Replacing transit compartments with the analytical solution of a partial differential equation in malaria liver-stage modeling

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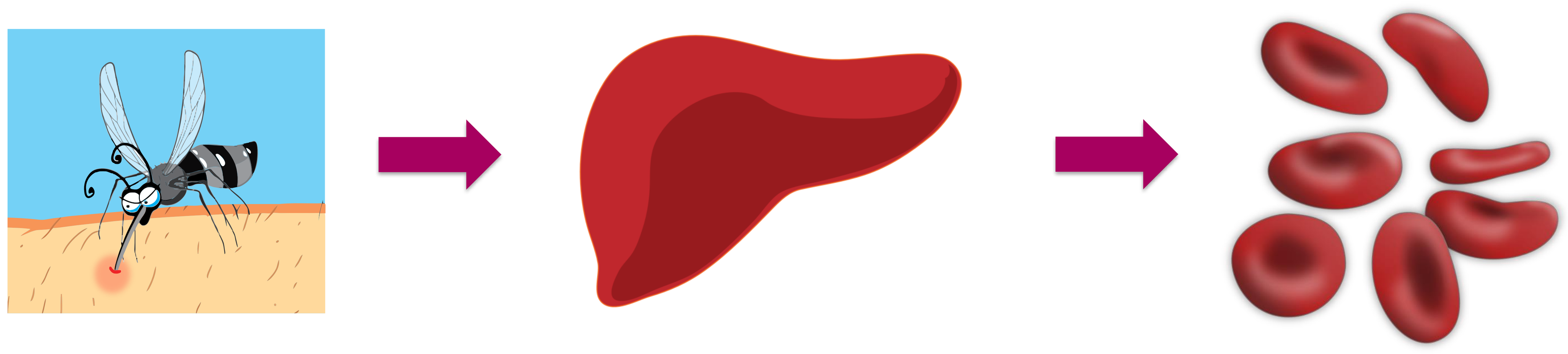
1. Background

After infection by a mosquito bite, malaria *P. falciparum* parasites go into the liver where they stay and replicate for over one week before invading the blood.



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2. Model of the liver stage

Parasite ageing in the liver can be modeled using a Partial Differential Equation (PDE) [1]. This is mathematically equivalent to a fluid (parasites) flowing through a pipe (age). In addition to ageing, parasites also replicate and are killed by drugs.

$$\frac{\partial p_L}{\partial t} + \frac{\partial p_L}{\partial a} = p_L(GR_L - Kill_L) \qquad P_L(t) = \int_0^{T_L} p_L(a,t)\,da$$

*Definitions in the **List of symbols** below.*

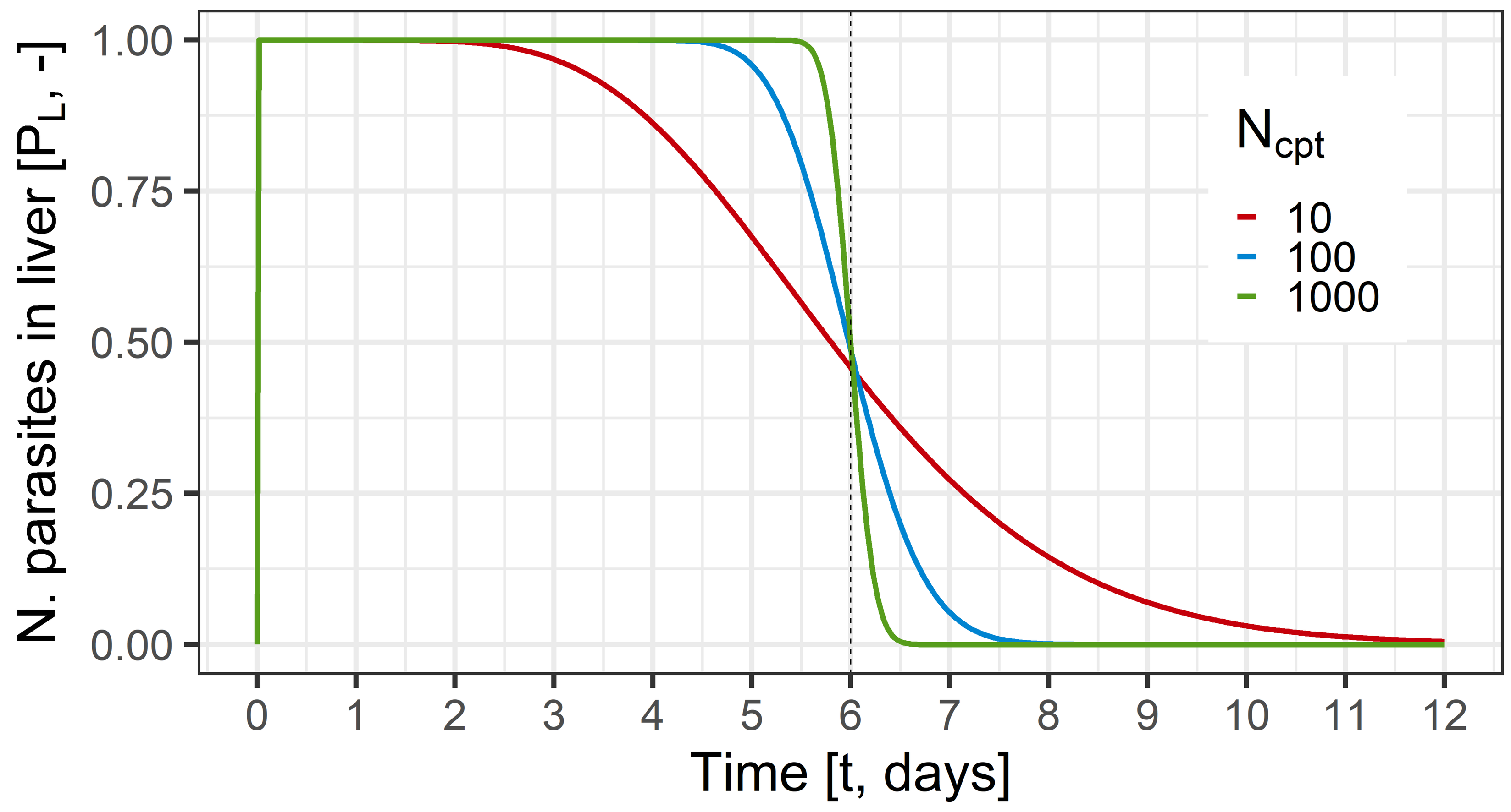
3. Solving the model: transit compartments

The PDE can be numerically approximated by a set of ODEs, mathematically equivalent to transit compartments.

$$\begin{aligned}
\frac{d}{dt}p_L^1(t) &= F_{inf}P_{spz}INPUT - k_{tr}p_L^1 + (\mathrm{GR_L} - Kill_L)p_L^1 \\
\frac{d}{dt}p_L^i(t) &= k_{tr}\left(p_L^{i-1} - p_L^i\right) + (\mathrm{GR_L} - Kill_L)p_L^i \\
\frac{d}{dt}p_L^{N_{cpt}}(t) &= k_{tr}p_L^{N_{cpt}-1} - (\mathrm{GR_L} - Kill_L)p_L^{N_{cpt}}
\end{aligned}$$

Where $k_{tr} = N_{cpt}/T_L$ and $i = 2 \ldots N_{cpt} - 1$. Parasites from different bites are passed as "input doses" to p_L^1.

Example: 1 bite at t = 0, $GR_L = Kill_L = 0$, T_L = 6 days, $F_{inf}P_{spz}$ = 1. Slope of liver escape determined by N_{cpt} (numeric diffusion).



4. Solving the model: analytical solution

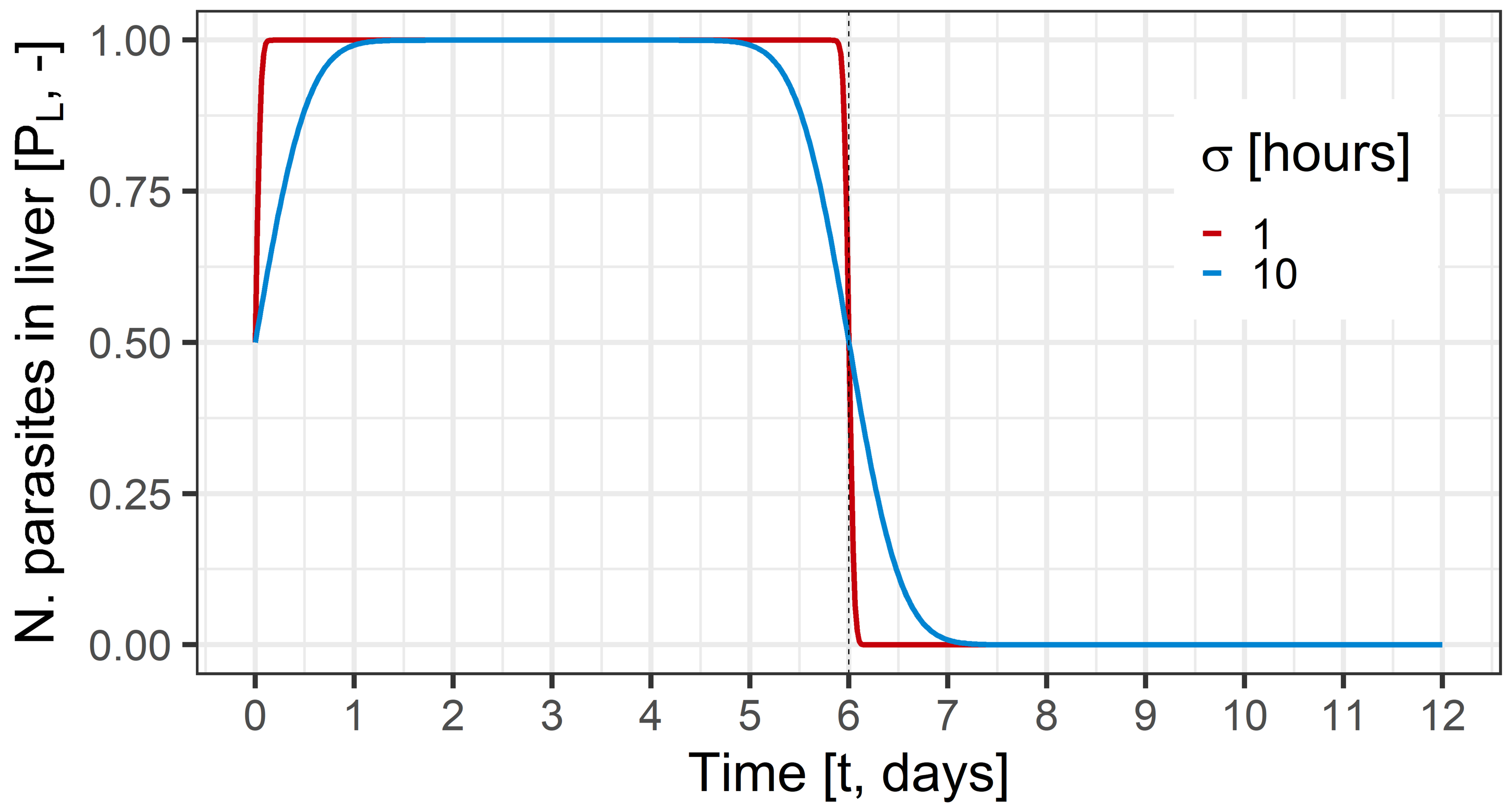
The PDE can be solved analytically.

$$p_L(a,t) = F_{inf}P_{spz}\sum_{n=1}^{N_{bites}} p_L(a-(t-t_n), t=t_n)\, e^{J_n}$$

$$\frac{dJ_n}{dt} = \begin{cases} 0, & t < t_n \\ GR_L - Kill_L, & t \geq t_n \end{cases}$$

We assume that the initial distribution of parasite ages $p_L(a, t = t_n)$ is the same for all bites. To perform simulations, we assume this is a (narrow) Gaussian, $p_L(a, t=t_n) = \frac{1}{\sqrt{2\pi}\sigma}e^{-\frac{1}{2}\left(\frac{a}{\sigma}\right)^2}$.

Example: 1 bite at t = 0, $GR_L = Kill_L = 0$, T_L = 6 days, $F_{inf}P_{spz}$ = 1. Slope of liver escape determined by σ.



5. Conclusions

- The analytical solution does not require to solve a possibly high number (N_{cpt}) of ODEs.
- The slope of liver escape is simply determined by σ, not numeric diffusion (via N_{cpt}).
- With limited computational effort, the analytical solution allows to track the dynamics of parasites from individual bites, useful to introduce "cure thresholds" (*i.e.* number of parasites from the same bite can be either ≥ 1 or 0).

List of symbols

p_L = parasite density in liver
a = parasite age
T_L = avg. time spent in liver
GR_L = growth rate in liver
$Kill_L$ = drug kill rate in liver
P_L = n. parasites in liver
$F_{inf}P_{spz}$ = n. parasites transferred to liver from single bite
t_n = time of n^{th} bite

References

[1] C. Barcelo, S. Jones, P. J. Lowe, J. J. Möhrle, N. Gobeau, and M. H. Cherkaoui-Rbati, *In Preparation*.

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