Immune response modeling with cytokine dosing for artificial lymph node organ-on-chip development

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August 2025

Pharmacokinetics Models used in data generation

Naive T-cell Dynamics

We model the Naive T-cell population using a logistic growth equation with an additional decay term.

Parameters

$$
\begin{aligned}
N_0 &: \text{Initial Naive T-cell count (cells)} \\
r &: \text{Growth rate (per second)} \\
d &: \text{Decay rate (per second)} \\
K &: \text{Carrying capacity (cells)} \\
V &: \text{Blood volume (L)} \\
N_A &: \text{Avogadro's number} \\
\sigma &: \text{Noise level (log-normal)} \\
t &: \text{Time (seconds)}
\end{aligned}
$$

Deterministic Dynamics

The expected (ideal) Naive T-cell count is given by the logistic growth with decay:

$$N_{\text{ideal}}(t) = \frac{K}{1 + \left(\frac{K - N_0}{N_0}\right) e^{-(r-d)t}}. \tag{1}$$

Stochastic Dynamics

To account for biological variability, we introduce log-normal multiplicative noise:

$$N_{\text{noisy}}(t) = N_{\text{ideal}}(t) \cdot \eta(t), \tag{2}$$

where

$$\eta(t) \sim \text{LogNormal}(0, \sigma). \tag{3}$$

Conversion to Molar Concentration

We convert cell counts to molar concentrations:

$$C_{\text{ideal}}(t) = \frac{N_{\text{ideal}}(t)}{N_A \cdot V}, \tag{4}$$

$$C_{\text{noisy}}(t) = \frac{N_{\text{noisy}}(t)}{N_A \cdot V}. \tag{5}$$

Activated T-cell Dynamics

We model the Activated T-cell population using an exponential growth model with multiplicative noise.

Parameters

$$
\begin{aligned}
N_0 &: \text{Initial T-cell count (cells)}\\
r &: \text{Growth rate (per second)}\\
t &: \text{Time (seconds)}\\
V &: \text{Blood volume (L)}\\
N_A &: \text{Avogadro's number}\\
\sigma &: \text{Noise level (log-normal)}
\end{aligned}
$$

Deterministic Growth

The ideal Activated T-cell count follows exponential growth:

$$N_{\text{ideal}}(t) = N_0\, e^{rt}. \tag{6}$$

Stochastic Dynamics

To account for biological variability, we introduce multiplicative log-normal noise:

$$N_{\text{noisy}}(t) = N_{\text{ideal}}(t) \cdot \eta(t), \tag{7}$$

where

$$\eta(t) \sim \text{LogNormal}(0, \sigma). \tag{8}$$

Conversion to Molar Concentration

We convert cell counts to molar concentrations by dividing by Avogadro's number and blood volume:

$$C_{\text{ideal}}(t) = \frac{N_{\text{ideal}}(t)}{N_A \cdot V}, \tag{9}$$

$$C_{\text{noisy}}(t) = \frac{N_{\text{noisy}}(t)}{N_A \cdot V}. \tag{10}$$

Naive B-cell Dynamics

We model the Naive B-cell population using logistic growth with a decay term, combined with stochastic noise.

Parameters

$$
\begin{aligned}
N_0 &: \text{Initial Naive B-cell count (cells)}\\
r &: \text{Growth rate (per second)}\\
d &: \text{Decay rate (per second)}\\
K &: \text{Carrying capacity (cells)}\\
t &: \text{Time (seconds)}\\
V &: \text{Blood volume (L)}\\
N_A &: \text{Avogadro's number}\\
\sigma &: \text{Noise level (log-normal standard deviation)}
\end{aligned}
$$

Deterministic Dynamics

The deterministic Naive B-cell population follows logistic growth with decay:

$$N_{\text{ideal}}(t) = \frac{K}{1 + \left(\frac{K - N_0}{N_0}\right) e^{-(r-d)t}}. \tag{11}$$

Stochastic Dynamics

To incorporate biological variability, we add multiplicative log-normal noise:

$$N_{\text{noisy}}(t) = N_{\text{ideal}}(t) \cdot \eta(t), \tag{12}$$

where

$$\eta(t) \sim \text{LogNormal}(0, \sigma). \tag{13}$$

Conversion to Molar Concentration

We convert cell counts into molar concentrations:

$$C_{\text{ideal}}(t) = \frac{N_{\text{ideal}}(t)}{N_A \cdot V}, \tag{14}$$

$$C_{\text{noisy}}(t) = \frac{N_{\text{noisy}}(t)}{N_A \cdot V}. \tag{15}$$

Plasma B-cell Dynamics

We model the Plasma B-cell population using an exponential growth model with stochastic fluctuations.

Parameters

$$\begin{aligned}
N_0 &: \text{Initial Plasma B-cell count (cells)} \\
r &: \text{Growth rate (per second)} \\
t &: \text{Time (seconds)} \\
V &: \text{Blood volume (L)} \\
N_A &: \text{Avogadro's number} \\
\sigma &: \text{Noise level (log-normal standard deviation)}
\end{aligned}$$

Deterministic Dynamics

The deterministic population follows exponential growth:

$$N_{\text{ideal}}(t) = N_0 \, e^{rt}. \tag{16}$$

Stochastic Dynamics

To account for biological variability, we introduce multiplicative log-normal noise:

$$N_{\text{noisy}}(t) = N_{\text{ideal}}(t) \cdot \eta(t), \tag{17}$$

where

$$\eta(t) \sim \text{LogNormal}(0, \sigma). \tag{18}$$

Conversion to Molar Concentration

We convert cell counts to molar concentrations:

$$C_{\text{ideal}}(t) = \frac{N_{\text{ideal}}(t)}{N_A \cdot V}, \tag{19}$$

$$C_{\text{noisy}}(t) = \frac{N_{\text{noisy}}(t)}{N_A \cdot V}. \tag{20}$$

Dendritic Cell Pulse Dynamics

We model mature dendritic cell (DC) recruitment as a transient pulse, given by the difference of two exponential processes (recruitment vs. clearance).

Parameters

$$\begin{aligned}
DC_0 &: \text{Baseline dendritic cell count (cells)} \\
A &: \text{Pulse amplitude (cells)} \\
\tau_r &: \text{Rise time constant (s)} \\
\tau_d &: \text{Decay time constant (s)} \\
t &: \text{Time (s)} \\
V &: \text{Blood volume (L)} \\
N_A &: \text{Avogadro's number} \\
\sigma &: \text{Noise level (log-normal standard deviation)}
\end{aligned}$$

Pulse Dynamics

The deterministic pulse is modeled as the difference of exponentials:

$$P(t) = \exp\left(-\frac{t}{\tau_d}\right) - \exp\left(-\frac{t}{\tau_r}\right), \tag{21}$$

clipped to ensure non-negativity:

$$P(t) = \max\{P(t), 0\}. \tag{22}$$

The ideal dendritic cell count is then:

$$N_{\text{ideal}}(t) = DC_0 + A \cdot \frac{P(t)}{\max_t P(t)}. \tag{23}$$

Stochastic Extension

We introduce multiplicative log-normal noise:

$$N_{\text{noisy}}(t) = N_{\text{ideal}}(t) \cdot \eta(t), \tag{24}$$

with

$$\eta(t) \sim \text{LogNormal}(0, \sigma). \tag{25}$$

Conversion to Molar Concentration

The cell counts are converted into molar concentrations as:

$$C_{\text{ideal}}(t) = \frac{N_{\text{ideal}}(t)}{N_A \cdot V}, \tag{26}$$

$$C_{\text{noisy}}(t) = \frac{N_{\text{noisy}}(t)}{N_A \cdot V}. \tag{27}$$

IL-2 Plasma Pharmacokinetics

We model the plasma concentration of interleukin-2 (IL-2) as a rise-and-decay function, scaled to match a specified peak concentration.

Parameters

$$\begin{aligned}
C_{\max} &: \text{Peak IL-2 concentration (ng/mL)} \\
t_{\text{peak}} &: \text{Time of peak concentration (h)} \\
\tau_r &: \text{Rise time constant (h)} \\
\tau_e &: \text{Elimination time constant (h)} \\
MW &: \text{Molecular weight of IL-2 (g/mol)} \\
\sigma &: \text{Noise level (log-normal standard deviation)} \\
t &: \text{Time (h)}
\end{aligned}$$

Ideal Concentration Curve

We first define a rise–decay function:

$$R(t) = \left(1 - e^{-t/\tau_r}\right) e^{-t/\tau_e}. \tag{28}$$

We then scale it to enforce the peak at $t = t_{\text{peak}}$:

$$C_{\text{ideal}}(t) = C_{\max} \cdot \frac{R(t)}{R(t_{\text{peak}})}. \tag{29}$$

Stochastic Extension

Biological variability is introduced via multiplicative log-normal noise:

$$C_{\text{noisy}}(t) = C_{\text{ideal}}(t) \cdot \eta(t), \tag{30}$$

where

$$\eta(t) \sim \text{LogNormal}(0, \sigma). \tag{31}$$

Unit Conversions

The model tracks concentration in several equivalent units:

$$C_{\text{pg/mL}}(t) = 1000 \cdot C_{\text{ng/mL}}(t), \tag{32}$$

$$C_{\text{pM}}(t) = C_{\text{ng/mL}}(t) \cdot \frac{10^{-6}}{MW} \cdot 10^{12}, \tag{33}$$

$$C_{\text{M}}(t) = C_{\text{pM}}(t) \cdot 10^{-12}. \tag{34}$$