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Write-up for malaria modeling project

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Background

Malaria, the most deadly human parasitic infection, causes more than 300 million new cases and 1 million deaths annually, however the efficacious vaccine against the infection are still in development. Vaccination of mice can induce variable numbers of memory CD8 T lymphocytes against liver-stage malaria parasites (sporozoites). Previous studies established that a high number of malaria-specific memory T cells can induce sterilizing protection against sporozoite challenge.

Objectives

To understand how vaccine-induced memory T cells protect against malaria infection and to estimate parameters determining probability of parasite clearance. .

Methods

We develop a simple mathematical model predicting the probability of clearing the infection as the function of the initial parasite dose and the efficacy of the immune response at finding and clearing parasite-infected cells. We used experimental data from infection of vaccinated mice with two species of malaria parasite, Plasmodium bergei and Plasmodium yoleii, to estimate model parameters.

1) Data: The data we used is from Nathan Schmidt's lab at UT, and the main measurements include the immunization type (DC, LM, DC+LM), the measured percent of peripheral blood lymphocytes that were malaria specific (%PBL), the strain (Plasmodium berghei and Plasmodium yoleii) and dose of pathogen (Number of sporozoites: Pb: N = 1000; Py: N = 10, 50, 100, 1000, 10000).
2) Model: The probability of clearing the infection by one pathogen cell p_0 can be described as

$$p_0 = 1 - e^{-KEbt}$$

where Eb is the %PBL, K is a constant representing the clearance rate of a single T cell, and t is the number of hours passed since a pathogen infected a hepatocyte, which has been fixed as 48 hours in our modeling.

Moving on to clearing the infection by more than one malaria pathogen we described $P_{clearance}$, the probability of clearing the infection with N pathogens as

$$P_{clearance} = p_0^N = (1 - e^{-KEbt})^N$$

Suppose the average number of pathogens varies according to a Poisson distribution, we got the Likelihood.

$$\sum_{i=0}^{N} P_c(i) \cdot P(i \mid N_e) = \sum_{i=0}^{N} (1 - e^{-KEbt})^i \cdot \frac{N_e^{\,i}}{i!} e^{-N_e} = \ldots = e^{-N_e \cdot e^{-KEbt}}$$

Then we use R programming to compute the maximum likelihood of the single parameter K and Ne.

Results

The distribution of %PBL is shown in Fig1-4.

Figure 1

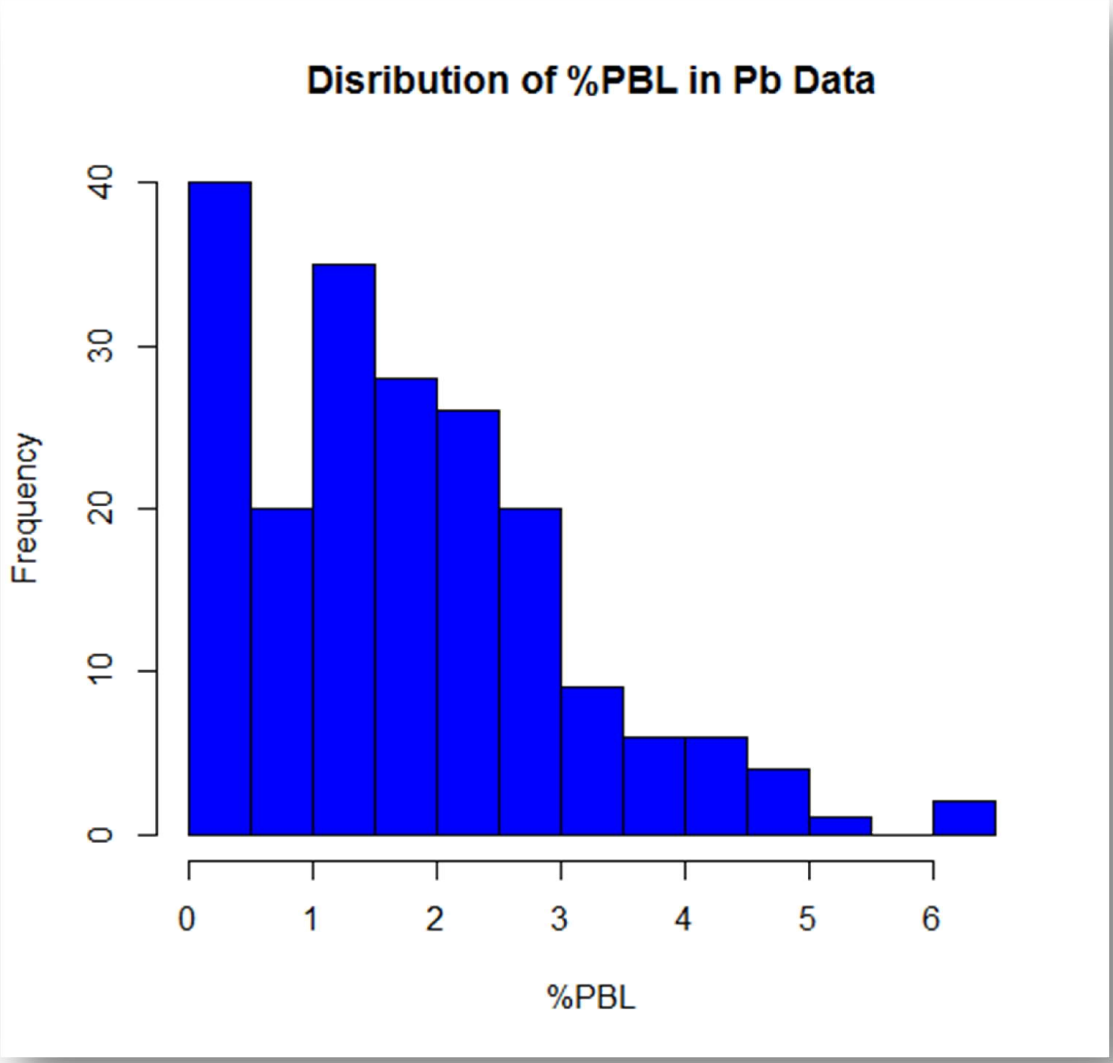

Disribution of %PBL in Pb Data
Frequency
0
10
20
30
40
0
1
2
3
4
5
6
%PBL

Figure 2

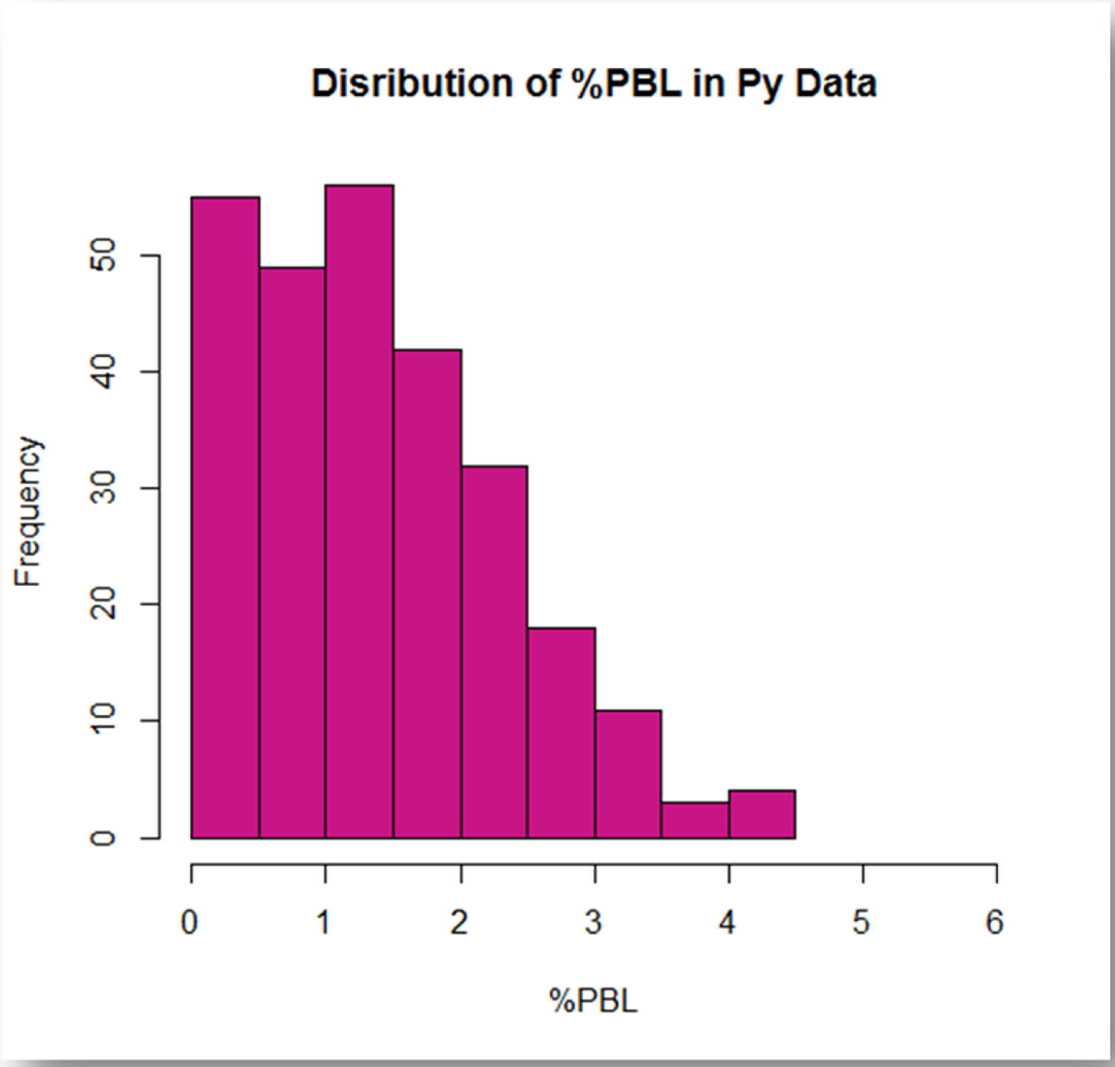

Disribution of %PBL in Py Data
Frequency
0
10
20
30
40
50
0
1
2
3
4
5
6
%PBL

Figure 3

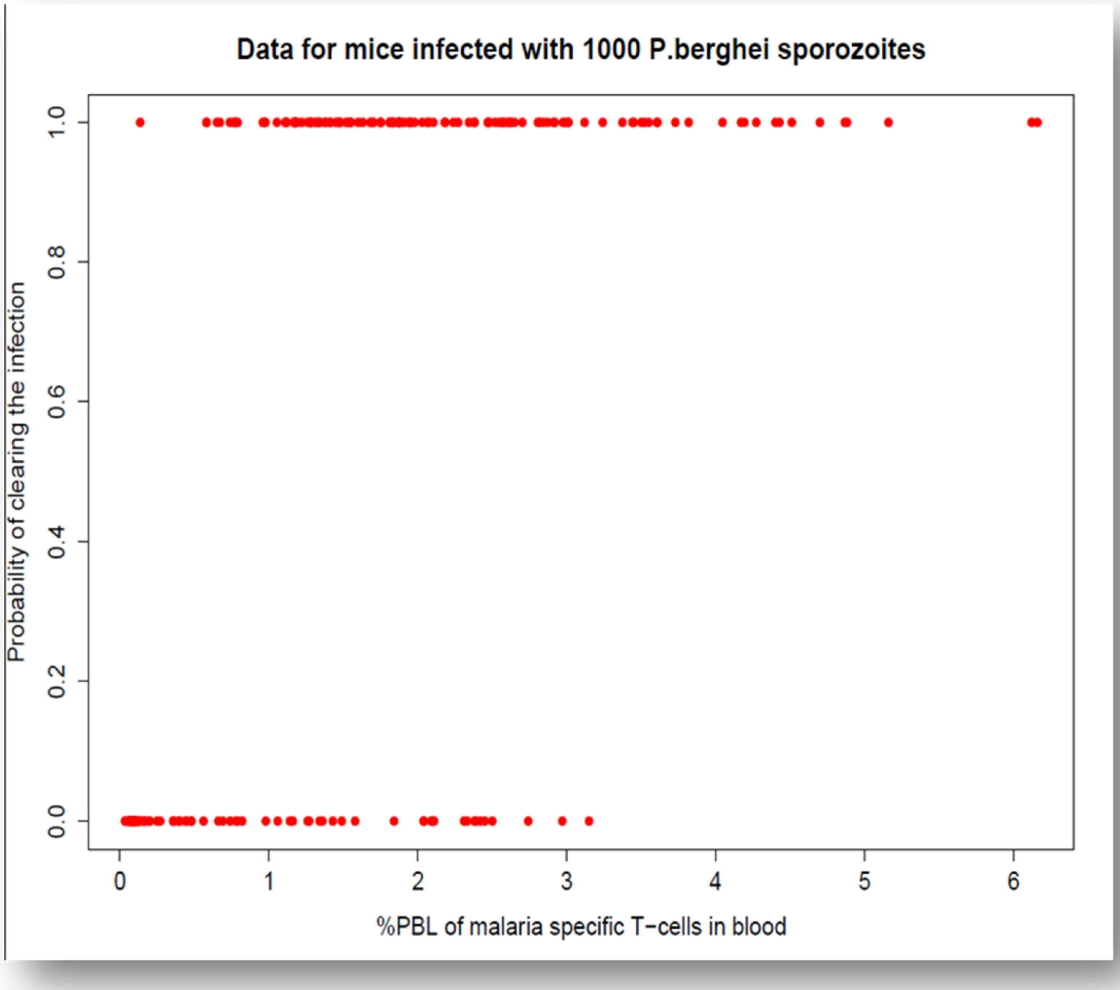
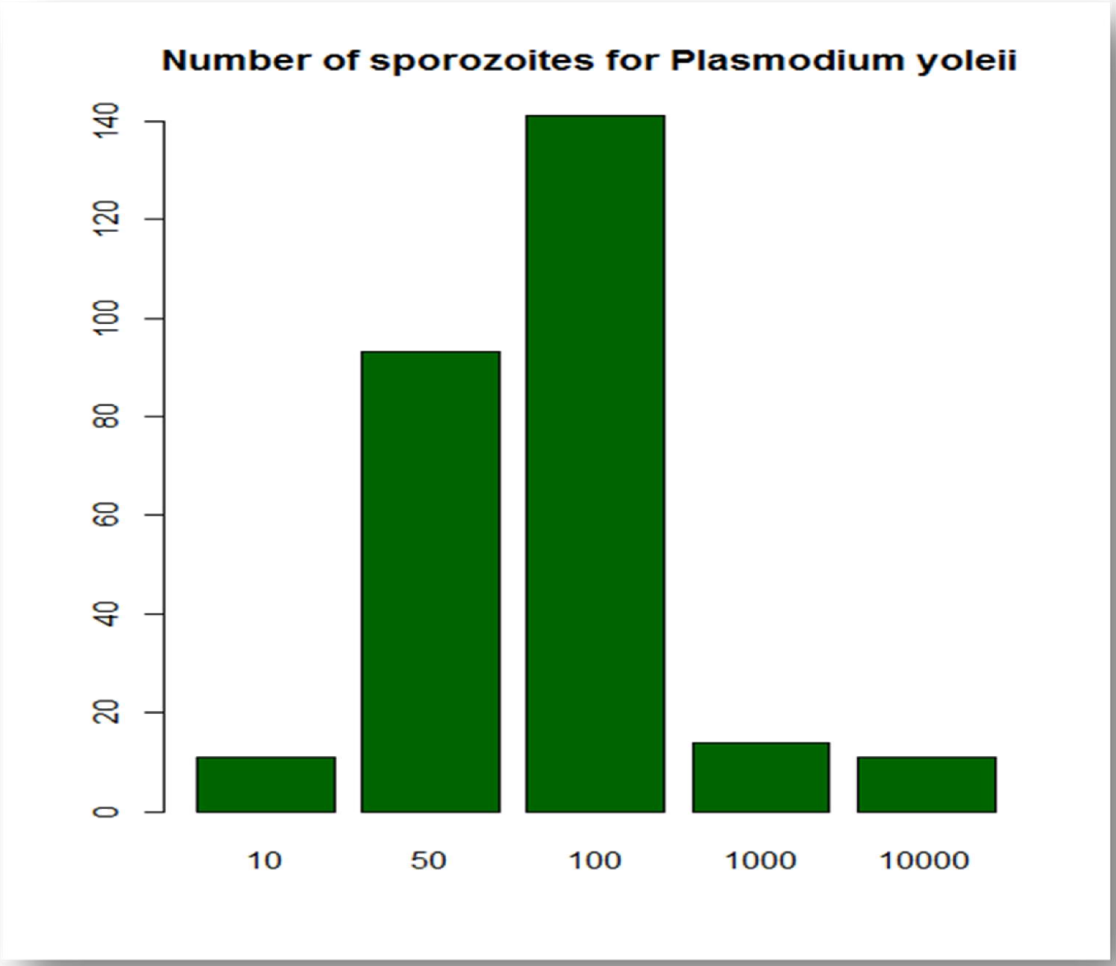

Data for mice infected with 1000 P.berghei sporozoites
Probability of clearing the infection
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
%PBL of malaria specific T−cells in blood

Figure 4

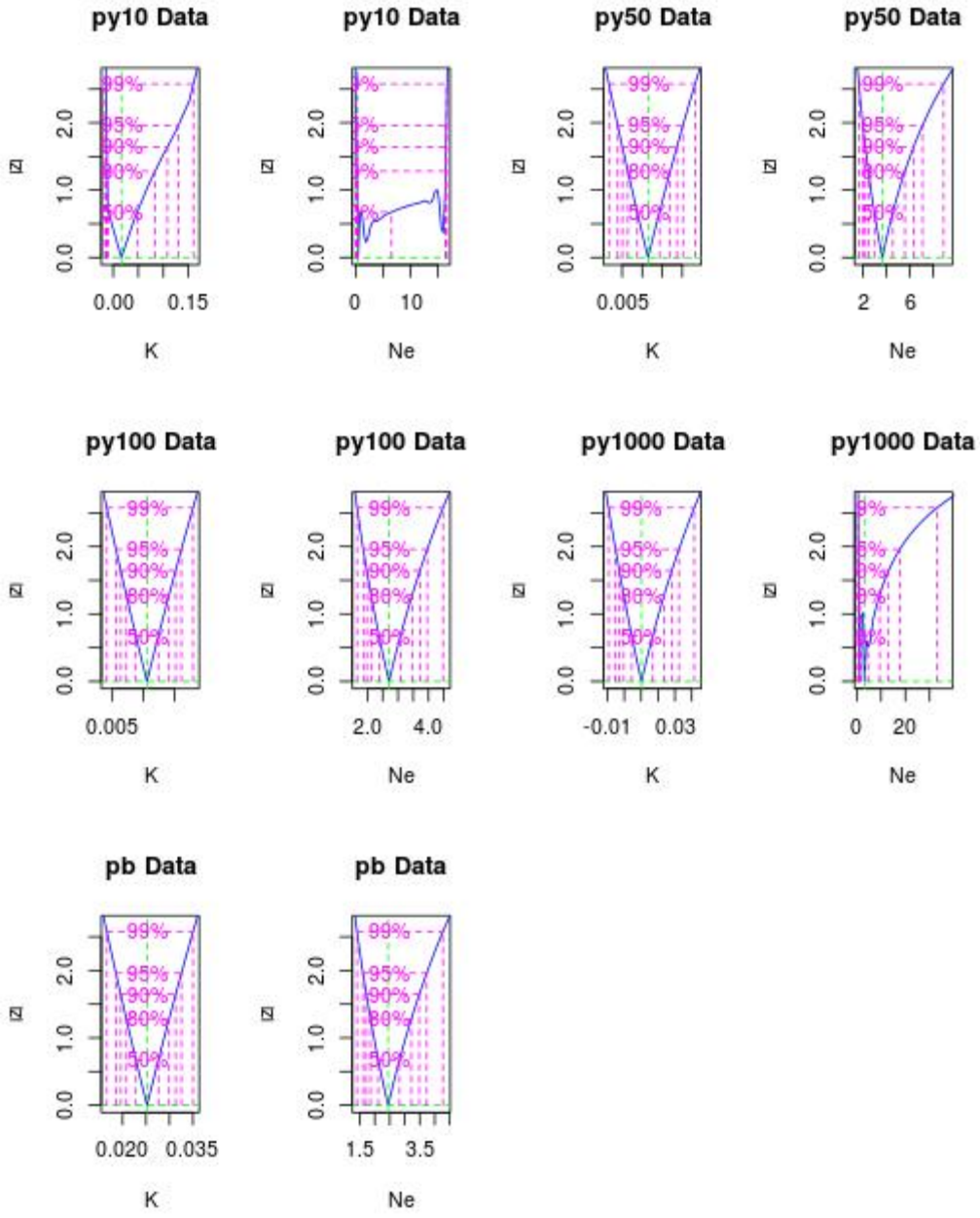


The parameters K, the clearance rate of a single T cell, and Ne, the actual number of pathogen-infected hepatocytes were calculated by maximum likelihood.

	num	K	Ne
pb	1000	0.025	2.45
py	10	0.016223	0.448641
	50	0.011473	3.65774
	100	0.010569	2.709049
	1000	0.010249	3.144458
	10000	-176.842	3.7317

Fig.5 shows the likelihood of estimated parameters.

Figure 5



The original data vs. fitted curve by modeling is shown in Fig.6-12.

Figure 6

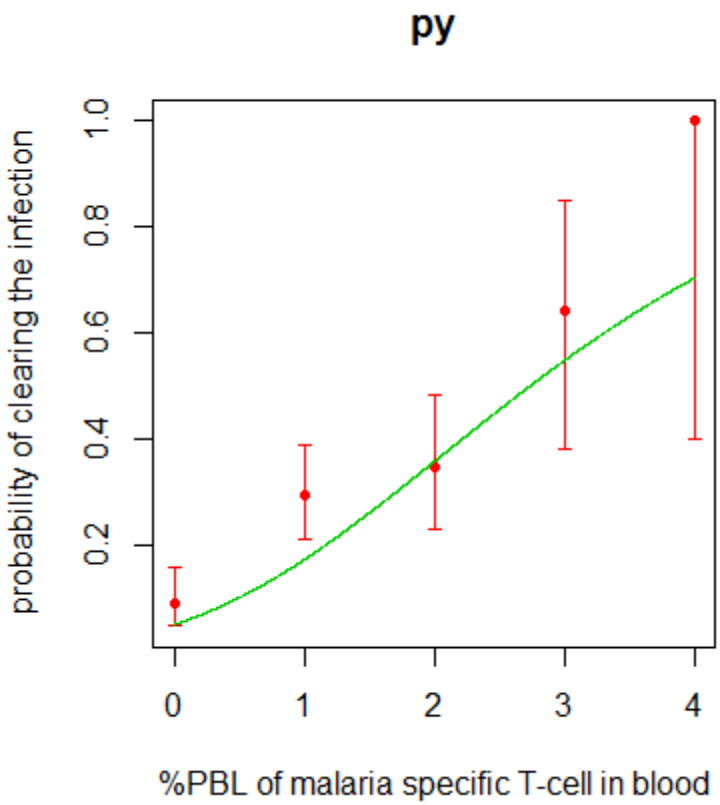

py
probability of clearing the infection
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
%PBL of malaria specific T-cell in blood

Figure 7

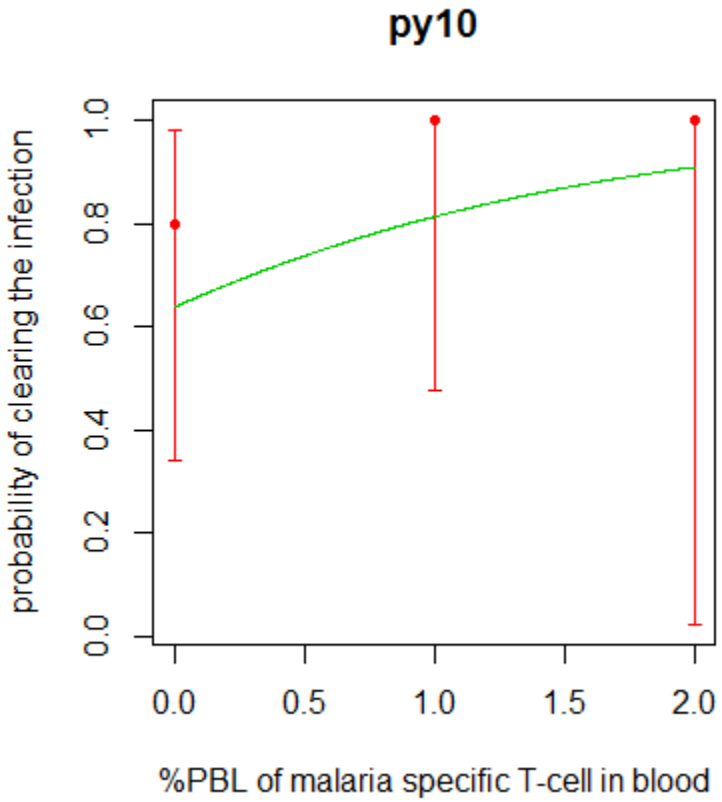

py10
probability of clearing the infection
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
%PBL of malaria specific T-cell in blood

Figure 8

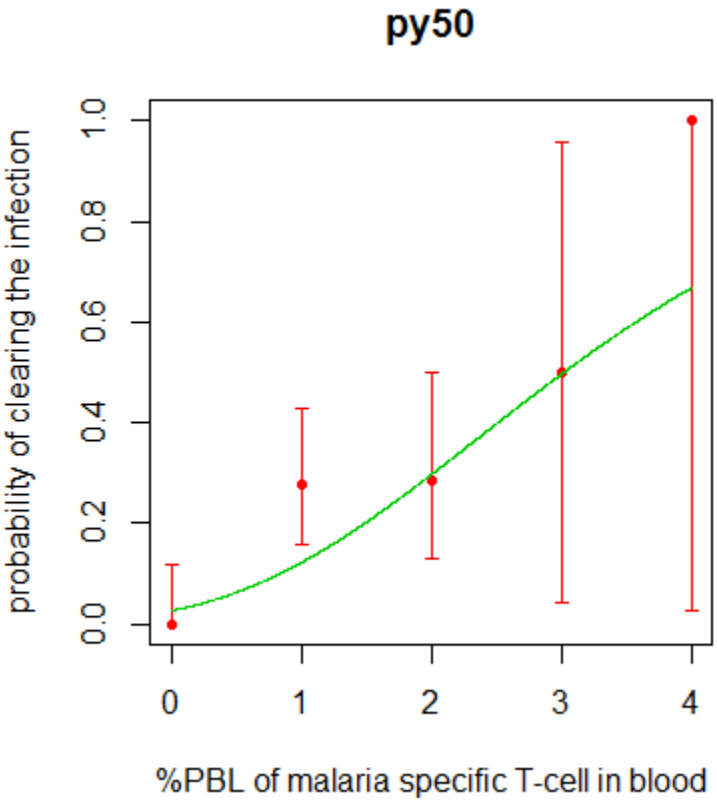

py50
probability of clearing the infection
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
%PBL of malaria specific T-cell in blood

Figure 9

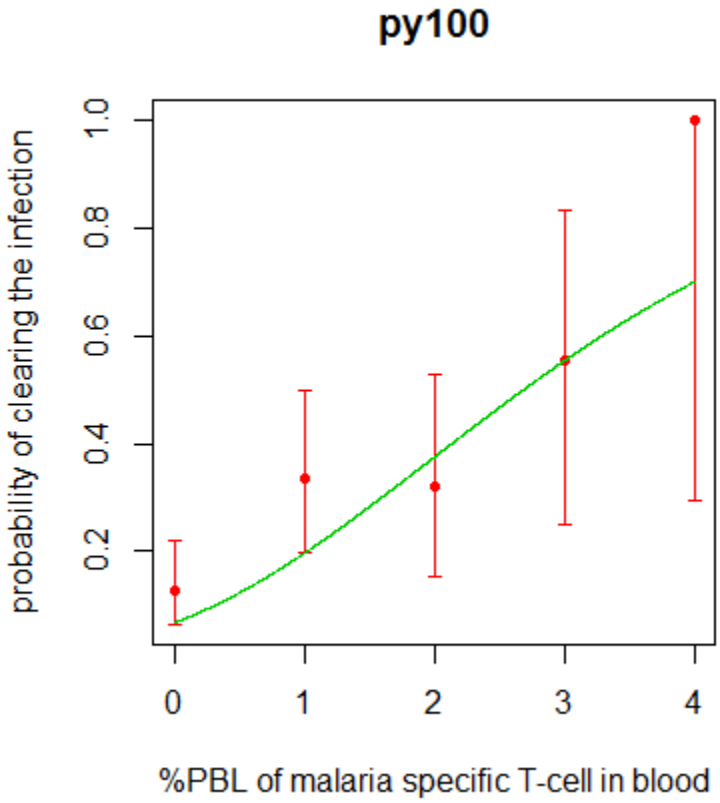

py100
probability of clearing the infection
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
%PBL of malaria specific T-cell in blood

Figure 10

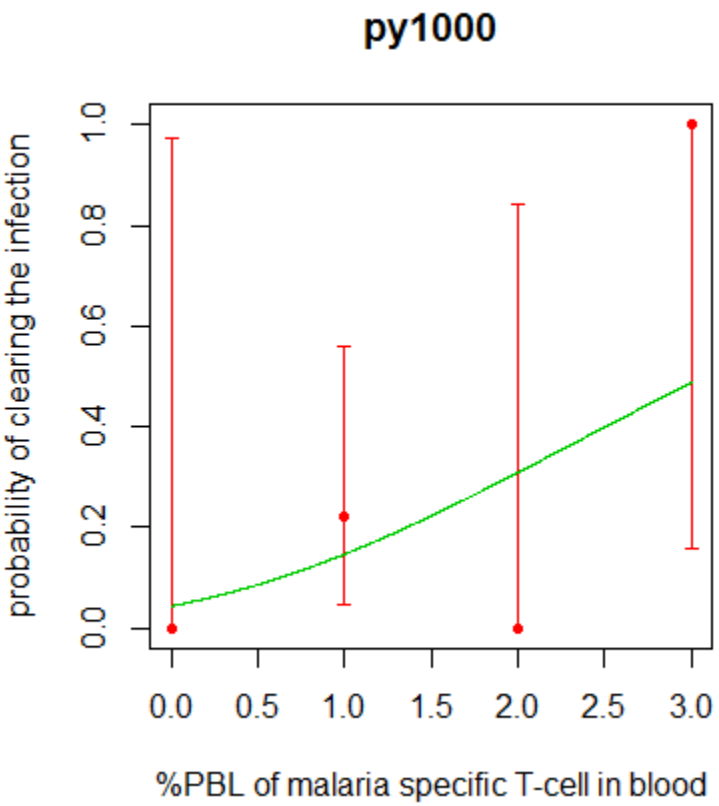

py1000
probability of clearing the infection
0.0
0.2
0.4
0.6
0.8
1.0
0.0
0.5
1.0
1.5
2.0
2.5
3.0
%PBL of malaria specific T-cell in blood

Figure 11

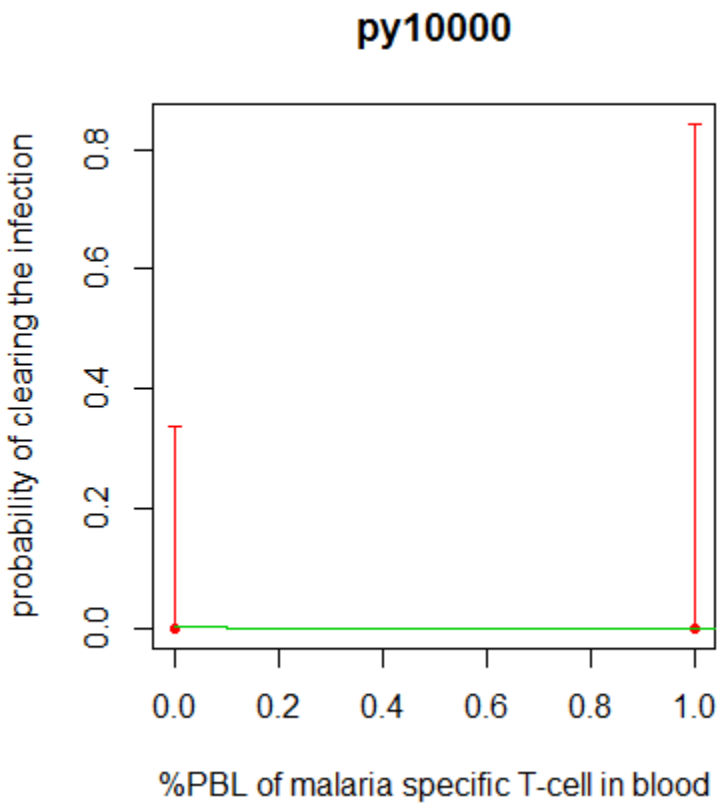
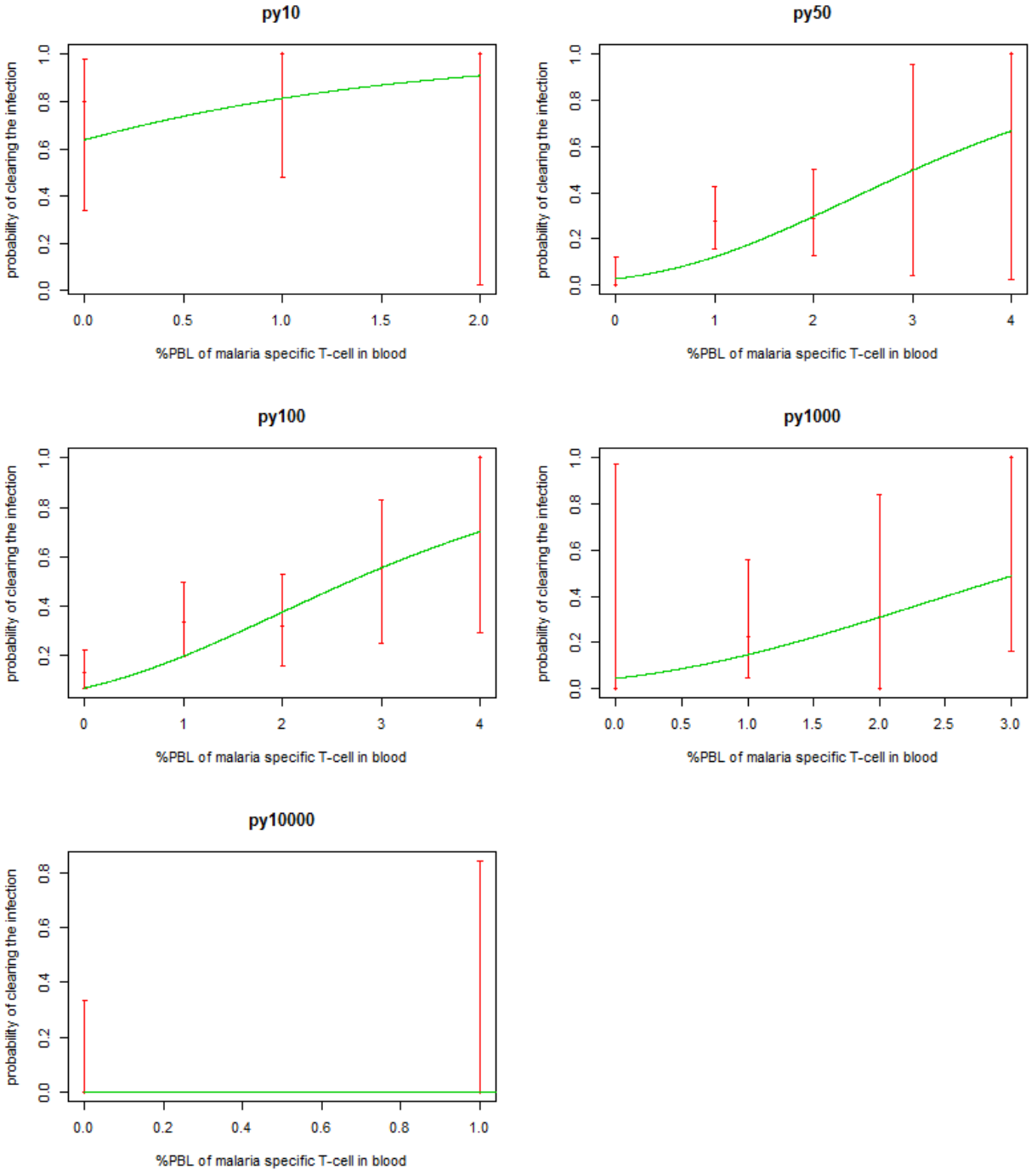
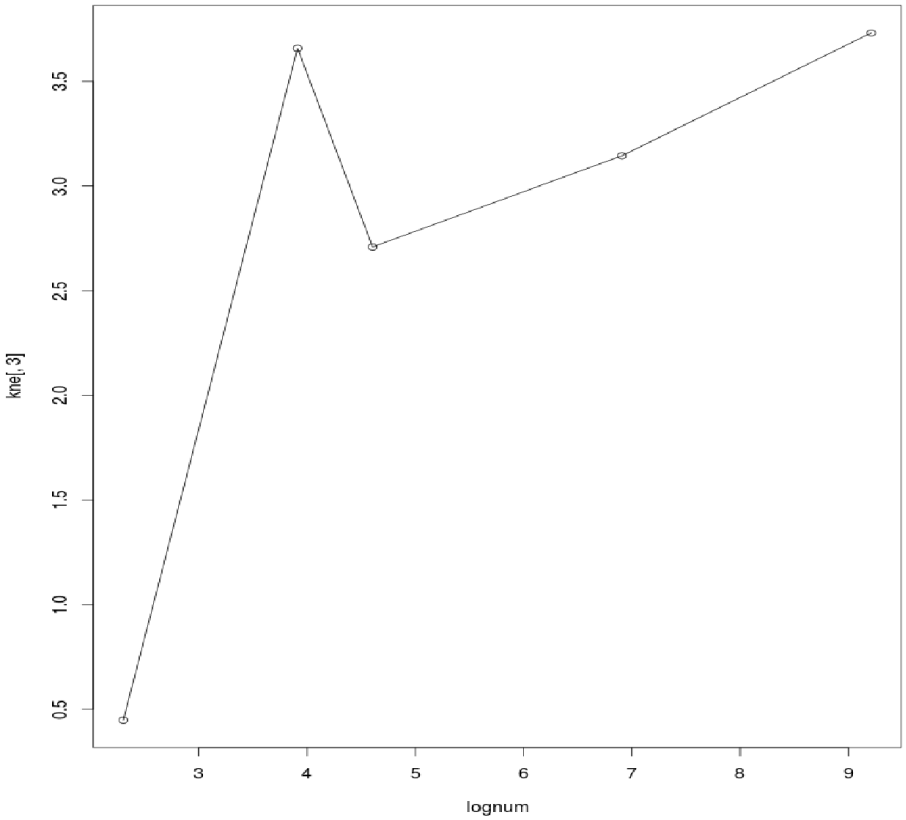

py10000
probability of clearing the infection
0.0
0.2
0.4
0.6
0.8
0.0
0.2
0.4
0.6
0.8
1.0
%PBL of malaria specific T-cell in blood

Figure 12


py10
probability of clearing the infection
%PBL of malaria specific T-cell in blood
py50
probability of clearing the infection
%PBL of malaria specific T-cell in blood
py100
probability of clearing the infection
%PBL of malaria specific T-cell in blood
py1000
probability of clearing the infection
%PBL of malaria specific T-cell in blood
py10000
probability of clearing the infection
%PBL of malaria specific T-cell in blood

The relationship between logN and Ne is shown in Fig.13

Figure 13



Conclusions

The resulting parameters and the model suggest that the effective number of infected hepatocytes is much smaller than the assumed number of pathogens injected. The significance of this work lies in the estimation of parameters in the process of malaria infection in mice, such as probability of clearance by CD8 cells in malaria liver-stage infection upon a given infection dose, which are experimentally not obtainable. The modeling of the relationship between the number of infected sporozoites and the probability of clearance by CD8+ cells will provide reference for vaccine strategy and validity surveillance.