Perspective

Decoding Communications between Cells in the Immune System Using Principles of Chemical Engineering

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Introduction

The core topics that define the discipline of chemical engineering are thermodynamics, kinetics, and transport phenomena. A special and rare feature of a chemical engineering education is that phenomenological descriptions of concepts pertinent to these subjects are buttressed by a strong foundation in the underlying molecular mechanisms. The resulting ability to think about the macroscopic manifestations of molecular events makes chemical engineers attractive to a wide range of corporate sectors and disciplines. Indeed, chemical engineers have played a key role in developing many technologies that have improved the human condition in the 20th century. This tradition continues and, in fact, the ability to think across length scales is even more important for emerging technologies of the 21st century (Breslow and Tirrell, 2003).

An in-depth understanding of thermodynamics, reaction kinetics, transport phenomena, and associated molecular concepts also allows chemical engineers to address fundamental scientific questions. Chemical engineers have contributed significantly toward answering fundamental questions in fluid dynamics (Leighton and Acrivos, 1987; Brady et al., 1988; Bentley and Leal, 1986; Scriven, 1960), nonlinear dynamics and chaos (Ottino, 1990), phase behavior of complex fluids (Prausnitz et al., 1999; Bates and Fredrickson, 1990), and instabilities in chemically reacting systems (Aris et al., 1991).

An important scientific challenge of our times is the quest for a mechanistic understanding of molecular and cell biology, and its larger-scale manifestations. Such knowledge is the foundation for developing new therapies, drugs, and biomimetic devices that can function with precision. The large-scale emergent properties that characterize many functioning biological systems are the result of cooperative events involving a myriad of interacting molecular components. Understanding how these systems work requires studying phenomena that occur across a wide spectrum of length and time scales. In particular, coarse-grained descriptions of large-scale phenomena based on an understanding of underlying molecular events need to be developed as biology becomes a quantitative and predictive science. Coarse-grained descriptions are necessitated by the fact that brute force atomistic simulation of phenomena that occur on cellular length scales in many minutes and hours will not be possible for many years. These coarse-grained descriptions must be based on detailed molecular pictures in order to represent a real biological system. The rare combination of molecular and phenomenological perspectives makes chemical engineers particularly well poised to elucidate the mechanisms underlying the function of complex biological systems.

In this perspective, I will focus on how cells in the immune system communicate with one another and make decisions to mount an immune response. The recent advances that I will outline are steps toward understanding the origin of pathologies that stem from misregulation of the immune response (lupus, arthritis, multiple sclerosis, etc.). These studies provide the scientific underpinnings that will guide the development of new therapeutic strategies for controlling aberrant regulation of the immune response. Understanding the mechanisms underlying the exquisite sensitivity with which cells in the immune system recognize antigen may also inspire the design of synthetic systems that can carry out biomimetic recognition tasks.

I hope that the work described here demonstrates that modern chemical engineering principles, in close synergy with genetic and biochemical experiments, can shed light on important questions in biology with far-reaching consequences (including the development of new therapies). While this perspective focuses on the elucidation of fundamental scientific issues, it is important to note that the use of chemical engineering principles to solve practical problems in biomedicine has led to a number of success stories; notable examples are provided by drug delivery technologies (Langer and Vacanti, 1993), tissue engineering (LaVan et al., 2002), and tumor biology (Jain, 1999). Some of these successes have impacted clinical practice, and others promise the development of new pharmaceutical products.

Immunological Synapse is a Specialized Cell-Cell Junction

Complex organisms, such as humans, differ from simpler organisms like invertebrates in a number of ways. One very important way

is that complex organisms have an adaptive immune system that can respond to pathogens that have not been encountered previously (Abbas et al., 2000). The orchestrators of adaptive immune responses are a class of cells called T lymphocytes (T cells). The importance of these cells is highlighted by the fact that HIV invades T cells and severely compromises the adaptive immune system. T cells have evolved to deal with pathogens that are no longer in the blood or on mucosal surfaces, but have invaded the organism's cells. Specialized cells (such as dendritic cells, B cells, and macrophages) that harbor pathogen are called antigen presenting cells (APCs), and they display a signature of the pathogen on their surfaces. During T cell-APC encounters, T cells detect the presence of pathogen and subsequently make a decision to mount an immune response.

In the preceding four years, enormous advances have been made in understanding the mysteries of what happens at the T cell-APC interface that allows detection of pathogen and the activation of T cells. In short, by eavesdropping on conversations between T cells and APCs, we are beginning to learn how to decode their communications. This has been made possible by concerted use of video microscopy experiments, biochemical and genetic experiments, and computational and theoretical studies. Indeed, employing such a battery of complementary tools seems necessary for parsing the mechanisms that underlie the function of complex biological systems.

A pathogen (e.g., virus or bacterium) inside a host cell begins to make its own proteins. These proteins are catabolized by enzymes (such as the proteosome or peptidases and proteases) into small peptide fragments that are about 10–20 amino acids in length (Abbas et al., 2000). Chromosome 6 in the human genome contains the major histocompatibility (MHC) gene complex that codes for a class of proteins called MHC. These proteins belong to the immunoglobin superfamily, and, if they can, they bind one or more of the peptide fragments that originate from the foreign protein (as well as self proteins). These MHC-bound peptides (pMHC) are then transported from the cytoplasm to the surface of the cell aided by chaperone molecules. Antigen-derived pMHC molecules are the signatures of the pathogen displayed on APC surfaces (Figure 1).

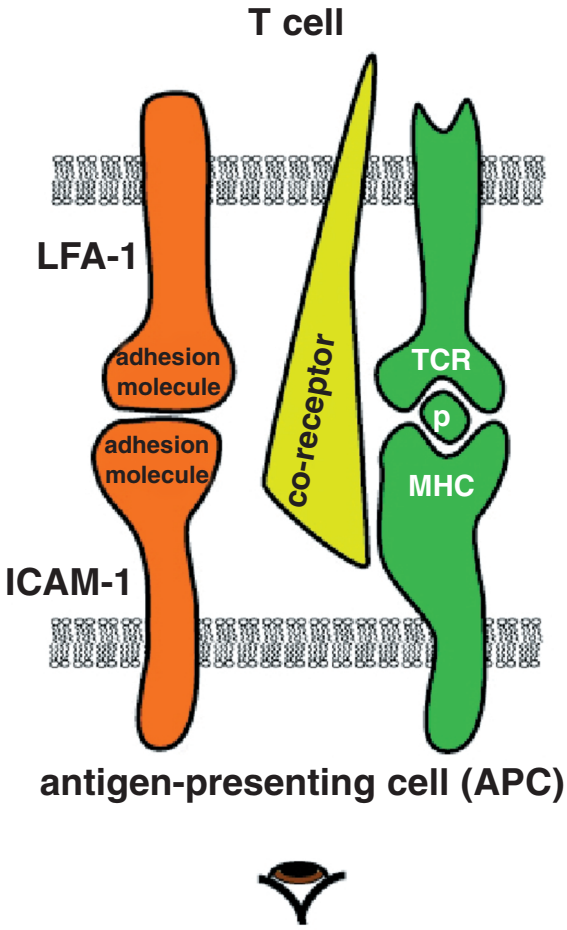

Figure 1. Examples of membrane proteins that bind across the T cell-APC interface.
TCR binding to pMHC (green) can lead to intracellular signaling that mediates T cell activation. LFA-1 and ICAM-1 (red) are integrin family proteins that bind across the cells. Other proteins (like co-receptors) are also known to bind to MHC. The cartoon of the eye at the bottom shows the view observed in microscopy studies looking *en face* at the intercellular junction.

T cells react to the protein component of pathogens by recognizing antigen-derived pMHC on APC surfaces. This recognition involves the binding of a membrane protein called the T cell receptor (TCR) expressed on the T cell surface to pMHC (Figure 1). The binding of TCR to pMHC can initiate an intracellular signaling cascade that can ultimately lead to T cell activation and an immune response. Thus, this molecular interaction has been studied extensively by molecular biologists and immunologists. X-ray crystallography has yielded the detailed structure of the TCR-pMHC complex (Garboczi et al., 1996). Kinetic studies have resulted in a database consisting of the kinetics of association (k_{on}) and dissociation (k_{off}) for various TCR clones and pMHC molecules. In other words, much is known about this molecular scale interaction that is necessary for mounting an immune response.

It has also been known for some time that various other molecules (such as the adhesion molecules LFA-1 and ICAM-1) also bind across the interface during T cell recognition of APC (Figure 1). Approximately four years ago, teams of immunologists carried out video microscopy experiments where the spatio-temporal evolution of membrane proteins at the T cell-APC interface and T cell shape were directly visualized (Monks et al., 1998; Grakoui et al., 1999; Krummel and Davis, 2002; van der Merwe, 2002). The resulting vivid images led to an important discovery. During T cell recognition of APC, different receptors and ligands that bind across the cells organize into a specific spatial pattern. This patterned collection of different receptors and ligands is several microns in size (Figure 2a). Since this recognition motif was hypothesized to be implicated in information transfer between T cells and APCs, in analogy with collections of proteins that form in the junction between nerve cells, it was called the immunological synapse. Figure 2a shows the remarkable rearrangement of membrane proteins and cell shape observed during the formation of the synapse. The mature immunological synapse is characterized by a stable central cluster of TCR and pMHC (called cSMAC) surrounded by a ring of adhesion molecules (called pSMAC). This morphology is stable for over an hour.

The discovery of the synapse sparked two broad questions. How does the synapse form (i.e., what are the forces involved in the formation of this structure)? What is the biological function of the synapse? In the following, I describe how chemical engineering principles, rooted in transport phenomena, reaction kinetics, and its molecular underpinnings (statistical mechanics) have contributed toward shedding light on these issues of central importance for understanding the immune response and developing new therapeutic strategies.

Forces that Drive Synapse Formation

Computer simulation of molecular phenomena has become an integral part of chemical engineering research (Chakraborty, 2001). However, using a standard molecular simulation method (such as molecular dynamics) to study synapse formation is not tractable since it forms over long times (~30 min) and involves thousands of molecules embedded in a deformable cell membrane; nor is such a simulation necessary for the question of primary concern, which is not about known molecular details, but about the time evolution of large-scale spatial patterns. Thus, it is appropriate to consider approximate coarse-grained models that are consistent with the underlying molecular phenomena.

A number of different processes occur on short (molecular) length scales during T cell-APC engagement. Different types of complementary receptors and ligands can bind across the cell-cell junction if they are spatially apposed in the membranes in which they live. Membrane proteins are mobile in the planes of the membranes that contain them. Intramembrane mobility can be due to diffusion. In the case of TCR, there is evidence that convected motion also occurs due to directed motion of the T cell cytoskeleton (Wulfing and Davis, 1998). The mean-field reaction-diffusion equations that describe these processes (Eqs. 1–6) are quintessential chemical engineering. In the system under consideration, there is a further complication that couples these reaction-diffusion equations to the collective shape fluctuations of the cell membranes.

To consider this issue, for pedagogical simplicity, consider experiments where the synapse forms between a living T cell and a supported lipid bilayer containing ligands for TCR (pMHC) and LFA-1 (ICAM-1). The phenomenology observed in this experimental system is the same as that at T cell-APC junctions. The TCR-pMHC complex is known to be 15 nm in size and the LFA-1-ICAM-1 complex is about 40 nm in size (Garboczi et al., 1996; Dustin and Shaw, 1999). This topographical size difference between the two kinds of receptor-ligand complexes couples strongly with the mechanics of the T cell membrane. The simplest way in which this couples the reaction-diffusion equations to the membrane mechanics is that complementary receptors and ligands, when apposed, can only bind when the intermembrane separation is roughly commensurate with the natural size of the corresponding complex (i.e., kon depends on intermembrane separation z in Eqs. 1–6). Other couplings originate from the fact that different membrane shapes correspond to different free energies. Shapes with higher interfacial area are penalized by interfacial tension (g). Shapes with high curvatures are unfavorable because of the finite bending rigidity of the membrane (k). In particular, bending of the membrane to accommodate the two kinds of receptor-ligand complexes (i.e., 15 and 40 nm) on length scales shorter than $\sqrt{k/g}$ is highly unfavorable. Finally, membrane shape changes that lead to the deformation of a bonded complex away from its natural length incur energy penalties that, in the harmonic approximation, are related to the curvature of the binding energy potentials. These effects can be incorporated into a functional that maps the membrane shape (z(r)) to a free energy (Eq. 8). Equation 7 describes the mem-

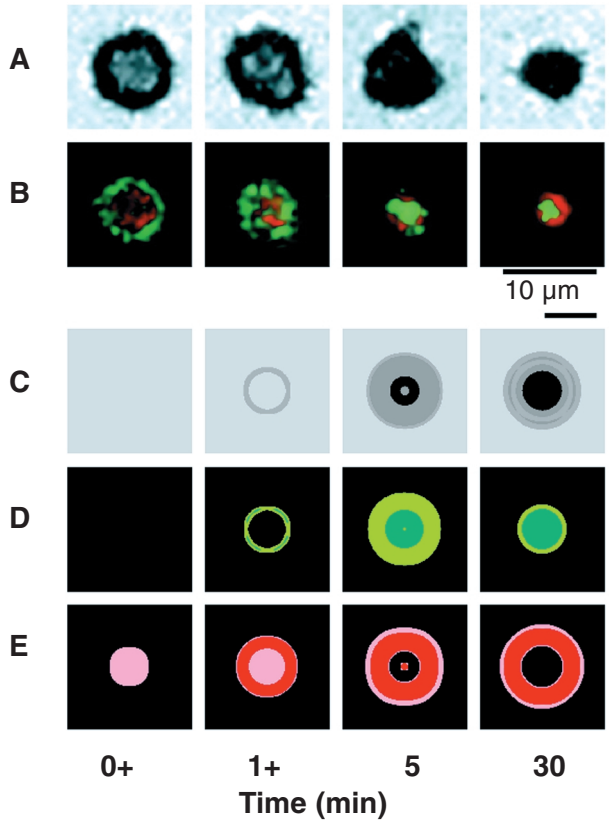

Figure 2. Immunological synapse formulation.
Panels A and B show results from experiments by Grakoui et al. (1999) where a T cell interacts with a supported bilayer mimic of the APC that contains ICAM-1 and pMHC. These *en face* images are taken looking up as shown in Figure 1. Panel A shows the time evolution of the shape of the T cell during synapse formation. The darker the color, the closer the apposition between the T cell membrane and the supported bilayer. Panel B is an overlay of MHCp (green) and ICAM (red) concentrations in the intercellular junction. Movies that make these observations of the spatio-temporal evolution of protein patterns and cell shape vivid can be seen at www.sciencemag.org/feature/data/1040037.shl. Panels C-E are the results of calculations (Qi et al., 2001) using the synapse assembly model. Panel C shows the evolution of cell shape. Again, the darker the color, the closer the apposition between the two membranes. Panel D shows the evolution of MHCp concentration (green). Panel E shows the evolution of ICAM concentration (red). The different shades of color in panels D and E reflect different levels of concentration, with darker colors corresponding to higher concentrations.

brane dynamics using the standard statistical mechanical form for hydrodynamic modes (Hohenberg and Halperin, 1977), and chemical engineers have used variants of such equations in a number of contexts. This time-dependent Landau Ginzburg equation is simply a Langevin equation for continuous fields, and includes thermal fluctuations.

The equations that describe the physico-chemical processes described above are (symbols defined in Table 1)

$$\frac{\partial C_T}{\partial t} = D_T \nabla^2 C_T - k_{\text{on}}(z) C_T C_M + k_{\text{off}}(1-P) C_{TM} - \vec{\nabla} \cdot \vec{V} C_T \quad (1)$$

$$\frac{\partial C_M}{\partial t} = D_M^2 C_M - k_{\text{on}}(z) C_T C_M + k_{\text{off}} C_{TM} \quad (2)$$

$$\frac{fC_{TM}}{ft} = D_{TM}^2 C_{TM} + \frac{1}{k_B T} \vec{\nabla} C_{TM} \cdot \vec{\nabla} \frac{\delta F}{\delta C_{TM}} + k_{\text{on}}(z) C_T C_M - k_{\text{off}} C_{TM} \quad (3)$$

$$\frac{\partial C_L}{\partial t} = D_L \nabla^2 C_L - k_{LI}(z) C_L C_I + k_{-LI} C_{LI} \quad (4)$$

$$\frac{\partial C_I}{\partial t} = D_I \nabla^2 C_I - k_{LI}(z) C_L C_I + k_{-LI} C_{LI} \quad (5)$$

$$\frac{\partial C_{LI}}{\partial t} = D_{LI}\left[\nabla^2 C_{LI} + \frac{1}{k_B T} \vec{\nabla} C_{LI} \cdot \vec{\nabla} \frac{\delta F}{\delta C_{LI}}\right] + k_{LI}(z) C_L C_I - k_{-LI} C_{LI} \quad (6)$$

$$\frac{\partial z}{\partial t} = -M \frac{\delta F}{\delta z} + \zeta \quad (7)$$

$$F = \frac{\lambda_{TM}}{2} \int\int dxdy C_{TM}(x, y, t)[z(x, y, t) - z_1]^2 + \frac{\lambda_{LI}}{2} \int\int dxdy C_{LI}(x, y, t)[z(x, y, t) - z_2]^2 + \frac{1}{2} \int\int dxdy[\gamma(\nabla z)^2 + \kappa(\nabla^2 z)^2] \quad (8)$$

This model (Eqs. 1–8) and its sophisticated descendants contain parameters that reflect the magnitude of forces due to the various processes that occur during T cell-APC encounters. As chemical engineers have long been aware, a model with a sufficiently large number of parameters can always fit any desired complex phenomenon. This model is, however, carefully crafted so that essentially all the parameters can be obtained directly from measurements or estimated with reasonable accuracy. Note that most of the parameters (e.g., binding kinetics) reflect molecular scale phenomena. It is important to remark that the parameters must reflect properties of the cellular environment. For example, the tension and bending rigidity of the cell membrane are not those of phospholipid bilayers, but rather, are those characteristic of a membrane connected to the cytoskeleton via proteins such as Talin. The tension and bending rigidity of cell membranes can therefore be as much as 75% higher than that for phospholipid bilayers (Simson et al., 1998).

Equations 1–8 describe a specific model for the ways in which various short length-scale processes are coupled to each other during synapse formation. Are these proposed mechanisms sufficient to describe synaptic pattern formation? This question has been addressed by solving the equations with values of estimated or measured parameters (Qi et al., 2001; Chakraborty, 2002; Lee et al., 2002b). Figure 2b shows that indeed much of the phenomenology observed in experiments is captured. Analyses of the model and the numerical results shed light on the important forces involved in synapse formation (Qi et al., 2001; Chakraborty, 2002; Hori et al., 2002; Lee et al., 2002b; Raychaudhuri et al., 2003). The resulting mechanistic insight can then be used to assess the consequences of specific molecular features going awry on synapse formation and T cell activation (Lee et al., 2002b).

Statistical field-theoretic analyses (Hori et al., 2002), functional renormalization group calculations (Raychaudhuri et al., 2003), and stability analysis (Hori et al., 2002) have revealed some (not all) of the basic mechanisms underlying the stunning observations shown in Figure 2. The adhesion molecules bind at the center of the junction at short times simply because they are longer. However, this makes it difficult for TCR to bind to pMHC in this region because it is shorter, and a uniform distribution of both kinds of receptors and ligands would require that the membrane adopt highly curved shapes with excursions between 40 nm and 15 nm occurring over short length scales. This is strongly penalized by the membrane mechanics. Thus, initially, TCR and pMHC bind at the edge of the junction. In other words, the topographical size difference between the two types of receptors and ligands coupled with the finite membrane mechanics provides a mechanism for sorting different types of receptors and ligands to different regions of the intercellular junction. There are two ways in which this sorting can take place: TCR/pMHC at the edge and adhesion molecules at the center or the opposite. As described above, at short times, the former pattern is obtained. The latter pattern, however, corresponds to a membrane shape with a lower free energy. This thermodynamic driving force, along with a directed motion of the TCR that is initiated by signaling events upon TCR-pMHC binding, results in the evolution of the pattern to form a stable cSMAC surrounded by a ring of adhesion molecules (Figure 2).

Table 1. Legend of Symbols in Equations

Symbol	Quantity
F	Free Energy
C_T	TCR concentration in *T*-cell membrane
C_M	MHC-peptide concentration in supported membrane
C_{TM}	Concentration of TCR/MHC-peptide complex
C_L	LFA-1 concentration in *T*-cell membrane
C_I	ICAM1 concentration in supported membrane
C_{LI}	Concentration of LFA-1/ICAM complex
k_{on}	On rate for TCR/MHC-peptide binding
k_{off}	Off rate for TCR/MHC-peptide binding
k_i	On rate for LFA-1/ICAM1 binding
k_{-i}	Off rate for LFA-1/ICAM1 binding
D_j	Diffusion coefficient of the *j*th protein in the appropriate membrane
Z	Local intermembrane separation
z_j	Natural length of *j*th protein complex
t	Time
γ	Interfacial tension of cell membrane
κ	Bending rigidity of cell membrane
ζ	Thermal noise
$k_B T$	Thermal energy at temperature T
M	Phenomenological constant for membrane response to free energy changes
λ_j	Curvature of binding energy well for *j*th protein complex
V	Speed of directed TCR transport

Function of the Immunological Synapse

While cellular experiments and the model described above provided insight into the forces that drive synapse formation, the biological function of the synapse

has been controversial and rather unclear. However, some recent studies are beginning to reveal a rather important function of the immunological synapse.

I begin this story by turning to an earlier stage in the life cycle of T cells. T cells are produced in the bone marrow. It is believed that most T cells that are produced express TCR molecules that would bind strongly to peptides derived from proteins from the organism (self peptides), and could potentiate autoimmunity (Abbas et al., 2000). Immature T cells (called thymocytes) interact with self pMHC molecules expressed on the surface of cells in the thymus. One of the consequences of these interactions is negative selection. This is a process via which thymocytes that express TCR that bind strongly to self-derived pMHC undergo programmed cell death (apoptosis). Thus, strong TCR-pMHC binding in the thymus results in an intracellular signaling cascade that leads to cell death. In contrast, later in their life cycle, when mature T cells bind strongly via their TCR to pMHC molecules derived from antigen, intracellular signaling results in activation followed by proliferation. Mature T cells and thymocytes have essentially the same set of intracellular signaling molecules. This presents the following conundrum. *How are such vastly different biological outcomes mediated by the same signaling molecules upon strong TCR binding at different stages of the life cycle of T cells?*

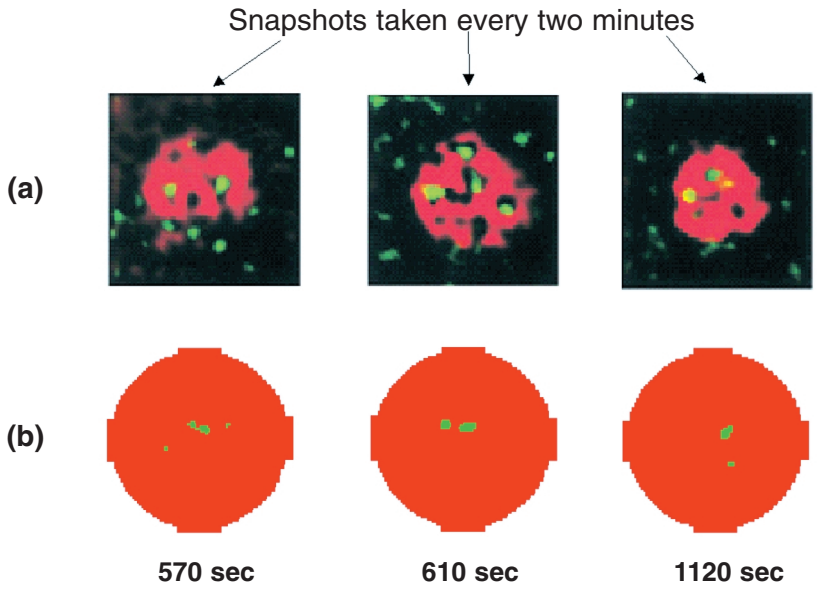

Figure 3. (a) Fluorescent video microscopy images of synapse formation at the intercellular junction between DP thymocytes and supported bilayers containing ICAM-1 and MHCp (Hailman et al., 2002); (b) snapshots in time from a trajectory calculated using a theoretical model for the same pMHC used in the experiments (Lee et al., 2003).
For (a), the images correspond to the same view as in Figure 2. The three images correspond to different time points spaced 2 min apart. Green corresponds to the spatial distribution of MHCp and red corresponds to the spatial distribution of ICAM-1. For (b), as in experiments, the TCR expression level is an order of magnitude smaller than in mature T cells (Figure 2). Calculations show that the low TCR expression coupled to thermal fluctuations results in the dynamic multifocal synapses seen in (a).

This question motivated experiments that visualized synaptic patterns formed at the junction between thymocytes and thymic stromal cells (Ritchie et al., 2002), as well as between thymocytes and lipid bilayers containing the requisite ligands (Hailman et al., 2002). While there are some differences in the morphology of the synaptic patterns formed in the two kinds of experiments, there are some important common elements. In both instances, a stable central cluster of TCR (cSMAC) does not form. Furthermore, the clusters of TCR and pMHC are dynamic. As shown in Figure 3a, for experiments using the bilayer platform, a dynamic multifocal synapse forms with clusters of TCR/pMHC in a sea of adhesion molecules; as time evolves, the clusters evanesce and then reappear in different locations.

Many possible explanations can be envisaged for the lack of a stable cSMAC in synapses formed by thymocytes. Models such as the one described above can assess the effects of different possibilities quickly, and focus in vitro and in vivo experimentation on the more plausible explanations. It is known that, both in vivo and in the cell lines used in the experiments described above, the concentration of TCR on the surface of thymocytes is about an order of magnitude smaller compared to mature T cells. Calculations (Lee et al., 2003) using a sophisticated descendent of the mathematical model for synapse formation described earlier show that low TCR expression results in the formation of dynamic multifocal synapses (Figure 3b).

Simple physical arguments and functional renormalization group calculations show how low TCR expression and thermal fluctuations conspire together to result in dynamic synapse patterns for thymocytes (Raychaudhuri et al., 2003; Lee et al., 2003). In fact, a simple explanation can be articulated in terms of an analogy with the phase behavior of a simple fluid—a subject that is understood by every chemical engineer. The binding of a receptor to its complementary ligand corresponds to a free energy minimum. From the standpoint of the cell membrane, TCR-pMHC binding corresponds to a free energy minimum at an inter-membrane separation of 15 nm. On the other hand, the binding of the adhesion molecules results in a free energy minimum corresponding to an inter-membrane separation of 40 nm. Thus, the system free energy as a function of intermembrane separation has two minima (at 15 nm and 40 nm). The depths of these minima are related to the propensity of binding. Thus, when the concentrations of all receptors and ligands are high (as in mature T cells), both minima are deep. The situation is analogous to the free energy profile of a simple fluid as a function of molar density near vapor-liquid coexistence. Thus, the two kinds of receptors/ligands "coexist" in the intercellular junction (Figure 2). It is amusing to note that in the case of a simple fluid, the liquid occupies the lower part of the space because of gravity. In an analogous fashion, the shorter

TCR/pMHC molecules are at the center of the synapse since this results in a lower membrane free energy. In other words, membrane mechanics plays a role analogous to gravity. Now, consider the situation when the TCR expression is lowered as in thymocytes. Then, the free energy corresponding to a membrane separation of 15 nm becomes shallower compared to that corresponding to the adhesion molecules. The situation is analogous to raising the temperature of a simple fluid above coexistence so that the vapor phase is favored. However, in this case, due to thermal density fluctuations, droplets of liquid do form, evanesce, and reappear at random locations. Similarly, in thymocytic synapses we observe dynamic clusters of TCR/pMHC due to fluctuations. As discussed in Lee et al. (2003), the dimensionality of the system and the characteristics of the membrane mechanics sets bounds on the size of the TCR/pMHC clusters.

The observation of different synapse patterns in thymocytes undergoing negative selection and mature T cells undergoing activation raises the following interesting question. *Is it possible that different spatial patterns of receptors can modulate the same intracellular signaling cascade differently, thus resulting in different biological outcomes?* Closely synergistic video microscopy experiments, biochemical and genetic experiments, and a computational model can address this question.

A computational model that can study whether different spatial patterns of extracellular receptors can differentially regulate the same intracellular signaling network must combine synapse assembly models (*vide supra*) with one that describes intracellular signaling. Intracellular signaling molecules can diffuse, bind to other molecules, catalyze reactions, and change state (e.g., undergo phosphorylation and dephosphorylation). These processes are not different, in principle, from the myriad of reacting systems that chemical engineers have studied in the past. Thus, it is not surprising that a computational model that can provide key insights into the function of the synapse must rely on methods that are an integral part of the modern chemical engineering discipline, viz., statistical mechanics of deformable manifolds and Monte-Carlo simulations (Newman and Barkeme, 1999). Stochastic simulations are required because the small number of signaling molecules makes the effects of noise important.

Summary and Future Directions

In addition to its biological importance, the studies I have described also lead to a tantalizing suggestion for the design of bioinspired systems. Studies of the immunological synapse suggest that different spatial patterns of cell surface receptors can differentially regulate the same intracellular signaling network. In other words, different spatial patterns of cell surface receptors can mediate different biological outcomes with the same intracellular machinery. Furthermore, when stimulated by ligands, the same extracellular receptors can form different spatial patterns by manipulating conditions such as receptor concentration. Thus, the aforementioned studies suggest that T cells manipulate conditions to affect different spatial patterns of receptors at different stages of their life cycle, which, in turn, mediates vastly different biological outcomes with the same signaling molecules. Can the same principles be used to design synthetic systems that can carry out biomimetic recognition tasks? One can imagine creating vesicles with surface receptors that make "synapses" characterized by different spatial patterns with different types of cells. This, in turn, results in a different response for each cell type with which the device interacts. Such synthetic devices could be useful in applications that include targeted drug delivery.

However, the creation of such devices is a target for the future, and the focus in this area currently remains on understanding the intricate mechanisms via which cells in the immune system communicate. In this perspective, I have tried to demonstrate the utility of modern chemical engineering principles for solving important problems in biology that involve emergent complexity in systems with many interacting components. In particular, I have tried to highlight how the chemical engineer's rare ability to think about phenomena that occur over a wide range of length and time scales is useful for studying complex problems in cellular and molecular immunology. Recently, in this journal, Ottino (2003) has made related remarks about other types of complexity.

There are numerous questions of far reaching significance in cellular and molecular immunology that remain unanswered. For example, one Holy Grail is to understand the mechanisms that underlie the extraordinary sensitivity with which T cells can recognize antigen-derived pMHC (about 20 antigen-derived pMHC in a sea of self pMHC can activate T cells (Irvine et al., 2002)). Given recent developments in experimental methods, I believe that this is exactly the right time to complement genetic and biochemical experiments with analyses based on modern chemical engineering principles in order to solve such important problems. Previously, available experiments were not asking detailed molecular and supramolecular mechanistic questions that chemical engineers are trained to answer. The ultimate challenge is, of course, to harness the knowledge base created by fundamental studies to develop therapeutic strategies and drugs that will alleviate human suffering. The rare combination of molecular and phenomenological perspectives of a chemical engineer can make significant contributions toward developing the mechanistic underpinnings that will allow such progress to occur. However, few chemical engineers are working closely with cellular and molecular immunologists to address these important questions (notable exceptions are K. D. Wittrup (Holler et al., 2000; Kieke et al., 2001) and D. Irvine (Irvine et al., 2002)). So, I close by quoting the physicist, Richard Feynman, who once remarked, "There is plenty of room at the bottom.".

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