Supplementary Information for: Modeling the effect of boost timing in prime-boost vaccines against malaria

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A. Outline of population mechanics

Population mechanics is based on the following assumptions:

1. T cell populations are elastic and show inertia. This statement is motivated by the dynamics of effector T cells during immune response to acute infections, specifically by the fact that T cells continue to proliferate even after the pathogen has been effectively neutralized (see figure below).

Inertia and elasticity draw clear analogies with models of Classical Mechanics, and call for the use of second order differential equations at the modeling level. From this viewpoint, the dynamics of a cell population results from the balance between opposite forces that tend to increase or decrease the number of cells. In particular, if a cell population $x$ is subject to $m$ different forces $F_1, \ldots, F_m$, then:

$$x''(t) = F_1 + \cdots + F_m$$

2. Proportional distribution of forces. If $n$ T cell populations compete for a given force $F(t)$, then the magnitude of the force perceived by population $i$ is given by:

$$F_i(t) = \frac{x_i(t)}{x_1(t) + \cdots + x_n(t)} F(t), \text{ for } i = 1, \ldots, n.$$  

where $x_i(t)$ is the number of cells of population $i$ at time $t$.

Models of population mechanics  Based on the previous assumptions, it is possible to model the dynamics of multiple cell populations that compete for different forces. For instance, let $x_1$, $x_2$ and $x_3$ three cell populations, and suppose that $x_1$ and $x_2$ compete for a given factor $F_a$, while a second factor $F_b$ is shared between populations $x_1$ and $x_3$. The corresponding mathematical model takes the following form:
the simulations. For more details about hybrid automata see: [this file](#). In case a population reaches value zero, it is reset to zero and removed from given state to another being governed by differential equations (see for instance Fig 1 in this file). Such systems are characterized by alternating between a collection of discrete states, with transitions from a given state to another being governed by differential equations (see for instance Fig 1 in this file). In case a population reaches value zero, it is reset to zero and removed from the simulations. For more details about hybrid automata see:

\[
\begin{align*}
x_1'(t) &= -c_1x_1(t) - k_1x_1 + \frac{x_1(t)}{x_1(t) + x_2(t)}\lambda_{1,a}F_a(t) + \frac{x_1(t)}{x_1(t) + x_3(t)}\lambda_{1,b}F_b(t) \\
x_2'(t) &= -c_2x_2(t) - k_2x_2 + \frac{x_2(t)}{x_1(t) + x_2(t)}\lambda_{2,a}F_a(t) \\
x_3'(t) &= -c_3x_3(t) - k_2x_3 + \frac{x_3(t)}{x_1(t) + x_3(t)}\lambda_{3,b}F_b(t) \\
x_4'(t) &= -c_4x_4(t) - k_4x_4 + \frac{x_4(t)}{x_1(t) + x_2(t) + x_4(t)}\lambda_{2,a}F_a(t) \\
F'_a(t) &= f_a(t; F_a, x_1, x_2) \\
F'_b(t) &= f_b(t; F_b, x_1, x_3)
\end{align*}
\]

Parameters $c_i$ and $k_i$ represent the damping and elastic coefficients of population $i$. Parameter $\lambda_{i,k}$ describes the intensity of the force perceived by population $i$ per unit of factor $F_k$. Finally, the dynamics of factors $F_a$ and $F_b$ is given by certain functions $f_a$ and $f_b$, which in turn may depend on the size of the cell populations.

Population mechanics models are of a modular nature and can be easily pieced together to account for additional populations. For instance, adding a fourth population that competes for factor $F_a$ in the previous example yields:

\[
\begin{align*}
x_1(t)'' &= -c_1x_1'(t) - k_1x_1 + \frac{x_1(t)}{x_1(t) + x_2(t) + x_4(t)}\lambda_{1,a}F_a(t) + \frac{x_1(t)}{x_1(t) + x_3(t)}\lambda_{1,b}F_b(t) \\
x_2(t)'' &= -c_2x_2'(t) - k_2x_2 + \frac{x_2(t)}{x_1(t) + x_2(t) + x_4(t)}\lambda_{2,a}F_a(t) \\
x_3(t)'' &= -c_3x_3'(t) - k_2x_3 + \frac{x_3(t)}{x_1(t) + x_3(t)}\lambda_{3,b}F_b(t) \\
x_4(t)'' &= -c_4x_4'(t) - k_4x_4 + \frac{x_4(t)}{x_1(t) + x_2(t) + x_4(t)}\lambda_{2,a}F_a(t) \\
F'_a(t) &= f_a(t; F_a, x_1, x_2, x_4) \\
F'_b(t) &= f_b(t; F_b, x_1, x_3)
\end{align*}
\]

We remark that solutions of the previous equations can eventually lead to negative values for some variables. Since negative values are meaningless in our current context, these models must be understood as hybrid dynamical systems. Such systems are characterized by alternating between a collection of discrete states, with transitions from a given state to another being governed by differential equations (see for instance Fig 1 in this file). In case a population reaches value zero, it is reset to zero and removed from the simulations. For more details about hybrid automata see:
- Johansson, K. H. and Lygeros, J. and Zhang, J. and Sastry, S. (2000) Hybrid automata: A formal paradigm for heterogeneous modeling. Proceedings of the 2000 IEEE International Symposium on Computer-Aided Control System Design

- Schaft A. J. van der and Schumacher J. M. (2000) An introduction to hybrid dynamical systems. Springer. New York, London.
Figure A: Hybrid automaton representation of equations 1. Equations 1 describe the situation of effector and memory T cells after activation. (1) Before an immune response both the memory pool $M$ and interleukin $H$ are at equilibrium. This equilibrium corresponds to the values $M = M^* = \varphi/\mu$ and $H = H^* = k/\lambda H M^*$ (see reference [37] in the main text for further details). The population of effector T cells expands owing to the antigenic force provided by the pathogen. (2) If effector T cells disappear before the end of the infection they are no longer considered in equations 1. (3) On the other hand, if the pathogen falls below a given threshold $P_m > 0$ the infection is controlled, and hence the antigenic force disappears. When this occurs the only force acting on effector T cells is the intrinsic elastic force, while memory T cells continue to compete for the homeostatic force $F_H$. (4) As consequence of the elastic force, effector T cells eventually disappear, and memory T cells eventually reach a steady state. (5) We will not consider situations in which the homeostatic interleukin or memory T cell populations go to zero. In any of these cases, the chosen set of parameters does not lead to a meaningful simulation.
Inoculation of prime agent ($P$)

$E'_a(0) = M'_a(0) = M'(0) = 0$

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Inoculation of boost

$E_a'' = -kE_a + \frac{E_a}{E_a + M_a} F_A$

$M_a'' = -cM'_a - kM_a + \frac{M_a}{E_a + M_a} F_A + \frac{M_a}{M + M_a} F_H$

$M'' = -cM' - kM + \frac{M}{M + M_a} F_H$

$H' = \varphi - \mu M - \mu M_a$

$P' = \alpha P - \beta (E_a + M_a) P$

T cell activation

$P(0) = P_0$

Figure B: Hybrid automata diagram of the model of homologous PB vaccines. Notation is consistent with the rest of the models presented in this work.
SM2. Experimental data

Characterization of clonal expansion and contraction

Table A: Number of effector T cells (%CD11ahi) after the inoculation of $10^4$ irradiated sporozoites (see Figure 6.A in the main text).

| Day | Mouse 1 | Mouse 2 | Mouse 3 | Mean | StDev |
|-----|---------|---------|---------|------|-------|
| 0   | 15      | 8       | 4       | 9    | 5.568 |
| 1   | 33      | 50      | 26      | 36.3 | 12.342|
| 2.5 | 50      | 51      | 50      | 50.3 | 0.577 |
| 4   | 61      | 45      | 50      | 52   | 8.185 |
| 5   | 46      | 72      | 71      | 63   | 14.468|
| 6   | 68      | 63      | 87      | 72.6 | 12.663|
| 7   | 30      | 41      | 20      | 30.3 | 10.504|
| 8   | 20      | 35      | 18      | 24.3 | 9.291 |
| 11  | 15      | 20      | 15      | 16.6 | 2.887 |

Table B: Number of effector T cells (%CD11ahi) after the inoculation of $10^5$ irradiated sporozoites (see Figure 6.B in the main text).

| Day | Mouse 1 | Mouse 2 | Mouse 3 | Mean | StDev |
|-----|---------|---------|---------|------|-------|
| 0   | 2       | 5       | 3       | 3.3  | 1.527 |
| 1   | 35      | 38      | 42      | 38.3 | 3.512 |
| 3   | 42      | 40      | 42      | 41.3 | 1.155 |
| 4   | 40      | 55      | 48      | 47.6 | 7.505 |
| 5   | 40      | 50      | 68      | 52.6 | 1.189 |
| 6   | 60      | 73      | 65      | 66   | 6.557 |
| 7   | 63      | 80      | 78      | 73.6 | 9.291 |
| 8   | 70      | 71      | 80      | 73.6 | 5.507 |
| 11  | 55      | 50      | 53      | 52.6 | 2.516 |
Formation of memory T cells

Table C: Memory T cell (% of Resident Memory T cells) formed in three vaccination protocols (P: single inoculation of $10^4$ irradiated sporozoites, $PB_1$: priming with $10^4$ and boosting three days later with $4 \times 10^4$ irradiated sporozoites, and $PB_2$: priming with $10^4$ and boosting seven days later with $4 \times 10^4$ irradiated sporozoites). These data are shown in Figure 6.C in the main text.

| Treatment | Mouse 1 | Mouse 2 | Mouse 3 | Mouse 4 | Mouse 5 | Mean | StDev |
|-----------|---------|---------|---------|---------|---------|------|-------|
| P         | 3       | 2       | 3       | 2       | 1       | 2.2  | 0.837 |
| Treatment | Mouse 6 | Mouse 7 | Mouse 8 | Mouse 9 | Mouse 10 | Mean | StDev |
| $PB_1$    | 3       | 4       | 1       | 4       | 6       | 3.6  | 1.817 |
| Treatment | Mouse 11 | Mouse 12 | Mouse 13 | Mouse 14 | Mouse 15 | Mean | StDev |
| $PB_2$    | 7       | 9       | 5       | 6       | 11      | 7.6  | 2.41  |

Table D: Memory T cell (% of Resident Memory T cells) formed in three vaccination protocols (P: single inoculation of $10^5$ irradiated sporozoites, $PB_1$: priming with $10^5$ and boosting three days later with $4 \times 10^4$ irradiated sporozoites, and $PB_2$: priming with $10^5$ and boosting seven days later with $4 \times 10^4$ irradiated sporozoites). These data are shown in Figure 6.D in the main text.

| Treatment | Mouse 1 | Mouse 2 | Mouse 3 | Mean | StDev |
|-----------|---------|---------|---------|------|-------|
| P         | 27      | 27      | 36      | 30.0 | 5.196 |
| Treatment | Mouse 4 | Mouse 5 | Mouse 6 | Mean | StDev |
| $PB_1$    | 17      | 17      | 15      | 16.33 | 1.155 |
| Treatment | Mouse 7 | Mouse 8 | Mouse 9 | Mean | StDev |
| $PB_2$    | 23      | 27      | 21      | 23.67 | 3.055 |