The Role of Energy Cost on Accuracy, Sensitivity, Specificity, Speed and Adaptation of T-Cell Foreign and Self Recognition

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The critical role of energy consumption in biological systems including T-Cell discrimination process has been investigated in various ways. The kinetic proofreading (KPR) in T-Cell recognition involving different levels of energy dissipation influences functional outcomes such as error rates and specificity. In this work, we study quantitatively how the energy cost influences error fractions, sensitivity, specificity, kinetic speed in terms of Mean First Passage Time (MFPT) and adaption errors. These provide the background to adequately understand T-Cell dynamics. It is found that energy plays a central role in the system that aims to achieve minimum error fractions and maximum specificity with the fastest speed under our kinetic scheme, but such an optimal condition is accomplished at significant amount cost of energy and sensitivity. Starting with the application of steady state approximation (SSA) to the evaluation of the concentration of each complex produced associated with KPR, which is used to quantify various observables, we present both analytical and numerical results in detail.

1 Introduction

One of the well known biological malfunctions is the deviation from the normal condition of being able to maintain the ability to efficiently differentiate foreign antigens from self-proteins attacking living cells. It may be associated with an abnormality of KPR processes, which prevents a bound form of “wrong” ligands from being dissociated at a sufficiently high rate.\textsuperscript{1} The affinity ratio of “correct” and “wrong” ligands with T-cell receptor is typically a measurable quantity that determines the efficiency of such dissociation. Hopfield and Nino developed KPR theory in biosynthetic processes.\textsuperscript{2,3} Hopfield formulated error fractions for protein synthesis.\textsuperscript{3} They elucidated that enzymes discriminate two different reaction pathways, leading to correct or incorrect products due to KPR. Since then, extensive researches on sensitivity and specificity associated with error fractions have been performed. Goldbeter et al found that covalent modification in protein involving biological systems affects a sensitivity amplification using Steady State Approximation (SSA).\textsuperscript{4}

A series of modifications after ligand binding in the KPR process involves extra steps which creates “time delay” τ. The extra steps leading to signaling are critical factors that allow for reduction in error rates, indicating high efficiency of kinetic discrimination.\textsuperscript{5} However, KPR also involves free energy cost for activation of an initially formed complex, which occurs in nonequilibrium states.\textsuperscript{1} The energy is also crucial in reducing the error rates and allowing increased specificity.\textsuperscript{2} Before KPR attracted great interests, there had been several studies focusing on the effect of energy cost for KPR in biological processes such as tRNA aminoacylation\textsuperscript{6,7} and so on.

Beyond the classical studies on discrimination process for biological systems such as Hopfileld,\textsuperscript{2} Nino,\textsuperscript{3} and McKeithan,\textsuperscript{8} there has been a fair amount of accomplishment on T-cell recognition with certain modifications,\textsuperscript{9–11} which make it possible to address several deficiencies found in existing models. For example, Qian calculated an error fraction depending on both KPR steps and energy cost using the Successive Rapid Equilibrium Approximation (SREA) by assuming that there is energy input for only the first cycle.\textsuperscript{9} Chen et al. are the ones provided a the formulation of T-Cell sensitivity and specificity in a quantitative manner, depending on the number of KPR steps using a SSA.\textsuperscript{12} There have been significant contributions from Cui\textsuperscript{10} and Banerjee,\textsuperscript{11} focusing on the detailed relationship between error rates and MFPTs. Despite their efforts on detailed analysis of the dynamics, their studies are based on the kinetic scheme in terms of only energy cost, lacking comprehensive information for which both KPR steps and energy dissipation are taken into consideration. For convenience, we use the term “KPR steps” instead of phosphorylation steps although technically a KPR process includes both phosphorylations and the dissociation of each intermediate product. Here, the following questions can be raised:

(1) If energy consumption plays an central role in reducing...
errors, how does energy influence sensitivity and specificity in T-Cell discrimination process, and what are the relationships among error fraction, sensitivity and specificity under identical conditions?

(2) Although two factors, the KPR steps and energy dissipation, both of which contribute to editing process of the system have opposite effects in terms of the time required to complete the associated process, the retardation due to the increased KPR steps may be mitigated by sufficient level of energy dissipation. Can the MFPT data provide adequate information to determine such energy level under the given condition?

(3) What is the appropriate stimulus signal that promotes adaptation of the corresponding system?

In order to answer the above questions, we design a kinetic model describing T-Cell discrimination process. After introducing the chosen model for our discussion, this paper shows a detailed procedure leading to analytical expressions for these quantities based on the SSA by imposing energy input in “every step” since a series of modifications that occur after ligand binding requires energy consumption and is out of equilibrium. Based on the kinetic model, we calculated error fractions, sensitivity and specificity in terms of both KPR steps and energy cost.

We also calculated the kinetic speed in terms of MFPT, the average time required to complete the signaling event starting from an initial state, depending on energy with given KPR steps. The entire picture of the dynamics in T-Cell recognition will still remain unclear with the only sensitivity and specificity data available until the consequences of MFPT are evaluated. This is because the MFPT provides information on the time required for signaling to be completed under energy dissipation. We also see how energy influences the adaptation errors in response to the shift of a particular parameter, which is the rate constant used in our kinetic model.

2 Kinetic Scheme describing T-Cell recognition

The following detailed kinetic scheme reflects KPR associated with the energy consumption. This scheme is based on the McKeithan’s kinetic model. The initial complex formed by a T-cell receptor and equal amounts of foreign and self ligands triggers a series of modifications, leading to signaling. Since the first complex reaches equilibrium rapidly, the values of governing rate constants \( k_1 \) and \( k_{-1} \) for the corresponding forward and backward reactions, respectively are substantially higher than the ones given by \( k_p \) and \( k_{-p} \) for the rest of the reactions. The dissociation events at each intermediate complex leading to its initial state with the rate of \( k_i \) (i=1,2,...N) allow for a reduction in the amount of ligand bound molecules. We set the same value of the dissociation constant \( k_{\text{disso}} \) for each intermediate complex for simplicity. There is a need to incorporate the rate constants governing the direct formation process, which leads to the development of the complexes without passing through earlier steps into the full “rate equation”. The direct formation constants denoted by \( m_i (i = 1, 2, \ldots, N) \) decrease with the KPR steps due to the higher energy intermediates as KPR progresses.

In addition to this, they also decrease with consumed energy according to the formula for energy dissipation. We allow variation of the backward rates and the direct formation rates so that they decrease with energy. However, the reverse rate constant \( k_{-1} \) that is associated with the fast equilibrium is unchanged. The transfer rate “W” is included in the irreversible process from the final complex to the absorbing site where the associated dynamics is completed. The equilibrium ATP and ADP concentrations are related to the rate constants:

\[
\frac{[ATP]_{eq}}{[ADP]_{eq}} = \frac{k_{p}^{0}C_1 [ATP]_0}{k_{p}^{0}[C_0]_{eq}} \frac{k_{p}^{m_1}m_1 k_{-1}}{k_{p}^{0}k_{1}^{0}_{\text{disso}}} (1)
\]

where \( k_p \) and \( k_{-p} \) are pseudo first order rate constants denoted by \( k_p = k_{p}^{0}[ATP] \) and \( k_{-p} = k_{p}^{0}[ADP] \) respectively.

The second equality comes from the relationship between the ratio of the equilibrium concentration and kinetic constants (i.e)

\[
\frac{[C_i]_{eq}}{[C_0]_{eq}} = \frac{k_i^{0}m_i}{k_{-1}^{0}}
\]

The free energy of ATP hydrolysis is given as

\[
\Delta G = \Delta G_D^{\text{DT}} + RT \ln \left( \frac{[ATP]}{[ADP]} \right) = RT \ln \left( \frac{k_p k_1 k_1^{*}}{k_{-1}^{0}m_1 k_{-1}^{0}} \right) (2)
\]

where

\[
\Delta G_D^{\text{DT}} = -RT \ln \left( \frac{[ATP]_{eq}}{[ADP]_{eq}} \right) (3)
\]

and we can define \( \gamma \) as the available free energy from each ATP hydrolysis as [9-13]

\[
\gamma = \frac{k_p k_1 k_1^{*}}{k_{-1}^{0}m_1 k_{-1}^{0}} \quad (N = 1) \quad (4)
\]

\[
\gamma = \frac{k_p k_{-(i+1)} m_i}{k_{-1}^{0}m_{i+1} k_{i}^{*}} \quad (N > 1) \quad (5)
\]

where \( k_{i}^{*} \) (i=1,2,...N) is all the same.

The affinity ratio between “wrong”(self-protein) and “correct”(foreign antigen) for targeting is given by

\[
\theta = \frac{C'}{C} = \frac{m_i}{m_{\text{disso}}} = \frac{k_{\text{disso}}}{k_1^{0}} = \frac{k_{-1}^{0}}{k_{-1}^{0}} \quad (6)
\]

assuming \( m_i \) is the same for both the correct and wrong ligands. The self-proteins bound to the receptor dissociate more quickly than the foreign antigens indicating that the affinity ratio is less than 1. We set the value of \( \theta \) to be 0.01.
Fig. 1 Schematics of the kinetic model for “N” kinetic proofreading process (a): foreign ligands (b): self ligands. Followed by receptor-ligand binding, a series of modifications triggers the T-Cell recognition signaling. At each intermediate state, self ligands dissociate $1/\theta$ ($\theta=0.01$ in our case) times faster than foreign ligands. $k_1$ and $k_{-1}$ are both forward and backward rate constants at fast equilibrium. After receptor-ligands binding process, the governing rate constants of the phosphorylation reactions and the reverse of the phosphorylation reactions between intermediate complexes are $k_p$ and $k_{-p}$ respectively. Each $m_i$ denotes the rate of the direct formation starting from free ligands. Coupling to energy source is considered in every step.
3 Results: Error Fractions

We apply the mass action law to express the time derivative of concentration for each bound state, which is given by

\[
\frac{dC_0}{dt} = k_1[R][L] - (k_{-1} + k_p)C_0 + k_pC_1
\]

\[
\frac{dC_1}{dt} = k_pC_0 - (k_p + k_{disso})C_1 + k_{-p}C_2
\]

\[
\frac{dC_2}{dt} = k_pC_1 - (k_p + k_{disso})C_2 + k_{-p}C_3 + m_2[R][L]
\]

\[
\frac{dC_{N-1}}{dt} = k_pC_{N-2} - (k_p + k_{disso})C_{N-1} + k_{-p}C_N + m_{N-1}[R][L]
\]

\[
\frac{dC_N}{dt} = k_pC_{N-1} - (k_p + k_{disso} + W)C_N + m_N[R][L]
\]

(7)

Here, [R] and [L] denote the concentrations of unbound TCR and ligands, respectively.

Applying the SSA to each intermediate including the final complex that contributes to signaling, we get

\[
C_0 = \frac{k_1[R][L] + k_{-p}C_1}{k_{-1} + k_p}
\]

(8)

\[
C_1 = \frac{k_pC_0 + k_{-p}C_2 + m_1[R][L]}{k_p + k_{disso}}
\]

(9)

\[
C_2 = \frac{k_pC_1 + k_{-p}C_3 + m_2[R][L]}{k_p + k_{disso}}
\]

(10)

The general expression for \(C_{N-1}\) just before the formation of a final complex is as follows.

\[
C_{N-1} = \frac{k_pC_{N-2} + k_{-p}C_N + m_{N-1}[R][L]}{k_p + k_{disso}}
\]

(11)

The initial concentration \(C_0\) given by above can be replaced by \(k_1[R][L]\) assuming \(k_{-1} >> k_p\) and \(k_1[R][L] >> k_pC_1\).

The concentration at the final state is given by

\[
C_N = \frac{k_pC_0 + m_1[R][L]}{k_p + k_{disso} + W} \quad (N = 1);
\]

\[
C_N = \frac{k_pC_0 + m_1[R][L] + m_2[R][L]}{k_p + k_{disso} + W} \quad (N > 1)
\]

(12)

(13)

Note that each series of \(C_N\) depends on the number of KPR steps, whose expression for \(N=2\) case has a recursion relationship that connects with a \(C_{N-2}\) term, generating additional terms successively (i.e) \(C_{N-4}, C_{N-6}, \ldots\) and so on with \(C_0\) for \(n=even\) and \(C_1\) for \(n=odd\). On the other hand, \(C_{N-2} = \frac{k_pC_{N-3} + k_{-p}C_{N-1} + m_2[R][L]}{k_p + k_{disso}}\) with substitution of the expression for \(C_{N-1}\) and \(C_{N-3}\) respectively.

Solving for \(C_{N-2}\) by ignoring the term \(k_{-p}C_N\) generated accordingly due to its negligibility compared to the other terms for taking the advantage of numerical calculation without producing significant errors, we get

\[
C_{N-2} = \frac{k_p^2C_{N-4} + k_{-p}m_{N-3}[R][L] + k_{-p}m_{N-1}[R][L]}{(k_p + k_{disso})^2 - 2k_{-p}k_p} + m_{N-2}[R][L](k_p + k_{disso})
\]

(14)

Applying the same trick to the rate expressions containing time derivative terms, \(\frac{dC_{N-2}}{dt}, \frac{dC_{N}}{dt}\) and so on, the initial concentration that controls the recursion relationship for \(C_{N-2}\) is

\[
C_1 = \frac{k_pC_0(k_p + k_{disso} + k_{-p}m_{1}[R][L])}{(k_p + k_{disso})(k_p + k_{disso} - k_{-p}k_p)} \quad (N = odd)
\]

(15)

\[
C_0 = \frac{k_1[R][L]k_p(k_p + k_{disso} + k_{-p}m_{1}[R][L])}{(k_{-1} + k_{-p}k_p)(k_p + k_{disso} - k_{-p}k_p)} \quad (N = even)
\]

(16)

The error fraction \(f\) is defined as the ratio of the rate of “wrong” product formation to the rate of “correct” product formation (i.e) \(C_{N,foreign}/C_{N,self}\) for T-Cell targeting. Therefore, its full expression for our N-cycle kinetic proofreading model is given by

\[
f = \frac{(k_pC_{0,Self} + m_1[R][L] + k_p + k_{disso} + W)}{(k_pC_{0,foreign} + m_1[R][L] + k_p + k_{disso} + W)} \quad (N = 1)
\]

(17)

\[
f = \frac{(\frac{k_pC_{N-2,foreign} + k_{-p}m_{N-1}[R][L]}{(k_p + k_{disso})^2 - 2k_{-p}k_p}) + m_{N-2}[R][L](k_p + k_{disso})}{(\frac{k_pC_{N-2,foreign} + k_{-p}m_{N-1}[R][L]}{(k_p + k_{disso})^2 - 2k_{-p}k_p}) + m_{N-2}[R][L](k_p + k_{disso})} \quad (N > 1)
\]

(18)

where

\[
C_{N-2,foreign} = \frac{k_p^2C_{N-4,foreign} + k_{-p}m_{N-3}[R][L] + k_{-p}m_{N-1}[R][L]}{(k_p + k_{disso})^2 - 2k_{-p}k_p} + m_{N-2}[R][L](k_p + k_{disso})
\]

(19)

\[
C_{N-2,self} = \frac{k_p^2C_{N-4,self} + k_{-p}m_{N-3}[R][L] + k_{-p}m_{N-1}[R][L]}{(k_p + k_{disso})^2 - 2k_{-p}k_p} + m_{N-2}[R][L](k_p + k_{disso})
\]

(20)

Again, the expression for \(C_{N-2}\) can be given in terms of either \(C_0\) for even \(n\) or \(C_1\) for odd \(n\).

We obtained the numerical results for error fractions depending on both number of KPR steps and energy dissipation, featuring their decrease with both factors. The error fractions gradually decline until energy \(\gamma\) reaches \(10^4\) without giving a significant difference in the numerical values for any KPR steps. However, drastic drops in error fractions are observed in higher energy cost regime above the branch point of the energy cost measured in \(\gamma\) and its salient feature is pronounced at higher KPR steps. It is also found that the error fraction converges to Hopfield limit \((\theta^{i+1})\) where \(i=1,2,\ldots N\) which is a minimum at large \(\gamma\) when
the absorption rate \( W \) approaches zero as suggested by Hopfield.\(^{22}\) T-Cell reduces error rates by recognizing foreign antigens with the help of multiple phosphorylation steps and energy expenditure even though the misrecognition of self-proteins as foreign peptides commonly occurs. Experimentally, it is well known that the typical error fraction is less than \( 10^{-6} \).\(^{11}\) Another study estimating the error rate based on a simple kinetic proofreading model suggests that the rate is approximately \( 10^{-4} \) at the affinity ratio of 0.01 for \( N=4.\(^{8}\) \)

4 Results: Sensitivity and Specificity

Both sensitivity and specificity based on the kinetic model were computed. Sensitivity is defined as the probability of having the number of foreign antigens sufficient to generate major signaling out of the total complex. On the other hand, specificity is defined as a factor to determine the ability to discriminate the correct ligands (foreign antigens) from the wrong ones (self-proteins) in their active states which contribute to major signaling.\(^{12}\) Chan et al. provided a simple expression for these quantities in kinetic proofreading in the context of T-Cell recognition in the following manner.\(^{12}\) We directly follow the procedures they present.

This implies the definition of sensitivity and specificity can be expressed as follows:

\[
\text{Sensitivity} = \frac{TP}{TP + FN} \\
\text{Specificity} = \frac{TP}{TP + FP}
\]

where

\( TP = \) The number of signaling events for a “correct” ligand  \\
\( FN = \) The number of zero signaling events for a “correct” ligand  \\
\( TN = \) The number of zero signaling events for a “wrong” ligand  \\
\( FP = \) The number of signaling events for a “wrong” ligand

If we simply use the fraction of the active complexes, taking \( C_{\text{total}} \) as \( \alpha^N \), then

\[
TP = C_{\text{total, foreign}} \alpha_{\text{correct}}^N \\
FN = C_{\text{total, foreign}} (1 - \alpha_{\text{correct}}^N) \\
TN = C_{\text{total, self}} (1 - \alpha_{\text{wrong}}^N)
\]

Therefore,

\[
\text{Sensitivity} = \frac{C_{\text{total, foreign}} \alpha_{\text{correct}}^N}{C_{\text{total, foreign}} \alpha_{\text{correct}}^N + C_{\text{total, self}} (1 - \alpha_{\text{correct}}^N)} \quad (21)
\]

\[
\text{Specificity} = \frac{C_{\text{total, foreign}} \alpha_{\text{correct}}^N}{C_{\text{total, foreign}} \alpha_{\text{correct}}^N + C_{\text{total, self}} \alpha_{\text{wrong}}^N} \quad (22)
\]

Here, \( C_{\text{total}} \) can be achieved by adding the concentrations of all intermediates including the ligand-receptor complex at the final state, which is taken from both foreign and self-ligands, sorted by different “\( N \)”. The associated concentrations of foreign ligands for the purpose of numerical calculation were taken from the equation (8) to (16).

Chan and et al.\(^{12}\) shows the feature of decrease in sensitivity depending on the number of KPR steps based on their idealized kinetic scheme for which reverse reactions between intermediate states are not taken into account without using energy \( \gamma \). They also obtained the result through increased specificity, reaching to 1.0 depending on the number of KPR steps. The trade-off between sensitivity and specificity is also observed in our model.\(^{12,17}\)
Our results show that the sensitivity decreases and converges to a certain minimum as the energy cost $\gamma$ increases with a given number of KPR steps. It is also found that the sensitivity decreases with the number of KPR steps for given energy as expected from the equation (21). A rapid drop in the sensitivity is observed in low energy regime, especially $\gamma<100$, but above that, it decreases gradually. In addition to this, its drastic decrease becomes prominent with the growth of KPR steps. The numerical results indicate that the concentration of the final complex formed by the foreign antigens for each $N$ drops steadfastly and reaches a minimum with the increase of $\gamma$, while the concentrations of all intermediates including the final products formed by both foreign antigens and self-proteins also approach a converged minimum rapidly for any $N$, resulting in the obtained minimum sensitivity at large $\gamma$. This observation can be interpreted as that a large amount of energy input which drives the forward reactions also involves the immediate dissociation at each intermediate complex, yielding lower value of sensitivity with elevation of energy. At the same time, the decreasing trend of the final concentration can be accelerated by reducing the rate of the direct formation with energy consumption. For this reason, the successive increment of the forward rate relative to the backward rate with the growth of KPR steps results in a sharp drop of in the sensitivity.

The specificity obtained from our model using SSA has the feature approaching a maximum value rapidly as the energy cost $\gamma$ increases. In addition to this, it is noticeable that the number of KPR steps does not affect the specificity in a significant manner with given energy $\gamma$, showing marginal growth of the quantity as $N$ increases. We observe the rapid increase of specificity converging to the approximate value of 1.0 (Exact value of 1.0 found at $N>4$) with energy.

Based on McKeithan’s kinetic model for T-Cell discrimination process, the estimated values of the sensitivity and specificity at the affinity ratio of 0.01 for $N=4$ are 0.68 and 0.9999 respectively when no energy is involved. The estimated sensitivity is not in agreement with our numerical results, which are $O(10^{-2})$ measured at the detailed balance condition. This is mainly due to the fact that the nature of these quantities are not robust, exhibiting large variations depending on several factors such as overall kinetic scheme and the values of specific parameters.
5 Results: Mean First Passage Time

The speed of KPR cascade associated with Mean First Passage Time (MFPT) provides information on how rapidly the immune system responds to the foreign ligand. More precisely speaking, it is the average time taken to produce the final product that contributes signaling immediately from foreign antigen.[10,18] It is the average time taken to produce the final product that contributes signaling immediately from foreign antigen.[10,18] We find that the energy input and the number of KPR steps are the major factors that determine the MFPT in KPR model. We start with the construction of the transition matrix governing the kinetic model in Laplace domain, followed by the calculation of the corresponding probability of each state. Our work in this part is directly towards the evaluation of MFPT depending on the energy consumption when the foreign ligands are involved in KPR. Similar works have been done by Banerjee et al. for the calculation of MFPT of DNA replication process.[11] However, it is based on a different style of biological network that takes separate mechanisms relying on the type of ligands, both correct and incorrect ones forming associated complexes.[11,16] In other words, the machinery completed by Banerjee et al. can be utilized to extract information such as first passage probability density of “correct” products among the coexistence of two types of ligands, which is different from our case. Basically, we follow the recipe from Bel et al.[19] for the evaluation of the MFPT. The detailed procedure to obtain the MFPT is given in the Appendix.

However, when the algebraic equations used for obtaining the parameters $\lambda_1$ and $\lambda_2$ are applied for each case, $N=1$ and $N>1$, we encounter the following problems.

(A) The equation (25) in Appendix is also relevant to the other case ($N>1$) since the dynamics at the product $C_0$ still affects the rest of intermediate complexes.

(B) Each equation (31) in Appendix which increases its degree as the number of the KPR steps grows has imaginary roots, which makes it cumbersome to find and collect appropriate real roots that determine the solution of the corresponding equation in Laplace domain.

How can we address the problems? Based on the numerical result, we have found that the MFPT for $N=1$ where the network is governed by the first ATP hydrolysis is much higher than the MFPT for $N>1$ at large energy due to the nature of kinetic scheme characterized by the inverse relationship between the rate of direct formation and energy consumption. To be specific, within the first ATP hydrolysis, the creation of the final product is only influenced by the forward rates $k_1$, $k_p$ and the direct formation rate $m_1$, while both the immediate dissociation events at the product and the direct formation rate that drastically decreases with the growth of energy make the signal to escape the loop difficult at large energy input. However, as the number of KPR steps increases, the forward rates, especially pronounced in high energy regime allow the system to make a completion in a much shorter time.

Based on this observation, we made an approximation to deal with the intractable situation by only imposing the quadratic equation (25), which allows two real roots to control the entire systems such that we can simply ignore the influence of other series of equations (31) because the rate determining process is associated with the kinetics within the first ATP hydrolysis due to the “trapping effect” discussed below.

Collecting all quantities including the expression for $E_1$ and $E_2$ to get the probability density at the absorbing state, which is given by $F(s) = WP_{N+1}(s)$ in the Laplace domain, the mean first passage time $T$ whose expression, in general, is $\int_0^\infty f(t) dt = (-1)\frac{dF(s)}{ds}|_{s=0}$ can be computed for our model. The expression for the MFPT probability density is given by $F(s) = W\left(E_1^{N+1} + E_2^{N+1}\right)$.

![Figure 5](image.png)

**Fig. 5** (a) The mean first passage time (MFPT) depending on energy input $\gamma$ with given the number of kinetic proofreading steps, $N=3$(red) and $N=6$(blue) respectively. (b) 3D plot of the MFPT dependent on both KPR steps and energy $\gamma$

The numerical results reveal that in general, the MFPT increases with the formation of more phosphorylated complexes, but decreases with the energy input. There is a steep drop in the escape time until the energy $\gamma$ reaches 100, but above the value, its variation is negligible for any KPR steps. However, as shown in the figure, such features are found to have deviations for small KPR steps ($N=3$) having long escape time at low energy compared to the case of higher KPR steps ($N=6$).
As discussed earlier, the consequence is directly associated with our kinetic scheme that allows the rate of direct formation to decrease with consumed energy, and the backward rate constant $k_{-1}$ still having a constantly large value regardless of the energy input, which makes it difficult for the signals to escape the first PdPC hydrolysis cycle as energy increases. Such a trap in the first hydrolysis affects the escape time for larger KPR steps, yielding higher values of MFPT for $N=3$, but other factors that facilitate the transport of signals such as successive forward rates become dominant in determining the escape time for $N>3$. Moreover, as indicated in the figure featuring the unusually drastic drop of the escape time for $N=3$, energy expenditure can be used to accelerate the rate of signal transduction. The change in the MFPT until the energy cost $\gamma$ approaches 100 for $N=3$ is approximately 1.5 sec, which is substantially greater than the case for $N=6$ whose corresponding time difference is $O(10^{-2})$ sec.

A very simple kinetic model without considering energy expenditure for TCR activation indicates that the estimated waiting time using a phosphorylation rate of $1.0s^{-1}$ with 10 KPR steps is around 10 sec.\textsuperscript{12} Compared to the particular estimation, the lower value of the MFPT for our case is mainly attributed to the drastic drop of the backward rate with the increase of the energy input.

\section*{6 Results: Adaptation Errors}

In biological systems, a stimulus signal generates corresponding outcomes. The change in output in response to the perturbation allows the systems to return to the original one whose output is measured without a signal input.\textsuperscript{20} For T-Cell recognition, a sudden shift of a given parameter leads to change in an output activity to some extent despite its eventual recovery. It is meaningful to find out how accurately a perturbed system returns to the unperturbed one depending on KPR steps and energy dissipation.

We take a slight change of forward rate constant $k_p$ associated with the phosphorylation process in PdPC as a signal input to monitor its response which is the concentration of all intermediate complexes for foreign antigens and self-proteins (total concentrations of foreign antigens and self-proteins). The adaptation error is defined as $|a-a_0|$, where $a_0$ is the amount of change in output activity without perturbation and $a$ is the amount of change in output activity due to perturbation, and the error is expected to decline with energy cost.\textsuperscript{20} Among several candidates as an output activity in response to a given input in order to measure the adaptation errors featuring decline, we have found that the total concentration of foreign antigens and self-proteins is the only one that displays a gradual drop in error with both KPR steps and the amount of energy cost when the forward rate is slightly enhanced.

The error becomes somewhat lower as more phosphorylated products are created with given energy, but conversely, we find a sharp growth of the error with KPR steps at equilibrium (zero energy input).

Such an opposite situation is attributed to the increase in concentration of the final products with the growth of KPR steps when the systems is perturbed at equilibrium, which is in contrast to the general decline of the concentration under the same condition when there is available energy cost. The increased forward rate as stimulation, combined with the relatively larger direct formation and backward rates at equilibrium compared to out of equilibrium is mainly responsible for the growth of each intermediate product, having a cumulative effect on the concentration of total complexes. This reveals its sharp increase as KPR proceeds, resulting in the salient feature of the adaptation error under the detailed balance condition. Our numerical results also show that there is a significant drop in the adaptation error in low energy regime ($\gamma<100$) but above it, the error declines gradually with increasing energy, converging to around 0.0194 when $\gamma>10^9$. On the other hand, when the backward rate is slightly enhanced as a stimulus signal, there is an increase of the adaptation error with KPR steps for all range of energy consumption although the error is reduced as more energy is involved for a given KPR step.

In this case, the adaptation error decreases and converges to a certain minimum for $N=5$, but for $N<5$, the error simply drops and reaches zero with increased energy.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure6}
\caption{(a) The adaptation error that measures the concentration of all intermediate complexes in response to perturbation of the forward rate $k_p$ displays its decrease, but featuring plateau with energy cost. (b) 3D plot of the corresponding adaptation errors dependent on both KPR steps and energy $\gamma$.}
\end{figure}
The general trend of the decreasing adaptation error with energy can be interpreted as a trade-off between two factors: There is a serial increment of each forward rates between intermediate complexes as perturbation, which increases the concentration of the final products drastically, yielding large errors. This becomes noticeable as KPR steps grows due to the additional elevation of the forward rate. However, the total concentration may be moderated by the successive decline of the direct formation rates with energy consumption, producing small errors in the regime of large energy cost.

When T-Cell dynamics, initially influenced by perturbation is under the condition where the lowest adaptation error is achieved, it means that the system has recovered most of the features of physical outcomes including error fractions, sensitivity and specificity. Such a feature can be pronounced when sufficient amount of energy is involved in T-Cell recognition process based on the model we design.

7 Discussion

It is difficult to predict the consequences of T-Cell dynamics without numerical calculation due to the complexity of our T-Cell scheme. For example, the dissociation event at each intermediate product and the direct process forming a phosphorylated complex without passing through previous intermediate stage are necessary elements to understand T-Cell recognition, as well as forward and backward rates between two products. Moreover, considering the nonequilibrium nature of living organisms, interacting with environments constantly, we had to incorporate energy source associated with ATP hydrolysis into our system. As used by Qian, the energy dissipation is expressed in terms of several kinetic rate constants, and it indicates that most of the rates governing our T-Cell system depend on the consumed energy, which makes the related dynamics more complex. Hence, it is important to take all the information into account to set up an appropriate model for understanding T-Cell recognition.

Despite existing studies on kinetic proofreading in T-Cell recognition, the lack of simultaneous comparisons of physical outcomes has prevented us from fully understanding the dynamics of the process in terms of energy input. As part of addressing such a problem, we present all the results regarding error rates, sensitivity, specificity, speed and adaptation errors in terms of energy dissipation with given KPR steps.

It has been found that the error fractions decrease with energy dissipation and KPR steps, and they have asymptotic behaviors, converging to certain minimum values when a sufficient amount of energy is supplied, which is consistent with the consequence of Hopfield's work. Compared to the numerical results of specificity, we have also found that the error rates determined at large amount of energy consumption lead to maximized specificity. Trade-off between sensitivity and specificity featured as the number of KPR steps grows is also observed when energy cost increases. In addition to this, the energy supply plays an central role in reducing the escape time accelerating the speed of signal transduction by minimizing the time-delay caused by the growth of KPR steps under the given kinetic scheme. Finally, the only measurable quantity where adaptation error gradually decreases with both KPR steps and energy cost when the system is perturbed is the total concentration of all intermediates.

Despite our efforts, the optimal condition that allows for the T-Cell discrimination process to work such that it is being made under maximum allowed efficiency is still not completely revealed. Nevertheless, it is found that such a condition characterized by the minimum error fractions, the minimum MFPT and the maximum specificity is obtained at high energy with loss of the sensitivity for our particular model.

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Appendix

The governing equation expressed as $p(t) = Ap(t)$ gives the series of probabilistic outcomes denoted by $p_0, p_1, \ldots$ and $p_{N+1}$ due to the stochastic nature of the system. The direct transition matrix for our Markovian model is given by

$$
\begin{pmatrix}
    p_{1}(t) \\
p_{2}(t) \\
p_{3}(t) \\
p_{N+1}(t) \\
p_{N}(t)
\end{pmatrix}
= 
\begin{pmatrix}
    -k_{c1} & k_{c1} & 0 & \cdots & 0 \\
    k_{d} & -k_{d} - k_{a1} & 0 & \cdots & 0 \\
    0 & k_{b} & -k_{b} - k_{c2} & \cdots & 0 \\
    \vdots & \vdots & \vdots & \ddots & \vdots \\
    0 & 0 & 0 & \cdots & -k_{c1}
\end{pmatrix}
\begin{pmatrix}
p_{1}(t) \\
p_{2}(t) \\
p_{3}(t) \\
p_{N+1}(t) \\
p_{N}(t)
\end{pmatrix}
$$

Performing Laplace transform, we get

$$
(s - A)P(s) =
\begin{pmatrix}
    s + k_{c1} + \sum_{i=2}^{N+1} k_{c1} & -k_{c1} & -k_{c1} & \cdots & -k_{c1} \\
    k_{d} & s + k_{d} + k_{a1} & -k_{a1} & \cdots & -k_{a1} \\
    0 & k_{b} & s + k_{b} + k_{c2} & \cdots & -k_{c2} \\
    \vdots & \vdots & \vdots & \ddots & \vdots \\
    0 & 0 & 0 & \cdots & -k_{c1}
\end{pmatrix}
\begin{pmatrix}
P(s) \\
P(s) \\
P(s) \\
P(s) \\
P(s)
\end{pmatrix}
$$

(23)

Each row in the above matrix has the value of $(1,0,0,\ldots,0,0)$ because of the relation $(s - A)P(s) = p(t = 0)$. Putting the general solution for the equation, given by

$$
P_{i}(s) = E_{i,1} \lambda_{i}^{1} + E_{i,2} \lambda_{i}^{2} \quad (i=1,2,\ldots,N)
$$

where $E_{i,1,2}$ are constants determined at boundaries into the “system controlling equation(s)(SCEs)”, we get algebraic equations in each $\lambda$ for two different number of kinetic proofreading cases(eqn (25) and (31) in Appendix for $N=1, N > 1$ respectively). Note that the SCEs are the series of equations that do not include the initial and final algebraic equations solely used for boundary conditions.

For $N=1$,

$$
\frac{k_{-p}}{s + k_{-1} + k_{p}} \lambda_{1}^{2} - \lambda_{1} + \frac{k_{1}}{s + k_{-1} + k_{p}} = 0
$$

(25)

Using the fact $E_{1,2}$ must satisfy the equations determined at boundaries ($i=0$ and $i=2$), the following relations are obtained.

$$
(s + k_{1} + m_{1} - k_{-1} \lambda_{1} - k_{diss} \lambda_{1}^{2}) E_{1} + (s + k_{1} + m_{1} - k_{-1} \lambda_{2} - k_{diss} \lambda_{2}^{2}) E_{2} = 1
$$

(26)
\[ k_k \lambda_1 - (s + k_p + k_{disso} + W) \lambda_1^2 + m_1 \] \[ E_1 = \left[ -k_k \lambda_2 + (s + k_p + k_{disso} + W) \lambda_2^2 - m_1 \right] E_2 \] (27)

Combining these two equations to solve for \( E_1 \) and \( E_2 \), we get

\[ E_2 = E_1 \left[ k_k \lambda_1 - (s + k_p + k_{disso} + W + \lambda^2) \lambda_1^2 + m_1 \right] - k_k \lambda_2 + (s + k_p + k_{disso} + W + \lambda^2) \lambda_2^2 - m_1 \] (28)

where \( \lambda_1 \) and \( \lambda_2 \) are given by

\[ \lambda_{1,2} = \frac{(s + k_{-1} + k_p) \pm \sqrt{(s + k_{-1} + k_p)^2 - 4k_1k_{-1}}}{2k_p} \] (30)

For \( N > 1 \),

\[ \lambda_{2,2} = \frac{E_{-1} \lambda_{1,2} - (s + k_p + k_{disso}) \lambda_{1,2}^2 + m_1}{k_k} \] (31)

In the same manner, the other equations determined at boundaries \( (i = 0 \) and \( i = N + 1 \)) where \( E_{i,2} \) must be expressed as follows.

\[ (s + k_1 + \sum_{i=1}^{N} m_i(E_{1,1} + E_{2,1}) - k_{-1}(E_{1,1} + E_{2,1}) - k_{disso} \left[ \lambda_{1,1}^2 (1 - \lambda_{1,1}^N) + \lambda_{1,2}^2 (1 - \lambda_{1,2}^N) \right] = 1 \] (32)

The expressions for \( E_1 \) and \( E_2 \) can be obtained as follows:

\[ E_1 = \frac{\lambda_{2,1}^N \left( s + k_p + k_{disso} + W \lambda_2 + 1 \right) - m_1}{2k_p} \] (34)

\[ E_2 = \frac{1}{A} \left[ \frac{\lambda_{2,1}^N \left( s + k_p + k_{disso} + W \lambda_2 + 1 \right) - m_1}{2k_p} \right] + B \] (35)

where

\[ A = s + k_1 + \sum_{i=1}^{N} m_i - k_{-1} \lambda_1 - k_{disso} \frac{\lambda_{1,1}^N (1 - \lambda_{1,1}^N)}{1 - \lambda_{1,1}} \] (36)

\[ B = s + k_1 + \sum_{i=1}^{N} m_i - k_{-1} \lambda_2 - k_{disso} \frac{\lambda_{1,2}^N (1 - \lambda_{1,2}^N)}{1 - \lambda_{1,2}} \] (37)

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