Supplementary Material

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1 Nature of Solution

In this study, we also investigated the late-time behavior of our models, focusing on the existence and uniqueness of steady states and convergence properties as $t \to \infty$. Specifically, we address the question: Does each choice of parameters yield a unique steady state, and do all solutions converge to this steady state in the long term? Our findings are as follows:

1. For system (1) (Occupancy Model), the answer is affirmative. Given that this system is effectively one-dimensional, the proof of convergence to a unique steady state is straightforward.

2. For systems (2) and (6) (KPR and KPR with stabilizing activation chain), convergence to a unique steady state is also established, applying the theorem by Sontag, as referenced in prior communications.

3. For systems (3), (4), and (9) (KPR with limited signaling, sustained signaling, and both), convergence to a unique steady state is confirmed based on the application of the Deficiency Zero Theorem, as demonstrated in the following sections.

4. For the system (5) (KPR with negative feedback), however, the answer is negative, which aligns with the earlier findings.

5. Lastly, for systems (7) and (8) (KPR with IFF, and limited signalling), the answer is affirmative. The convergence to a unique steady state is proven below.

1.1 Kinetic Proofreading

Within this framework, a pMHC ligand (L) can bind reversibly to a TCR receptor (R), resulting in the formation of a pMHC-TCR complex denoted as C_0. Once formed, this TCR-pMHC complex (C_0) undergoes a series of biochemical changes to achieve a signaling-competent state represented as C_N. If a pMHC detaches from a TCR at any intermediate stage, all modifications are instantly undone, causing the TCR to return to its original, unmodified state. T cell activation is directly proportional to the quantity of TCRs in the C_N state.

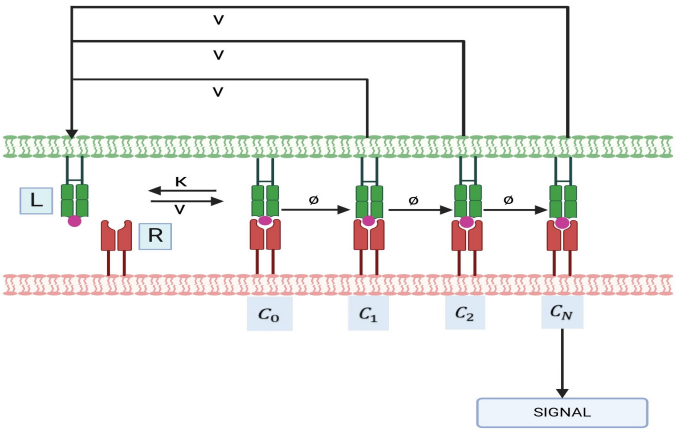
$$\frac{dL}{dt} = -\kappa LR - v\sum_{i=0}^{N} C_i$$

$$\frac{dR}{dt} = -\kappa LR - v\sum_{i=0}^{N} C_i$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi + v)C_0$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \leq i \leq N-1$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - vC_N$$



Mathematical Formulation

The above equations can be rewritten as:

$$\frac{dC_0}{dt} = \kappa(L_T - \sum_{i=0}^{N} C_i)(R_T - \sum_{i=0}^{N} C_i) - (\phi + v)C_0 \tag{1}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \leq i \leq N-1 \tag{2}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - vC_N \tag{3}$$

Here R_T and L_T are the total concentrations of the receptor and the ligand.
From equations (1)-(3), it can be deduced that if $\Sigma_1 = \sum_{i=0}^{N} C_i$

$$\frac{d\Sigma_1}{dt} = \kappa(L_T - \Sigma_1)(R_T - \Sigma_1) - v\Sigma_1 \tag{4}$$

Lemma 1.1. *Let $(C_0(t), C_1(t), \ldots, C_N(t))$ be a solution of (1)-(3) contained in the closure K of the biologically relevant region. Then any ω-limit point $(C_0^*, C_1^*, \ldots, C_N^*)$ of this solution is contained in the interior of K. In particular, any steady state is contained in the interior of K.*

Proof. For the proof we use Lemma 2.1(main text). It follows from equation (4) that $\sum_{i=0}^{N} C_i^*$ is strictly less than L_T and R_T. It then follows from (1) that $C_0^* > 0$. This in turn implies using (2) and (3) that $C_i^* > 0$ for $1 \leq i \leq N$.

Stability of the solutions

In case of KPR, the binding reaction is of the form $L + R = C_0$. The bound receptor C_0 undergoes a series of phosphorylations to reach the signalling competent state C_N. Each C_i can decay releasing L, R and the phosphate groups. The network is weakly reversible. In our system, there are $n = N + 2$ complexes, and it contains only a single linkage class, which means $l = 1$. To show that the deficiency of the above weakly reversible network is zero it will be sufficient to show that the rank of the above system is $s = N + 1$.

There are $N + 2$ complexes $\{L + R, C_0, C_1, C_2, ..., C_N\}$.

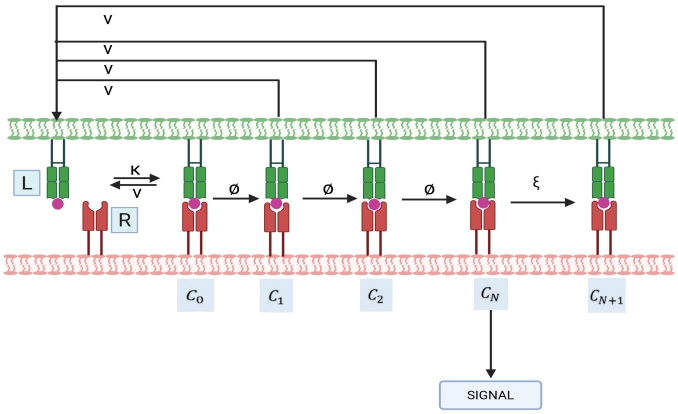
The stoichiometric matrix is given by:

$$\begin{bmatrix} a_1 & a_2 & \ldots & a_{N+1} & b_1 & b_2 & \ldots & b_N & c_1 \\ 1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 & -1 \\ 1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 & -1 \\ -1 & 0 & \ldots & 0 & -1 & 0 & \ldots & 0 & 1 \\ 0 & -1 & \ldots & 0 & 1 & -1 & \ldots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & -1 & 0 & 0 & \ldots & 1 & 0 \end{bmatrix}$$

The first $N+1$ columns of this matrix are linearly independent. Hence for this model $s \geq N+1$. Hence $\delta \leq (N+2) - (N+1) - 1 = 0$. Since δ is always non-negative this implies that $\delta = 0$.

1.2 Kinetic proofreading with limited signaling

This model extends the kinetic proofreading concept, suggesting that once a TCR reaches the signaling-competent state C_N, the bound TCR shifts to a non-signalling state C_{N+1} at a rate ξ.



Mathematical formulation

$$\frac{dC_0}{dt} = \kappa(L_T - \sum_{i=0}^{N+1} C_i)(R_T - \sum_{i=0}^{N+1} C_i) - (\phi + v)C_0 \tag{5}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \leq i \leq N-1 \tag{6}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (v + \xi)C_N \tag{7}$$

$$\frac{dC_{N+1}}{dt} = \xi C_N - vC_{N+1} \tag{8}$$

Here R_T and L_T are the total concentrations of receptor and the ligand.
Let $\Sigma_1 = \sum_{i=0}^{N+1} C_i$. Then, from Equations (5)-(8), we have:

$$\frac{d\Sigma_1}{dt} = \kappa(L_T - \Sigma_1^*)(R_T - \Sigma_1) - v\Sigma_1 \tag{9}$$

Lemma 1.2. *Let $(C_0(t), C_1(t), \ldots, C_{N+1}(t))$ be a solution of (5)-(8) contained in the closure K of the biologically relevant region. Then an ω-limit point $(C_0^*, C_1^*, \ldots, C_{N+1}^*)$ of this solution is contained in the interior of K. In particular, any steady state is contained in the interior of K.*

Proof. For the proof we use Lemma 2.1(main text). It follows from equation (9) that $\sum_{i=0}^{N+1} C_i^*$ is strictly less than L_T and R_T. It then follows from (5) that $C_0^* > 0$. This in turn implies inductively, using (5)-(8) that $C_i^* > 0$ for $1 \leq i \leq N-1$.

We have proved the deficiency of this weakly reversible network is zero as in section **??**.

1.3 Kinetic proofreading with sustained signalling:

This model extends the KPR scheme by integrating experimental findings that indicate signalling-competent TCRs can maintain signaling for a defined time frame, even once pMHC unbinding occurs. In this framework, T-cell receptors (TCRs) in the signalling-capable state C_N persist in signaling for a designated period (T) following the detachment of pMHC, subsequently returning to their baseline state at a rate λ.

Mathematical Formulation

$$\frac{dC_0}{dt} = \kappa(L_T - \sum_{i=0}^{N} C_i(t))(R_T - \sum_{i=0}^{N} C_i(t) - R^*(t)) - (v+\phi)C_0(t) \tag{10}$$

$$\frac{dC_i}{dt} = \phi C_{i-1}(t) - (\phi + v)C_i(t); \quad 1 \le i \le N-1 \tag{11}$$

$$\frac{dC_N}{dt} = \phi C_{N-1}(t) - vC_N(t) + \kappa(L_T - \sum_{i=0}^{N} C_i(t))R^*(t) \tag{12}$$

$$\frac{dR^*}{dt} = vC_N(t) - \kappa(L_T - \sum_{i=0}^{N} C_i(t))R^*(t) - \Omega R^*(t) \tag{13}$$

Here R_T and L_T are the total concentrations of receptors and the ligand.
If $\Sigma_1 = \sum_{i=0}^{N+1} C_i$ then it follows from equations (10)-(13) that:

$$\sum_{i=0}^{N} \frac{dC_i}{dt} = \kappa(L_T - \sum_{i=0}^{N} C_i)(R_T - \sum_{i=0}^{N} C_i - R^*) - v\sum_{i=0}^{N} C_i + \kappa(L_T - \sum_{i=0}^{N} C_i)R^* \tag{14}$$

and

$$\frac{d\Sigma_1}{dt} = \kappa(L_T - \Sigma_1)(R_T - \Sigma_1 - R^*) + \kappa R^*(L_T - \Sigma_1) - v\Sigma_1 \tag{15}$$

Lemma 1.3. *Let $(R^*(t), C_0(t), C_1(t), \ldots, C_N(t))$ be a solution of (10)-(13) contained in the closure K of the biologically relevant region. Then any ω-limit point $(R^{**}, C_0^*, C_1^*, \ldots, C_N^*)$ of this solution is contained in the interior of K. In particular, any steady state is contained in the interior of K.*

Proof. For the proof we use Lemma 2.1(main text). It follows from (15) that $\sum_{i=0}^{N} C_i^*$ is strictly less than L_T. Suppose now that $\sum_{0}^{N} C_i + R^{**} = R_T$. Then it follows from (10) that $C_0^* = 0$. This implies, using (11) that $C_i^* = 0$ for all $1 \le i \le N-1$. The sum of (12) and (13) then implies that $R^{**} = 0$. Substituting this back in (12) shows that $C_N^* = 0$. Putting these facts together we see that $\sum_{i=0}^{N} C_i + R^{**} = 0$, contradicting our assumption. Thus in fact $\Sigma_1 + R^{**} < R_T$. Once this has been established it follows from (10) that $C_0^* > 0$. Then (11) implies that $C_i^* > 0$ for $1 \le i \le N-1$. From (12) we can conclude that $C_N^* > 0$ and from (13) that $R^{**} > 0$.

Stability of the Solutions of system:

In the case of kinetic proofreading (KPR) with sustained signaling, the binding reaction follows $L + R = C_0$, where the bound receptor complex C_0 undergoes a sequence of phosphorylation steps to reach the signaling-competent state C_N. Unlike in limited signaling, here the TCRs continue to signal even after pMHC dissociates. The rate at which these unbound yet signaling-competent TCRs revert to their unmodified state is governed by a factor Ω. In this model, T cell activation depends on both C_N and R^*. Each intermediate state C_i can decay, releasing L, R, R^*, and phosphate groups, making the network weakly reversible.

Our system consists of $n = N + 3$ complexes with a single linkage class ($l = 1$). To establish that the deficiency of this weakly reversible network is zero, it suffices to show that its rank is $s = N + 2$.

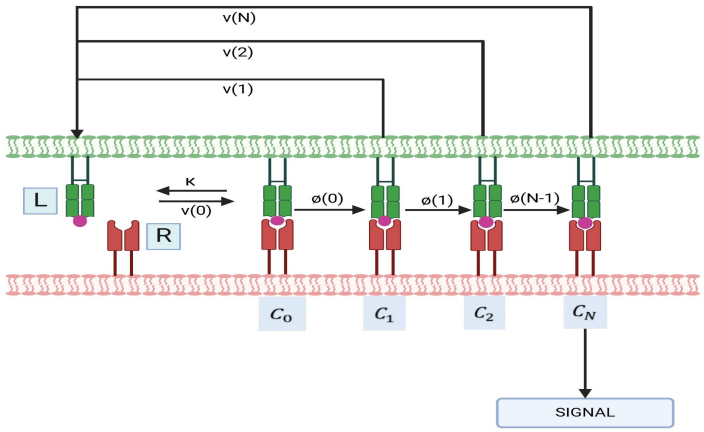
The network comprises $N + 3$ complexes: $\{L + R, C_0, C_1, C_2, \ldots, C_N, L + R^*\}$.

$$\begin{bmatrix} a_1 & a_2 & \dots & a_N & a_{N+1} & b_1 & b_2 & \dots & b_N & c_1 & c_2 & c_3 \\ 1 & 1 & \dots & 1 & 1 & 0 & 0 & \dots & 0 & -1 & -1 & 0 \\ 1 & 1 & \dots & 1 & 0 & 0 & 0 & \dots & 0 & -1 & 0 & 1 \\ -1 & 0 & \dots & 0 & 0 & -1 & 0 & \dots & 0 & 1 & 0 & 0 \\ 0 & -1 & \dots & 0 & 0 & 1 & -1 & \dots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \dots & -1 & 0 & 0 & 0 & \dots & -1 & 0 & 0 & 0 \\ 0 & 0 & \dots & 0 & -1 & 0 & 0 & \dots & 1 & 0 & 1 & 0 \\ 0 & 0 & \dots & 0 & 1 & 0 & 0 & \dots & 0 & 0 & -1 & -1 \end{bmatrix}$$

The first $N+2$ columns of this matrix are linearly independent. Hence for this model $s \geq N+2$. Hence $\delta \leq (N+3) - (N+2) - 1 = 0$. Since δ is always non-negative this implies that $\delta = 0$.

1.4 Kinetic Proofreading with Stabilizing Activation Chain

The model indicates that KPR complexes enhance the stability of foreign peptides while reducing their affinity for self-peptides. This selective strengthening and weakening of the C_i complexes, as well as differences in activation timing, are represented through changes in the respective rate constants $v(i); (i = 0, 1, ..., N)$ and $\phi(i); (i = 0, 1, ..., N-1)$ as the proofreading process advances.



Mathematical formulation

$$\frac{dC_0}{dt} = \kappa(L_T - \sum_{i=0}^{N} C_i)(R_T - \sum_{i=0}^{N} C_i) - (\phi(0) + v(0))C_0 \tag{16}$$

$$\frac{dC_i}{dt} = \phi(i-1)C_{i-1} - (\phi(i) + v(i))C_i; \quad 1 \leq i \leq N-1 \tag{17}$$

$$\frac{dC_N}{dt} = \phi(N-1)C_{N-1} - v(N)C_N \tag{18}$$

In this model for simplicity $v(0)$ is denoted as $v(= 1/\tau)$ which is dissociation time, and $\phi(0)$ denotes the propagation rate for the first step $C_0 \to C_1$. Now for next steps these rates are given by

$$v(i) = \frac{(1+i)}{(1+ri)} v; r > 1 \qquad \phi(i) = \phi r^i; r > 1$$

Let $\Sigma_1 = \sum_{i=0}^{N} C_i$. From Equations (16)-(18), we get:

$$\frac{d\Sigma_1}{dt} = \kappa \left(L_T - \Sigma_1\right)\left(R_T - \Sigma_1\right) - \Sigma_1 \sum_{i=0}^{N} v(i) \tag{19}$$

Lemma 1.4. *Let $(C_0(t), C_1(t), \ldots, C_N(t))$ be a solution of (16)-(18) contained in the closure K of the biologically relevant region. Then any ω-limit point $(C_0^*, C_1^*, \ldots, C_N^*)$ of this solution is contained in the interior of K. In particular, any steady state is contained in the interior of K.*

Proof. For the proof we use Lemma 2.1(main text). It follows from (19) that $\sum_{i=0}^{N} C_i^*$ is strictly less than L_T and R_T. It then follows from (16) that $C_0^* > 0$. This in turn implies using (17) and (18) that $C_i^* > 0$ for $1 \leq i \leq N$.

Stability of the solutions

In the case of KPR with a stabilizing activation chain, the binding reaction follows $L+R = C_0$, where the bound receptor complex C_0 undergoes a sequence of phosphorylation steps to reach the signaling-competent state C_N. T cell activation is determined by C_N. Each intermediate state C_i can decay, leading to the release of L, R, and phosphate groups, making the network weakly reversible.

Our system consists of $n = N + 2$ complexes with a single linkage class ($l = 1$). To establish that the deficiency of this weakly reversible network is zero, it suffices to show that its rank is $s = N + 1$.

The network comprises $N + 2$ complexes: $\{L + R, C_0, C_1, C_2, \ldots, C_N\}$.

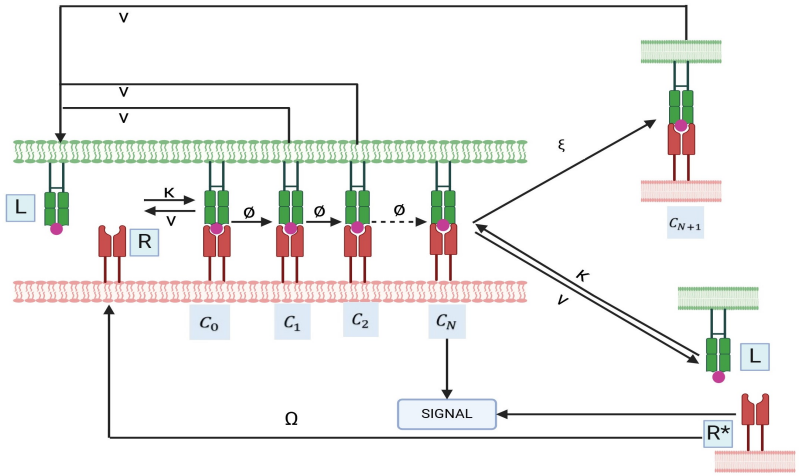
The stoichiometric matrix is given by:

$$\begin{bmatrix} a_1 & a_2 & \ldots & a_{N+1} & b_1 & b_2 & \ldots & b_N & c_1 \\ 1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 & -1 \\ 1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 & -1 \\ -1 & 0 & \ldots & 0 & -1 & 0 & \ldots & 0 & 1 \\ 0 & -1 & \ldots & 0 & 1 & -1 & \ldots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & -1 & 0 & 0 & \ldots & 1 & 0 \end{bmatrix}$$

The first $N + 1$ columns of this matrix are linearly independent. Hence for this model $s \geq N + 1$. Hence $\delta \leq (N + 2) - (N + 1) - 1 = 0$. Since δ is always non-negative this implies that $\delta = 0$.

1.5 Kinetic Proofreading with Limited and Sustained Signaling

This model is a combination of two models KPR with limited and KPR with sustained signaling.



Mathematical formulation

$$\frac{dC_0}{dt} = \kappa(L_T - \sum_{i=0}^{N+1} C_i)(R_T - \sum_{i=0}^{N+1} C_i - R^*) - (\phi + v)C_0 \tag{20}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \leq i \leq N - 1 \tag{21}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (v+\xi)C_N + \kappa(L_T - \sum_{i=0}^{N+1} C_i)R^* \tag{22}$$

$$\frac{dC_{N+1}}{dt} = \xi C_N - vC_{N+1} \tag{23}$$

$$\frac{dR^*}{dt} = vC_N - \kappa(L_T - \sum_{i=0}^{N+1} C_i)R^* - \Omega R^* \tag{24}$$

Define $\Sigma_1 = \sum_{i=0}^{N+1} C_i$. From equations (20)-(23) it follows that:

$$\frac{d\Sigma_1}{dt} = \kappa\left(L_T - \Sigma_1\right)\left(R_T - \Sigma_1 - R^*\right) - v\sum_{i=0}^{N+1} C_i - \Omega R^* \tag{25}$$

Lemma 1.5. *Let $(C_0(t), C_1(t), \ldots, C_{N+1}(t), R^*(t))$ be a solution of (20)-(23) contained in the closure K of the biologically relevant region. Then any ω-limit point $(C_0^*, C_1^*, \ldots, C_{N+1}^*, R^{**})$ of this solution is contained in the interior of K. In particular, any steady state is contained in the interior of K.*

Proof. For the proof we use Lemma 2.1(main text). It follows from (25) that $\sum_{i=0}^{N+1} C_i$ is strictly less than L_T. Suppose now that $\sum_{i=0}^{N} C_i + R^{**} = R_T$. Then it follows from (20) that $C_0^* = 0$. This implies, using (21) that $C_i^* = 0$ for all $1 \leq i \leq N-1$. The sum of (22), (23) and (24) implies that $R^{**} = 0$. Substituting this back into (23) gives $C_{N+1} = 0$ and substituting this into (12) gives $C_N = 0$. Putting these facts together we see that $\sum_{i=0}^{N+1} C_i^* + R^{**} = 0$, contradicting our assumption. Thus in fact $\sum_{i=0}^{n+1} C_i + R^{**} < R_T$. Once this has been established it follows from (20) that $C_0^* > 0$. Then (21) implies that $C_i^* > 0$ for $1 \leq i \leq N-1$. From (22) we can conclude that $C_N^* > 0$, from (23) that $C_{N+1}^* > 0$ and from (24) that $R^{**} > 0$.

Stability of the solutions

In case of KPR with limited and sustained signalling the binding reaction is of the form $L + R = C_0$. The bound receptor C_0 undergoes a series of phosphorylations to reach signalling competent state C_N. In this model, T cell activation is determined by both C_N and R^*. Each C_i can decay releasing L ,R, R^*, and the phosphate groups. The network is weakly reversible. In our system we have $n = N + 4$ complexes; there is only one linkage class i.e., $l = 1$. To show that the deficiency of the above weakly reversible network is zero. It will be sufficient to show that the rank of the above system is $s = N + 3$.

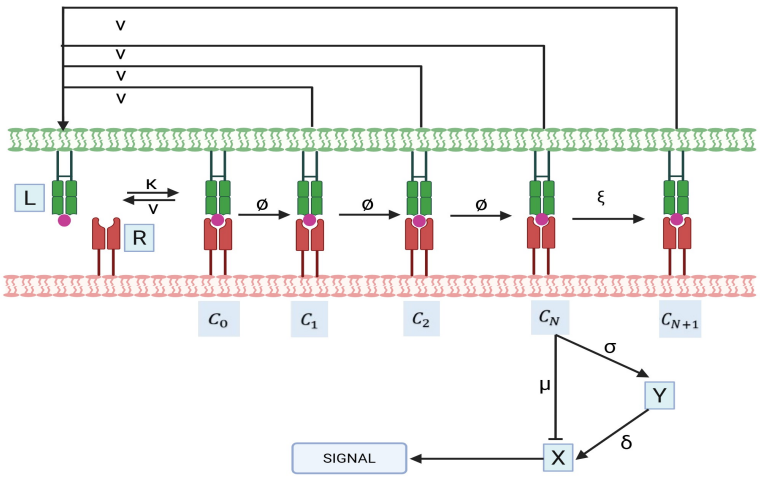
There are $N + 4$ complexes $\{L + R, C_0, C_1, C_2, ..., C_{N+1}, L + R^*\}$.

The stoichiometric matrix is given by:

$$\begin{bmatrix}
a_1 & a_2 & \ldots & a_{N+2} & b_1 & b_2 & \ldots & b_{N+1} & c_1 & c_2 & c_3 \\
1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 & -1 & -1 & 0 \\
1 & 1 & \ldots & 1 & 0 & 0 & \ldots & 0 & -1 & -1 & 1 \\
0 & 0 & \ldots & 0 & 0 & 0 & \ldots & 0 & 0 & 0 & -1 \\
-1 & 0 & \ldots & 0 & -1 & 0 & \ldots & 0 & 1 & 0 & 0 \\
0 & -1 & \ldots & 0 & 1 & -1 & \ldots & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & \ldots & 0 & 0 & 0 & \ldots & -1 & 0 & 1 & 0 \\
0 & 0 & \ldots & -1 & 0 & 0 & \ldots & 1 & 0 & 0 & 0
\end{bmatrix}$$

The first $N + 3$ columns of this matrix are linearly independent. Hence for this model $s \geq N + 3$. Hence $\delta \leq (N + 4) - (N + 3) - 1 = 0$. Since δ is always non-negative this implies that $\delta = 0$.

1.6 Kinetic proofreading with limited signaling and incoherent feed forward loop



This model is an extension of KPR with an incoherent feed forward loop, it has been assumed that signalling is limited and after reaching the signalling competent state the bound TCR transits to a non-signalling transit state.

$$\frac{dC_0}{dt} = \kappa(L_T - \sum_{i=0}^{N+1} C_i)(R_T - \sum_{i=0}^{N+1} C_i) - (\phi + v)C_0() \tag{26}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \leq i \leq N-1 \tag{27}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (v + \xi)C_N \tag{28}$$

$$\frac{dC_{N+1}}{dt} = \xi C_N - vC_{N+1} \tag{29}$$

$$\frac{dY}{dt} = a(m - Y) - bY + \sigma C_N(m - Y) \tag{30}$$

$$\frac{dX}{dt} = c(l - X) - dX + \delta Y(l - X) - \mu C_N X \tag{31}$$

We aim to demonstrate that the system, an extension of the kinetic proofreading (KPR) model, is globally asymptotically stable. The system consists of two sets of variables: Z_1, consisting of the C_i, which satisfies a closed system of equations

$$\frac{dZ_1}{dt} = f(Z_1),$$

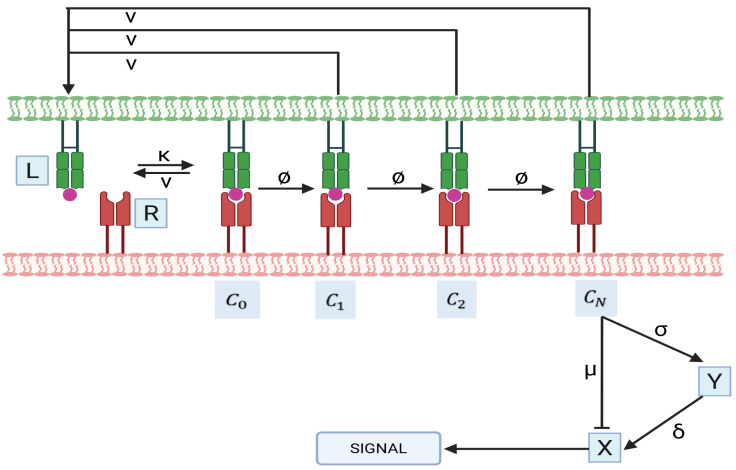
and Z_2, consisting of X and Y, governed by

$$\frac{dZ_2}{dt} = g(Z_1, Z_2).$$

It has already been proven that the system for Z_1 has a unique steady state, and that all solutions for Z_1 converge to this steady state as $t \to \infty$. In other words, as $t \to \infty$ each $C_i(t)$ converges to some $C_i^* > 0$. Consider any ω-limit point of a solution (C_i, X, Y) of (26)-(31) and the solution starting at that point for $t = 0$. It lies entirely in the ω-limit set of that solution and so C_i has the constant value C_i^* for all i. This means that this solution satisfies the equations obtained from (30) and (31) by replacing C_N by C_N^*. Equation (30) is an equation for Y alone and so it it easy to see that the solution converges to $Y^* = \frac{a+b+\lambda C_N^*}{a+\lambda C_N^*}$ as $t \to \infty$. Now we can again pass to a solution starting at an ω-limit point to see that

for the resulting solution X solves the equation obtained from (31) by replacing C_N by C_N^* and Y by Y^*. Thus the solution converges to $X^* = \frac{(c+\delta l)Y^*}{c+d+\delta Y^*+\mu C_N^*}$ as $t \to \infty$. Since these statements hold for all ω-limit points it follows that any solution of (26)-(31) converges to (C_i^*, Y^*, X^*) as $t \to \infty$. For this system the unique positive steady state is globally asymptotically stable.

1.7 Kinetic proofreading with incoherent feed forward loop



For this model there is a unique steady state in each stoichiometric compatibility class which is globally asymptotically stable. The proof of this is based on the fact that we have already proved global asymptotic stability for the kinetic proofreading model and otherwise the proof is just as in the previous example.

1.8 Analytical observations on results:

Occupancy model :

Response as a Monotonic Function of Dissociation Time:

In the context of the occupancy model, we analyze the response by examining T cell activation as a function of receptor-ligand complex concentration, C, which is derived from the equilibrium concentrations of ligand and receptor. It satisfies the equation:

$$C = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2} \tag{32}$$

and is this model C is a measure of the T cell activation.

C is a solution to a quadratic equation of the form:

$$C^2 - aC + b = 0 \tag{33}$$

where

$$a = L_T + R_T + K_D > 0, \quad b = L_T R_T > 0$$

Only the negative square root gives a relevant solution, since $C < L_T$ and $C < R_T$ and therefore $C < a$.

The above equation can be reformulated as follows:

$$C = \frac{a - \sqrt{a^2 - 4b}}{2} \tag{34}$$

Analysis of the solution

Differentiating the expression for C with respect to K_D gives

$$\frac{dC}{dK_D} = \frac{\partial C}{\partial a} \cdot \frac{da}{dK_D}$$

C is a decreasing function of a since

$$\frac{\partial C}{\partial a} = \frac{1}{2}\left(1 - \frac{a}{\sqrt{a^2 - 4b}}\right) < 0$$

and combining this with

$$\frac{da}{dK_D} = 1 > 0$$

we have:

$$\frac{dC}{dK_D} < 0$$

Relationship with Dissociation Time

The dissociation constant K_D is related to the dissociation rate constant k_{off} and the association rate constant k_{on}:

$$K_D = \frac{k_{\text{off}}}{k_{\text{on}}}$$

Additionally, the dissociation time τ is inversely proportional to the dissociation rate constant:

$$\tau = \frac{1}{k_{\text{off}}}$$

As the dissociation time τ increases, the dissociation rate constant k_{off} decreases, resulting in a decrease in K_D. Given that C is a decreasing function of K_D, it follows that C becomes an increasing function of the dissociation time τ.

This relationship demonstrates that as ligand-receptor binding stabilizes, resulting in a longer dissociation time, T cell activation increases, highlighting the importance of bond longevity in cellular activation responses.

Response as monotonic function of ligand concentration

To determine how C depends on L_T, we differentiate C with respect to L_T:

$$\frac{dC}{dL_T} = \frac{\partial C}{\partial a} \cdot \frac{da}{dL_T} + \frac{\partial C}{\partial b} \cdot \frac{db}{dL_T}$$

We have $\frac{da}{dL_T} = 1$ and $\frac{db}{dL_T} = R_T$. Differentiating C with respect to b gives:

$$\frac{\partial C}{\partial b} = \frac{1}{2}\left(\frac{2}{\sqrt{a^2 - 4b}}\right)$$

Sign of $\frac{dC}{dL_T}$

Analyzing the derivative $\frac{dC}{dL_T}$:

$$\frac{dC}{dL_T} = \frac{1}{2}\left(1 - \frac{a}{\sqrt{a^2 - 4b}}\right) + \frac{R_T}{\sqrt{a^2 - 4b}} > 0.$$

Thus, the equilibrium concentration of the pMHC-TCR complex (C) is an increasing function of the ligand concentration (L_T). As the ligand concentration increases, the number of available binding sites increases, which directly enhances the formation of the complex (C). Therefore, in the occupancy model, the response function is positively dependent on the ligand concentration.

Response of KPR model as increasing function of dissociation time

In the kinetic proofreading model the response function is given by:

$$\text{Response} = a^N C_T$$

where

$$a = \frac{\phi}{(\phi + v)}$$

and

$$C_T = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2}$$

Similar to the argument in occupancy model it is clear that for this model C_T satisfies the same equation as C does in the occupancy model. Thus it is a decreasing function of k_{off}, which follows that it is an is an increasing function of the dissociation time (τ).

Response of KPR model as increasing function of ligand concentration

That the response with respect to ligand concentration is monotone in the kinetic proofreading model can be attributed again to the fact that in this case C_T is increasing (similar to the argument in the case of the occupancy model) and α is constant. Thus R is increasing.

2 Mathematical Formulation and analysis

2.1 Occupancy Model

In this model a pMHC ligand (L) can reversibly bind a T cell receptor (R) to form a pMHC-TCR complex (C).

$$\frac{dC}{dt} = \kappa LR - vC \tag{35}$$

where

$$k_{\text{on}} = \kappa \qquad \text{and} \qquad k_{\text{off}} = v$$

and at equilibrium $\frac{dC}{dt} = 0$ and hence

$$LR = K_D C \tag{36}$$

where $K_D = \frac{v}{\kappa}$
Also the total amount of ligand L_T and total amount of receptor TCR R_T are conserved quantities

$$L_T = L + C \quad R_T = L + C \tag{37}$$

By inserting these in equation in (36) we get

$$C = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2}$$

$$\text{T cell activation} = C$$

Calculating the $E_{\max}$
The $E_{\max}$ can then be found by finding C in the limit of L_T tending to infinity. In this limit, we have

$$\lim_{L_T \to \infty} \frac{K_D}{L_T} = 0 \quad \lim_{L_T \to \infty} \frac{R_T}{L_T} = 0$$

$$\begin{aligned}
E_{\max} &= \lim_{L_T \to \infty} C \\
&= \lim_{L_T \to \infty} \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2} \\
&= \lim_{L_T \to \infty} \frac{2L_T R_T}{L_T + R_T + K_D + \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}} \\
&= \lim_{L_T \to \infty} \frac{2R_T}{1 + \frac{R_T}{L_T} + \frac{K_D}{L_T} + \sqrt{(1 + \frac{R_T}{L_T} + \frac{K_D}{L_T})^2 - 4\frac{R_T}{L_T}}} \\
&= R_T
\end{aligned}$$

Hence

$$E_{\max} = R_T$$

Calculation for EC_{50}
At half the maximal response, we have $L_T = EC_{50}$.
Also, T cell activation =

$$E_{\max}/2 = R_T/2$$

which implies

$$C = R_T/2$$

Using equation (36) we have

$$(L_T - C)(R_T - C) = K_D C$$

hence

$$(L_T - R_T/2)(R_T - R_T/2) = K_D R_T/2$$

Rearranging we get

$$L_T = K_D + R_T/2$$

Hence

$$EC_{50} = K_D + R_T/2$$

2.2 Kinetic Proofreading

In this model, a pMHC ligand (L) can reversibly associate with a TCR receptor (R) to form a pMHC-TCR complex, denoted as C_0. Once formed, this complex undergoes a series of biochemical modifications, progressively transitioning towards a signaling-competent state, labeled as C_N. If the pMHC dissociates from the TCR at any intermediate stage, all modifications are rapidly undone, causing the TCR to revert to its original, unmodified state. The level of T cell activation is directly linked to the quantity of TCRs in the fully modified C_N state.

$$\frac{dL}{dt} = -\kappa LR - v\sum_{i=0}^{N} C_i \tag{38}$$

$$\frac{dR}{dt} = -\kappa LR - v\sum_{i=0}^{N} C_i \tag{39}$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi + v)C_0 \tag{40}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \leq i \leq N-1 \tag{41}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - vC_N \tag{42}$$

We have the total amount of ligand L_T and total amount of receptor TCR R_T as conserved quantities:

$$L_T = L + C_T \quad R_T = L + C_T$$

where $C_T = \sum_{i=0}^{N} C_i$

Using values of L_T and R_T in equation (38) we get

$$C_T = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2} \quad \text{where} \quad K_D = \frac{v}{\kappa}$$

Let

$$a = \frac{\phi}{(\phi + v)}$$

Hence, at equilibrium

$$\begin{aligned} C_T &= \sum_{i=0}^{N} C_i \\ &= \sum_{i=0}^{N-1} C_i + C_N \\ &= \sum_{i=0}^{N-1} a^i C_0 + C_N \\ &= \frac{(1-a^N)}{(1-a)} C_0 + C_N \\ &= \frac{(1-a^N)}{(1-a)} (1-a) C_T + C_N \\ &= \frac{1}{a^N} C_N \end{aligned}$$

$$C_T = \frac{1}{a^N} C_N$$

Hence

$$\begin{aligned} \text{T cell activation} &= C_N \\ &= a^N C_T \end{aligned}$$

Calculation for $E_{\max}$

$$\begin{aligned} E_{\max} &= \lim_{L_T \to \infty} C_T \\ &= \lim_{L_T \to \infty} \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4 L_T R_T}}{2} \\ &= \lim_{L_T \to \infty} \frac{2 L_T R_T}{L_T + R_T + K_D + \sqrt{(L_T + R_T + K_D)^2 - 4 L_T R_T}} \\ &= \lim_{L_T \to \infty} \frac{2 R_T}{1 + \frac{R_T}{L_T} + \frac{K_D}{L_T} + \sqrt{(1 + \frac{R_T}{L_T} + \frac{K_D}{L_T})^2 - 4 \frac{R_T}{L_T}}} \\ &= R_T \end{aligned}$$

So $E_{\max} = a^N R_T$

Calculation for EC_{50}
At half the maximal response, T cell activation =

$$E_{\max}/2 = a^N R_T/2$$

which implies

$$a^N C_T = a^N R_T/2$$

$$C_T = R_T/2$$

Since, $L_T = L + C_T \quad R_T = L + C_T$ Using this equation in equation (38)

$$\begin{aligned}\kappa(L_T - C_T)(R_T - C_T) - v\sum_{i=0}^{N} C_i = 0\\ (L_T - C_T)(R_T - C_T) = K_D C_T\\ L_T = K_D + R_T/2\end{aligned}$$

2.3 Kinetic proofreading with limited signaling

It is an extension of the kinetic proofreading model that proposes that when a TCR has reached signalling competent state C_N, the bound TCR transits to a non signalling state C_{N+1} with rate ξ.

$$\frac{dL}{dt} = -\kappa LR - v\sum_{i=0}^{N+1} C_i \tag{43}$$

$$\frac{dR}{dt} = -\kappa LR - v\sum_{i=0}^{N+1} C_i \tag{44}$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi + v)C_0 \tag{45}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \le i \le N-1 \tag{46}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (v + \xi)C_N \tag{47}$$

$$\frac{dC_{N+1}}{dt} = \xi C_N - vC_{N+1} \tag{48}$$

Here $C_T = \sum_{i=0}^{N+1} C_i$, and T cell activation is given by C_N.

$$\begin{aligned}C_T &= \sum_{i=0}^{N-1} C_i + C_N + C_{N+1}\\ &= \sum_{i=0}^{N-1} a^i C_0 + C_N + \frac{\xi}{v}C_N\\ &= \frac{(1-a^N)}{(1-a)}(1-a)C_T + \frac{v+\xi}{v}C_N\end{aligned}$$

Hence

$$C_T = \frac{1}{a^N}\left(\frac{v+\xi}{v}\right)C_N.$$

and

$$C_N = \left(\frac{v}{v+\xi}\right) a^N C_T$$

Calculating the $E_{\max}$

Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$ Hence

$$E_{\max} = \left(\frac{v}{v+\xi}\right) a^N R_T$$

Calculating the EC_{50}

At half the maximal response, T cell activation

$$\frac{E_{\max}}{2} = \left(\frac{v}{v+\xi}\right) a^N \frac{R_T}{2}$$

which implies

$$\left(\frac{v}{v+\xi}\right) a^N C_T = \left(\frac{v}{v+\xi}\right) a^N \frac{R_T}{2}$$

Hence

$$C_T = \frac{R_T}{2}$$

Since, $L_T = L + C_T \quad R_T = R + C_T$ Using this equation in (43)

$$\kappa(L_T - C_T)(R_T - C_T) - v\sum_{i=0}^{N+1} C_i = 0$$
$$(L_T - C_T)(R_T - C_T) = K_D C_T$$
$$L_T = K_D + R_T/2$$

2.4 Kinetic proofreading with sustained signaling

It is another modification of the kinetic proofreading model, according to this model, T-cell receptors (TCRs) in the signaling-competent state C_N, persist in signaling for a certain duration (T) after the unbinding of pMHC. Subsequently, they return to the basal state (T) with a rate of λ.

$$\frac{dL}{dt} = -\kappa LR + v\sum_{i=0}^{N} C_i - \kappa LR^* \tag{49}$$

$$\frac{dR}{dt} = -\kappa LR + v\sum_{i=0}^{N-1} C_i + \Omega R^* \tag{50}$$

$$\frac{dR^*}{dt} = vC_N - \kappa LR^* - \Omega R^* \tag{51}$$

$$\frac{dC_0}{dt} = \kappa LR - (v+\phi)C_0 \tag{52}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \le i \le N-1 \tag{53}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - vC_N + \kappa LR^* \tag{54}$$

The conservation equations are:

$$L_T = L + C_T \quad R_T = R + C_T + R^*$$

$$\text{T cell activation} = C_N + R^*$$

From equation (51) at the steady state

$$R^* = \frac{vC_N}{\kappa L + \Omega} \tag{55}$$

Also substituting (55) into (50) at steady state we get

$$-(v+\phi)C_0 + v\sum_{i=0}^{N-1} C_i + \Omega R^* = 0$$

$$-(v+\phi)C_0 + v\sum_{i=0}^{N-1} a^i C_0 + \Omega \frac{vC_N}{\kappa L + \Omega} = 0$$

$$-(v+\phi)C_0 + v\frac{1-a^n}{1-a} C_0 + \Omega \frac{vC_N}{\kappa L + \Omega} = 0$$

upon rearrangement and solving we get

$$C_0 = \frac{\Omega(1-a)}{a^n(\kappa L + \Omega)} C_N$$

Also,

$$\begin{aligned} C_T &= \sum_{i=0}^{N} C_i \\ &= \sum_{i=0}^{N-1} C_i + C_N \\ &= \sum_{i=0}^{N-1} a^i C_0 + C_N \\ &= \frac{1-a^n}{1-a} C_0 + C_N \\ &= \left(\frac{1-a^n}{1-a}\right) \frac{\Omega(1-a)}{a^n(\kappa L + \Omega)} C_N + C_N \end{aligned}$$

Solving this we get:

$$C_N = \frac{\kappa L + \Omega}{\Omega + a^n \kappa L} a^n C_T \tag{56}$$

Hence from equation (55) and (56), T cell activation is given by

$$\begin{aligned} &\text{T cell activation} \\ &\quad = C_N + R^* \\ &\quad = \frac{\kappa L + \Omega}{\Omega + a^n \kappa L} a^n C_T + \frac{vC_N}{\kappa L + \Omega} \\ &\quad = \left(\frac{\kappa L + v + \Omega}{\Omega + a^n \kappa L}\right) a^n C_T \end{aligned}$$

Calculating the $E_{\max}$

Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$ where C_T is given by:

$$C_T = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2}$$

$$\begin{aligned} E_{\max} &= \lim_{L_T \to \infty} \left(\frac{\kappa L + v + \Omega}{\Omega + a^n \kappa L} \right) a^n C_T \\ &= \lim_{L_T \to \infty} \left(\frac{\kappa (L_T - C_T) + v + \Omega}{\Omega + a^n \kappa (L_T - C_T)} \right) a^n C_T \\ &= a^n R_T \lim_{L_T \to \infty} \left(\frac{\kappa (1 - C_T/L_T) + v/L_T + \Omega/L_T}{\Omega/L_T + a^n \kappa (1 - C_T/L_T)} \right) \\ &= R_T \end{aligned}$$

Hence $E_{\max} = R_T$

Calculating the EC_{50}

At half the maximal response
T cell activation

$$\frac{E_{\max}}{2} = \frac{R_T}{2}$$

which implies

$$\frac{R_T}{2} = \left(\frac{\kappa (L_T - C_T) + v + \Omega}{\Omega + a^n \kappa (L_T - C_T)} \right) a^n C_T$$

Rearranging and solving for L_T we get:

$$L_T = \left(\frac{a^n C_T (v + \Omega - \kappa R_T/2) - \Omega R_T/2}{a^n \kappa (R_T/2 - C_T)} \right)$$

2.5 Kinetic proofreading with negative feedback

Kinetic Proofreading with Negative Feedback extends the KPR scheme by introducing the notion that the rates of complex formation in the activation chain can be modulated at intermediate stages and/or within the final signaling state C_N. This modulation is achieved through a single negative feedback mechanism mediated by Src homology 2 domain phosphatase-1 (SHP-1).

$$\frac{dL}{dt} = -\kappa LR + v \sum_{i=0}^{N} C_i \tag{57}$$

$$\frac{dR}{dt} = -\kappa LR + v \sum_{i=0}^{N} C_i \tag{58}$$

$$\frac{dC_0}{dt} = \kappa LR + (b + \gamma S) C_1 - (\phi + v) C_0 \tag{59}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} + (b + \gamma S) C_{i+1} - (\phi + v + b + \gamma S) C_i; \quad 1 \le i \le N - 1 \tag{60}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (b + \gamma S + v) C_N \tag{61}$$

$$\frac{dS}{dt} = \alpha C_1 (S_T - S) - \beta S \tag{62}$$

The conservation equations are:

$$L_T = L + C_T \quad R_T = R + C_T$$

Here $C_T = \sum_{i=0}^{N+1} C_i$, and T cell activation is given by C_N.

$$\text{T cell activation} = C_N$$

Now C_N can be expressed in form of C_T as in eq (4.17) in [1],

$$C_N = \frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} r_-^N C_T \tag{63}$$

where

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

Therefore, the cell activation is given by

$$\text{T cell activation} = \frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} r_-^N C_T \tag{64}$$

$$\tag{65}$$

Calculation for $E_{\max}$
Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$ where C_T is given by:

$$C_T = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2}$$

$$\begin{aligned} E_{\max} &= \lim_{L_T \to \infty} \left(\frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} \right) r_-^N C_T \\ &= \left(\frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} \right) r_-^N R_T \end{aligned}$$

Calculation for EC_{50}
At half the maximal response
T cell activation

$$\frac{E_{\max}}{2} = \left(\frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} \right) \frac{r_-^N R_T}{2}$$

$$\left(\frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} \right) r_-^N C_T = \left(\frac{1 - r_-/r_+}{1 - (r_-/r_+)^{N+1}} \right) \frac{r_-^N R_T}{2}$$

which implies

$$C_T = \frac{R_T}{2}$$

Since, $L_T = L + C_T \quad R_T = L + C_T$, using this equation in equation (57)

$$\kappa(L_T - C_T)(R_T - C_T) - v\sum_{i=0}^{N} C_i = 0$$
$$(L_T - C_T)(R_T - C_T) = K_D C_T$$
$$L_T = K_D + R_T/2$$

2.6 Kinetic proofreading with stabilizing activation chain

In this model a pMHC ligand (L) binds to a TCR receptor (R) to form a pMHC-TCR complex C_0, which undergoes series of chemical modifications to reach signalling competent state C_N.

This stabilization/destabilization of the C_i complexes and variation in the time taken for activation, are articulated by variations in the values of corresponding rate constants $v(i); (i = 0, 1, ..., N)$ and $\phi(i); (i = 0, 1, ..., N-1)$ as the proofreading progresses.

$$\frac{dL}{dt} = -\kappa LR - \sum_{i=0}^{N} v(i)C_i \tag{66}$$

$$\frac{dR}{dt} = -\kappa LR - \sum_{i=0}^{N} v(i)C_i \tag{67}$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi(0) + v(0))C_0 \tag{68}$$

$$\frac{dC_i}{dt} = \phi(i-1)C_{i-1} - (\phi(i) + v(i))C_i; \quad 1 \le i \le N-1 \tag{69}$$

$$\frac{dC_N}{dt} = \phi(N-1)C_{N-1} - v(N)C_N \tag{70}$$

$$v(i) = \frac{(1+i)}{(1+ri)}v; r > 1 \qquad \phi(i) = \phi r^i; r > 1$$

where $v(0) = 1.5$ and $\phi(0) = 1.3$. In this model for simplicity $v(0)$ is denoted as $v(= 1/\tau)$ which is dissociation time, and $\phi(0)$ denotes the propagation rate for first step $C_0 \to C_1$. Now for next steps these rates are given by

$$v(i) = \frac{(1+i)}{(1+ri)}v; r > 1 \qquad \phi(i) = \phi r^i; r > 1$$

The conservation equations are:

$$L_T = L + C_T \quad R_T = R + C_T \quad C_T = \sum_{i=0}^{N} C_i$$

Here we have from [2]

$$C_0 = \frac{C_T}{\mu}; \quad C_i = \gamma C_0, 1 \le i \le N-1; \quad C_N = \delta C_T$$

where

$$\mu = 1 + \frac{\phi(N-1)}{v(N)}\gamma(N-1) + \sum_{i=0}^{N-1}\gamma_i$$

$$\gamma_i = \alpha_1 \times ... \times \alpha_i = \prod_{j=1}^{i} \alpha_i; \qquad \alpha_i = \frac{\phi(i-1)}{\phi(i) + v(i)}$$

$$\delta = \frac{1}{\mu} \frac{\phi(N-1)}{v(N)} \gamma(N-1)$$

and where C_T is the number of bound receptors or ligands $C_T = \sum_{i=0}^{N} C_i$ which is given by

$$C_T = \frac{2L_T R_T}{L_T + R_T + \epsilon + \sqrt{(L_T + R_T + \epsilon)^2 - 4L_T R_T}}; \qquad \epsilon = \frac{1}{\mu} \frac{v(0) + \phi(0)}{\kappa}$$

$$\begin{aligned} \text{T cell activation} &= C_N \\ &= \delta C_T \end{aligned}$$

Calculating the $E_{\max}$
Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$
Hence

$$E_{\max} = \delta R_T$$

Calculating the EC_{50}
At half the maximal response
T cell activation

$$\frac{E_{\max}}{2} = \delta R_T / 2$$

which implies

$$\delta C_T = \delta R_T / 2 \quad C_T = R_T / 2$$

Since

$$C_T = \frac{2L_T R_T}{L_T + R_T + \epsilon + \sqrt{(L_T + R_T + \epsilon)^2 - 4L_T R_T}}; \qquad \epsilon = \frac{1}{\mu} \frac{v(0) + \phi(0)}{\kappa}$$

Substituting $C_T = R_T/2$ in above equation and solving for L_T we get

$$L_T = 2R_T + 4\epsilon$$

Hence potency

$$Potency = 2R_T + 4\epsilon$$

2.7 Kinetic proofreading with incoherent feed forward loop

Although the actual model [3] considered the KPR with limited signalling combined with incoherent feed forward loop. We first considered the KPR with incoherent feed forward loop only for the plotting.

$$\frac{dL}{dt} = -\kappa LR - v \sum_{i=0}^{N} C_i \tag{71}$$

$$\frac{dR}{dt} = -\kappa LR - v \sum_{i=0}^{N} C_i \tag{72}$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi + v) C_0 \tag{73}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v) C_i; \quad 1 \le i \le N-1 \tag{74}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - vC_N \tag{75}$$

$$\frac{dY}{dt} = a(m-Y) - bY + \sigma C_N(m-Y) \tag{76}$$

$$\frac{dX}{dt} = c(l-X) - dX + \delta Y(l-X) - \mu C_N X \tag{77}$$

where $C_T = \sum_{i=0}^{N} C_i$, and T cell activation is given by X.

$$C_N = \alpha^n C_T$$

$$Y = \frac{(1+\sigma C_N/a)m}{1+b/a+\sigma C_N/a} \quad X = \frac{(1+\delta Y/c)l}{1+d/c+\delta Y/c+\mu C_N/d}$$

Calculating the $E_{\max}$

Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$
Hence

$$\begin{aligned} E_{\max} &= \lim_{L_T\to\infty}\left(\frac{(1+\delta Y/c)l}{1+d/c+\delta Y/c+\mu_\alpha^n C_T/c}\right) \\ &= \left(\frac{(1+\delta Y/c)l}{1+d/c+\delta Y/c+\mu\alpha^n R_T/c}\right) \end{aligned}$$

Calculating the EC_{50}

At half the maximal response
T cell activation

$$\frac{E_{\max}}{2} = \left(\frac{(1+\delta Y/c)l}{2(1+d/c+\delta Y/c+\mu\alpha^n R_T/c)}\right)$$

which implies

$$\left(\frac{(1+\delta Y/c)l}{1+d/c+\delta Y/c+\mu\alpha^n C_T/c}\right) = \left(\frac{(1+\delta Y/c)l}{2(1+d/c+\delta Y/c+\mu\alpha^n R_T/c)}\right)$$

$$2(1+d/c+\delta Y/c+\mu\alpha^n R_T/c) = 1+d/c+\delta Y/c+\mu\alpha^n C_T$$

Rearranging and solving for C_T

$$C_T = 2R_T + \left(\frac{1+d/c+\delta Y/c}{\mu\alpha^n}\right)$$

Since, $L_T = L + C_T \quad R_T = R + C_T$ Using this equation in (71)

$$\kappa(L_T - C_T)(R_T - C_T) - v\sum_{i=0}^{N+1} C_i = 0$$
$$(L_T - C_T)(R_T - C_T) = K_D C_T$$

Using value of C_T in above equation and solving. we get:

$$L_T = \frac{2R_T^2 + 3R_T U - U^2 - 2K_D R_T - UK_D}{R_T + U}$$

where

$$U = \left(\frac{1 + d/c + \delta Y/c}{\mu \alpha^n} \right)$$

2.8 Kinetic proofreading with limited signaling and incoherent feed forward loop

This model is an extension of KPR with incoherent feed forward loop, it has been assumed that signalling is limited and after after reaching the signalling competent state the bound TCR transits to non-signalling transit state.

$$\frac{dL}{dt} = -\kappa LR - v \sum_{i=0}^{N+1} C_i \tag{78}$$

$$\frac{dR}{dt} = -\kappa LR - v \sum_{i=0}^{N+1} C_i \tag{79}$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi + v) C_0 \tag{80}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v) C_i; \quad 1 \leq i \leq N-1 \tag{81}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (v + \xi) C_N \tag{82}$$

$$\frac{dC_{N+1}}{dt} = \xi C_N - v C_{N+1} \tag{83}$$

$$\frac{dY}{dt} = a(m - Y) - bY + \sigma C_N (m - Y) \tag{84}$$

$$\frac{dX}{dt} = c(l - X) - dX + \delta Y (l - X) - \mu C_N X \tag{85}$$

where $C_T = \sum_{i=0}^{N} C_i$, and T cell activation is given by X.
Here

$$C_N = \left(\frac{v}{v + \xi} \right) \alpha^n C_T$$

$$Y = \frac{(1 + \sigma C_N/c)m}{1 + d/c + \sigma C_N/c} \quad X = \frac{(1 + \delta Y/c)l}{1 + d/c + \delta Y/c + \mu C_N/c}$$

Calculating the $E_{\max}$
Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$
Hence

$$\begin{aligned} E_{\max} &= \lim_{L_T \to \infty} \left(\frac{(1 + \delta Y/c)l}{1 + d/c + \delta Y/c + v\mu\alpha^n C_T/(v + \xi)c} \right) \\ &= \left(\frac{(1 + \delta Y/c)l}{1 + d/c + \delta Y/c + v\mu\alpha^n R_T/(v + \xi)c} \right) \end{aligned}$$

Calculating the EC_{50}
At half the maximal response
T cell activation

$$\frac{E_{\max}}{2} = \left(\frac{(1 + \delta Y/c)l}{2(1 + d/c + \delta Y/c + v\mu\alpha^n R_T/(v + \xi)c)} \right)$$

which implies

$$\frac{(1+\delta Y/c)l}{1+d/c+\delta Y/c+v\mu\alpha^n C_T/(v+\xi)c} = \left(\frac{(1+\delta Y/c)l}{2(1+d/c+\delta Y/c+v\mu\alpha^n R_T/(v+\xi)c)}\right)$$

$$2(1+d/c+\delta Y/c+v\mu\alpha^n R_T/(v+\eta)c) = 1+d/c+\delta Y/c+v\mu\alpha^n C_T/(v+\xi)c$$

Rearranging and solving for C_T

$$C_T = 2R_T + \left(\frac{(c+d+\delta Y)(v+\xi)}{\mu v\alpha^n}\right)$$

Since, $L_T = L + C_T \quad R_T = R + C_T$, using this equation in (78)

$$\kappa(L_T - C_T)(R_T - C_T) - v\sum_{i=0}^{N} C_i = 0$$
$$(L_T - C_T)(R_T - C_T) = K_D C_T$$

Using value of C_T in above equation and solving. we get:

$$L_T = \frac{2R_T^2 + 3R_T W - W^2 - 2K_D R_T - WK_D}{R_T + W}$$

where

$$W = \left(\frac{(c+d+\delta Y)(v+\xi)}{\mu v\alpha^n}\right)$$

2.9 Kinetic proofreading with Limited and Sustained Signaling

It as a combination of two models KPR with limited signaling and KPR with sustained signaling.

$$\frac{dL}{dt} = -\kappa LR - \kappa LR^* - v\sum_{i=0}^{N+1} C_i \tag{86}$$

$$\frac{dR}{dt} = -\kappa LR + v\sum_{i=0}^{N-1} C_i + vC_{N+1} + \Omega R^* \tag{87}$$

$$\frac{dC_0}{dt} = \kappa LR - (\phi + v)C_0 \tag{88}$$

$$\frac{dC_i}{dt} = \phi C_{i-1} - (\phi + v)C_i; \quad 1 \le i \le N-1 \tag{89}$$

$$\frac{dC_N}{dt} = \phi C_{N-1} - (v+\xi)C_N + \kappa LR^* \tag{90}$$

$$\frac{dC_{N+1}}{dt} = \xi C_N - vC_{N+1} \tag{91}$$

$$\frac{dR^*}{dt} = vC_N - \kappa LR^* - \Omega R^* \tag{92}$$

The conservation equations are:

$$L_T = L + C_T \quad R_T = R + C_T + R^*$$

where $C_T = \sum_{i=0}^{N+1} C_i$

$$\text{T cell activation} = C_N + R^*$$

From (92) at the steady state

$$R^* = \frac{vC_N}{\kappa L + \Omega} \tag{93}$$

Now, using it and (88) at a steady state; for (87) at a steady state we have

$$-(\phi + v)C_0 + v\sum_{i=0}^{N-1} C_i + vC_{N+1} + \Omega\frac{vC_N}{\kappa L + \Omega} = 0$$

$$-(\phi + v)C_0 + vC_T - vC_N + \Omega\frac{vC_N}{\kappa L + \Omega} = 0$$

$$C_0 = \frac{v}{(\phi + v)}C_T - \frac{v}{(\phi + v)}C_N + \frac{v}{(\phi + v)}\frac{\Omega C_N}{\kappa L + \Omega}$$

$$C_0 = (1-a)C_T - (1-a)C_N + (1-a)\frac{\Omega C_N}{\kappa L + \Omega}; \qquad \text{where} \quad a = \frac{\phi}{(\phi + v)}$$

As C_T is given by:

$$\begin{aligned}
C_T &= \sum_{i=0}^{N+1} C_i \\
&= \sum_{i=0}^{N-1} C_i + C_N + C_{N+1} \\
&= \sum_{i=0}^{N-1} a^i C_0 + C_N + \frac{\xi}{v}C_N \\
&= \frac{1-a^n}{1-a}C_0 + C_N + \frac{\xi}{v}C_N \\
&= \left(\frac{1-a^n}{1-a}\right)\left((1-a)C_T - (1-a)C_N + (1-a)\frac{\Omega C_N}{\kappa L + \Omega}\right) + C_N + \frac{\xi}{v}C_N \\
&= \frac{1}{a^n}\frac{(a^n\kappa L + \Omega v + \xi\kappa L + \xi\Omega)}{v(\kappa L + \Omega)}C_N
\end{aligned}$$

Which implies C_N is given by:

$$C_N = \frac{v(\kappa L + \Omega)}{(a^n\kappa L + \Omega v + \xi\kappa L + \xi\Omega)}a^n C_T \tag{94}$$

T cell activation

$$\begin{aligned}
&= C_N + R^* \\
&= C_N + \frac{vC_N}{\kappa L + V} \\
&= \frac{\kappa L + \Omega + v}{\kappa L + \Omega}C_N \\
&= \frac{v(\kappa L + \Omega + v)}{(a^n\kappa L + \Omega v + \xi\kappa L + \xi\Omega)}a^n C_T
\end{aligned}$$

Calculating the $E_{\max}$
Similar to the case of kinetic proofreading model, it can be shown that when $L_T \to \infty$ $C_T \to R_T$ where C_T is given by:

$$C_T = \frac{L_T + R_T + K_D - \sqrt{(L_T + R_T + K_D)^2 - 4L_T R_T}}{2}$$

$$\begin{aligned}
E_{\max} &= \lim_{L_T \to \infty} \left(\frac{v(\kappa L + \Omega + v)}{(a^n \kappa L + \Omega v + \xi \kappa L + \xi \Omega)} \right) a^n C_T \\
&= \lim_{L_T \to \infty} \left(\frac{v(\kappa (L_T - C_T) + \Omega + v)}{(a^n \kappa (L_T - C_T) + \Omega v + \xi \kappa (L_T - C_T) + \xi \Omega)} \right) a^n C_T \\
&= a^n R_T \lim_{L_T \to \infty} \left(\frac{v(\kappa (1 - C_T/L_T) + \Omega/L_T + v/L_T)}{(a^n \kappa (1 - C_T/L_T) + \Omega v/L_T + \xi \kappa (1 - C_T/L_T) + \xi \Omega/L_T)} \right) \\
&= \frac{v}{a^n + \xi} a^n R_T
\end{aligned}$$

Calculating the EC_{50} At half the maximal response
T cell activation

$$\frac{E_{\max}}{2} = \frac{\frac{v}{a^n + \xi} a^n R_T}{2}$$

which implies

$$\frac{\frac{v}{a^n + \xi} a^n R_T}{2} = \left(\frac{v(\kappa (L_T - C_T) + \Omega + v)}{(a^n \kappa (L_T - C_T) + \Omega v + \xi \kappa (L_T - C_T) + \xi \Omega)} \right) a^n C_T$$

Rearranging and solving for L_T we get:

$$L_T = \frac{R_T (a^n \kappa C_T - \Omega v + \xi \kappa C_T - \xi \Omega) + 2(a^n + \xi)(\Omega + v - \kappa C_T)}{R_T a^n \kappa + \xi \kappa R_T - 2(a^n + \xi) \kappa C_T}$$

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