Modeling Collective & Intelligent Decision Making of Multi-cellular Populations

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***Abstract*— In the presence of unpredictable disturbances and uncertainties, cells intelligently achieve their goals by sharing information *via* cell-cell communication and making collective decisions, which are more reliable compared to individual decisions. Inspired by adaptive sensor network algorithms studied in communication engineering, we propose that a multi-cellular adaptive network can convert unreliable decisions by individual cells into a more reliable cell-population decision. It is demonstrated using the effector T helper (a type of immune cell) population, which plays a critical role in initiating immune reactions in response to invading foreign agents (e.g., viruses, bacteria, etc.). While each individual cell follows a simple adaptation rule, it is the combined coordination among multiple cells that leads to the manifestation of "self-organizing" decision making *via* cell-cell communication.**

I. Introduction

All living systems, including microscopic cells (bacteria, animal cells, etc.), live in environments that are uncertain, dynamically-changing, and even hostile. However, it is remarkable that these systems survive and achieve their goals by exhibiting "intelligent" features such as adaptation and robustness. A multi-cellular population is composed of dynamically interacting cells or "agents" distributed over physical space and robustly adapting to environmental changes. Understanding distributed sensing, collective decision making, and cooperative control of such an intelligent multi-agent system is an interesting research topic not only for biology but also for many engineering fields, including adaptive sensor network and swarm robotics [1-3].

A. Multi-cellular intelligence emerges via self-organization

One of the main goals of hematopoietic stem cells in a multi-cellular organism is to control cell number in response to dynamically changing demands. However, this population control can be disturbed by many factors as the environment is full of disturbances and uncertainties that are hard to predict in advance. In the presence of such disturbances and uncertainties, cells "intelligently" achieve their goal by constantly sensing (identifying) the current state and actively controlling it so that they can stably reach the target state. They gather information using sensors (e.g., cell surface receptor), make decisions using complex intracellular molecular processes including gene expression, and take actions (e.g., cell division). Interestingly, although each cell determines its own action given local information, a higher, population-level behavior or pattern that achieves the target emerges *via* self-organization, 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 [4].

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B. Multi-cellular intelligence involves complex intracellular mechanisms

As mentioned earlier, cells make "intelligent" decisions using complex intracellular molecular parts and processes. However, intelligent behaviors are often hard to explain using a reductionistic approach. For example, today's microprocessor can be made up of billion transistors. Using the device, we can create an artificial intelligence program that can recognize fingerprints as shown in **Figure 1.** When a fingerprint recognition program is running on a computer, it would not be possible (or even meaningful) to examine how billion transistors are functioning over time. Similarly, precisely describing how intracellular parts are working while a cell exhibits intelligent behaviors (adaptation and robustness) might be an impossible to task to do (**Fig. 1**). However, traditional biological research approaches hardly allow models whose molecular mechanisms are not well defined. It has been suggested that unknown complex molecular mechanisms for intelligent multi-cellular behaviors can be modeled using mathematical algorithms derived from system identification and feedback control theory [5-10].

C. Adaptive sensor network and collective decision making

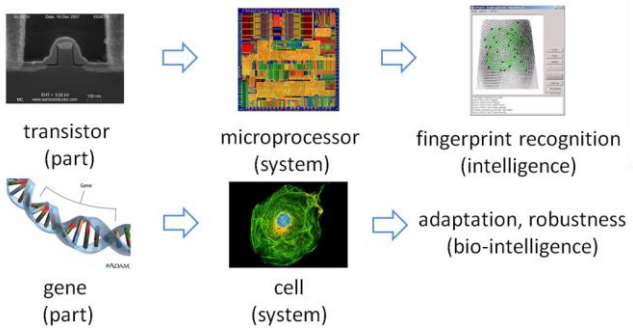

Figure 1. System and intelligence.

An adaptive sensor network consists of a set of nodes or sensors that make a detection decision using a collection of

individual sensing decisions. Its main features include adaptive mechanism (of individual sensors) and self-organizing behavior [1,2,11,12], suggesting that its mathematical formulation might be useful for modeling self-organizing behavior of a multi-cellular population in which each cell adapts to its changing environment. Previously, we have demonstrated that the effector T helper cell (T_{eff}), which plays an important role in alarming the whole immune system in response to invasion by foreign agents (e.g., viruses, bacteria, etc.), can be modeled using an adaptive network algorithm [5]. The similarity between engineered adaptive sensor network and the T_{eff} population has prompted us to investigate the mechanism of collective decision making of the T_{eff} population shown in this study.

D. An adaptive model for the T_{eff} population

In response to antigenic stimulation, T_{eff} cells secrete IL-2. When secreted, IL-2 molecules can feed back and bind the 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 (gene expression) of IL-2 [5].

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 individual T_{eff} cells, it has been suggested that they obey a simple adaptation rule [5]. 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 [5]. 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 a more accurate cell-population decision to trigger an immune response.

II. Results

A. Mathematical Model

In this study, we use an adaptive structure for modeling the evolution of the extracellular IL-2 concentration, based on our previous model [5]. We focus on extracellular IL-2 because it has been reported that the extracellular IL-2 levels play an important role in initiating an immune response [13]. Assume we have m by n T_{eff} cells in a plane with m rows and n columns. Each cell is denoted as cell(m,n). The intracellular IL-2 concentration of cell(m,n) can be expressed as:

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

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) that represents antigenic strength. $w1_{m,n}(i)$ 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. $w2_{m,n}(i)$ 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 parameter 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:

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

where c is the diffusion factor, which was not present in our previous model [5]. **Figure 2** shows that the $o2_{m,n}$ levels are dependent on how fast IL-2 molecules diffuse in the extracellular space under identical conditions (except for the diffusion factor). As the diffusion factor increases the T_{eff} cells maintain lower levels of extracellular IL-2 for a shorter period of time. Denoting $\boldsymbol{w}_{m,n}$ as the parametric 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:

$$w_{m,n}(i+1) = w_{m,n}(i) + \mu_{m,n}(i) \cdot e_{m,n}(i) \cdot u_{m,n}(i) \qquad (3)$$

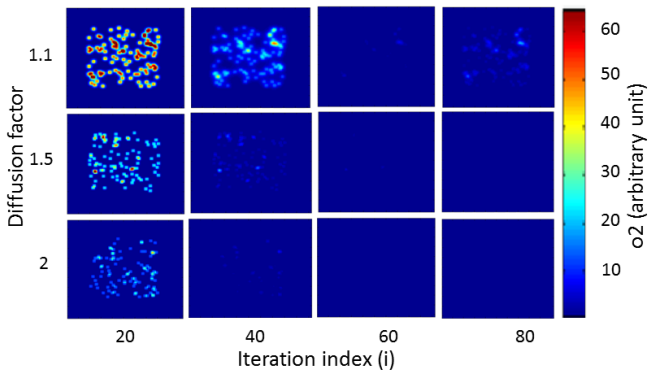

Figure 2. The effects of the diffusion factor on the extracellular IL-2. As the diffusion factor increases the T_{eff} cells maintain lower levels of extracellular IL-2 for a shorter period of time.

where the error term $e_{m,n}$ is computed by subtracting $i2_{m,n}(i)$ from $o2_{m,n}(i)$:

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

and $\mu_{m,n}(i)$ is computed using:

$$\mu_{m,n}(i) = \frac{\mu_0}{\varepsilon + \left\| u_{m,n}(i) \right\|^2} \quad (5)$$

where μ_0 is the iteration step size (0.1 was used for the simulated experiments) and ε in the denominator is a small positive constant that avoids division by zero. Observe that cells influence each other through the averaging that is performed in (2) to determine the $o2_{m,n}$, which plays an important role in initiating an immune response as stated previously. We will show that our adaptive model 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, thus converting unreliable decisions by individual cells into a more reliable cell-population decision to trigger an immune response.

B. Immune response triggering based on collective decision making

Our 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 its intracellular IL-2 level will adapt to the near-zero extracellular IL-2 concentration (due to the diffusion process). 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 other words, the IL-2 production/secretion of each cell is substantially affected by the density of neighbor cells that detect antigen. This is illustrated in **Figure 3**. In **Figure 3A**, simulated experiment results are shown for two cases when antigen-detecting cells are sparsely (top) and densely (bottom) distributed. The number of cells selected for antigenic stimulation is identical (20) for both cases. The figure shows that, while very sparse or isolated responses (top) rapidly subside, the cells maintain higher levels of extracellular IL-2 for a longer period of time when the cell density is increased (bottom). These findings indicate that the density-dependent mechanism can filter sparse or isolated responses (possibly due to errors) while synergistically enhancing dense responses, thus converting unreliable decisions by individual cells into a more reliable cell-population decision. **Figure 3B** shows when antigen-detecting cells are densely distributed, their extracellular IL-2 levels can rise above the arbitrary threshold shown, thus triggering an immune response.

We also applied uniformly distributed background noise $v(i)$ to the model to examine the effect of environmental noise to our model (Eq. 6). $v(i)$ generates random numbers that are uniformly distributed in the interval (0,10). **Figure 4** displays the result which indicates that the existence of noise in the background does not affect the behavior of cells in terms of their collective decision making.

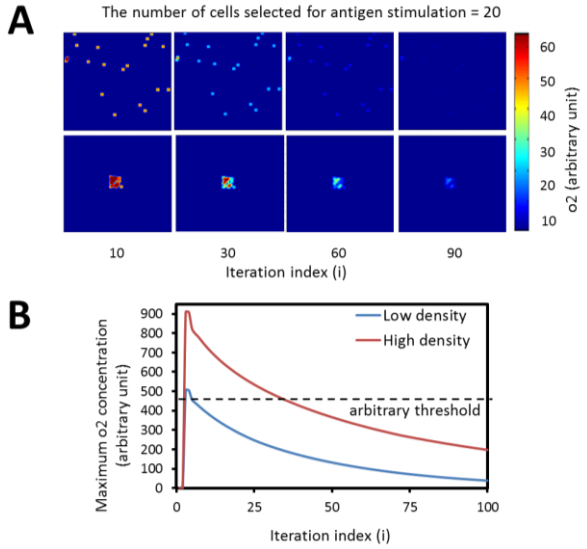

Figure 3. Density-dependent immune response triggering. (A) Simulated experiment results are shown for two cases when antigen-detecting cells are sparsely (top) and densely (bottom) distributed. The number of cells selected for antigenic stimulation is identical (20) for both cases. The figure shows that when the cell density is increased (bottom) the cells maintain higher levels of extracellular IL-2 for a longer period of time and very sparse or isolated responses (top) rapidly subside. These findings indicate that the density-dependent mechanism can filter sparse or isolated responses (possibly due to noise) while synergistically enhancing dense responses, thus converting unreliable decisions by individual cells into a more reliable cell-population decision. (B) When antigen-detecting cells are densely distributed, their extracellular IL-2 levels can rise above the arbitrary threshold shown, thus triggering an immune response.

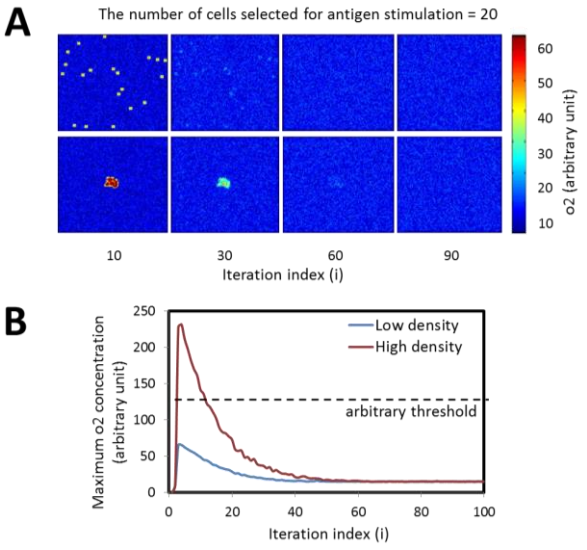

Figure 4. Uniformly distributed background noise has been applied to the model. (A) Simulated experiment results are shown for two cases with noise when antigen-detecting cells are sparsely (top) and densely (bottom) distributed. (B) When antigen-detecting cells are densely distributed, their extracellular IL-2 levels can rise above the arbitrary threshold shown unaffected by the existence of noise, thus triggering an immune response. However, threshold level decreases significantly in the presence of background noise.

$$o2_{m,n}(i+1) = \frac{1}{9c}\left[\sum_{j=m-1}^{m+1}\sum_{k=n-1}^{n+1} i2_{j,k}(i)\right] + v(i) \quad (6)$$

III. Conclusion

In the presence of unpredictable disturbances and uncertainties, cells intelligently achieve their goals by sharing information *via* cell-cell communication and making "collective" decisions, which can reduce errors in decision making. In this study, we proposed an adaptive network model that can convert unreliable decisions by individual cells into a more reliable cell-population decision using the T_{eff} population as an example. The study of collective decision-based sensing is a challenging problem in many biological fields. For example, the mechanism has recently been reported as a previously unrecognized survival strategy by which bacterial pathogens evade antimicrobial defenses and overwhelm the host [14]. Human stress hormones and cytokines can be detected by bacterial collective or 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. There also have been studies that suggest collective sensing may play an important role in cancer and stem cell biology. For instance, it has also reported that disruption of a collective sensing mechanism triggers tumorigenesis in mammary cancer stem cells [15]. These studies indicate that computational modeling of multi-cellular behaviors using our collective decision making model may lead to useful insights not only into immunology but also into other related biological fields, including microbial pathogenesis, embryonic development, tumor formation, drug resistance, etc. Furthermore, finding similar patterns in such diverse systems suggest that our adaptive approach is one of the "social interaction motifs" that may be commonly shared by many biological systems [16].

However, it is important to note that our model is a simplified one that does not take into account some of important biological complications. Among which is the time consuming nature of protein production after detecting the need for readjustment, i.e., our adaptive feedback model does not consider the unavoidable delay in protein production in order to adapt intracellular IL-2 concentration to extracellular IL-2 concentration. Furthermore, cell population dynamic mechanisms such as cell movement, division and apoptosis are shown to have considerable impacts and their effects need to be considered [17,18]. The physics of cellular microenvironment is another important aspect that should be considered. Considering the fact that cells interact and communicate through an aqueous environment, diffusion and/or fluid dynamics equations can also be incorporated into the model [19]. In conclusion, in order to have a more realistic model we need to address the aspects and complications mentioned above. Moreover, there are ways to modify our model using other adaptive algorithms like distributed Kalman filters [20, 21]. Finally, experiments should be carried out to validate our model.

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