Supplementary Material S1: Investigating the Role of T-Cell Avidity and Killing Efficacy in Relation to Type 1 Diabetes Prediction

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\section{A Model Scaling}

\subsection{A.1 Scaled one-clone model}

By making the following substitutions: \( t_c = T_c/\tilde{R} \) (here \( \tilde{R} := (\alpha^{1/2} - \delta^{1/2}_{T_c})^2/\epsilon \)), \( b = \eta_0 B/\gamma \), \( p_c = \delta_P P_c/\gamma \), \( i_g = \delta_I g P_c/(a_2 \gamma) \), \( p = \delta_P P/(R \tilde{R} \beta_0) \) (here \( \beta_0 \) is the initial number of beta cells), \( \beta_s = \beta/\beta_0 \), we get

\begin{align}
\frac{dt_c}{dt} &= \alpha t_c \frac{p}{p + k} - \delta_T t_c - (\alpha^{1/2} - \delta^{1/2}_T)^2 \epsilon c \\
\frac{db}{dt} &= \eta_0 + (-\eta_2 p t_c + \eta_1 p - \eta_0)b \\
\frac{dp_c}{dt} &= \delta_P \left[ \eta_2 p t_c b/\eta_0 - p_c \right] \\
\frac{di_g}{dt} &= \delta_I g \left[ \ell b + p_c - i_g \right] \\
\frac{d\beta_s}{dt} &= -\kappa R t_c \beta_s \\
\frac{dp}{dt} &= \delta_P \left[ t_c \beta_s - p \right],
\end{align}

where \( k = \delta_P \tilde{k}/(R \tilde{R} \beta_0) \), \( \eta_2 = \tilde{\eta}_2 R \tilde{R}^2 \beta_0/\delta_P \), \( \eta_1 = \tilde{\eta}_1 R \tilde{R} \beta_0/\delta_P \), and \( \ell = a_1 \delta_P/(a_2 \eta_0) \).
A.2 Reduced/scaled one-clone model

Substituting the variables \( b, i_g \) and \( p \) by their steady states (fast variables) and assuming that \( \beta_s \) is roughly a constant (slow variable), i.e. \( \beta_s = 1 \), generates the following two-variable model

\[
\begin{align*}
\frac{dt_c}{dt} &= \alpha t_c \frac{t_c}{t_c + \bar{k}} - \delta t_c t_c - (\alpha^{1/2} - \delta^{1/2} t_c)^2 t_c^2 \\
\frac{dp_c}{dt} &= \delta p_c \left[ \frac{\eta_2 t_c^2}{\eta_1 t_c + \eta_0} - p_c \right],
\end{align*}
\]

(S2a)

where \( \bar{k} = k/\beta_s (= k) \) (can be shown analytically to satisfy \( 0 \leq \bar{k} \leq 1 \), see Section B) and \( \eta_0 = \eta_0/\beta_s (= \eta_0) \).

A.3 Scaled two-clone model

By applying the following substitutions \( t_{cj} = T_{cj}/\bar{R} \) (here \( \bar{R} := (\alpha^{1/2} - \delta^{1/2} t_c)^2/\epsilon \)), \( b_j = \eta_0 j B_j/\gamma_j \), \( p_{cj} = \delta P_{cj} P_{cj}/\gamma_j \), \( i_{gj} = \delta i_{gj} \beta_{gj} I_{gj}/(a_{2j} \gamma_j) \) and \( p_j = \delta P_j P_j/(R_j \bar{R} \beta_0) \) \( (j = 1, 2) \), we obtain

\[
\begin{align*}
\frac{dt_{cj}}{dt} &= \alpha_{t_{cj}} t_{cj} \frac{p_{cj}}{p_{cj} + k_{1j}} - \delta_{t_{cj}} t_{cj} - (\alpha_{21}^{1/2} - \delta_{21}^{1/2} t_{cj})^2 t_{cj} (t_{c11} + t_{c12}) \\
\frac{dt_{cj}}{dt} &= \alpha_{t_{cj}} t_{cj} \frac{p_{cj}}{p_{cj} + k_{2j}} - \delta_{t_{cj}} t_{cj} - (\alpha_{21}^{1/2} - \delta_{21}^{1/2} t_{cj})^2 t_{cj} (t_{c21} + t_{c22}) \\
\frac{dp_{cj}}{dt} &= \delta_{p_{cj}} \left[ \frac{\eta_2 p_{cj} G(t_{c11}, t_{c12}, t_{c21}, t_{c22})}{\eta_0} + \eta_1 p_{cj} - \eta_0 \right] b_j \\
\frac{dp_{cj}}{dt} &= \delta_{p_{cj}} \left[ \frac{\eta_2 p_{cj} G(t_{c11}, t_{c12}, t_{c21}, t_{c22}) b_j}{\eta_0} - p_{cj} \right] \\
\frac{dp_{cj}}{dt} &= \delta_{i_{gj}} \left[ \ell_j b_j + p_{cj} - i_{gj} \right] \\
\frac{dp_{cj}}{dt} &= -\kappa \bar{R} G(t_{c11}, t_{c12}, t_{c21}, t_{c22}) \beta_s \\
\frac{dp_{cj}}{dt} &= \delta_{P_j} \left[ G(t_{c11}, t_{c12}, t_{c21}, t_{c22}) \beta_s - p_j \right],
\end{align*}
\]

(S3a)

(S3b)

(S3c)

(S3d)

(S3e)

(S3f)

(S3g)

where \( k_j = \delta_{P_j} \bar{k}_j/(R_j \bar{R} \beta_0) \), \( \eta_{2j} = \bar{\eta}_{2j} R_j \bar{R}^2 \beta_0/\delta_{P_j} \), \( \eta_{1j} = \bar{\eta}_{1j} R_j \bar{R} \beta_0/\delta_{P_j} \), \( \ell_j = a_{1j} \beta_{P_j}/(a_{2j} \eta_0) \) (recall that \( G \) is linear).
B Theoretical Results

B.1 Nullclines and steady states

We focus in this section on the reduced model described by Eqs. (S2a)-(S2b) to find its steady states and determine under what conditions these steady states are stable. In order to do so, we examine the $t_c$ and $p_c$-nullclines and their points of intersections (steady states).

$$f_1(t_c) := \frac{\alpha}{t_c + \bar{k}} = \delta_{T_c} + (\alpha^{1/2} - \delta_{T_c}^{1/2})^2 t_c = 0$$

$$f_2(t_c, \bar{k}) := -k \left[ \delta_{T_c} + (\alpha^{1/2} - \delta_{T_c}^{1/2})^2 t_c \right].$$

Equation (S2a) is independent of $p_c$, therefore its nullclines are vertical lines. Clearly, $t_c = 0$ is one $t_c$-nullcline. For additional $t_c$-nullclines, we must have

$$\alpha \frac{t_c}{t_c + \bar{k}} = \delta_{T_c} + (\alpha^{1/2} - \delta_{T_c}^{1/2})^2 t_c = 0 \iff \left( \alpha^{1/2} - \delta_{T_c}^{1/2} \right)^2 t_c^2 - (\alpha - \delta_{T_c}) t_c = -k \left[ \delta_{T_c} + (\alpha^{1/2} - \delta_{T_c}^{1/2})^2 t_c \right].$$

Let $f_1(t_c) := (\alpha^{1/2} - \delta_{T_c}^{1/2})^2 t_c^2 - (\alpha - \delta_{T_c}) t_c$ and $f_2(t_c, \bar{k}) := -k \left[ \delta_{T_c} + (\alpha - \delta_{T_c}) t_c \right]$. Fig. S1 shows typically the graphs of these two functions $(f_1, f_2)$ intersecting at two points when the avidity of T cells is high.
enough (i.e., when $k$ is small enough) and do not intersect otherwise. To determine the parameter range for $k$ in which the two curves $f_1, f_2$ intersect, we solve for the roots of $t_c$ from the quadratic Eqn. (S4). By letting $a := \alpha^{1/2} - \delta_{T_c}^{1/2} > 0$ and $b := \alpha^{1/2} + \delta_{T_c}^{1/2}$, we deduce that the roots of Eqn. (S4) are

$$t_{cr} = \frac{a(b - a\bar{k}) \pm \sqrt{a^2(b - a\bar{k})^2 - 4a^2\bar{k}\delta_{T_c}}}{2a^2}. \tag{S5}$$

To obtain real roots, we require the quantity inside the square root to be non-negative, i.e. $(b - a\bar{k})^2 - 4\bar{k}\delta_{T_c} \geq 0$. It follows that

$$b^2 - 2ab\bar{k} + a^2\bar{k}^2 - 4\bar{k}\delta_{T_c} \geq 0 \quad \iff \quad b^2 - 2(\alpha - \delta_{T_c})\bar{k} + a^2\bar{k}^2 - 4\delta_{T_c}\bar{k} \geq 0 \quad \iff \quad b^2 - 2\alpha\bar{k} + a^2\bar{k}^2 - 2\delta_{T_c}\bar{k} \geq 0.$$ 

But $-2\alpha\bar{k} - 2\delta_{T_c}\bar{k} = -2\bar{k}(\alpha + \delta_{T_c}) = -\bar{k}(a^2 + b^2)$. Hence

$$a^2\bar{k}^2 - (a^2 + b^2)\bar{k} + b^2 \geq 0 \quad \iff \quad a^2\bar{k}(\bar{k} - 1) - b^2(\bar{k} - 1) \geq 0,$$

which implies that

$$(a^2\bar{k} - b^2)(\bar{k} - 1) \geq 0. \tag{S6}$$

Inequality (S6) is satisfied either when $\bar{k} \geq (b/a)^2 > 1$ or $0 \leq \bar{k} \leq 1 < (b/a)^2$. If $\bar{k} \geq (b/a)^2$, then one of the $t_{cr} < 0$, a physiologically irrelevant case. However, if $0 \leq \bar{k} \leq 1$, then both $t_{cr} > 0$ and the graphs of the two functions $f_1, f_2$ intersect at either one point (i.e. they are tangential to each other) when $\bar{k} = 1$, or intersect at two points when $0 \leq \bar{k} < 1$, as demonstrated in Fig. S1. Thus, two physiologically relevant $t_c$-nullclines (vertical lines) are obtained in the interval $\bar{k} \in [0, 1)$.

By solving for $p_c$ in Eqn. (S2b), we obtain the $p_c$-nullcline, given by

$$p_c = \frac{\eta_2 t_{c}^2}{\eta_2 t_{c}^2 - \eta_1 t_{c} + \eta_0}.$$ 

The points of intersection of the $t_c$- and $p_c$-nullclines are the steady states of Eqs. (S2a)-(S2b). There are three such intersections; namely, the point $S_1 := (0, 0)$, corresponding to a healthy state (with no effector CD8$^+$ T-cell, CD4$^+$ T-cell or plasma-cell accumulation); the point $U$, whose $t_c$-component is the left
black dot shown in Fig. S1; and the point $S_2$, corresponding to an autoimmune state (with elevated level of CD$^8^+$ T cells, CD$^4^+$ T cells and plasma cells), whose $t_c$-component is the right black dot in Fig. S1. These steady states can all coexist provided that $\bar{k} \in [0, 1)$. We demonstrate below that $S_1$ and $S_2$ are stable, while $U$ is unstable.

Fig. S1 reveals that increasing T-cell avidity (i.e. decreasing $\bar{k}$ within $[0, 1)$) shifts the right black dot of intersection (and thus the corresponding $t_c$-nullcline) to the right. This shift is accompanied by an elevation in the level of autoreactive T cells in the autoimmune state $S_2$. The left black dot of intersection, on the other hand, is shifted to the left against the origin, compressing the basin of attraction of the healthy state $S_1$. Details of these various configurations are explained in detail in the main text.

Notice that the denominator in the equation of $p_c$-nullcline could be zero (in which case, the $p_c$-nullcline will have a vertical asymptote). This may lead to an unbounded increase in the level of T cells in the autoimmune state $S_2$ while varying $\bar{k}$, a feature considered unrealistic biologically (see Fig. S1(a)). To avoid this situation, we impose the condition $\eta_1^2 < 4\eta_2\bar{\eta}_0$

### B.2 Stability analysis

The Jacobian matrix of Eqs. (S2a)-(S2b) is given by

$$J = \begin{pmatrix}
\frac{2\alpha t_c}{t_c + \bar{k}} - \frac{\alpha t_c^2}{(t_c + \bar{k})^2} - 2(\alpha^{1/2} - \delta^{1/2}_{T_c})^2 t_c & 0 \\
\delta_{P_c} \left[ \frac{2\eta_2 t_c}{\eta_2 t_c^2 - \eta_1 t_c + \bar{\eta}_0} - \frac{\eta_2 t_c^2 (2\eta_2 t_c - \eta_1)}{(\eta_2 t_c^2 - \eta_1 t_c + \bar{\eta}_0)^2} \right] & -\delta_{P_c}
\end{pmatrix}.$$  

The eigenvalues of $J|_{S_1}$ are $\lambda_1 = -\delta_{T_c}$ and $\lambda_2 = -\delta_{P_c}$, both of which are negative, so the healthy state is always stable. In the presence of the two other steady states, the autoimmune state $S_2$ is also stable while the steady state $U$ is unstable. The $t_c$-nullcline passing through $U$ is the separatrix between the basins of attraction of the two states $S_1$ and $S_2$.

### B.3 B-cell-dependent T-cell activation

In one of the model assumptions stated in the main text, we ignored the direct role of B cells in activating T cells and assumed that the three types of APCs under consideration (DCs, macrophages and B cells)
act uniformly on the T-cell population. We also assumed that the population size of APCs is roughly constant. Here we show that having a separate pool of B cells that acts directly on T cells as APCs for activation and cell replication, does not significantly alter the general behaviour of the reduced one-clone model.

To verify this, we modify Eqn. (S2a) to account for B-cell activation of T cells, as follows

$$\frac{dt_c}{dt} = (\alpha_B b + \alpha)t_c \frac{t_c}{t_c + \bar{\kappa}} - \delta T_c t_c - (\alpha^{1/2} - \delta^{1/2} T_c)^2 t_c^2,$$

where $\alpha_B bt_c^2/(t_c + \bar{\kappa})$ is the B-cell-dependent T-cell activation occurring at a rate $\alpha_B$ and satisfying $\alpha_B b + \bar{\alpha} \approx \alpha$. (This equation derives from the non-scaled form as done before.) Including such terms in the dynamic equation of $t_c$ generates a cubic-shaped $t_c$-nullcline by joining the two right vertical nullcline associated with Eqs. (S2a)-(S2b) (see Fig. S2. Increasing the value of $a_B$ decreases the steepness of this cubic nullcline and slightly alters the location of the steady states $S_2$ and $U$, but does not alter their stability. This suggests that the approximation used in Eqn. (S2a) is justifiable.

Fig. S2: The phase plane of Eqs. (S7) and (S2b), displaying the $t_c$- and $p_c$-nullclines for $a_B = 0.5$ ($t_c = 0$ nullcline is not shown because the $c$-axis is in logarithmic scale). The two gray lines are the $t_c$-nullclines, while the Hill-like black line is the $p_c$-nullcline. The stable steady state $S_2$, shown as black dot, is the autoimmune state as before, while the unstable steady state $U$ is shown as a white dot. (The healthy state $S_1$ is not shown.) Including the term $\alpha_B bt_c^2/(t_c + \bar{\kappa})$ in the dynamic equation of $t_c$ modified the shape of the $t_c$-nullclines only slightly.