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Using an Adaptive Gene Network Model for Self-Organizing Multicellular Behavior

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Abstract— **Using the transient interleukin (IL)-2 secretion of effector T helper (T_{eff}) cells as an example, we show that self-organizing multicellular behavior can be modeled and predicted by an adaptive gene network model. Incorporating an adaptation algorithm we established previously, we construct a network model that has the parameter values iteratively updated to cope with environmental change governed by diffusion and cell-cell interactions. In contrast to non-adaptive models, we find that the proposed adaptive model for individual T_{eff} cells can generate transient IL-2 secretory behavior that is observed experimentally at the population level. The proposed adaptive modeling approach can be a useful tool in the study of self-organizing behavior observed in other contexts in biology, including microbial pathogenesis, antibiotic resistance, embryonic development, tumor formation, etc.**

I. Introduction

A. Self-organization

Self-organization is a process in which a structural and/or functional pattern at the higher level of a system emerges from interactions among the autonomously acting, lower-level components of the same system [1]. Without reference to the global pattern, each component responds or "adapts" to environmental changes sensed at the local level. Self-organization is essential for many biological processes that are multicellular in nature and depend on cell-cell interactions within the population. Understanding how molecular networks, which adapt to the environment at the single-cell level, define population behavior via self-organization is an interesting yet challenging research topic. While each gene regulatory network in individual cells is not capable of complex behavior, it is the combined coordination among multiple gene networks that leads to the manifestation of sophisticated order at the population level. It has been known that cells use a variety of means to communicate with one another for such self-organizing behavior, including quorum sensing [2, 3].

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B. Quorum Sensing

Quorum sensing is a type of decision-making process used by decentralized cell populations to coordinate behavior. For example, many species of bacteria use quorum sensing to coordinate their gene expression according to the local density of their population and eventually the behavior of the entire community [4, 5]. Quorum sensing bacteria produce small signal molecules called autoinducers (Fig. 1A). They also have receptors that can specifically bind to (and detect) them. When autoinducers are secreted from bacteria, diffusion reduces their concentration in the surrounding medium (extracellular space) almost to zero unless neighboring bacteria in the vicinity also release them. This implies that if the cell-population density is sufficiently high, the extracellular autoinducer concentration may increase even in the presence of the ongoing diffusion process. When a critical extracellular autoinducer concentration is reached due to a dense cell-population, the receptor-bound autoinducers can feed back and regulate the expression of specific genes, including the autoinducer gene, coordinating a self-organizing behavior of the bacterial population. Note that the gene expression of an individual cell is closely coupled with the dynamical change in the extracellular autoinducer

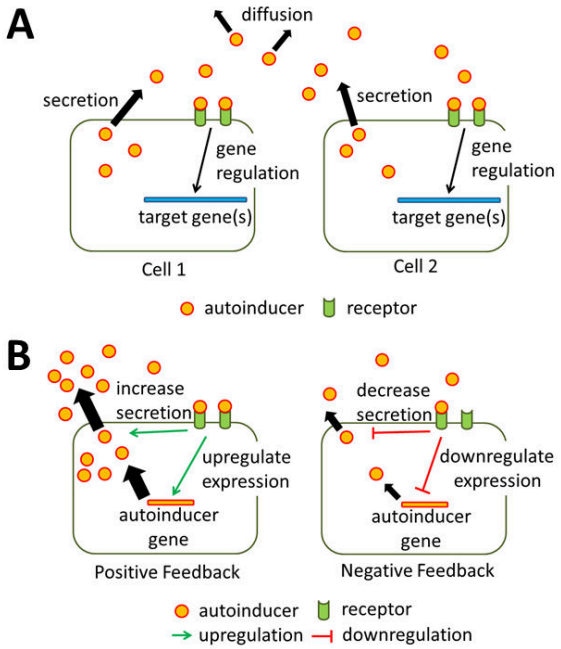

Figure 1. Quorum sensing. (A) Quorum sensing bacteria produce autoinducers that bind to receptors of neighboring cells and regulate their gene expression. (B) Two types of feedback mechanisms: positive (left) and negative (right).

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concentration, which is governed by the diffusion process and by contributions from the cell and its neighbors.

There are two known types of "feedback" mechanisms, positive and negative, that the receptor-bound autoinducer may use to regulate its own production and/or secretion (Fig. 1B) [1]. Positive feedback is a mechanism known to generate amplification and bistability [6, 7]. Negative feedback can stabilize a system by removing the effects of environmental fluctuations [8] and generate oscillations [9, 10]. However, recent protein and genetic interaction mapping studies have demonstrated that the architecture of an interactome can be substantially re-wired during a cellular or adaptive response (reviewed in [11]). These studies indicate that each feedback mechanism alone may not be sufficient to explain the complex adaptive nature of self-organization and the use of a flexible, adaptive network model is required even though the underlying molecular mechanisms are not completely known. One useful example of such a modeling approach is an artificial neural network (ANN), which changes its parameters by a process of adaptation to a set of training patterns [12]. Nevertheless, it is important to consider more flexible network structures that allow for more adaptation and interaction among the network components.

C. Adaptive Networks

There have been research efforts that attempt to link self-organization to adaptive networks [13], namely, to networks where the evolution of the topology is linked to the state of the network. Such adaptive networks appear in many biological systems, including immune and neural systems. Revealing the principles of self-organization in the context of adaptive networks may provide useful insights into the understanding of complex self-organizing behavior. Adaptive networks also appear in other contexts, including in the study of social networks [14-19]. These earlier works generally do not consider what algorithms and what processing needs to be done by the individual nodes to result in an adaptive network behavior, and how to endow the individual elements with learning abilities. In this article, we propose to use an adaptive network to model self-organizing multicellular behavior and propose algorithms at the cellular level to induce the self-organized pattern at the global level. Such adaptive networks were introduced in [20, 21] and they have been used in [22, 23] to model forms of self-organized behavior arising in biological networks such as fish schooling and bird flight formations. In these adaptive networks, the individual agents are assumed to be learning nodes and they continuously interact with their immediate neighbors through in-network processing. The result of these interactions is a diffusion process that allows information to ripple through the network. The agents iteratively and continuously adjust or "adapt" the model parameters based on the error between the measured and predicted data. We have recently proposed building adaptive models for gene networks using related adaptive filtering techniques in [24]. In this article, we propose to use the adaptive diffusion network approach to model self-organization of cell populations via quorum sensing, using the transient interleukin (IL)-2 secretion of effector T helper cells as an example.

II. Results

A. Adaptive Model for Transient IL-2 Secretion

In contrast to innate (native) immunity, which responds to repeated infections in the same way, adaptive immunity can adjust its defensive capabilities with each successive exposure to a particular infecting agent [25]. Adaptive immunity has an extraordinary capacity to distinguish among different foreign substances called antigens, which induce specific immune responses. The components of adaptive immunity are lymphocytes (B cells, T cells, etc.) and their products including interleukins, small cell-signaling molecules extensively used in intercellular communication, which can be considered as autoinducers in the context of quorum sensing.

In response to antigenic stimulation, a type of T cell called effector T helper cell (T_{eff}) secretes IL-2, a growth factor that can stimulate the proliferation and differentiation of the T cells, as well as other cells such as B cells, natural killer (NK) cells, etc [25]. When secreted, IL-2 molecules (autoinducers) bind IL-2 receptors (IL-2R) of T_{eff} cells. As a result, intracellular STAT5 (Signal Transducer and Activator of Transcription 5) molecules become phosphorylated STAT5 (pSTAT5), which promotes cell survival and regulates the production of IL-2 (Fig. 2A). Interestingly, even in the presence of prolonged antigen stimulation, IL-2 secretion and its accumulation in the shared, extracellular space are transient [26]. The molecular mechanisms underlying this brevity remain unclear. The extracellular IL-2 concentration decreases by the diffusion process. However, as long as the T_{eff} cells produce IL-2 continuously upon antigen binding, the concentration eventually reaches a steady-state value as the effects of secretion and diffusion balance out. In other words, as long as antigen-binding causes IL-2 production/secretion, the transient IL-2 behavior experimentally observed can hardly be achieved. In this context, it has been suggested that T_{eff} cells may control the IL-2 production/secretion by altering the strength of the antigenic stimulus available to each cell [26].

It has been also proposed that another type of T cell, regulatory T cell (T_{reg}), which has IL-2R that consumes IL-2 but does not produce IL-2, can drop the extracellular IL-2 concentration resulting in transient accumulation of secreted IL-2 [7]. However, the transient behavior has been observed in the absence of T_{reg} cells and it has been suggested that IL-2 feeds back negatively on its own expression via pSTAT5 within the T_{eff} cells, enabling pulse-like IL-2 production/secretion (Fig. 2A) [27, 28]. As stated earlier, negative feedback is known to generate oscillatory behavior and not transient behavior [9, 10], which can be understood intuitively as follows. When IL-2 secretion is increased pSTAT5 also increases (Fig. 2A). As pSTAT5 is increased, IL-2 production and the ensuing secretion are decreased due to the negative feedback mechanism. As IL-2 secretion is decreased, pSTAT5 is also decreased and no longer suppresses IL-2 production. As a result, IL-2 secretion is increased again and the cycle either continues (undamped oscillation) or dies out reaching steady-state (damped

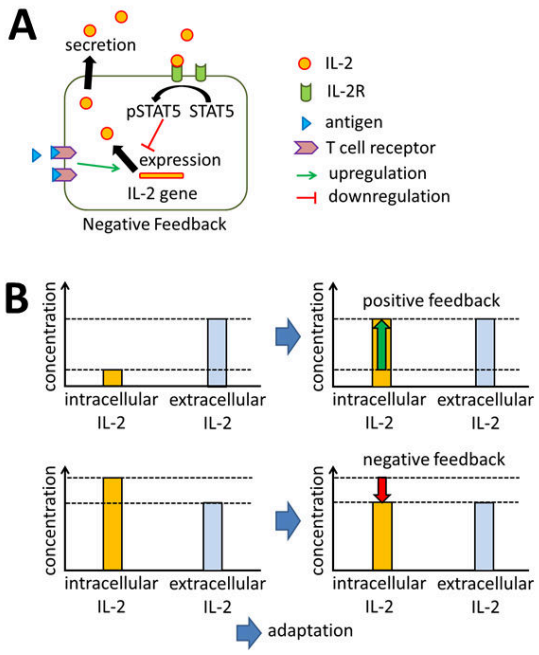

Figure 2. Transient IL-2 secretion by T_{eff} cells. (A) A schematic illustration of the feedback gene network (a negative feedback model is shown). (B) An adaptive model. Although the extracellular IL-2 concentration remains the same, the intracellular IL-2 concentration can either increase (positive feedback) or decrease (negative feedback) depending on its current value with respect to the extracellular IL-2 concentration.

oscillation). Note that, like the previous case, the extracellular IL-2 concentration reaches steady-state and does not drop to zero even in the presence of the diffusion process, as long as the antigen binding sustains IL-2 production. There are other findings that suggest the negative feedback model is not sufficient. Among different gene network motifs, an incoherent type 1 feed forward loop is known to create a pulse-like transient behavior and it is unlikely that cells utilize a negative feedback motif to generate such behavior [29]. Furthermore, a recent study reports that pSTAT5 may increase IL-2 secretion indicating that there can also be a positive feedback mechanism involved [30].

One interesting feature of self-organization is that complex behavior at the system level emerges when each system element follows a simple "adaptation rule" in response to environmental change sensed at the local level. For example, a skein of geese self-organizes into V-formation when they need to travel long distances [23]. A trailing bird constantly adjusts or "adapts" its position with respect to the position of the bird ahead without reference to the global pattern. For individual T_{eff} cells, we assume that they obey a simple adaptation rule as follows. Each cell adjusts or "adapts" the production/secretion of IL-2 with respect to the extracellular IL-2 concentration sensed via IL-2R so that both intracellular and extracellular IL-2 concentrations become similar. Note that this adaptive mechanism responds not to the absolute value of the extracellular IL-2 level but to its relative value compared to that of the intracellular IL-2 concentration. Fig. 2B shows that although the extracellular IL-2 concentration remains the same, the intracellular IL-2 concentration can either increase (positive feedback) or decrease (negative feedback) depending on its current value with respect to the extracellular IL-2 concentration. This adaptive model predicts that if a T_{eff} cell detects antigen while neighboring cells do not, the cell will soon stop producing IL-2 since the near-zero extracellular IL-2 concentration will be adaptively reflected on its intracellular Il-2 level. On the other hand, if a T_{eff} cell does not detect antigenic stimulus while many of its neighboring cells do, it will start producing IL-2 to adapt its intracellular IL-2 concentration to higher extracellular IL-2 concentration. In fact, this simple adaptive algorithm executed by individual T_{eff} cells can filter isolated responses (possibly due to noise) of individual cells to antigenic stimulus while enhancing responses when the neighbor cells also detect the stimulus simultaneously, suggesting that adaptation of individual cells may have a critical role in converting unreliable decisions by individual cells into an accurate cell-population decision to trigger or suppress an immune response [2].

B. Mathematical Model

In the previous section, it was mentioned that there are several issues that suggest the negative feedback model is not sufficient. First, negative feedback is not appropriate for generating a pulse-like, transient behavior [29]. Second, both negative and positive feedback mechanisms have been reported [30] and these mechanisms may be differentially used under different conditions although they are not completely understood [11]. Third, the negative feedback model cannot explain the termination of IL-2 production/secretion in the presence of sustained antigenic stimulus [26]. In this section, based on ideas from our previous works [20, 21, 24], we propose an adaptive model that addresses these issues.

Assume we have m by n T_{eff} cells on a plane with m rows and n columns and each cell can be denoted as cell(m,n). The intracellular IL-2 concentration of cell(m,n) can be expressed as:

$$i2_{m,n}(i+1) = w1_{m,n}(i) \cdot o2_{m,n}(i) + w2_{m,n}(i) \cdot a_{m,n}(i) \quad (1)$$

where i is the iteration index, $i2_{m,n}$ is the intracellular IL-2 concentration of cell(m,n), $o2_{m,n}$ is the extracellular IL-2 concentration at cell(m,n), and $a_{m,n}$ is the amount of antigen detected by cell(m,n). Moreover, $w1_{m,n}(i)$ is a parameter that shows how the current extracellular IL-2 value, $o2_{m,n}(i)$, determines the next intracellular IL-2 value, $i2_{m,n}(i+1)$, by controlling the production and/or secretion of IL-2, while $w2_{m,n}(i)$ shows how strongly the current receptor-bound antigen level, $a_{m,n}(i)$, is related to the next intracellular IL-2 value, $i2_{m,n}(i+1)$. Note that both $w1_{m,n}(i)$ and $w2_{m,n}(i)$ are not fixed values and can change adaptively at every iteration.

If we assume the concentration of secreted IL-2 at cell(m,n) is equivalent to its intracellular IL-2 concentration and the extracellular IL-2 concentration at cell(m,n) is the average of secreted IL-2 concentrations of the cell(m,n) and its eight adjacent cells (nine cells in total), the extracellular IL-2 concentration at cell(m,n) can be represented as:

$$o2_{m,n}(i+1) = \frac{1}{9}\left[\sum_{j=m-1}^{m+1}\sum_{k=n-1}^{n+1} i2_{j,k}(i)\right] \quad (2)$$

Denoting $\boldsymbol{w}_{m,n}$ as the parameter vector $[w1_{m,n}, w2_{m,n}]$ and $\boldsymbol{u}_{m,n}$ as the data vector $[o2_{m,n}, a_{m,n}]$, $\boldsymbol{w}_{m,n}$ can be adaptively updated using the NLMS (Normalized Least Mean Squares) algorithm [24, 31]:

$$\boldsymbol{w}_{m,n}(i+1) = \boldsymbol{w}_{m,n}(i) + \mu_{m,n}(i) \cdot e_{m,n}(i) \cdot \boldsymbol{u}_{m,n}(i) \quad (3)$$

where the error term $e_{m,n}$ is computed by subtracting $i2_{m,n}(i)$ from $o2_{m,n}$ (4) and $\mu_{m,n}(i)$ is computed using (5).

$$e_{m,n}(i) = o2_{m,n}(i) - i2_{m,n}(i) \quad (4)$$

$$\mu_{m,n}(i) = \frac{\mu}{\varepsilon + \left\|\boldsymbol{u}_{m,n}(i)\right\|^2} \quad (5)$$

where μ is an iteration step size (0.1 was used for the simulated experiments) and ε in the denominator is a very small positive constant that avoids division by zero.

C. Simulated Experiment Results

We used MATLAB (Mathworks, USA) for running simulated experiments: 1,000 cells were randomly selected from 10,000 (m = 100, n =100) T_{eff} cells for continuous antigenic stimulus. Fig. 3A shows that the average extracellular concentration (o2) of 10,000 cells exhibits a transient behavior when the adaptive model is used. In contrast, the negative feedback model reaches a non-zero steady-state after a brief damped oscillation. The simulation results varied to some extent (e.g., more or less damping) depending on the simulation parameters, including the number of cells selected for antigenic stimulus and the amount of antigen applied, etc., but the results in general were consistent with the data shown in Fig. 3A.

Fig. 3B illustrates how individual cells behave adaptively in response to the changing environment. Cell(51,45) is one of randomly selected cells for antigenic stimulus. Both the intracellular (i2) and extracellular (o2) IL-2 concentrations exhibit a transient behavior. However, o2 is much lower than i2, indicating that some of its neighbors may not be detecting any antigen. The parameter w1, which shows how o2 affects i2, converges to a negative value near -0.1. This means o2 is less than i2 and there is negative feedback (Fig. 2B). The parameter w2 informs the strength at which antigenic stimulus increases IL-2 production/secretion and our simulation result shows that it drops down to zero even though the antigenic stimulation is present throughout the simulation. This result addresses one of the issues raised in the previous section that the negative feedback model cannot explain the termination of IL-2 production/secretion in the presence of sustained antigenic stimulus.

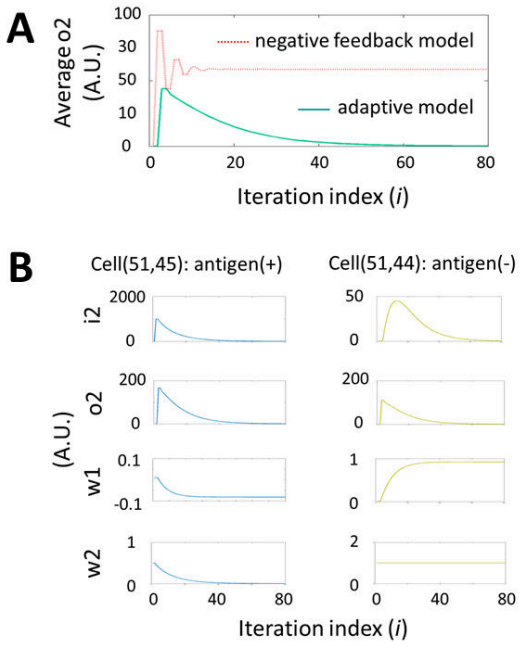

Figure 3. Simulated experiment results (A.U.: Arbitrary Unit). (A) The adaptive model exhibits a transient behavior while the negative feedback model reaches a non-zero steady-state value after a brief damped oscillation. (B) Adaptive behavior of individual cells.

Fig 3B also shows the simulation results of Cell(51,44), one of neighboring cells of Cell(51,45), which detects no antigen. Note that this cell produces IL-2 (positive i2 values) although it has no antigenic stimulus because o2 feeds back positively. This is confirmed by the fact that w1 converges to a positive value around 1. Our results show that both negative and positive feedback mechanisms are differentially used under different conditions. Since there is no antigenic stimulus (zero value), w2 is not affected by the adaption process and its initial value (one) is maintained.

III. Conclusion

Quorum sensing has been reported as a survival strategy by which bacterial pathogens evade antimicrobial defenses and overwhelm the host [32]. Human stress hormones and cytokines can be detected by bacterial quorum sensing systems, and by this mechanism, the pathogen can detect the physiologically stressed host, providing an opportunity to invade when the patient is most vulnerable. Furthermore, there have been studies that suggest quorum sensing may play an important role in cancer, stem cell, and immune system biology. For instance, a hypothesis that cancer cells may use a quorum-sensing mechanism to regulate multicellular functions and control steps in metastatic colonization has been proposed [33]. It has also been reported that disruption of a quorum-sensing mechanism triggers tumorigenesis in mammary cancer stem cells [34]. These studies indicate that computationally modeling self-organization using adaptive networks may lead to useful insights in diverse biological fields.

IV. ACKNOWLEDGEMENT

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