Dynamical modeling

We describe a detailed model of the interactions between three cell types: conventional CD4+ T cells (Tconvs), regulatory T cells (Tregs), and dendritic cells (DCs). The variables and parameters of the model can be found in Tables 1 and S1.
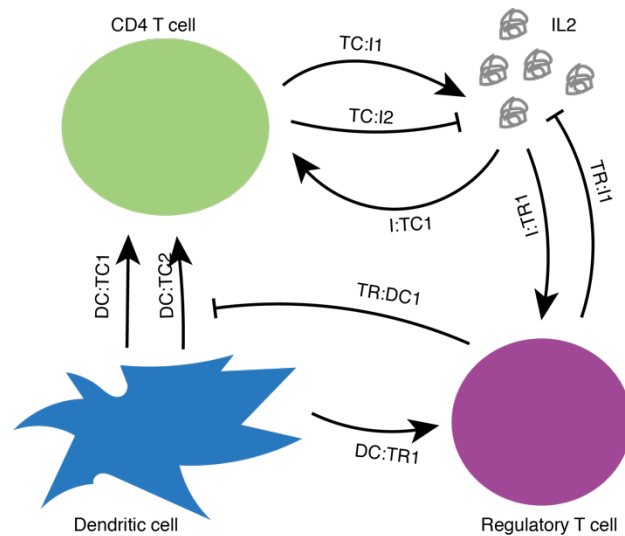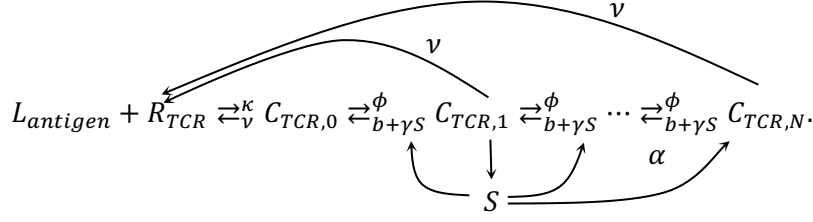

Figure 1. Model schematic

1. TCR signaling (DC:TC1)

This component consists of kinetic proofreading of antigen recognition and the effective signaling strength that regulates downstream pathways, including production of IL-2, and IL-2Rα (Francois et al., 2013; Voisinne et al., 2015). To make the model description self-contained, we lay out the detailed derivation from (Francois et al., 2013).

1.1 Kinetic proofreading

1.1.1 Reactions

$$L_{antigen} + R_{TCR} \underset{v}{\overset{\kappa}{\rightleftarrows}} C_{TCR,0} \underset{b+\gamma S}{\overset{\phi}{\rightleftarrows}} C_{TCR,1} \underset{b+\gamma S}{\overset{\phi}{\rightleftarrows}} \cdots \underset{b+\gamma S}{\overset{\phi}{\rightleftarrows}} C_{TCR,N}.$$

(with v arrows and α, S indicated)

1.1.2 Equations

Corresponding equations are as bellow:

$$\frac{dS_{SHP1}}{dt} = \alpha C_{TCR,1}\left(S_{SHP1,T} - S_{SHP1}\right) - \beta S_{SHP1},$$

$$\frac{dC_{TCR,0}}{dt} = \kappa\left(L_{antigen} - \sum_{i=0}^{N} C_{TCR,i}\right)\left(R_{TCR} - \sum_{i=0}^{N} C_{TCR,i}\right) + (b + \gamma S_{SHP1})C_{TCR,1}$$

$$- (\phi + v)C_{TCR,0},$$

$$\frac{dC_{TCR,j}}{dt} = \phi C_{TCR,j-1} + (b + \gamma S_{SHP1})C_{TCR,j+1} - (\phi + b + \gamma S_{SHP1} + v)C_{TCR,j},$$

$$\frac{dC_{TCR,N}}{dt} = \phi C_{TCR,N-1} - (b + \gamma S_{SHP1} + v)C_{TCR,N},$$

where *j* runs from 1 to N-1.

At steady states, the summation of equations for $C_{TCR,j}$ above leads to:

$$\kappa\left(L_{antigen} - \sum_{i=0}^{N} C_{TCR,i}\right)\left(R_{TCR} - \sum_{i=0}^{N} C_{TCR,i}\right) = v\sum_{i=0}^{N} C_{TCR,i}.$$

Assuming $\sum_{i=0}^{N} C_{TCR,i} \ll R_{TCR}$, we obtain

$$\kappa L_{antigen} R_{TCR} = (\kappa R + v)v\sum_{i=0}^{N} C_{TCR,i},$$

$$v\sum_{i=0}^{N} C_{TCR,i} = L_{antigen}\frac{\kappa R_{TCR}}{v + \kappa R}.$$

Other equations become

$$S_{SHP1} = S_{SHP1,T} \frac{C_{TCR,1}}{C_{TCR,1} + C_{TCR,*}}, \text{where } C_{TCR,*} = \frac{\beta}{\alpha},$$

$$0 = L_{antigen} \frac{\kappa R_{TCR}}{v + \kappa R} + (b + S_{SHP1})C_{TCR,1} - (\phi + v)C_{TCR,0},$$

$$0 = \phi C_{TCR,j-1} + (b + S_{SHP1})C_{TCR,j+1} - (\phi + b + S_{SHP1} + v)C_{TCR,j},$$

$$0 = \phi C_{TCR,N-1} - (b + S_{SHP1} + v)C_{TCR,N}.$$

To solve for $C_{TCR,j}$'s, we first obtain solutions of

$$0 = \phi + (b + S_{SHP-1})r^2 - (\phi + b + S_{SHP1} + v)r = f(r)$$

as

$$r_{\pm} = \frac{\phi + b + S_{SHP1} + v \pm \sqrt{(\phi + b + S_{SHP1} + v)^2 - 4\phi(b + S_{SHP1})}}{2(b + S_{SHP1})}$$

Finally, $C_{TCR,j}$ can be expressed as

$$C_{TCR,j} = a_+ r_+^j + a_- r_-^j.$$

Since $f(1) = -v < 0 < \phi = f(0)$, it is always the case that $r_+ > 1 > r_- > 0$. To obtain a_+

and a_-, we manipulate the following two equations.

$$0 = L_{antigen} \frac{\kappa R_{TCR} v}{v + \kappa R_{TCR}} + a_+\big((b + S_{SHP1})r_+ - \phi - v\big) + a_-\big((b + S_{SHP1})r_- - \phi - v\big)$$

$$= L_{antigen} \frac{\kappa R_{TCR} v}{v + \kappa R_{TCR}} + \frac{a_+ v}{r_+ - 1} + \frac{a_- v}{r_- - 1},$$

$$\sum_{i=0}^{N} C_{TCR,i} = \frac{\kappa R_{TCR} L_{antigen}}{v + \kappa R_{TCR}} = \frac{a_+(r_+^{N+1} - 1)}{r_+ - 1} + \frac{a_-(r_-^{N+1} - 1)}{r_- - 1}.$$

Finally, we obtain

$$a_+ = -a_- \left(\frac{r_-}{r_+}\right)^{N+1} \frac{r_+ - 1}{r_- - 1},$$

$$a_- = (1 - r_-)\frac{\kappa R_{TCR}L_{antigen}}{\nu + \kappa R_{TCR}}\left(1 - \left(\frac{r_-}{r_+}\right)^{N+1}\right)^{-1},$$

$$a_+ = (r_+ - 1)\frac{\kappa R_{TCR}L_{antigen}}{\nu + \kappa R_{TCR}}\left(\frac{r_-}{r_+}\right)^{N+1}\left(1 - \left(\frac{r_-}{r_+}\right)^{N+1}\right)^{-1}.$$

Other variables at steady state can be obtained as,

$$C_{TCR,N} = a_+ r_+^N + a_- r_-^N = a_- r_-^N \left(1 - \frac{r_-(r_+ - 1)}{r_+(r_- - 1)}\right)$$

$$= \frac{\kappa R_{TCR}L_{antigen}}{\nu + \kappa R_{TCR}}\left(1 - \left(\frac{r_-}{r_+}\right)\right)r^N\left(1 - \left(\frac{r_-}{r_+}\right)^{N+1}\right)^{-1},$$

$$C_{TCR,1} = a_+ r_+ + a_- r_- = a_- \left(r_- - \left(\frac{r_-}{r_+}\right)^{N+1}\frac{r_+ - 1}{r_- - 1}\right)$$

$$= \frac{\kappa R_{TCR}L_{antigen}}{\nu + \kappa R_{TCR}}r_-(1 - r_-)\left(1 + \frac{(r_-/r_+)^{N+1}(r_+ - 1)}{r_- - r_-^2}\right)\left(1 - \left(\frac{r_-}{r_+}\right)^{N+1}\right)^{-1}.$$
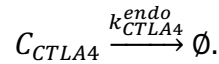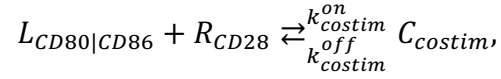
Once S_{SHP1} is determined using $S_{SHP1} = S_{SHP1,T}\frac{C_{TCR,1}}{C_{TCR,1}+C_{TCR,1}^*}$, other variables follow from it.

2. Costimulatory signaling and inhibition by CTLA4 (DC:TC2 and TR:DC1)

This component describes binding kinetics of CD80|CD86, CD28, and CTLA4 and the trans-endocytosis of CD80|CD86 by CTLA4 (Collins et al., 2002; Jansson et al., 2005; Khailaie et al., 2017; Larsen et al., 2005; Qureshi et al., 2011; Sugar et al., 2017; van der Merwe et al., 1997).

2.1 CD28-CD80|CD86 binding kinetics

2.1.1 Reactions for both Tconvs and Tregs

$$L_{CD80|CD86} + R_{CD28} \underset{k_{costim}^{off}}{\overset{k_{costim}^{on}}{\rightleftarrows}} C_{costim},$$

$$L_{CD80|CD86} + R_{CTLA4} \underset{k_{CTLA4}^{off}}{\overset{k_{CTLA4}^{on}}{\rightleftarrows}} C_{CTLA4},$$

$$C_{CTLA4} \xrightarrow{k_{CTLA4}^{endo}} \emptyset.$$

We assumed the expression level of CD28 in the plasma membrane of Tconvs remains fixed. The cycling of CTLA4 is maintained at steady state for Tregs. Also, once the complexes of CTLA4 and CD80|CD86 are internalized, the complexes are instantly degraded.

2.1.2 Equations

2.1.2.1 Tconvs

We assumed that the Tconv:DC engagement ceases before the considerable accumulation of CTLA4 by the Tconv. Thus, $R_{CTLA4} = 0$ for the whole time.

$$\frac{dC_{costim}}{dt} = k_{costim}^{on} \left(\frac{L_{CD80|CD86}}{S_{DC}} - C_{costim} \right) \left(\frac{R_{CD28}}{S_T} - C_{costim} \right) - k_{costim}^{off} C_{costim}.$$

At steady state,

$$C_{costim}$$

$$= \frac{1}{2}\left(R_{CD28}/S_T + +L_{CD80|CD86}/S_{DC} + k_{costim}^{off}/k_{costim}^{on}\right.$$

$$\left. - \sqrt{\left(R_{CD28}/S_T + L_{CD80|CD86}/S_{DC} + k_{costim}^{off}/k_{costim}^{on}\right)^2 - 4R_{CD28}/S_T \cdot L_{CD80|CD86}/S_{DC}}\,\right).$$

C_{costim} was assumed to be the determinant of immune synapse formation. Once C_{costim} falls below a threshold (set to 5 in the simulation), the Tconv stops engaging with the DC and receiving signals of TCR and costimulation.

2.1.2.2 Tregs

We assumed that Tregs maintain a constant CTLA4 level in their cell membranes. This assumption slightly underestimates the actual value during active negative feedback regulation, given our data that IL-2 signaling increases CTLA4 expression by Tregs.

$$\frac{dC_{costim}}{dt} = k_{costim}^{on}\left(\frac{L_{CD80|CD86}}{S_{DC}} - C_{costim} - C_{CTLA4}\right)\left(\frac{R_{CD28}}{S_T} - C_{costim}\right) - k_{costim}^{off}C_{costim},$$

$$\frac{dC_{CTLA4}}{dt} = k_{CTLA4}^{on}\left(\frac{L_{CD80|CD86}}{S_{DC}} - C_{costim} - C_{CTLA4}\right)\left(\frac{R_{CTLA4}}{S_T} - C_{CTLA4}\right) - k_{CTLA4}^{off}C_{CTLA4}$$

$$- k_{CTLA4}^{endo}C_{CTLA4}.$$

At steady states, given k_{costim}^{on}, k_{costim}^{off}, k_{CTLA4}^{on}, and $k_{CTLA4}^{off} \gg k_{CTLA4}^{endo}$,

$$k_{costim}^{on}\left(L_{CD80|CD86}/S_{DC} - C_{costim} - C_{CTLA4}\right)\left(R_{CD28}/S_T - C_{costim}\right) - k_{costim}^{off}C_{costim} = 0,$$

$$k_{CTLA4}^{on}(L_{CD80|CD86}/S_{DC} - C_{costim} - C_{CTLA4})(R_{CTLA4}/S_T - C_{CTLA4}) - k_{CTLA4}^{off}C_{CTLA4} = 0,$$

which can be solved numerically for C_{costim} and C_{CTLA4}.

2.2 Detailed description of trans-endocytosis of CD80|CD86 by Tregs

We further implemented the regulation of the trans-endocytosis efficiency by costimulation with the assumption that costimulation strength upregulates the trans-endocytosis efficiency. This assumption was based on the fact that CD28 signaling increases the adhesion of T cells to DCs and therefore, is likely to increase the efficiency of CTLA-4-mediated trans-endocytosis (Thauland et al., 2014).

$$\frac{dL_{CD80|CD86}}{dt} = -k_{CTLA4,eff}^{endo}C_{CTLA4,tot}$$

$$= -k_{CTLA4}^{endo}\left(f_{cont_{low}} + \left(f_{cont_{high}} - f_{cont_{low}}\right)\left(1 + \frac{K_{CD28,tr\rightarrow Umin}}{C_{costim,tr}}\right)^{-1}\right)$$

$$\times V_{neighbor}n_{tr}S_{DC:TR}C_{CTLA4},$$

where $k_{CTLA4,eff}^{endo}$ is the effective rate of endocytosis of CTLA4 and $C_{CTLA4,tot}$ is the total number of the CD80|CD86:CTLA4 complexes in the immune synapses formed by Tregs and a DC.
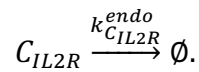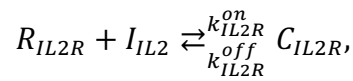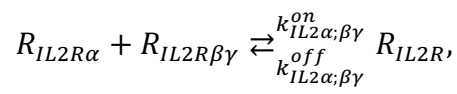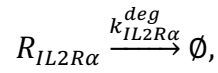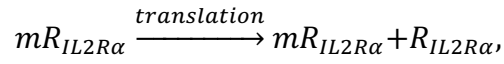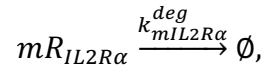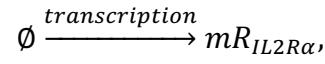
3. *Competition for IL-2 between a Tconv and Tregs (TC:I1, TC:I2, and TR:I1)*

In this component, we describe the dynamics of IL2Ra production, IL-2 production, secretion, and diffusion, and IL-2-IL2R binding and endocytosis.

3.1 IL2 receptor production and IL-2-IL2 receptor binding dynamics

We follow the descriptions by: (Busse et al., 2010; Feinerman et al., 2010; Tkach et al., 2014; Voisinne et al., 2015)

3.1.1 Reactions

$$\emptyset \xrightarrow{transcription} mR_{IL2R\alpha},$$

$$mR_{IL2R\alpha} \xrightarrow{k^{deg}_{mIL2R\alpha}} \emptyset,$$

$$mR_{IL2R\alpha} \xrightarrow{translation} mR_{IL2R\alpha} + R_{IL2R\alpha},$$

$$R_{IL2R\alpha} \xrightarrow{k^{deg}_{IL2R\alpha}} \emptyset,$$

$$R_{IL2R\alpha} + R_{IL2R\beta\gamma} \underset{k^{off}_{IL2\alpha;\beta\gamma}}{\overset{k^{on}_{IL2\alpha;\beta\gamma}}{\rightleftarrows}} R_{IL2R},$$

$$R_{IL2R} + I_{IL2} \underset{k^{off}_{IL2R}}{\overset{k^{on}_{IL2R}}{\rightleftarrows}} C_{IL2R},$$

$$C_{IL2R} \xrightarrow{k^{endo}_{C_{IL2R}}} \emptyset.$$

3.1.2 Equations

$$\frac{dmR_{IL2R\alpha}}{dt} = k_{mIL2R\alpha}^{transcription(basal)} + k_{mIL2R\alpha}^{transcription(TCR,costim)} P_{TCR,costim \to IL2R\alpha}^{on}$$

$$+ k_{mIL2R\alpha}^{transcription(pSTAT5)} P_{JAK \to pSTAT5}^{on} - k_{mIL2\alpha}^{deg} mR_{IL2R\alpha},$$

where

$$P_{TCR,costim \to IL2R\alpha}^{on} = \left(1 + \left(\left(\frac{C_N}{K_{TCR \to IL2R\alpha}}\right)^{n_{TCR \to IL2R\alpha}} + \left(\frac{C_{costim}}{K_{costim \to IL2R\alpha}}\right)^{n_{costim \to IL2R\alpha}}\right)^{-1}\right)^{-1},$$

$$P_{JAK \to pSTAT5}^{on} = \frac{1}{1 + \left(\frac{K_{JAK \to pSTAT5}}{S_{JAK}}\right)^{n_{JAK \to pSTAT5}}} (1 - P_{TCR \to IL2R\alpha}^{on}),$$

$$S_{JAK} = \frac{R_{IL2\alpha}}{R_{IL2\alpha} + R_{IL2\alpha,0}} \cdot \frac{I_{IL2}}{I_{IL2} + K_{IL2 \to JAK}(R_{IL2\alpha})},$$

$$K_{IL2 \to JAK}(R_{IL2\alpha}) = K_{IL2 \to JAK}^{high} \frac{R_{IL2\alpha}}{R_{IL2\alpha} + R_{IL2\alpha,0}} + K_{IL2 \to JAK}^{low} \frac{R_{IL2\alpha,0}}{R_{IL2\alpha} + R_{IL2\alpha,0}}.$$

The rest of the differential equations are

$$\frac{dR_{IL2R\alpha}}{dt} = k_{IL2R\alpha}^{translation} mR_{IL2R\alpha} - k_{IL2R\alpha}^{deg} R_{IL2R\alpha},$$

$$\frac{dR_{IL2R}}{dt} = k_{IL2\alpha;\beta\gamma}^{on}(R_{IL2R\alpha} - R_{IL2R})(R_{IL2R\beta\gamma} - R_{IL2R}) - k_{IL2\alpha;\beta\gamma}^{off} R_{IL2R},$$

$$\frac{dC_{IL2R}}{dt} = k_{IL2R}^{on}(R_{IL2R} - C_{IL2R})I - k_{IL2R}^{off} C_{IL2R} - k_{C_{IL2R}}^{endo} C_{IL2R}.$$
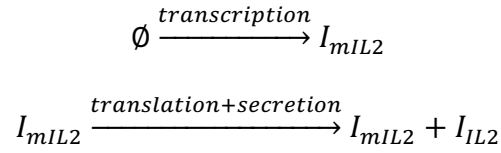
Thus, at steady state,

$$R_{IL2R} = \frac{1}{2}\left(\left(R_{IL2R\alpha} + R_{IL2R\beta\gamma} + K_{IL2R\alpha:\beta\gamma,d}\right)\right.$$

$$\left. - \sqrt{\left(R_{IL2R\alpha} + R_{IL2R\beta\gamma} + K_{IL2R\alpha:\beta\gamma,d}\right)^2 - 4R_{IL2R\alpha}R_{IL2R\beta\gamma}}\right),$$

$$C_{IL2R} = \frac{I_{IL2}R_{IL2R}}{K_{C_{IL2R}} + I_{IL2}}, \text{where } K_{C_{IL2R}} = \frac{k_{IL2R}^{off}}{k_{IL2R}^{on}} \approx 10pM.$$

3.2 IL2 production dynamics

We follow the descriptions by: (Tkach et al., 2014; Voisinne et al., 2015)

3.2.1 Reactions

$$\emptyset \xrightarrow{transcription} I_{mIL2}$$

$$I_{mIL2} \xrightarrow{translation+secretion} I_{mIL2} + I_{IL2}$$

3.2.2 Equations

$$\frac{dI_{mIL2}}{dt} = k_{mIL2}^{transcription(TCR,costim)} P_{TCR,costim \to IL2}^{on} - k_{mIL2}^{deg} I_{mIL2}$$

where

$$P_{TCR,costim \to IL2}^{on} = \frac{1}{1 + \left(\frac{K_{TCR \to IL2}}{C_N}\right)^{n_{TCR \to IL2}}} \cdot \frac{1}{1 + \left(\frac{K_{costim \to IL2}}{C_{costim}}\right)^{n_{costim \to IL2}}} \cdot \left(1 - P_{pSTAT5 \to IL2}^{on}\right)$$
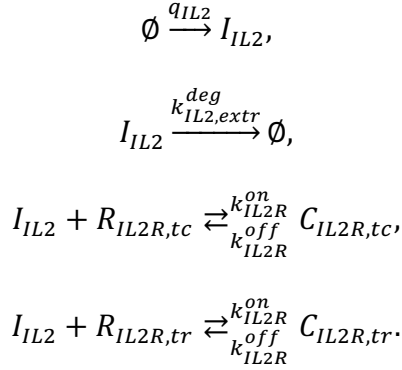
for CD4 T cells (Lim et al., 2015).

The secretion rate of IL-2 is

$$q_{IL2} = k_{IL2}^{translation} I_{mIL2}.$$

3.3 IL-2 secretion, diffusion, and consumption dynamics

We integrated models from (Busse et al., 2010; Oyler-Yaniv et al., 2017; Shvartsman et al., 2001; Thurley et al., 2015) into a partial differential equation (PDE). Ordinary differential equations (ODEs) in the previous subsection are linked to the model component introduced here.

3.3.1 Reactions

$$\emptyset \xrightarrow{q_{IL2}} I_{IL2},$$

$$I_{IL2} \xrightarrow{k_{IL2,extr}^{deg}} \emptyset,$$

$$I_{IL2} + R_{IL2R,tc} \underset{k_{IL2R}^{off}}{\overset{k_{IL2R}^{on}}{\rightleftarrows}} C_{IL2R,tc},$$

$$I_{IL2} + R_{IL2R,tr} \underset{k_{IL2R}^{off}}{\overset{k_{IL2R}^{on}}{\rightleftarrows}} C_{IL2R,tr}.$$

3.3.2 Equations

The density of IL-2 is modeled through a reaction-diffusion equation.

$$\frac{\partial I_{IL2}}{\partial t} = D_{IL2} \nabla^2 I_{IL2} - n_{tr} j_{IL2,tr}^{consum} - k_{IL2,extr}^{deg} I_{IL2},$$

where

$$j_{IL2,tr}^{consum} = k_{IL2R}^{on} I_{IL2R} R_{IL2R,tr} - k_{IL2R}^{off} C_{IL2R,tr},$$

$$(\text{assuming steady state}) = k_{C_{IL2R}}^{endo} C_{IL2R,tr} = k_{C_{IL2R}}^{endo} \frac{I_{IL2} R_{IL2R,tr}}{K_{C_{IL2R}} + I_{IL2}}.$$

Boundary conditions are

$$-4\pi\rho^2 D_{IL2} \left. \frac{\partial I_{IL2}}{\partial r} \right|_{r=\rho} = q_{IL2} - k_{IL2R}^{on} I_{IL2R} R_{IL2R,tc} + k_{IL2R}^{off} C_{IL2R,tc}$$

and

$$I(r = \infty, t) = 0.$$

4. *Spatiotemporal dynamics of Tregs and their internal states described by coupled partial differential equations.*

In this component, we describe the spatial dynamics of Tregs and their internal states, resulting in coupled partial differential equations along with the equations in 3.3.2.

4.1 Treg movement

There are three possible mechanisms of the dynamical spatiotemporal regulation of Treg density: 1) chemo-attraction or chemo-repulsion due to cytokines or chemokines secreted by responding Tconvs or DCs (Chavanis, 2008; Rapp et al., 2019) , 2) proliferation induced by IL-2 sensing (Amado et al., 2013), and 3) decrease of motility upon engagement with DCs (Thauland et al., 2014). All of these possibilities are taken into account as:

$$\frac{\partial n_{tr}}{\partial t} = -\nabla \cdot \left(n_{tr} \chi_0 \left(1 - \frac{n_{tr}}{K_{cc}} \right) \nabla a \right) + \nabla \cdot \left(n_{tr} \nabla U \left(1 - \frac{n_{tr}}{K_{cc}} \right) \right) + \nabla \cdot (D_{tr} \nabla n_{tr})$$

$$+ k_{IL2 \to treg}^{prolif} \frac{P_{JAK \to pSTAT5,tr}^{on}}{\left(K_{IL2 \to treg}^{prolif} + P_{JAK \to pSTAT5,tr}^{on} \right)} n_{tr} \left(1 - \frac{n_{tr}}{K_{cc}} \right),$$

where U is the attractive potential describing the decrease of Treg motility due to the engagement with DCs and regulated by costimulation and pSTAT5 levels of Tregs (Chinen et al., 2016; Thauland et al., 2014):

$$U(r) = -U_{min}\left(1 + \left(\frac{C_{costim,tr}}{K_{CD28,tr \to Umin}} + \frac{P^{on}_{JAK \to pSTAT5,tr}}{K_{pStat5,tr \to Umin}}\right)^{-1}\right)^{-1}\left(1 - \frac{r^{n_U}}{r_{half} + r^{n_U}}\right),$$

where $\left(1 - \frac{n_{tr}}{K_{cc}}\right)$ is the carrying capacity estimated based on the physical volume of Tregs,

and a is an arbitrary cytokine or chemokine inducing chemoattraction or chemorepulsion.

D_{tr} is also assumed to be a function of r as

$D_{tr}(r)$

$$= \begin{cases} D_{tr,high} - \left(D_{tr,high} - D_{tr,low}\right)\left(1 + \left(\frac{C_{costim,tr}}{K_{CD28,tr \to Umin}} + \frac{P^{on}_{JAK \to pSTAT5,tr}}{K_{pStat5,tr \to Umin}}\right)^{-1}\right)^{-1} &, r < 15 \; um \\ D_{tr,high}, \quad r > 15 \; um \end{cases}.$$

The boundary condition is

$$-n_{tr}\chi_0\left(1 - \frac{n_{tr}}{K_{cc}}\right)\nabla a + n_{tr}\nabla U\left(1 - \frac{n_{tr}}{K_{cc}}\right) + D_{tr}\nabla n_{tr} = 0,$$

at $r = \rho$ and ∞.

4.2 Time evolution of internal states of Tregs

The internal states of Tregs evolve over time upon receiving signals from secreted IL-2 or other sources such costimulatory ligands or pMHCII of DCs. We developed a general mathematical description of the internal dynamics of an entity described as a frequency using PDEs. In general, the number density of a molecular species R in Tregs is written as $n_R = R \cdot n_{tr}$, where R is the number of a molecular species per cell. Then, the time evolution of n_R is described as

$$\frac{\partial n_R}{\partial t} = \frac{\partial R}{\partial t}n_{tr} + R\frac{\partial n_{tr}}{\partial t} = \left(f_{prod} + f_{deg}\right)n_{tr} + \frac{n_R}{n_{tr}}\frac{\partial n_{tr}}{\partial t},$$

where f_{prod} and f_{deg} are production and degradation rates of R, respectively. The suitable form this equation for implementing in the pdepe function of the MATLAB software is

$$\frac{n_{tr}}{n_R} \frac{\partial n_R}{\partial t} = \frac{n_{tr}^2}{n_R}\left(f_{prod} + f_{deg}\right) + \frac{\partial n_{tr}}{\partial t}$$

$$= \nabla \cdot \left(n_{tr}\left(1 - \frac{n_{tr}}{K_{cc}}\right)(\nabla U - \chi_0 \nabla a) + D_{tr}\nabla n_{tr}\right) + \frac{n_{tr}^2}{n_R}\left(f_{prod} + f_{deg}\right)$$

$$+ k_{IL2 \to treg}^{prolif} \frac{P_{JAK \to pSTAT5,tr}^{on}}{\left(K_{IL2 \to treg}^{prolif} + P_{JAK \to pSTAT5,tr}^{on}\right)} n_{tr}\left(1 - \frac{n_{tr}}{K_{cc}}\right),$$

where

$$c \equiv \frac{n_{tr}}{n_R},$$

$$f \equiv n_{tr}\left(1 - \frac{n_{tr}}{K_{cc}}\right)(\nabla U - \chi_0 \nabla a) + D_{tr}\nabla n_{tr},$$

$$s \equiv \frac{n_{tr}^2}{n_R}\left(f_{prod} + f_{deg}\right) + k_{IL2 \to treg}^{prolif} \frac{P_{JAK \to pSTAT5,tr}^{on}}{\left(K_{IL2 \to treg}^{prolif} + P_{JAK \to pSTAT5,tr}^{on}\right)} n_{tr}\left(1 - \frac{n_{tr}}{K_{cc}}\right).$$

Specifically, we implemented dynamics of $mIL2R\alpha$ (mRNA of $IL2R\alpha$) and $IL2R\alpha$ as

$$\frac{\partial n_{mIL2R\alpha,tr}}{\partial t} = \frac{\partial mR_{IL2R\alpha,tr}}{\partial t} n_{tr} + mR_{IL2R\alpha,tr} \frac{\partial n_{tr}}{\partial t}$$

$$= \left(k_{mIL2R\alpha,tr}^{transcription(basal)} + k_{mIL2R\alpha}^{transcription(pSTAT5)} P_{JAK \to pSTAT5,tr}^{on} - k_{mIL2\alpha}^{deg} n_{mIL2R\alpha,tr}/n_{tr}\right) n_{tr}$$

$$+ \frac{n_{mIL2R\alpha,tr}}{n_{tr}} \frac{\partial n_{tr}}{\partial t},$$

$$\frac{\partial n_{IL2R\alpha,tr}}{\partial t} = \frac{\partial R_{IL2R\alpha,tr}}{\partial t} n_{tr} + R_{IL2R\alpha,tr} \frac{\partial n_{tr}}{\partial t}$$

$$= \left(k_{IL2R\alpha}^{translation} n_{mIL2R\alpha,tr}/n_{tr} - k_{IL2R\alpha}^{deg} n_{IL2R\alpha,tr}/n_{tr}\right) n_{tr} + \frac{n_{IL2R,tr}}{n_{tr}} \frac{\partial n_{tr}}{\partial t},$$

where

$$P_{JAK \to pSTAT5,tr}^{on}(r) = \cfrac{1}{1 + \left(\cfrac{K_{JAK \to pSTAT5}}{S_{JAK,tr}(r)}\right)^{n_{JAK \to pSTAT5}}},$$

$$S_{JAK,tr}(r) = \cfrac{\cfrac{n_{R_{IL2\alpha}}}{n_{tr}}}{\cfrac{n_{R_{IL2\alpha}}}{n_{tr}} + R_{IL2\alpha,0}} \cfrac{I_{IL2}}{I_{IL2} + K_{IL2 \to JAK}\left(\cfrac{n_{R_{IL2\alpha}}}{n_{tr}}\right)},$$

$$K_{IL2 \to JAK}\left(n_{R_{IL2\alpha}}/n_{tr}\right) = K_{IL2 \to JAK}^{high} \cfrac{n_{R_{IL2\alpha}}/n_{tr}}{n_{R_{IL2\alpha}}/n_{tr} + R_{IL2\alpha,0}} + K_{IL2 \to JAK}^{low} \cfrac{R_{IL2\alpha,0}}{n_{R_{IL2\alpha}}/n_{tr} + R_{IL2\alpha,0}}.$$