Appendix

Numerical method

The T cells zone is considered to be a square domain denoted $\Omega$ where the reaction-diffusion equations describing extracellular cytokines concentrations are solved. We apply Dirichlet conditions to the four borders of the square domain ($\Gamma$). The numerical implementation of the reaction-diffusion equations was done using the finite difference method. Let us consider the boundary value problem ($P$) for the extracellular cytokine field $I$. We numerically solve the problem using the alternating direction implicit method. We briefly recall the procedure to be followed below.

\[
(P_1): \quad \begin{cases}
\frac{\partial I}{\partial t} = D \Delta I + W - \sigma I, & \text{in } \Omega \\
I(x, y, 0) = \phi(x, y), & \text{in } \Omega \\
I = I_0 & \text{on } \Gamma,
\end{cases}
\]

where $D$ is the diffusion coefficient, $W$ and $\sigma$ are the production and degradation factors respectively, $\phi(x, y)$ represents the initial condition condition for $I$, $I_0$ is a constant prescribed value at the boundaries. We consider the grid $(x_i, y_j, t_n) = (ih, jh, n\delta t)$, where $h$ and $\delta t$ are the space and time steps respectively. We denote $i = 1, 2, ..., N_x$ and $j = 1, 2, ..., N_y$. To begin with, we rewrite the problem ($P$) in the following form:

\[
(P_1): \quad \begin{cases}
\frac{\partial I}{\partial t} = \frac{D}{2} \left( \frac{\partial^2 I}{\partial x^2} + \frac{\partial^2 I}{\partial y^2} \right) + \frac{D}{2} \left( \frac{\partial^2 I}{\partial x^2} + \frac{\partial^2 I}{\partial y^2} \right) + W - \sigma I, & \text{in } \Omega \\
I(x, y, 0) = \phi(x, y), & \text{in } \Omega \\
I = I_0 & \text{on } \Gamma,
\end{cases}
\]

We split the first equation of the problem ($P_1$) into two sub-steps as follows:

\[
\begin{align*}
I_{i,j}^{n+1/2} - I_{i,j}^n &= D \frac{I_{i+1,j}^{n+1/2} - 2I_{i,j}^{n+1/2} + I_{i-1,j}^{n+1/2}}{h^2} + D \frac{I_{i,j+1}^{n+1/2} - 2I_{i,j}^{n+1/2} + I_{i,j-1}^{n+1/2}}{h^2} + W - \sigma I_{i,j}^{n+1/2} \\
I_{i,j}^{n+1} - I_{i,j}^{n+1/2} &= D \frac{I_{i+1,j}^{n+1} - 2I_{i,j}^{n+1} + I_{i-1,j}^{n+1}}{h^2} + D \frac{I_{i,j+1}^{n+1} - 2I_{i,j}^{n+1} + I_{i,j-1}^{n+1}}{h^2} + W - \sigma I_{i,j}^{n+1}.
\end{align*}
\]

We solve the first equation for each fixed $j$ to obtain $I_{i,j}^{n+1/2}$. Next, we solve the second to obtain $I_{i,j}^{n+1}$. Let us consider the first equation:

\[
\frac{I_{i,j}^{n+1/2} - I_{i,j}^n}{\delta t/2} = D \frac{I_{i+1,j}^{n+1/2} - 2I_{i,j}^{n+1/2} + I_{i-1,j}^{n+1/2}}{h^2} + D \frac{I_{i,j+1}^{n+1/2} - 2I_{i,j}^{n+1/2} + I_{i,j-1}^{n+1/2}}{h^2} + W - \sigma I_{i,j}^{n+1/2}.
\]

Rearranging the terms we obtain:

\[
\begin{align*}
&\frac{D}{h^2} I_{i-1,j}^{n+1/2} + \left( -\frac{2D}{h^2} - \frac{1}{\delta t/2} - \sigma \right) I_{i,j}^{n+1/2} + \frac{D}{h^2} I_{i+1,j}^{n+1/2} = \\
&\frac{D}{h^2} I_{i,j}^{n+1/2} - \left( -\frac{2D}{h^2} - \frac{1}{\delta t/2} - \sigma \right) I_{i,j}^{n+1/2} + \frac{D}{h^2} I_{i,j}^{n+1/2} = \\
&\frac{D}{h^2} I_{i,j}^{n+1/2} - W.
\end{align*}
\]
Therefore, we can write the first equation of the system \(1\) in the form:

\[
a_{i,j}I_{i-1,j}^{n+1/2} + b_{i,j}I_{i,j}^{n+1/2} + c_{i,j}I_{i+1,j}^{n+1/2} = f_{i,j},
\]

for each fixed \(j, j = 1, 2, ..., N_y - 1\), we solve numerically:

\[
a_iI_{i-1}^{n+1/2} + b_iI_{i}^{n+1/2} + c_iI_{i+1}^{n+1/2} = f_i, \quad \forall i = 1, 2, ..., N_x - 1
\]  

(2)

with the boundary conditions \(I_{i=0}^n = I_{0,1}, I_{i=N_x}^n = I_{0,2}\). We solve the equation (2) using Thomas algorithm. For that, we write the left boundary condition \(I_{i=0}^n = I_{0,1}\) as follows:

\[
I_{0}^{n+1/2} = L_{1/2}I_1 + K_{1/2},
\]

where \(L_{1/2} = 0\) and \(K_{1/2} = I_{0,1}\). Then from the equation (2) for \(i = 1\):

\[
a_1I_{0}^{n+1/2} + b_1I_{1}^{n+1/2} + c_1I_{2}^{n+1/2} = f_1,
\]

we obtain \(I_{1}^{n+1/2}\):

\[
I_{1}^{n+1/2} = L_{3/2}I_{1,1} + K_{3/2},
\]

where we denote \(L_{3/2} = \frac{-c_1}{b_1}, K_{3/2} = \frac{a_1I_{0,1} - f_1}{-b_1}\). We continue this process for \(i = 2, 3, ..., N_x - 1\):

\[
I_{i} = L_{i+1/2}I_{i+1} + K_{i+1/2},
\]  

(3)

where \(L_{i+1/2} = \frac{-c_i}{b_i + a_iL_{i-1/2}}, K_{i+1/2} = \frac{f_i + a_iK_{i-1/2}}{b_i + a_iL_{i-1/2}}\). We first obtain the coefficients \(L_{i+1/2}, K_{i+1/2}\) using the formula (2). Next, we find the solution \(I^{n+1/2}\) for the sub-step \(n+1/2\) by backward sweep using the equation (3). We apply the same procedure on the second equation of the system \((1)\) to compute the next step solution \(I^n\).

**Numerical implementation**

The source code was written in the Object Oriented Programming (POO) form under C++. The considered time and space units in the model are the minute and the domain length (L) respectively. The library wxWidgets was used to implement a user-friendly interface and visualize the simulations in real-time. The CPU time of numerical simulations was 3 – 4 hours on a computer with four cores and 6GB of RAM.

**Values of parameters**

The number of T cells in the computational domain is \(\sim 3 \times 10^3\) with the proportions of CD4\(^+\) and CD8\(^+\) T cells being 2 : 1, and the number of APCs ranging from 30 to 300 cells.

For APC, T-cells and infected cells models, the parameters were fitted with experimental data:

1. \(k_1\) The rate of T-cells production and release into the body: 1.8 /hr;
2. \(k_2\) The death rate of T-cells in the body: 0.12 /hr.
3. $k_3$ The elimination rate of the infected cells by T-cells $1.8 \times 10^{-6} \text{/hr}$.
4. $a$ A growth rate parameter of infected cells: $0.00024 \text{/hr}$.
5. $h$ A parameter in the growth function of infected cells: $0.006 \text{/hr}$.

For the IL-2 controlled processes the following parameter values were used taken from [43]:

1. $n_T$ - the number of IL-2 molecules internalized by T cells via IL-2 receptors: 2000-5000 per T cell;
2. $I_t^*$ - the saturation concentration of IL-2 for T cell division in vitro: $6 \times 10^{10}$ molec/ml for $5 \times 10^4$ cells/ml;
3. $\rho_{IL2}$ - the secretion rate of IL-2 by single CD4$^+$ T cell: $7 \times 10^5$ molec/hr;
4. $b_1$ - the degradation rate of extracellular IL-2: 0.5 1/hr;

For illustrative purpose, we assume that the degradation of the IL-2 effect on the intracellular activation $d_{inIL2}$ is equal to $d_{Tact}$.

For the type I IFN controlled processes the following parameter values were used taken from [29]:

1. $\rho_{IFN}$ - the secretion rate of type I IFN by single activated APC (plasmacytoid dendritic cell): $1.6 \times 10^4$ molec/hr;
2. $b_2$ - the degradation rate of extracellular type I IFN: 0.012 1/hr;
3. $D_{IL}, D_{IFN}$ - the diffusion coefficients of IL-2 and type I IFN. As the molecular weights of IL-2 and type I IFN are close to that of myoglobin, we used the following estimate of the diffusion coefficient $0.16 \text{mm}^3/\text{h}$.

The quantitative specification of the effect of signalling on gene activation requires a separate study. To illustrate the model performance, it was enough to assume some reference values as follows: $\alpha_1 \sim \alpha_2 \sim 1/(\text{molec hr})$ and $d_1 \sim d_2 \sim 0.1/(\text{hr})$
The proliferation and differentiation thresholds have been arbitrarily set to be $I_t^* = 100 \text{ Units(U)}$ and $C_t^* = 2000 \text{ U}$. 