaccination) on disease severity.
- **Model II** (2-spp/ strains) of different drug sensitivity allows to examine in-host competition and the effect of **drug treatment** on the onset of **resistance**.
- **Model III** allows multiple P. strains of varying virulence, cross-regulated by immunity, and vertically transmitted over several generations (as in recent mice experiments ). It demonstrates the development of **virulence due to persistent vaccination**. Another “single-strain” version of III was used along with cross-sectional survey data in PNG to estimate model a “hypothetical” community, coupled via mosquito transmission.

## I. Stochastic N-A-S (disease) model

We use highly simplified “in-host parasitemia” with 3 “**disease states**”: N (non-infected), A (asymptomatic), S (symptomatic), and allow **random transitions** among those with probabilities  $\{p_{ij} : i,j=N,A,S\}$ . The latter depend on the immune status (“effector variable”  $J$ ), which in turn is stimulated by A,S states

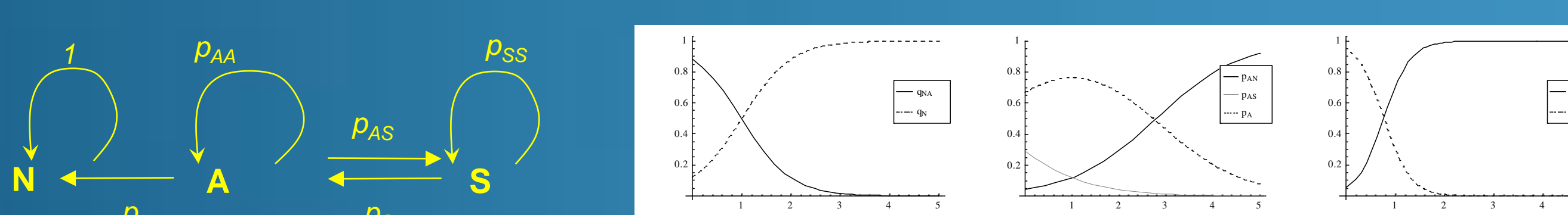


Fig.1: NAS transitions (left), and probability functions  $\{p_{ij}(J)\}$  (right)

A typical 2-year disease history under random inoculation (EIR) with discrete time-step shows intermittent patterns with possible stretches of several consecutive S-state (**severe episodes**).

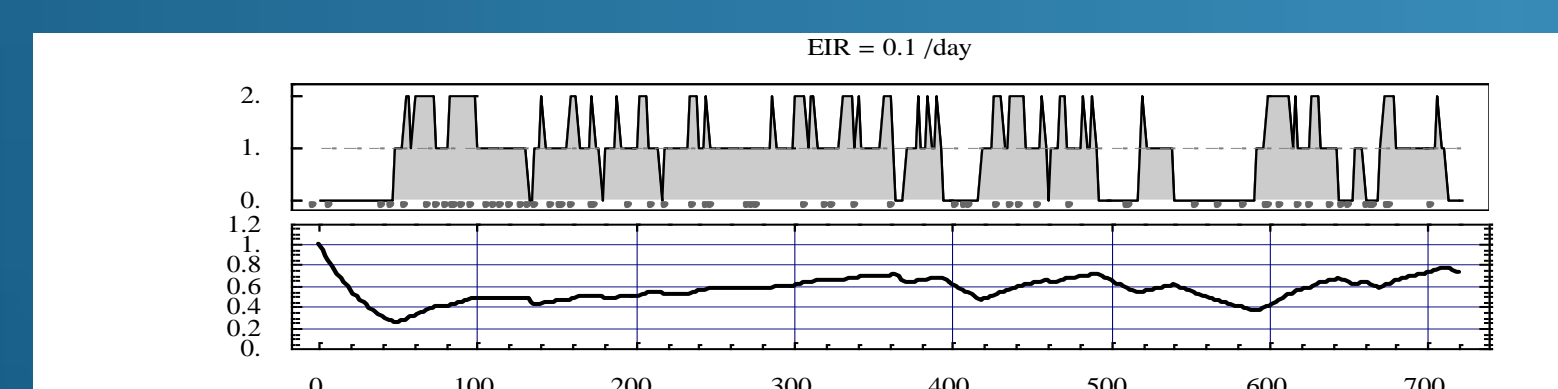
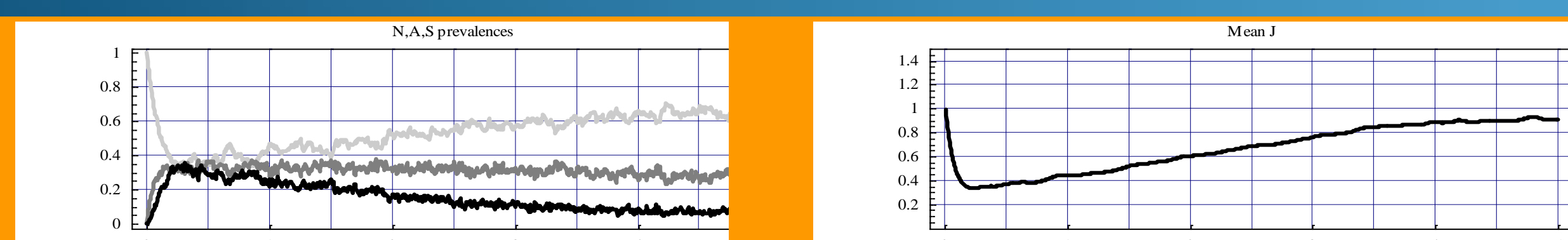


Fig.2: Typical 2-year disease history: “NAS={0,1,2}” (top), and  $J$  (bottom panel).

Next we apply to a heterogeneous cohort of 500 young hosts (ages 0-5), subjected to random EIR, and show mean **NAS-prevalences**, and mean **acquired immunity J**



## Disease severity and interventions

**Severity index** is defined total duration of severe episodes over a given 1-year time period.

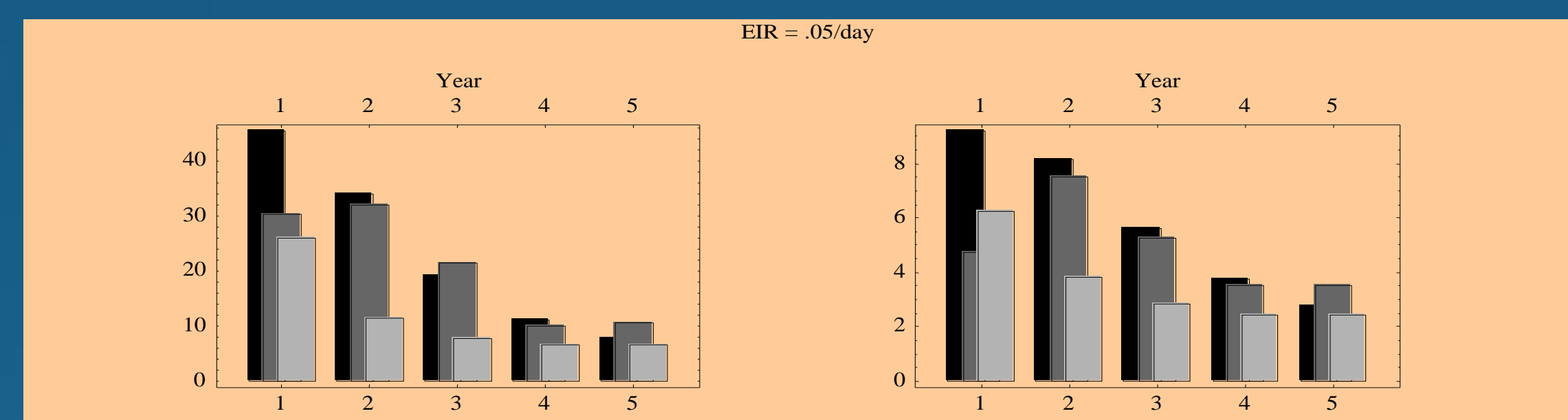
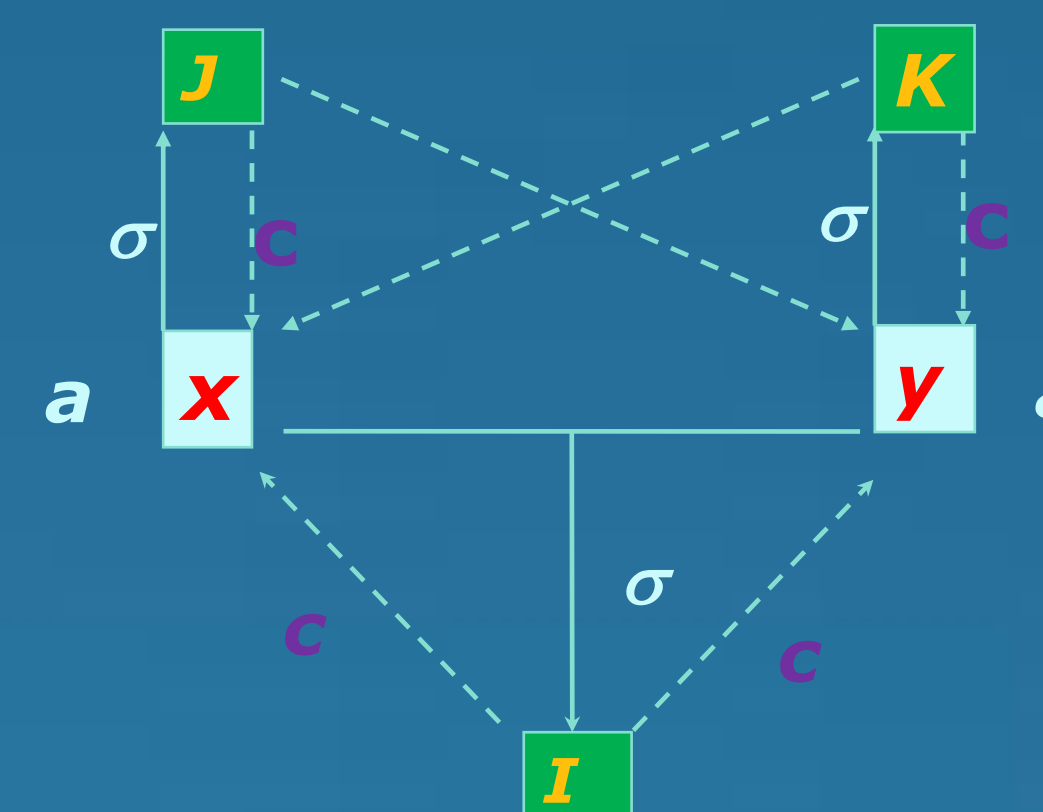


Fig. 6: Comparison of mean **severity index** (left) and **count** (right) for a 500-cohort subjected to  $EIR=0.05/day$ : untreated (black); vs. preventive drug-treatment (gray), vs. vaccination (light grey) in the 1st year .

**Note:** Preventive treatment lowers severity in the 1<sup>st</sup> year, but increases it in the following 5-year period.

## II. Two-strain competition

The system combines 2 parasite spp  $x,y$  with intrinsic growth rates  $a_i$ , and 3 immune effectors: innate  $I$  and specific  $J,K$ , with stimulation / clearing parameters  $\sigma/c$ , and possible cross-reactions (“ $J$  on  $y$ ” and “ $K$  on  $x$ ”).



Immune effectors decay (deactivate) at certain rates. 5 variables obey a coupled differential system [2,3]

Fig.2: Two-species ‘parasite-immune effector’ scheme

## Analysis of competition [2-3]

System (1) is a “**2-prey + 3-predator**” model, where immunity ‘predates’ on  $x,y$ , while species indirectly compete through their cross-reactive immunities. The outcome depends on **fitness parameter** (relative growth rate):  $\alpha = a_2/a_1$ , as well as cross-reactivities. Its **equilibrium parasitemia states** are approximately given by the classical **Volterra-Lotka competition**

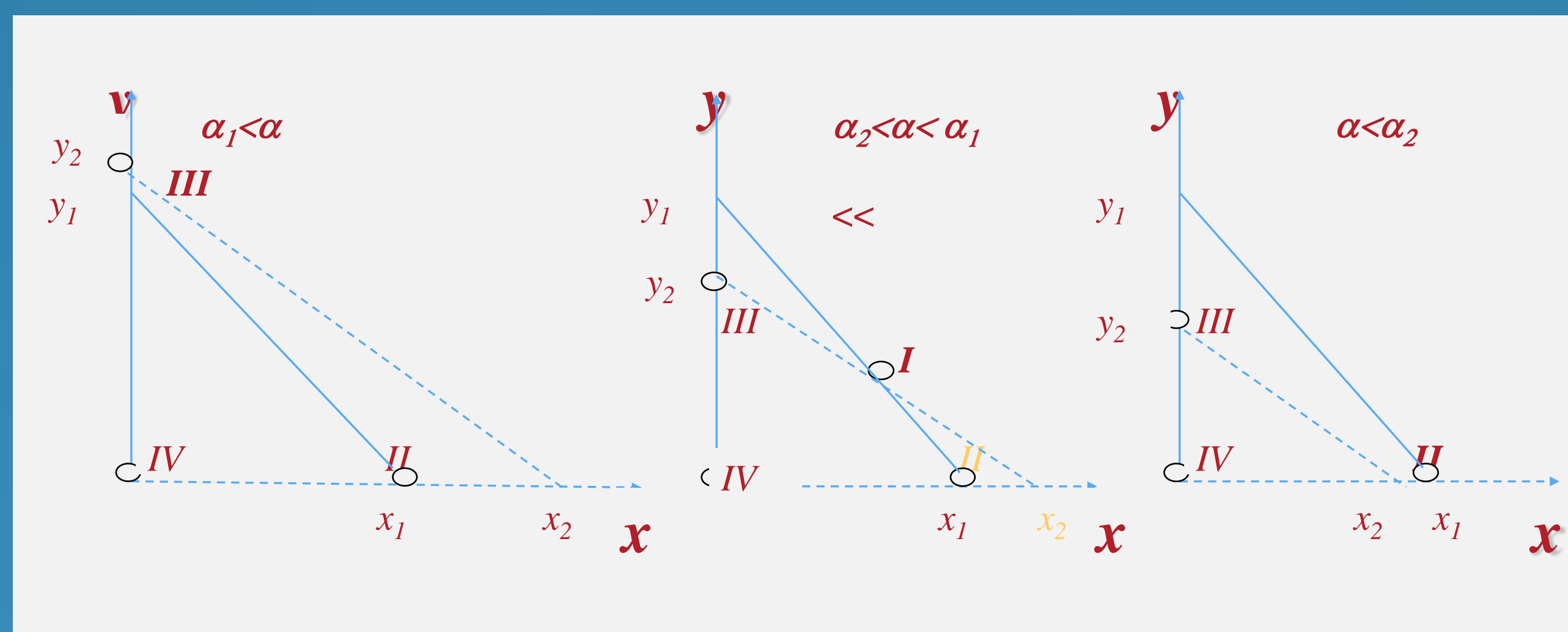


Fig. 3: Phase-plane portraits of reduced system (1), stable equilibrium marked in black. Depending on parameters we get either species domination ( $x$  right, or  $y$  - left), or coexistence (middle).

## Drug treatment and resistance

We take 2 strains with **different drug sensitivities**, naturally fit “sensitive”  $y$  vs. inferior “resistant”  $x$ , and subject such host to various **treatment** regimens, e.g. periodically spaced **prophylactic treatment** [3]

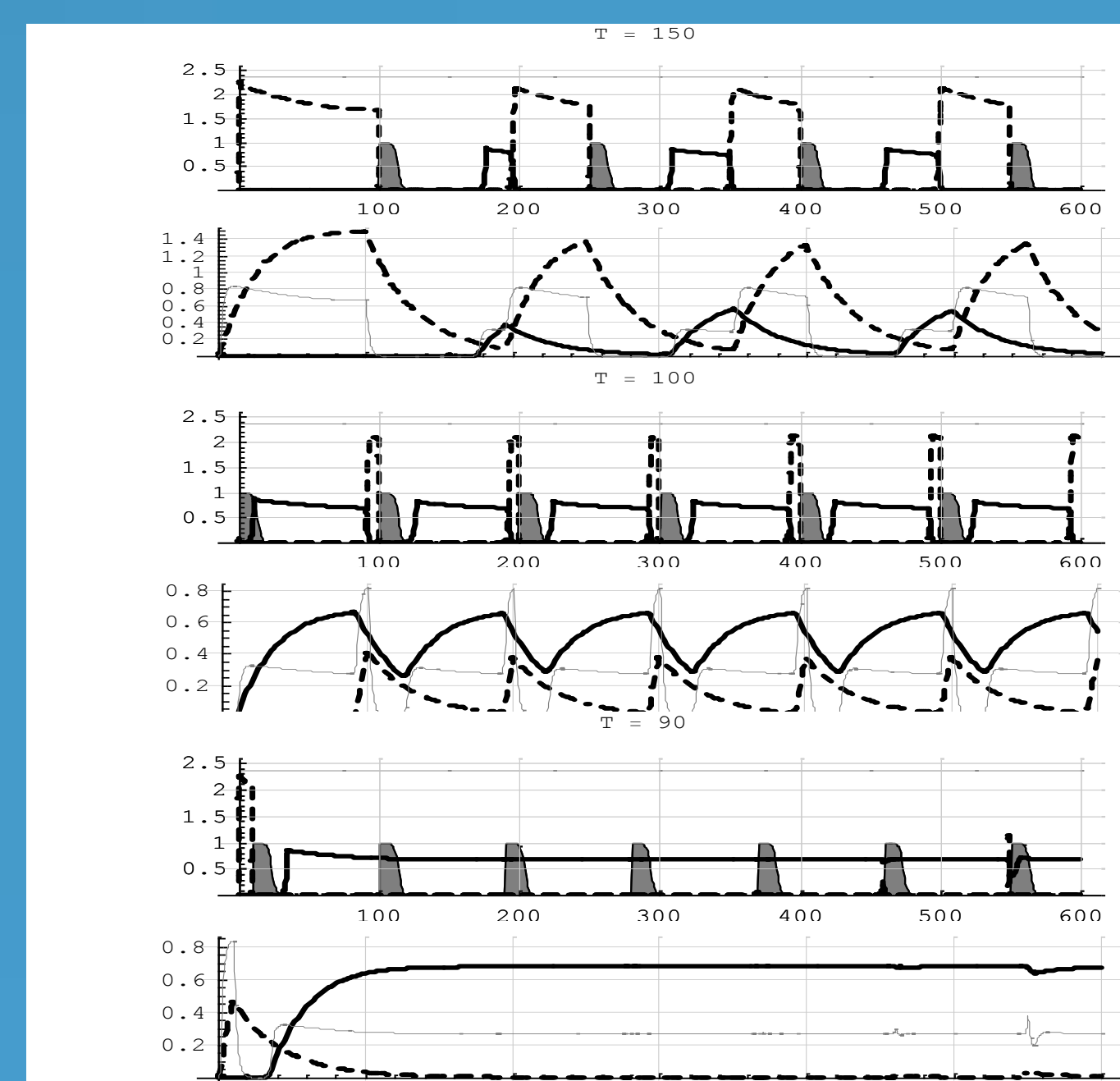
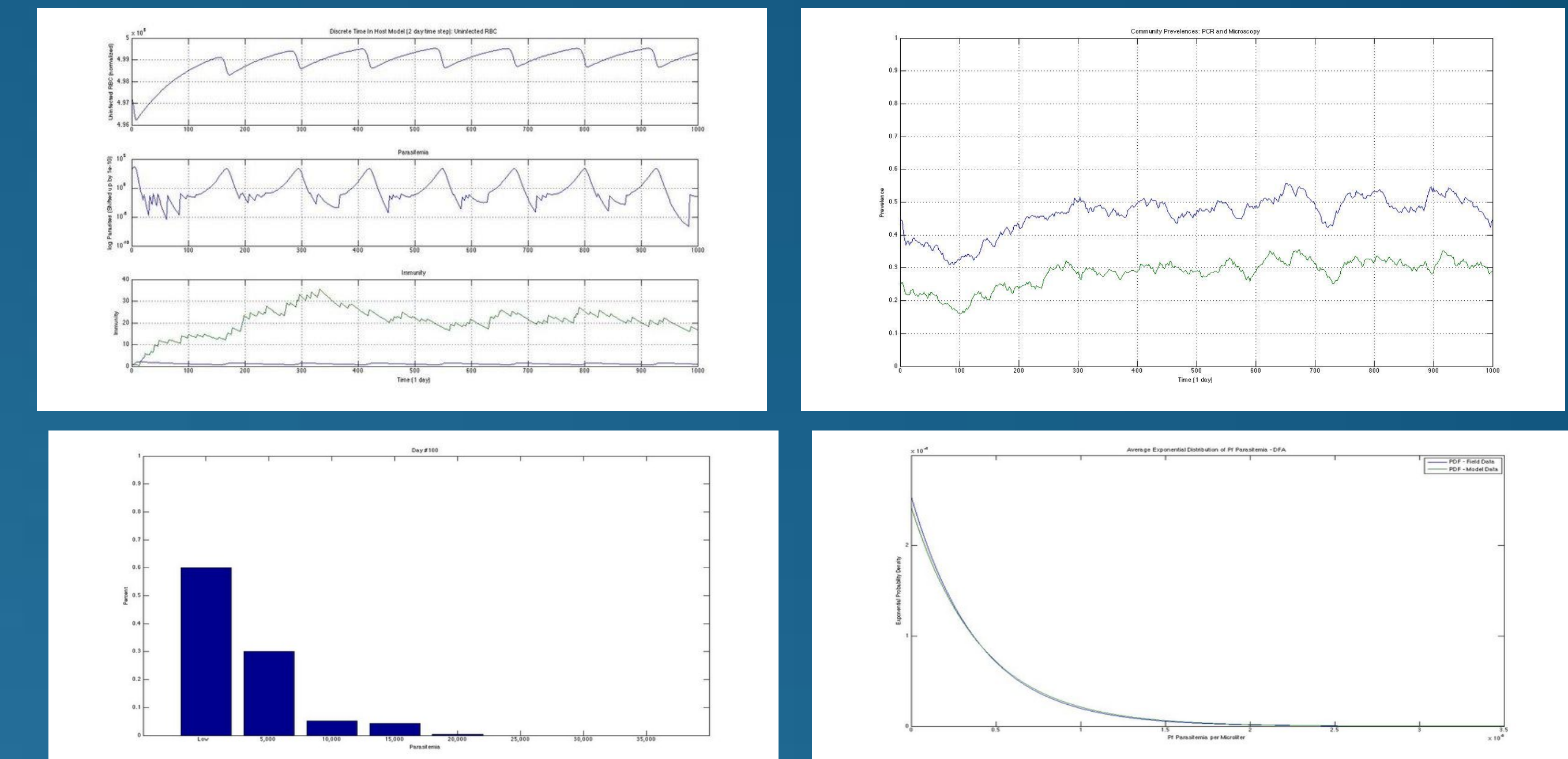


Fig.4: Increased frequency of treatment ( $1/T$ ) bring about a transition (top to bottom) from ‘dominant  $y$ ’ (dashed) to ‘dominant  $x$ ’ (solid) . In each plot upper panel shows parasitemia, lower one – immune effectors, and shaded regions - drug application.

One can further quantify the combined effect of ‘drug+ immunity+ inoculation’ on the long-term competition (see [3]).

## III. Individual based community

We set up a community based on a single strain version of (II), subjected to a fixed EIR, and used cross-sectional PNG data (high LM and low PCR parasitemia) to estimate “in-host” parameters. Plot below illustrate (i) typical in-host history; (ii) high (PCR) and low (LM) resolution prevalences; (iii) typical parasitemia distribution in the community; (iv) exponential fit for PNG data and our estimated model.



## IV. Multi-strain system for virulence

Here the in-host dynamics includes several additional factors and processes:

- Homeostatic **RBC –production/death**
- Density dependent **merozoite invasion** of RBC (young stage)
- Random survival** through old stage depending on immune level  $J$  (similar to model (II)), and replication
- Immune **stimulation/ clearing**

We allow **multiple cross-reactive strains** of variable virulence (in terms of immune threshold for survival).

- Random mutations** whereby each strain gives rise to a .5% progeny of higher or lower virulence

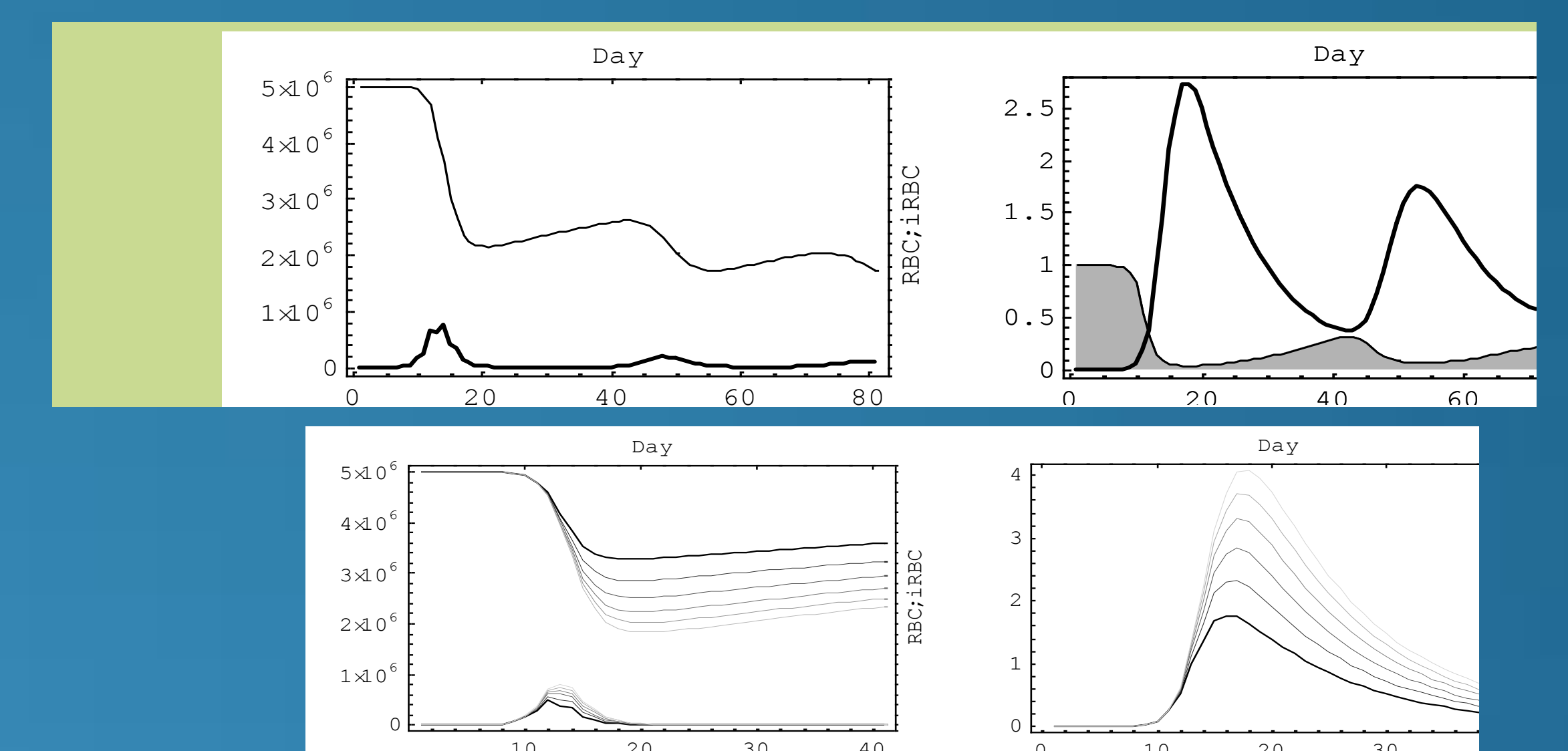
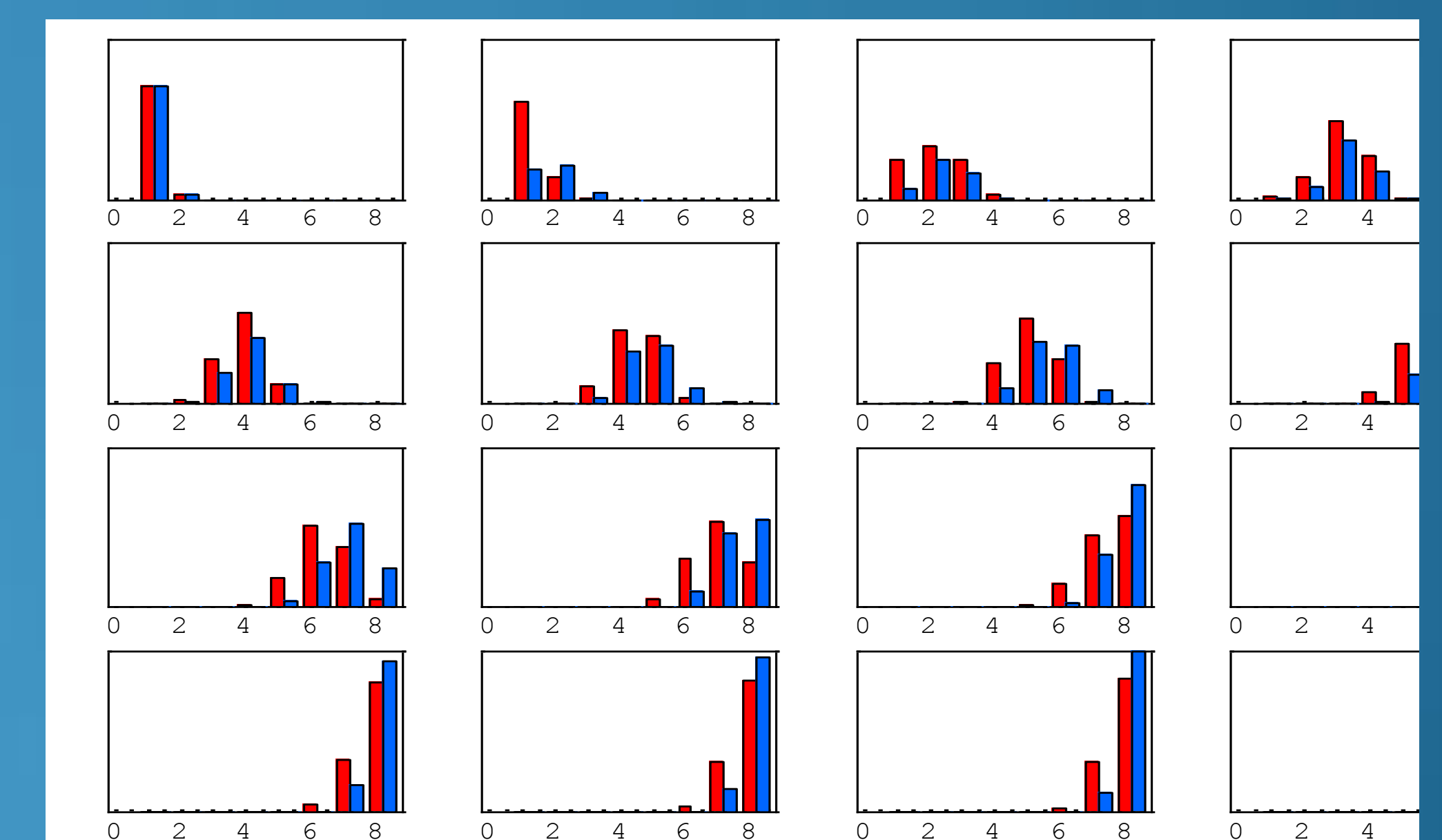


Fig. 5: Typical disease history after inoculation. Left: uninfected RBC (thin) and total infected ones (thick). Right: immune effector (thick) and survival probability of the dominant strain (shaded). Bottom plot compares several virulent strains in separate identical hosts (indicated by increased RBS depletion)

Next simulation looks at the effect of serial passage of multi-strain infection over several generations of inbred mice ([4]). It compares 2 groups: “naïve” and “partially vaccinated” ones. Each mice is inoculated with a mixture of spp. developed in its predecessor after 20 days (past the peak parasitemia).



We observe overall **evolution of virulence** in both groups (transition from low to high strain). But vaccinated group (blue) does it faster.

## References

- D. Gurarie, E. McKenzie, Math Bio. Sci, 2007
- D. Gurarie, P. Zimmerman, C. King, JTB, 240 (2006)
- D. Gurarie, E. McKenzie, Malaria J., 5:86 (2006)
- M. Mackinnon, A. Read, PloS Biol. 2, 9 (2004)