Priming and Activation of T Cells as a Miscibility Phase Transition

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How T cells can be activated in a controlled and precise fashion against foreign antigens has been a longstanding question in immunology. Here, we consider T cell quorum activation in the lymph node as a miscibility phase transition where conventional T cells and regulatory T cells separate into spatially distinct regions. We review theories that have been used to describe both the static equilibrium and the relaxation dynamics of the miscibility phase transition and make several experimental predictions based on this model.

I. INTRODUCTION

As a part of the adaptive immune system, T cells recognize peptides bound to the major histocompatibility complex (pMHC) on neighbouring cell surfaces and mounts a response involving direct cytotoxic activity, activation of additional classes of immune cells, or creation of immunogenic environments through cytokine secretion [1]. Naive T cells are primed in the secondary lymphoid organs (SLOs), where they are present in high density and sample pMHCs on antigen presenting cells (APCs). It has been proposed that activation of not one, but a quorum of multiple T cells, is required to mount a productive response [2]. It has also been observed that the density of T cells can lead to differential outcomes in their differentiation and proliferation [3, 4], substantiating the quorum sensing model. This context suggests that local density of T cells can be important for immune function.

On the other hand, simultaneously present in the SLOs are immunosuppressive regulatory T cells (T_{reg}), which circulate and engage transiently with APCs at steady state with a relatively uniform spatial distribution in the T cell zone [5]. At the same time, they have been shown to localize to spuriously activated conventional T cells (T_{conv}) and inhibit their further activation and proliferation [6, 7]. In this sense, T_{conv} activation requires the formation of a localized high density region that, to some extent, excludes T_{reg} cells. This phenomenon is reminiscent of a phase separation between immiscible materials such as oil and water. In the biological context, formation of dense phases of protein or RNA within the cytoplasm has also been viewed in this light, where it is commonly studied as a liquid-liquid phase separation [8]. Here, we review models of miscibility phase transitions and examine the implications of this interpretation for T_{conv}/T_{reg} interactions and the dynamics of T cell immunity.

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II. EQUILIBRIUM MODELS

We first consider equilibrium models for miscibility phase transitions. Although the immune response, and biological processes in general, are out-of-equilibrium, full activation and effector function occurs over the time scale of tens of hours, while spatial reorganization within the SLO can be observed within hours [7]. It it thus reasonable to hope that equilibrium models can still yield valuable insight.

A. Landau-Ginzburg Theory

The classic Landau-Ginzburg free energy can be written as [9]

$$f_{LG} = \frac{r}{2}\psi^2 + u\psi^4 + \frac{K}{2}(\nabla\psi)^2 \tag{1}$$

For models of a binary mixture, the order parameter $\psi(x)$ can be taken to be the difference between the concentration fields of the two species [10], that is

$$\psi(x) = c_A(x) - c_B(x) \tag{2}$$

Spontaneous symmetry breaking occurs for $r < 0$ and, in the saddle point approximation, yields stable states of

$$\psi(x) = \sqrt{-\frac{r}{4u}} \tag{3}$$

The parameter r is related to the strength of interaction between neighbouring cells. The miscibility transition predicted by this model is of the Ising universality class.

B. Regular Solution Model

From a lattice model of a conserved binary mixture with equal composition, the free energy density can be written as [9, 11]

$$f(\phi) = \phi\ln(\phi) + (1-\phi)\ln(1-\phi) + \chi\phi(1-\phi) + \frac{K}{2}(\nabla\phi)^2 \tag{4}$$

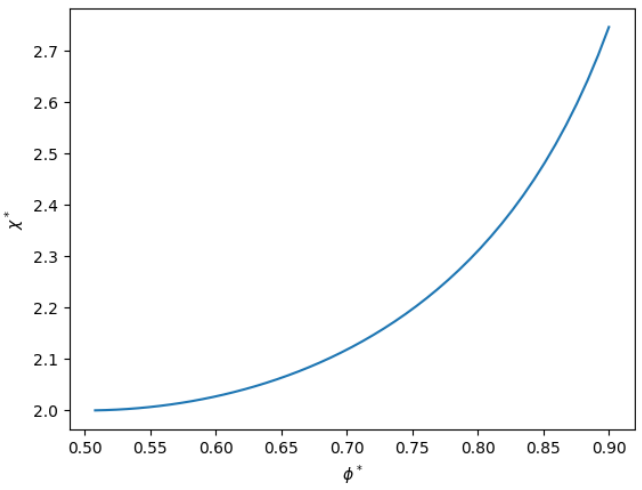

FIG. 1. Eq. 7, minimum couplings χ^* to achieve the activation threshold ϕ^* under the regular solution model.

where ϕ is the concentration field of a species, and the interaction parameter is defined by

$$\chi = \frac{z}{2k_BT}(2\epsilon_{AB} - \epsilon_{AA} - \epsilon_{BB}) \tag{5}$$

with z the coordination number of the lattice and ϵ_{ij} the strength of interaction between species i and j.

Under the saddle point approximation, for $\chi < 2$, there is no spontaneous demixing and the free energy minimum is found for an homongenous equal mixture at $\phi = \frac{1}{2}$. For $\chi > 2$, the minimum is given by

$$\ln\left(\frac{\phi}{1-\phi}\right) + \chi(1-2\phi) = 0 \tag{6}$$

In our model of activation, we can expect a threshold of ϕ^* for activation of the conventional cells. We can rearrange Eq. 6 to obtain a χ^* for the minimum coupling to achieve that threshold as (Fig. 1)

$$\chi^* = \frac{\ln(\frac{1}{\phi^*} - 1)}{1 - 2\phi^*} \tag{7}$$

Since the well-studied interactions in the system are those of T_{conv}/T_{conv} and T_{conv}/T_{reg}, we focus on these terms and neglect the T_{reg}/T_{reg} interactions. Achieving ϕ^* requires

$$\epsilon_{rc} > \frac{\epsilon_{cc}}{2} + \frac{\chi^* k_B T}{z} \tag{8}$$

Keeping in mind that $\epsilon > 0$ are repulsive interactions, this suggests that formation of T_{conv}-dense regions requires that attractive interactions among T_{conv}s must be stronger than those between T_{conv}s and T_{reg}s.

There are several interesting predictions that can be made based on Eq. 8. First, decreasing z, or allowing fewer contacts between T cells, can require greater interaction strengths for activation. This can be realized by introducing inert cells in the system, in which case stronger signaling in the T cell might be required for mounting an immune response. We also expect that decreasing the activation threshold ϕ^*, which can potentially be achieved by weakening inhibitory functions of T_{reg}s, should allow for activation with weaker T_{conv}/T_{conv} interactions.

Near the critical point, Eq. 4 can be expanded into the Landau-Ginzburg form as

$$f(\phi) = \frac{\chi}{4} - \ln 2 + (\chi - 2)(\phi - \frac{1}{2})^2 + \frac{4}{3}(\phi - \frac{1}{2})^4 + \frac{K}{2}(\nabla\phi)^2 \tag{9}$$

There is thus a correspondance between the two models with $\psi = \phi - \frac{1}{2}$, $r = 2(\chi - 2)$ and $u = \frac{4}{3}$. We also note that the LG form is most useful in analyzing behaviour near the critical point.

C. Phase stability under density fluctuations

If we consider some small fluctuation ε from the uniform field $\bar{\psi}$, the change in free energy to lowest order in ε is given as

$$\delta f(\epsilon) = \varepsilon^2(\frac{r}{2} + 6u\bar{\psi}^2) \tag{10}$$

Thus for $\bar{\psi} < \sqrt{-\frac{r}{12u}}$, fluctuations in the concentration field decrease the free energy and are spontaneous. This allows the system to demix without nucleation, and is commonly referred to as the spinodal decomposition [11].

The biological significance of this regime in the context of T cell activation might be limited, however. Initial signaling to the T cell receptor occurs through interaction with pMHC complexes on APCs, which are most commonly dendritic cells in the SLOs. This localization effect thus already serves as a nucleating event, bypassing this step even when demixing is not spontaneous.

III. DYNAMICAL MODELS

We next analyze dynamical relaxation models of miscibility phase transitions and discuss their significance in the context of T cell immunity.

A. Time-dependent Landau-Ginzburg Model

The relaxation dynamics of a field can be modelled as a particle diffusing in a potential defined by the free energy landscape, that is [12, 13]

$$\frac{\partial\psi}{\partial t} = -\Gamma_0\frac{\delta f}{\delta\psi} + \eta(\mathbf{x}, t) \tag{11}$$

where η is a Gaussian random noise term defined by

$$\langle \eta(\mathbf{x},t)\rangle = 0 \tag{12}$$

$$\langle \eta(\mathbf{x},t)\eta(\mathbf{x}',t')\rangle = 2\Gamma_0\delta(\mathbf{x}-\mathbf{x}')\delta(t-t') \tag{13}$$

The functional derivative providing a guiding force to the energy minimum

$$-\frac{\delta f}{\delta\psi} = -r\psi - 4u\psi^3 - K\nabla^2\psi \tag{14}$$

In the Gaussian limit (u=0), these relations can be written in Fourier space as

$$\frac{\partial\tilde{\psi}}{\partial t} = -\Gamma_0(r+Kq^2)\tilde{\psi} + \tilde{\eta}(\mathbf{q},t) \tag{15}$$

$$\langle \tilde{\eta}(\mathbf{q},t)\tilde{\eta}(\mathbf{q}',t')\rangle = 2\Gamma_0(2\pi)^d\delta^d(\mathbf{q}+\mathbf{q}')\delta(t-t') \tag{16}$$

This suggests a relaxation timescale given by

$$\tau(q) = \frac{1}{\Gamma_0(r+Kq^2)} \tag{17}$$

For modes with small q, the relaxation time diverges as the system approaches the critical point $r=0$, suggesting that the system dynamics slow down significantly near criticality.

This model is commonly referred to with the classification by Hohenberg and Halperin as model A [12].

B. Conserved Order Parameter

For a mixture with no exchange of material with the bath, the order parameter is conserved, that is

$$\frac{d}{dt}\int d^3\mathbf{x}\psi(\mathbf{x},t) = 0 \tag{18}$$

The conservation condition can be enforced by

$$-\lambda_0\nabla^2 \leftarrow \Gamma_0 \tag{19}$$

and the relaxation timescale in the Gaussian limit is given by

$$\tau(q) = \frac{1}{\lambda_0 q^2(r+Kq^2)} \tag{20}$$

which gives similar divergence of correlation time as Eq. 17, except with a different exponential dependence in q. This model is named model B [12].

C. Fluid Model

Model H explicitly models the advective flow with a velocity field $\mathbf{v}(\mathbf{x},t)$, in which case the dynamical equations become [12]

$$\frac{\partial\psi}{\partial t} + \mathbf{v}\cdot\nabla\psi = -\lambda_0\nabla^2\frac{\delta f}{\delta\psi} + \eta(\mathbf{x},t) \tag{21}$$

The velocity field for an incompressible fluid is given by [9, 14]

$$\rho\big(\frac{\partial\mathbf{v}}{\partial t} + (\mathbf{v}\cdot\nabla)\mathbf{v}\big) = \nu\nabla^2\mathbf{v} - \nabla p - \psi\nabla\frac{\delta f}{\delta\psi} \tag{22}$$

where ρ is the density, ν is the viscosity, and p is the pressure.

The associated relaxation timescale in the regime where $\mathbf{v}$ dynamics are much faster than ψ dynamics is [15]

$$\tau(q) \propto \begin{cases} \frac{\xi}{q^2} & k\xi < 1 \\ \frac{1}{q^3} & k\xi > 1 \end{cases} \tag{23}$$

which is again divergent near criticality.

D. Implications for T cell immunity

The lengthening of relaxation time scales near phase transition critical points is referred to as a critical slowing-down and has found applications to a range of systems near criticality [16, 17]. In the context of T cell activation, these changes may be reflected in increased transit or dwell time of cells in the SLO, which can be observed by two-photon microscopy [5]. Slowing-down may also be observed in longer delays in intracellular processes of signaling and gene expression. Time-course studies both *in vitro* and *in vivo* may provide evidence for these changes.

However, as noted above, T cell quorum activation may be more appropriately understood as surpassing a threshold density in the T_{conv}-dense phase rather than simply any degree of symmetry breaking. Therefore, while a slowing-down of T cell dynamics is expected at some level of interaction strength based on the miscibility phase transition interpretation, this critical point does not necessarily define the threshold for full-scale activation. In fact, activation of T cell immunity involves a highly dynamic program of proliferation and differentiation, which may not be compatible with a slowed-down system.

IV. CONCLUSION

Above, we have reviewed several static and dynamical models that describe the density field associated with a miscibility phase transition. While this this an extremely simplistic view of the biological system in the context of the multitude of secreted signals, receptor-ligand interactions, signaling timescales, and proliferation and differentiation outcomes, we have made a few experimentally verifiable predictions that can lead to a better understanding of T cell activation in SLOs. More careful modelling and analysis of the system may yield even more fruitful biological insights.

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