Effective Feedback in the Immune System[†]

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The immune system is an interesting natural example of a multi-agent system. It is composed of a large number and variety of components distributed throughout the body. Individual actions of vast numbers of cells, and their interactions with even larger numbers of molecular mediators, determine the course of an infection. In most cases, this distributed collection of agents protects organisms against a wide variety of attacks. Understanding the principles by which this system works is important not only for learning to control diseases, but also for understanding control of distributed systems in general.

Cell actions are governed largely by molecular signals. Each cell expresses on its surface an enormous number of receptors for a variety of different chemicals. These receptors bind to extracellular molecules, or molecules on the surfaces of other cells. Which subsets of receptors are bound determines whether cells die, divide, move, differentiate, or produce molecules for secretion or expression on their surfaces. As each type of receptor is specific for a certain kind of molecule, its expression determines whether a cell is 'listening' for a specific kind of information. Intracellular signalling mechanisms connected to these receptors determine the response to each such signal. In addition, interactions between intracellular signalling pathways cause the cell's response to be a function of combinations of external signals.

Segel and Bar-Or (Segel and Bar-Or 1999) demonstrated how certain kinds of molecular signals can provide feedback to tune the immune system response. In addition to eliminating an invading pathogen, an immune response often causes incidental damage to the host. Recruitment of immune system effectors to an infected area results in inflammation, with negative effects on blood circulation and local tissue integrity. Toxins required to kill certain pathogens may also damage host cells. Segel and Bar-Or presented this as a case of conflicting goals: the immune response should kill dangerous pathogens but should not harm the host. They showed how chemical signals indicating when pathogens were being killed and when host cells were being damaged could be used to adjust the response so as to minimize both kinds of damage. Here, we expand on this earlier work by using genetic algorithms to explore what forms of feedback information are most useful in the model system.

A standard approach to modeling the immune system, and the one taken by Segel and Bar-Or, is to derive a set of differential equations that describe the changes in concentrations of the relevant cell and molecule types over time. These equations describe the average behavior of the system, assuming ideal mixing.

Segel and Bar-Or's minimal model includes one kind of pathogen P and one kind of immune system effector E, which kills pathogens by secreting a toxic chemical N (such as nitric oxide). N damages host cells as well as killing pathogens. This is a simplified model of the dual nature of inflammatory responses in general. If pathogens cause damage at rate h_P, and the noxious chemical causes damage at rate h_N, then we can represent the total damage done during an immune response as:

$$\int h_P P + h_N N \tag{1}$$

The concentration of effectors grows in proportion to pathogen levels (with coefficient μ_P) up to some saturation limit E_{max}, and decays at a fixed rate g_E:

$$\frac{dE}{dt} = \mu_P P E(1 - \frac{E}{E_{max}}) - g_E E$$

N is secreted by effectors at rate s and decays at rate

[†]In Genetic and Evolutionary Computation Conference Workshop Program, Morgan-Kaufmann, pp. 329-332 (2001).

g_N:

$$\frac{dN}{dt} = sE - g_N N$$

Pathogens reproduce at fixed rate r. For pathogen killing, a "mass action" encounter rate EP is assumed and the killing effectiveness of an encounter is taken proportional to N, with coefficient a.

$$\frac{dP}{dt} = rP - aEPN$$

The secretion rate s is critical in this model: if it is too low, the pathogen will not be controlled and will do too much damage; if it is too high, the amount of incidental damage by the immune response will be high. An optimal value of s is one resulting in the minimum damage to the system; but this optimal value is dependent on pathogen virulence and susceptibility to effectors. No fixed secretion rate will perform well in all situations.

Segel and Bar-Or reasoned that the immune response, and in particular the secretion rate of N, should be controlled by feedback indicating whether damage is occurring to the host, and whether effectors are successful in eliminating pathogens. This information could be represented by two chemicals: K, created during pathogen killing, and H, created during host damage. c_K and c_H are the respective rates of production of these chemicals. (See (Segel and Bar-Or 1999) for specific molecules and evidence that they may function as 'kill indicators' or 'harm indicators'.) Each chemical also has a fixed decay rate, g_K and g_H:

$$\frac{dK}{dt} = c_K(aEPN) - g_K K$$

$$\frac{dH}{dt} = c_H(h_P P + h_N N) - g_H H$$

H is composed of damage done by both pathogens and the immune response; one way to provide an estimate of each of the two components is given by:

$$H_P = \frac{H}{1 + k_P N}$$

$$H_N = H - H_P = \frac{k_P N H}{1 + k_P N}$$

Segel and Bar-Or chose the following form for s:

$$\begin{aligned} s &= s_1 + \frac{s_2 K H_P}{1 + s_3 H_N + s_4 K H_P} \\ &= s_1 + \frac{s_2 K H}{1 + k_P N + s_3 k_P N H + s_4 K H} \end{aligned} \tag{2}$$

This makes the secretion rate dependent on information about the current state of the system. Indications that dangerous pathogens are being killed (KH_P term) upregulate the response to some saturation level, while damage done by the immune response downregulates the response. This should allow the immune response to adapt to different pathogenic challenges. Indeed, Segel and Bar-Or found that this adaptive secretion rate also caused less total damage during a response to a single pathogen than the optimal secretion rate for that pathogen (Segel and Bar-Or 1999).

In this paper, we explore methods for automatically discovering and optimally quantitating such adaptive response mechanisms. The general approach is to make the system flexible enough to respond to many kinds of available information, then select specific forms that are particularly effective at achieving the goals of the system. In the given model, there are a number of different ways that feedback could be used. Given the goal of minimizing damage to the host, how should effectors use the available chemical signals to adjust the secretion rate of N appropriately? Even in this rather simple case, there are many possible interactions, and nonlinearity in the equations makes it difficult to predict the overall results of these interactions. We use an evolutionary search to explore this rather large and irregular space.

We implemented the model described above in Gepasi, a biochemical simulator package developed by Pedro Mendes (Mendes 1997). Gepasi incorporates several tools to handle numerical integration, optimization and plotting of model dynamics. We used Gepasi's genetic algorithm, which encodes each parameter in floating-point representation. It uses multipoint crossover, performed only at gene boundaries. Mutation adds a random value chosen from a normal distribution with zero mean and standard deviation of 10% of the parameter value (but not exceeding boundaries on that parameter). Tournament selection is used, with each individual competing with 20% of the population, chosen at random. The number of generations is fixed. If the fittest individual remains the same for several generations, the least fit individuals in the population are replaced by randomly-generated individuals. Equation (1) for the total damage was used as the fitness function.

We started with a general form for s that allowed excitatory and/or inhibitory influences from all of the molecules in the system, some in combination; this is shown in equation (3). Values for all of the parameters in the above equation were allowed to vary between 0.0 and 2.0, except for m_7, which was required

$$s = s_1 + s_2 \frac{m_1 + m_2 K + m_3 H + m_4 N + m_5 NH + m_6 KH}{m_7 + m_8 K + m_9 H + m_{10} N + m_{11} NH + m_{12} KH} \tag{3}$$

$$s = s_1 + s_2 \frac{m_1 + m_2 K + m_3 H + m_4 N + m_5 NH + m_6 KH + n_1 NK + n_2 P + n_3 E}{m_7 + m_8 K + m_9 H + m_{10} N + m_{11} NH + m_{12} KH + n_4 NK + n_5 P + n_6 E} \tag{4}$$

to be nonzero to avoid divide-by-zero errors. The initial concentrations and parameters other than those in the equation for s were set as in the previous work [1] (Segel and Bar-Or 1999). We used a population size of 100 and 100 generations.

Although the adaptive secretion rate suggested by Segel and Bar-Or (equation (2)) is a special case of equation (3), the GA does not reproduce equation (2). There are some similarities, but the best solutions resulted in less total damage than that produced by equation (2). As expected, many of the parameters were set to zero (or extremely low values indistinguishable from zero for our purposes), leaving an expression of the form:

$$s = s_2 \frac{m_3 H + m_6 KH}{m_7 + m_{10} N + m_{11} NH}$$

Parameter values in the best solution were as follows: $s_2 = 0.008$, $m_3 = 0.001$, $m_6 = 0.735$, $m_7 = 0.05$, $m_{10} = 1.967$, $m_{11} = 0.001$.

Figure (1) shows how the secretion rate and its contributing terms vary over the course of the simulation. The $m_3 H$ term is very small, but essential for causing the initial secretion of N. It replaces the fixed base secretion rate s_1 in equation (2). Remember that K is produced when pathogens are killed, which cannot happen until N is produced, so if m_3 were zero, no N would ever be secreted. However, once production has begun, the second term of the numerator becomes the primary positive influence on N secretion. A similar term was used in equation (2); in both cases, upregulation depends on indications that dangerous pathogens are being destroyed.

The primary negative influence on N secretion is presence of N itself. Since N always does damage to the system in this model, it makes sense that its production should depend on the levels already available. This is an example of direct negative feedback, but is used in combination with other forms of feedback.

[1] $h_P = 1.0$, $h_N = 1.0$, $\mu_P = 0.1$, $E_{max} = 100$, $g_E = 0.1$, $g_N = 1.0$, $r = 0.1$, $a = 0.02$, $c_K = 5.0$, $g_K = 1.0$, $c_H = 1.0$, $g_H = 1.0$, $k_P = 1.0$. Initially: $P = 10$, $E = 1$, $N = K = H = 0$.

In the general form for s given in equation (3), terms dependent on cellular concentrations P and E were not included. In the real system, concentrations of molecules make them better candidates for feedback signals, but effector cells are also capable of detecting pathogens and other effectors directly. To see what difference this capability might make, we tried another form of s, shown in equation (4). None of the solutions found by the GA for this equation were better than that described above (which is also a specific instance of this equation). At least for this specific problem, the additional information does not seem to offer any advantage.

Although we have treated this as an optimization problem, we do not claim that evolution optimizes the immune response in this way. The exact values and forms of the above equations are not as important as the understanding of which kinds of feedback signals have some evolutionary advantage and why. These examples show us how feedback in the immune system *could* work, and the kinds of effects different signals might have on the developing response. They suggest certain mechanisms to look for in the immune systems of real organisms.

The above tests are just a beginning; they were all performed with a single set of parameters describing the characteristics of the pathogen and effectors. In other words, our model immune system was only tested against a single kind of pathogen, under one set of initial conditions. To evaluate whether the adaptive secretion strategies described above are truly adaptive, a wider range of pathogen parameters and initial conditions must be explored. Ideally, individuals in the GA would be challenged with multiple pathogens of varying virulence. The fitness measure would then be a composite of results from each individual 'infection'; this would ensure that the best individuals used broadly applicable feedback strategies.

Another important area for future research is in applying the results of such a survey to spatial models. Differential equations only approximate the dynamics of a spatially distributed system of discrete agents. It is unlikely that the exact parameter values will map directly to agent-based systems. However, they do pro-

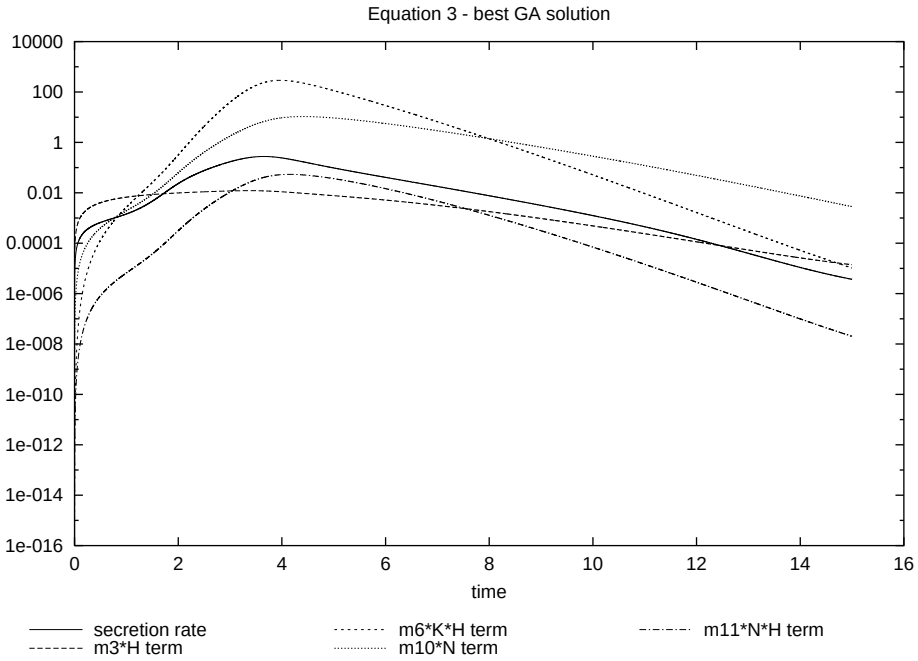

Figure 1: Time course of the simulated immune response, using the parameter values for the best GA solution found (shown in the text). The plot shows the magnitude of the secretion rate s and its variable component terms. Note the logarithmic scale in the y axis.

vide a measure of the relative importance of different signals and interactions.

Although there is a great deal of work left to be done on this specific problem, the current work illustrates an interesting approach to design of multi-agent systems. Many systems of interest have a number of conflicting goals like those described above, and require similar kinds of 'diffuse feedback' to resolve those goals (Segel 2000). A mathematical formulation of the system, together with an evolutionary strategy for evaluating different approaches, allows broad exploration of possible designs. This can be much less time-consuming than experimenting with designs individually.

References

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