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A nonequilibrium phase transition in immune response*

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The dynamics of immune response correlated to signal transduction in immune thymic cells (T cells) is studied. In particular, the problem of the phosphorylation of the immune-receptor tyrosine-based activation motifs (ITAM) is explored. A nonlinear model is established on the basis of experimental observations. The behaviours of the model can be well analysed using the concepts of nonequilibrium phase transitions. In addition, the Riemann–Hugoniot cusp catastrophe is demonstrated by the model. Due to the application of the theory of nonequilibrium phase transitions, the biological phenomena can be clarified more precisely. The results can also be used to further explain the signal transduction and signal discrimination of an important type of immune T cell.

Keywords: nonequilibrium phase transitions, ITAM, cusp catastrophe
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1. Introduction

The mechanisms underlying equilibrium phase transitions are well known and understood. The main concepts in this field, such as correlations, criticality, scale invariance and self-similarity, have been used in many systems. As a matter of fact, most of the universe is not in equilibrium. In contrast to those equilibrium systems, many complex systems of interest are often open and out of the thermodynamic equilibrium state. Nonequilibrium states appear possibly in open systems. The simplest states in nonequilibrium systems are the steady states. Here, constant flows of energy and/or matter are typically involved and are not determined solely by external constraints but also depends upon their history. For open systems far from equilibrium, we may observe nonequilibrium phase transitions given rise by appropriate change of control parameters.[1,2]

Nonequilibrium phase transitions are ubiquitous in physics, chemistry, biology and social science. Such transitions have been shown in the Belousov–Zhabotinskii reaction, the laser system and the Benard convection and so forth. When we study the signal transduction in immune systems, we also find nonlinear phase transitions.

When a biological problem is explored using physical language, the biological background should be briefly clarified first. The immune system is a complex system that can protect the individuals from attack by virus.[3] Immune responses are mediated by membrane bound receptors, the crosstalk of various receptors expressed on the same cell and by direct and/or indirect interactions of the immune competent cells.[4] The proceeding of the signal transduction is promoted by the multisubunit immune recognition receptors such as antigen receptors of thymic cells (TCRs). It is strictly dependent on the modulator located in the cytoplasmic part of the receptor subunits termed immunoreceptor tyrosine-based activation motif (ITAM). ITAMs consist of semiconserved sequences of amino that contain two appropriately spaced tyrosines. In general, phosphorylation of both tyrosines within an ITAM is thought to be essential for signalling transduction.[3] Engagement of the TCR evokes a series of signal transduction events that are critical to the activation of T cell functions for the immune response and T cell development in the thymus. Experimental observations showed that the ITAMs can be phosphorylated into two states.[5]

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This point has greatly improved our understanding of many types of signal transduction.

The application of the theory dealing with nonequilibrium phase transition can provide more clear explanation for the relationships between the phosphorylation of ITAMs and the signal transduction in immune systems.

2. The model

T cells are an important component in immune systems. The TCRs are expressed on the surface of T cells. Invading antigens form ligands for TCRs. In the beginning, the TCR recognizes and binds the ligand. The TCR is associated with signaling transmembrane protein chains. These chains all contain a certain amount of ITAMs.[3,6] Each ITAM consists of semiconserved sequences of amino that contain two appropriately spaced tyrosines. At first, the ITAM is only mono-phosphorylated by the protein tyrosine kinases (PTKs). In general, phosphorylation of both tyrosines within an ITAM is thought to be essential for effective signalling transduction.[4,5] The present study will concentrate on the multiplicity and phosphorylation of ITAMs.

The main assumption of this model is that the two tyrosines within an ITAM will be phosphorylated in two steps after the antigen invasion. In this paper, three variables are selected to describe the development of ITAMs. As shown in Fig.1, I_0, I_1 and I_2 indicate the concentrations of non-phosphorylated ITAMs, mono-phosphorylated ITAMs and dually-phosphorylated ITAMs, respectively. The mechanisms are depicted as follows: (1) After the TCR binds the ligand, one of the initial events is the phosphorylation of ITAMs,[5] which turns I_0 to I_1. The increasing rate of I_1 in this event can be formulated using $a_1 I_0 L$, where L denotes the concentration of the ligands and parameter a_1 indicates the affinity of the TCR with the ligand. (2) It is well known that phosphatases can make I_1 dephosphorylate to I_0. This process can be described by $\mathrm{d}I_1$ where parameter d contains a constant level of phosphatases. (3) The mono-phosphorylated ITAMs binding with activated Src-family PTKs may phosphorylate I_1 to evolve to I_2.[7] Thus the increasing rate of I_2 is related to $a_2 I_1^2$ with parameter a_2. (4) Dually-phosphorylated ITAMs binding to activated Zap-70s catalyse mono-phosphorylated ITAMs to dually-phosphorylated to accommodate more Zap-70s.[8] This binding results in more dually-phosphorylated ITAMs being produced. The related production rate of dually-phosphorylated ITAMs can be described by $a_3 I_1 I_2$. Parameter a_3 reflects the influence of Zap-70s on the production of dually-phosphorylated ITAMs. (5) CD4 molecules are also expressed on the surface of T cells. The interaction between the TCR and CD4 greatly improves the phosphorylation of mono-phosphorylated ITAMs.[9] Then we have the increasing rate of component I_2 described by $a_4 I_1$. Here, parameter a_4 can be thought of as the intensity of the interaction between TCRs and CD4s. (6) Dually-phosphorylated ITAMs binding to Zap-70s with high affinity can avoid dephosphorylation. If Zap-70s are lacking, the dually-phosphorylated ITAMs would be dephosphorylated with the help of some phosphatase-like factors.[10] As to this process, it can be considered that the phosphatase-like factor and dually-phosphorylated ITAM play the roles of enzyme and substrate, respectively. This dephosphorylation can be characterized using a quasi-steady-state approximation of the Michaelis–Memten approach,[11] i.e. $\dfrac{vI_2}{k+I_2}$, in which v and k are constants. $\dfrac{vI_2}{k+I_2}$ describes the migration from I_2 to I_1.

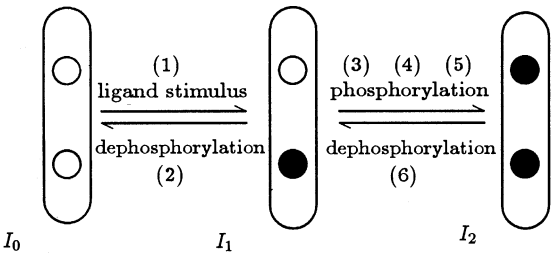


Fig.1. The development of ITAMs. I_0, I_1 and I_2 describe non-phosphorylated ITAM, mono-phosphorylated ITAM and dually-phosphorylated ITAM, respectively. Open circles denote non-phosphorylated tyrosines. Closed circles indicate phosphorylated tyrosines. Numbers 1, 2, 3, 4, 5 and 6 correspond to those appearing in the text, respectively. The mechanisms of ITAM phosphorylation are explained by (1), (2), (3), (4), (5) and (6) in the text.

The kinetic equations read as

$$\frac{\mathrm{d}I_0}{\mathrm{d}t} = -a_1 L I_0 + dI_1, \tag{1}$$

$$\frac{\mathrm{d}I_1}{\mathrm{d}t} = a_1 L I_0 - dI_1 - a_2 I_1^2 - a_3 I_1 I_2 - a_4 I_1 + \frac{vI_2}{k+I_2}, \tag{2}$$

$$\frac{\mathrm{d}I_2}{\mathrm{d}t} = a_4 I_1 + a_2 I_1^2 + a_3 I_1 I_2 - \frac{vI_2}{k+I_2}. \tag{3}$$

The above equations are similar to those describing PTKs.[11] This can be explained by the fact that both ITAM and PTK are phosphorylated. Taking the sum of Eqs.(1), (2) and (3), we have

$$I_0 + I_1 + I_2 = I_{\rm T}. \tag{4}$$

Constant $I_{\rm T}$ represents the total concentration of ITAM. $I_{\rm T}$ can be very large but must be limited. The variables are now scaled by the maximal total concentration $I_{\rm TM}$ such that $1 \geq I_{\rm T} \geq 0$. Because of the scaling, some of the parameters would depend upon $I_{\rm TM}$, i.e.

$$a_2 I_{\rm TM} \to a_2, \quad a_3 I_{\rm TM} \to a_3, \quad a_5 I_{\rm TM} \to a_5,$$

$$\frac{v}{I_{\rm TM}} \to v, \quad \frac{k}{I_{\rm TM}} \to k.$$

The quantity in the right-hand side of each above expression should be replaced by the one in the left-hand side. The standard parameter data are shown in Table 1. The present study provides an insight into the possible behaviours of the ITAM multiplicity. No attempt is made to relate parameter values to detailed experimental data.

Table 1. Units and parameter values.

Time unit: second	Concentration unit: mole/μm^2
$a_1 = 1$	$d = 0.6$
$a_2 = 4$	$k = 0.02$
$a_3 = 32$	$v = 2$
$a_4 = 3$	$L = 0.5$

3. Main results

The steady states of the kinetics given by Eqs.(1)–(3) satisfy the following equations:

$$-a_1 L I_{00} + d I_{10} = 0, \tag{5}$$

$$a_1 L I_{00} - d I_{10} - a_2 I_{10}^2 - a_3 I_{10} I_{20} - a_4 I_{10} + \frac{v I_{20}}{k + I_{20}} = 0,$$

$$a_4 I_{10} + a_2 I_{10}^2 + a_3 I_{10} I_{20} - \frac{v I_{20}}{k + I_{20}} = 0. \tag{7}$$

If there is no external stimulus ($L = 0$), we obtain the trivial steady states $I_{00} = I_{10} = I_{20} = 0$. The nontrivial steady states and the stability of them are studied using the Mathematica 4.

3.1. The cusp catastrophe

We first report that the model demonstrates Riemann–Hugoniot cusp catastrophe in the space spanned by I_{20}, a_1 and $I_{\rm T}$, as shown in Fig.2(a). TCR ligation is the essential prerequisite of the ITAM phosphorylation and the important parameter a_1, the affinity between TCR and its ligand, has a threshold. If $a_1 < 1.8$, bistability appears, as shown in Fig.2(b). Here the lower steady state represents the inactive phase and the higher steady state represents the active phase of the immune signal transduction. At point $I_{\rm T} = I_{\rm T0}$, the higher and lower steady states are in equilibrium. In interval $(I_{\rm T1}, I_{\rm T0})$, the lower steady state is stable but the higher one is metastable. Only if $I_{\rm T} > I_{\rm T0}$ does the higher steady state become stable (Fig.2(c)). It is seen that the system undergoes a first-order phase transition through the coexistence between the metastable phase and a stable phase. There is a critical value $a_1 = 1.8$. At this point, the second-order phase transition will take place and $a_1 = 1.8$ plays a role of critical point. If $a_1 > 1.8$, the nontrivial steady state is always stable and no phase transition takes place. It is also clearly seen that an increase in total phosphorylated ITAMs is obviously of benefit to the increase in dually-phosphorylated ITAMs and the activation of the signal transduction.

I_{10} and I_{00} are closely related to I_{20}. Thus the cusp catastrophe is also found in the space spanned by I_{10}, a_1 and $I_{\rm T}$, similar to that in the space spanned by I_{00}, a_1 and $I_{\rm T}$. The numerical simulations also show that the behaviour of I_{00} is qualitatively similar to that of I_{10}. If $a_1 < 1.8$, bistability is seen and if $a_1 > 1.8$, I_{10} and I_{00} are always stable. Because the maximum of $I_{\rm T}$ is a constant, I_{20} expands as I_{10} and I_{00} reduce. In the bistability scheme, in contrast to the case of I_{20}, if a_1 increases, I_{10} and I_{00} become relatively smaller.

Parameter a_1 reflects the affinity between TCR and its ligand. Thus it is found that the ITAM multiplicity combined with a stronger affinity of the antigen with TCR would promote the ITAM dual-phosphorylation and consequently promote the signal transduction.[7]

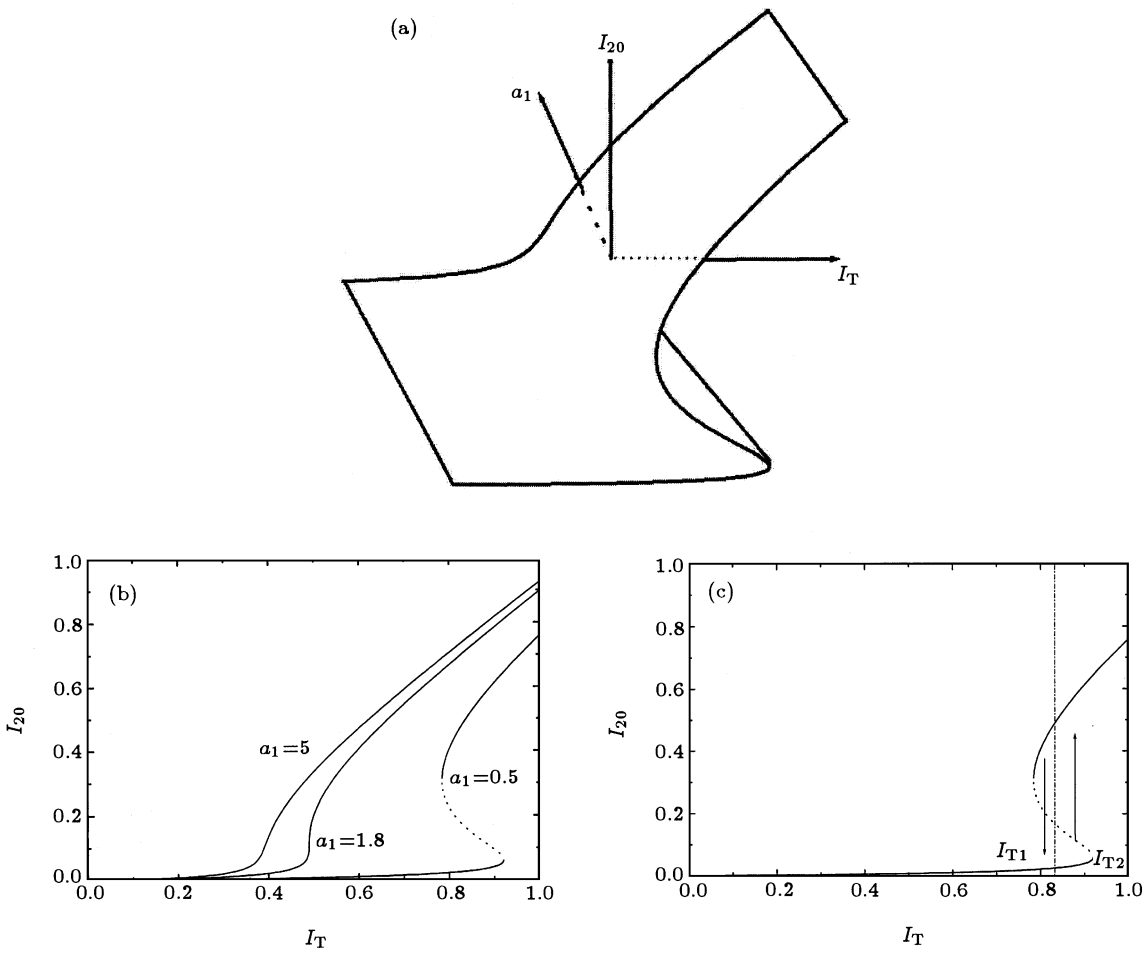


Fig.2. (a) A qualitative description of the Riemann–Hugoniot cusp catastrophe appearing in the space spanned by I_{20}, a_1 and I_T. (b) The projection of Fig.2(a) on the plane I_{20}–I_T for a given a_1. (c) The bistability structure: in interval $I_T < I_{T0}$, the upper steady state is metastable; only if $I_T > I_{T0}$ does the upper steady state become stable. The parameter data selected in all of the figures in this paper can be found in Table 1, except for those varying in certain ranges as shown in related figures.

Parameter a_4, the intensity of the interaction between TCR and CD4, also plays an important role. In the space spanned by I_{20}, a_4 and I_T, we also observe the cusp catastrophe. As shown in Fig.3, the change of a_4 leads the system to suffer a distinct change of stability of the steady states. At the critical point, $a_4 = 2.8$, there appears a second-order phase transition. When $a_4 < 2.8$, the first-order phase transition takes place. We find the bistability in which the lower steady state is stable for $I_T < I_{T0}$, but the higher steady state is metastable and the higher steady states appear stable for $I_T > I_{T0}$ while the lower ones are metastable. If $a_4 > 2.8$, no phase transition takes place and the steady states of higher I_{20} always remain stable and I_{20} increases as I_T rises.

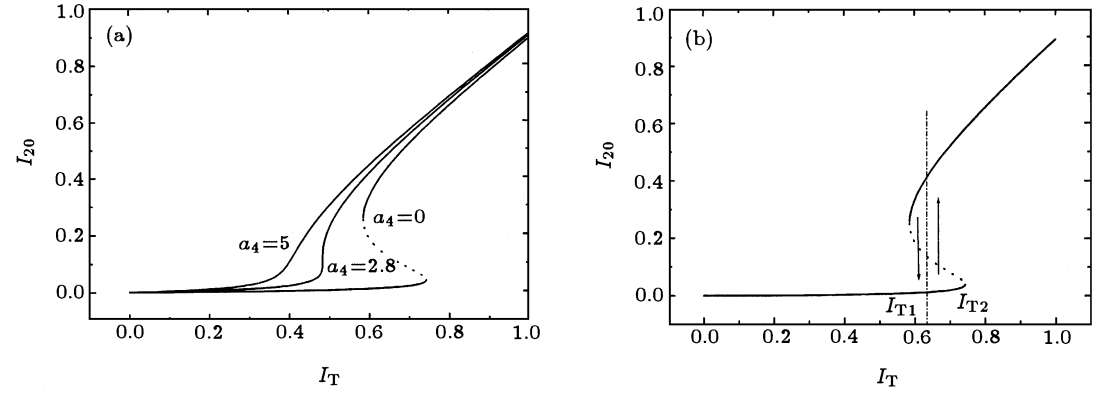


Fig.3. The Riemann–Hugoniot cusp catastrophe appearing in the space spanned by I_{20}, a_4 and I_T, which is projected onto the plane I_{20}–I_T for a given a_4.

3.2. Influence of parameters on variable I_2

We now study the effects of parameters a_1, a_2, a_3 and a_4 on the ITAM phosphorylation at a given value of I_T. The meanings of a_1 and a_4 have been explained above; a_2 is related to the production of I_2 promoted by I_1-Src complexes; a_3 is related to the production of I_2 promoted by I_1-Zap-70 complexes. From Fig.4(a), it is seen that an increase in a_1 leads to a rapid growth of I_{20}. We next study the influence of a_3. Figure 4(c) shows that I_{20} rises slowly as a_3 increases, however, I_{20} almost always remains at a higher level when a_3 expands. Thus a_3 also makes an important contribution to the ITAM phosphorylation. Figures 4(b) and (d) demonstrate that I_{20} increases slowly when a_2 grows but I_{20} expands fast as a_4 increases. All these four factors promote the increase in dual-phosphorylated ITAMs. However, these influences have different characteristics.

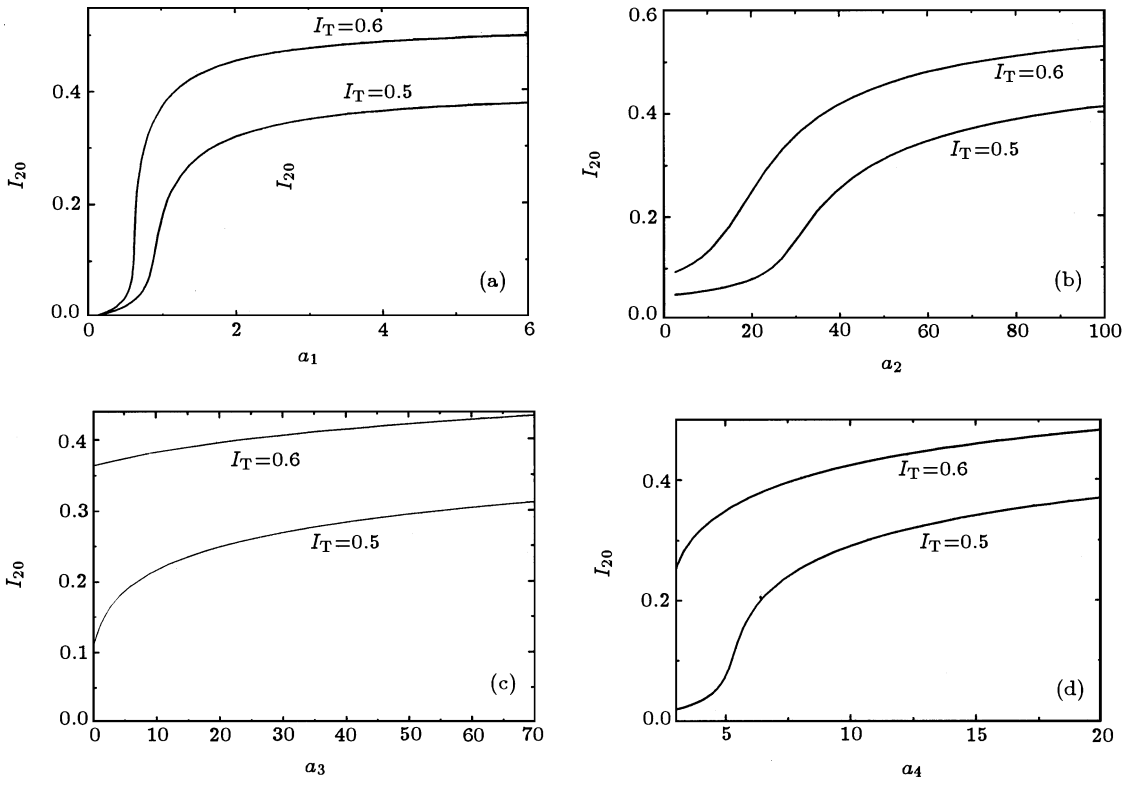


Fig.4. The effects of parameters a_1, a_2, a_3 and a_4 on dual-phosphorylation of ITAMs. The fixed values of I_T are given in the figures, in which $I_T = 0.5$ and I_T=0.6.

4. Conclusion

In this paper we have made a modelling study for the phosphorylation of ITAMs related to the signal transduction of T cell immunity. Except for classical samples, such as Belousov–Zhabotinskii reaction, laser system and Benard convection and so forth, as in Ising/Heisenberg spin system,[12] we provide the phosphorylation of ITAMs related to the signal transduction as a new example of nonequilibrium phase transitions.

We introduced the concept of stability to the phosphorylation of ITAMs. The higher level of dually-phosphorylated ITAMs plays a role of the active phase, and the lower level of them appears as the inactive phase. These two phases can be stable and metastable, and as the appropriate parameter changes, the metastable one can transform into the stable one or vice versa. After the concepts in physics, such as the cusp catastrophe, the first-order and second-order phase transitions are introduced into the research of the immunity system, it is found that the situation of signal transduction can be described more distinctly and quantitatively.

In this approach, we have to face a large amount of ITAMs. In the bistability scheme, if the number of dually-phosphorylated ITAMs reaches the upper steady state the system is in the active phase and if the number of dually-phosphorylated ITAMs is only

located on the lower steady state the system should be in the inactive phase. If the number of dually-phosphorylated ITAMs is just located between the upper and lower steady states, the system should be in the state of coexistence between active phase and inactive phase. It can be seen that the application of the first-order phase transition is reasonable and appropriate.

Obviously, the affinity of TCR with its ligand and the intensity of the interaction of TCR with CD4 play key roles in the immune recognition system.

In this paper only the early stage of signal transduction is involved. According to the experimental results, we have known that the events in the early stage are most important in determining the properties of signal transduction. Thus the results obtained in this paper are of interest to the research of immunology. In particular, they are useful for the study of the signal amplification and discrimination of immune systems.

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