BIOREPS Problem Set #13
How a well-adapted immune system is organized

1 Background

The adaptive immune system protects organisms from a great variety of pathogens by maintaining a population of specialized cells, each specific to particular challenges. Together these cells cover the array of potential threats. To recognize pathogens, the immune system relies on receptor proteins expressed on the surface s main constituents, the B and T lymphocytes. These receptors interact with antigens (small molecular elements making up pathogens), recognize them through specific binding, and initiate the immune response. Each lymphocyte expresses a unique receptor formed from random combinations encoded in the genome. The receptors later undergo selection through the death and division of the lymphocytes that express them, as well as mutations in the case of B lymphocytes. The diversity of the receptor repertoire determines the range of threats that the adaptive immune system can target in relation to the adaptive repertoire and the pathogenic environment.The adaptive immune system uses the experience of past infections to prepare its limited repertoire of specialized receptorsto protect organisms from future threats. We will attempt to calculate the best, most efficient way of doing this. Building a theoretical framework from first principles, we can predict the composition of receptor repertoires that are optimally adapted to minimize the cost of infections from a given pathogenic environment. A naive repertoire can reach these optima through a biologically plausible competitive mechanism. Our findings will begin to explain how limited populations of immune receptors can self-organize to provide effective immunity against highly diverse pathogens.

To find the optimal repertoire distribution we must consider the nature of antigen-receptor interactions and a penalty that the immune system pays for not recognizing antigens. This penalty must reflect the facts that recognition should happen within a reasonable time, before the pathogen colony can significantly increase its size; the interactions between the immune receptors and antigen are probabilistic; and not all antigens are equally frequent. We assume that, although the immune system cannot predict precisely which antigens it will encounter and when, it incorporates an estimate of the probabilities of their occurrences. We also take these probabilities to be constant in time. This is an idealization grounded in a separation of timescales, which assumes the distribution of antigens remains constant on timescales on which the immune system adapts.

During its time in the periphery, an antigen a will encounter and possibly interact with receptors at a rate $\lambda(t)$ that increases with time as the pathogen population grows. $f_{r,a}$ is the probability with wchich that antigen is recognized by the receptor, in other words the chance that there will be a reaction to a given encounter. For our purposes $f_{r,a}$ will be set at 1, meaning that everytime a receptor encounters the correct antigen it detects it and marks it for destruction.

Mathematically, let us define the encounter rate, λ as equal to the inital concentration of cells at time = 0, times the growth of the antigen: $\lambda_a(t) = \lambda_a(0)e^{\nu'_a t}$

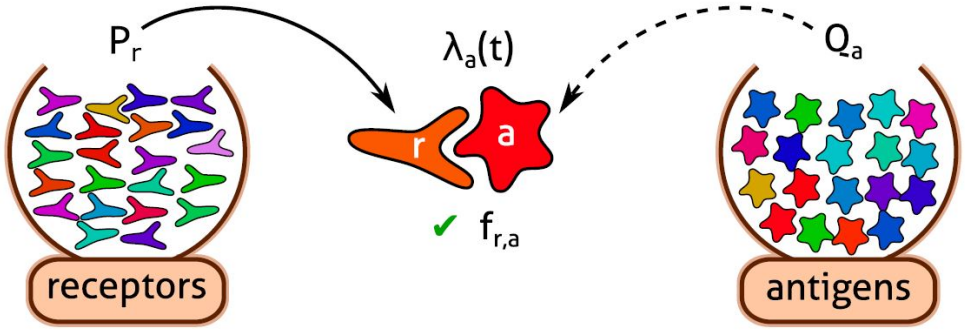

Figure 1: Schematic of a statistical model of antigen recognition by the adaptive immune system. After infection, antigen a encounters immune receptor r at random with a rate $\lambda(t)$. An encounter leads to a successful recognition with a probability fr,a that reflects the matching between a given antigen receptor pair. Image credit: Ref. [1].

References

[1] Andreas Mayer, Vijay Balasubramanian, Thierry Mora, and Aleksandra M. Walczak. *How a well-adapted immune system is organized*. PNAS, 112(19):5950-5955, 2015.

2 Questions

2.1 Finding the harm done

a) During its time in the periphery, an antigen *a* will encounter and possibly interact with receptors at a rate $\lambda_a(t)$,that increases with time as the pathogen population grows. Each encounter will occur with a different receptor r drawn from P_r. The mean number of encounters between antigens and receptors after a time *t*, which we call effect time, is given as $m_a(t) = \lambda_a(0)(e^{\nu'_a t} - 1)/\nu'_a$, where $\lambda_a(0)$ is the constant rate $\lambda_a(t)$ at $t = 0$. To find the cost function, we need to first derive $t_a(m)$ in terms of m_a. In other words, we need to find the inverse function of $m_a(t)$
Hint: Take log on both sides of the equation. To make your life easier, assume $t \gg \frac{1}{\nu'_a}$, so you can ignore some terms in order to simplified the expression.

b) The more antigens there are at the time of the immune reaction,the more damage they can potentially do. The cost function is also expected to grow exponentially in time:

$$F_a(t) = F_a(0)e^{\nu'_a t} \tag{1}$$

Substitute the expression for $t_a(m)$ into the above equation to derive the cost function in terms of m_a. Please show that $F_a(t) \propto m_a^{\alpha}$, with $\alpha = \nu_a/\nu'_a$.

2.2 Finding the average harm

In the previous part, we derived F_a, the harm done when the first recognition is at time t. In order to find the mean harm done, $\bar{F}_a$, we must perform a time integral of the product of harm done at time t, $F_a(t)$, and the probability that the first recognition is at time t, $H_a(t)$.

That is,

$$\bar{F}_a = \int_0^\infty dt H_a(t) F_a(t) \tag{2}$$

a) We need to calculate $H_a(t)dt$, the probability that the first recognition of the the antigen is between time t and time $t+dt$. It is easiest to approach this problem by discretizing the interval into n timesteps of length dt and then later finding the limit as these timesteps become infinitesimally small. $H_a(t)dt$ is a product of three parameters

1. The probability of an encounter between time t and time $t + dt$
2. The probability a given receptor recognizes antigen a
3. The probability of there not being any prior recognition events

The first two parameters we've dealt with already in this problem set, but the third parameter is less straightforward. One way to think of this third parameter is to picture it as the product of a recognition event not occurring in each of the n timesteps between time 0 and time t.

Hint: For this third parameter, you can ignore all terms of order $\mathcal{O}(dt^2)$ or higher. This will result in the probability of there not being any prior recognition events as 1 minus a sum of n terms. If you use the identity $1 - x \approx e^{-x}$ for small x, and take the limit of the sum as dt is made infinitesimally small, you should ultimately find that

$$H_a(t) = \lambda_a(t) P_a e^{-P_a m_a(t)} \tag{3}$$

and therefore

$$\bar{F}_a = \int_0^\infty \lambda_a(t) P_a e^{-P_a m_a(t)} F_a(t) \tag{4}$$

2.3 Minimizing the cost function

Suppose that there are two antigens in the body antigen a and antigen b. These antigens have corresponding receptors in our bodies specifically engineered to bind with and mark that antigen for destruction via the immune system. Therefore for each antigen we have, there exists a unique receptor, in our case: receptors a and b. With these given starting conditions, what is the optimal repertoire for the body to defend itself against attack. In other words, what is the most efficient and effective balance of receptor to have in order to fight any given attack. In order to calculate for optimality, we must first develop a Cost function based on the the probability that pathogen will show up and the harm that it will subsequently cause if allowed to go on unchecked. This "harm" that the pathogen creates has two components to it: μ is the virulence, or how deadly a pathogen is and Q we will simplify both of these into $\kappa = \mu Q_a$. Harm, as used in our cost function is dependent on how many there are and how long it is not detected, not on virulence μ

Now that we have solved for the harm functions for an average number of encounters and before the first recognition event, we are now tasked with the problem of finding the probability of receptors for a given antigen. To solve this minimalization problem, we need to pull from parts 2.1 and 2.3 and make certain substitutions. The main function we will work with will be labeled as the cost function where

$$Cost \equiv \langle F \rangle = \sum_a Q_a \bar{F}_a P_a \tag{5}$$

a) From equation 4 use Jacobians to convert $\bar{F}_a(t) \rightarrow \bar{F}_a(m)$ and substitute this into the Cost function.

b) From part 2.1, substitute $F_a(t) \propto m_a^\alpha$ for the value of F_a(m) and finally arrive at the following equation:

$$Cost = \sum_a \kappa_a P_a \int_0^\infty e^{-P_a m} m_a^\alpha dm \tag{6}$$

c) From this simplification, we will expand equation (4) to arrive at the following result:

$$Cost = \kappa_a P_a \int_0^\infty e^{-P_a m} m^\alpha dm + \kappa_b P_b \int_0^\infty e^{-P_b m} m^\alpha dm \tag{7}$$

The rate of harm for a respective pathogen is ν_a, and the rate of growth for the same pathogen as ν'_a. Combining these two variable we get: $\alpha = \nu_a / \nu'_a$ Again, to make the calculations stomachable, we will assume that for every pathogen: $\nu_a = \nu'_a$. Therefore, α is always equal to 1.

Show that this Cost equation Equals the following equation.

$$Cost = \kappa_a / P_a + \kappa_b / P_b \tag{8}$$

d) Now that we have a simplified equation for the Cost function, we can solve it for P_a and P_b. To sovle this equation, take the derivative of equation (8) with respect to P_a and set it equal to 0. solve for P_a. *hint: because this is a two anitgen system let* $P_b = 1 - P_a$

Conditions: $\kappa_a = 10$ and $\kappa_b = 3$ While these numbers are arbitrary, they are suppose to represent the products of the virulency and the frequency of these diseases.

The result of this calculation should produce a larger P_a value than P_b because of the larger κ_a value. This P value represents the probability of finding a receptor for antigen a in the repertoire of the immune system.