# Systems medicine Lecture notes Uri Alon (2020)

# Lecture 6

# The immune system detects exponential threats

[Sontag Cell Systems 2017 "A Dynamic Model of Immune Responses to Antigen Presentation"] -

**Introduction:**

Congratulations! We have successfully completed part 1 of this course, devoted to the design principles of hormone circuits. We saw how a regulatory motif allows hormone circuits to achieve size control of the glands, and to buffer variations in parameters in order to maintain homeostasis. We studied how biphasic control eliminates mutants in the glucose-insulin system, but leads to fragility to type-2 diabetes. We saw how a combination of two such motifs appears in the HPA stress-response pathway, leading to oscillatory phenomena that may play a role in bipolar disorder. The HPA circuit has a fold-change detection property that plays a role in addiction. We still need to understand the autoimmune disease called type-1 diabetes in which the body kills the beta-cells that secrete insulin - we will do so soon.

We now enter part 2, devoted to immune defenses and their associated diseases. In this lecture, we will set the stage.

**A major task of the immune systems is to fight pathogens like bacteria and viruses.** These pathogens make more of themselves - bacteria divide, and viruses use host cells to make more viruses. Thus, they **grow exponentially in time**, $e^{\alpha t}$. Since pathogens cause damage to cells, their exponential nature is very dangerous. They can rise quickly and thus threaten our lives. Without the immune system we quickly die of infection, as in AIDS in which the HIV virus destroys immune cells, or unfortunate germline mutations that abolish the immune system (baby in a bubble).

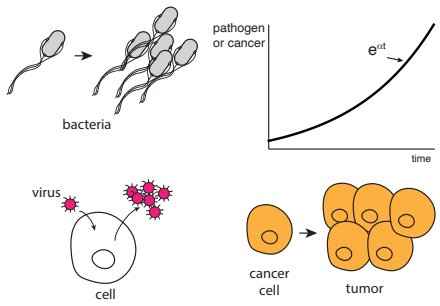


*Figure 6.1*

**Another exponential threat is cancer.** Cancer cells are mutant cells that divide without control. Their number, at least at first, grows exponentially. The immune system is a major mechanism to fight cancer, and in fact eliminates most cancers before we even notice them.

The immune system causes damage to the body, and thus we must keep it under control. Its responses cannot too strong or costs will outweigh benefits. All of us have immune cells that can attack our own cells, called **self-reactive immune cells**. These must be inhibited or we may get autoimmune disease, like type-1 diabetes.

**Thus, the immune system must operate within tight constraints**: it must quickly kill exponentially rising threats, without causing too much damage to self.

In this lecture our goal is to understand how the immune system can recognize exponential signals $e^{\alpha t}$ and respond strongly, while ignoring constant signals even if they are very strong, like self-tissues. The concept of fold-change detection from the previous lecture will play a role. Then, we will discuss which factors decide whether a given virus or tumor ends up killing the host or ends up eliminated by the immune system.
In this lecture we will use a bit more math than usual, and build the stage for the next lecture, which will explain why self-reactive cells and autoimmune diseases exist in the first place.

So first an outline of the immune system, and then a simple model of how it can detect exponential threats.

**Outline of the immune system**

The immune response has two main arms: **innate immunity** which is rapid and general, and **adaptive immunity** which is slower and specific (Fig 6.1). Both destroy pathogens: they eat up pathogens if they are outside our cells, and destroy infected cells when the pathogen is inside them.
The innate immune system is triggered by damaged cells. Damaged cells secrete signal molecules called **cytokines**. Important cytokines include IL1 and IL6. The innate system works in minutes to hours. The main response is **inflammation**, in which blood vessels open up little windows to let fluid with anti-bacterial proteins and white-blood cells into the tissue. These white blood cells, including phagocytes like macrophages and neutrophils, kill and eat up bacteria. Other cells called natural killer (NK) cells kill damaged cells including cells infected by virus and cancer cells. To detect bacteria, innate immune cells have sensors for the common denominators of all bacteria, such as bacterial cell wall component LPS. These sensors arose by evolution over half a billion years.

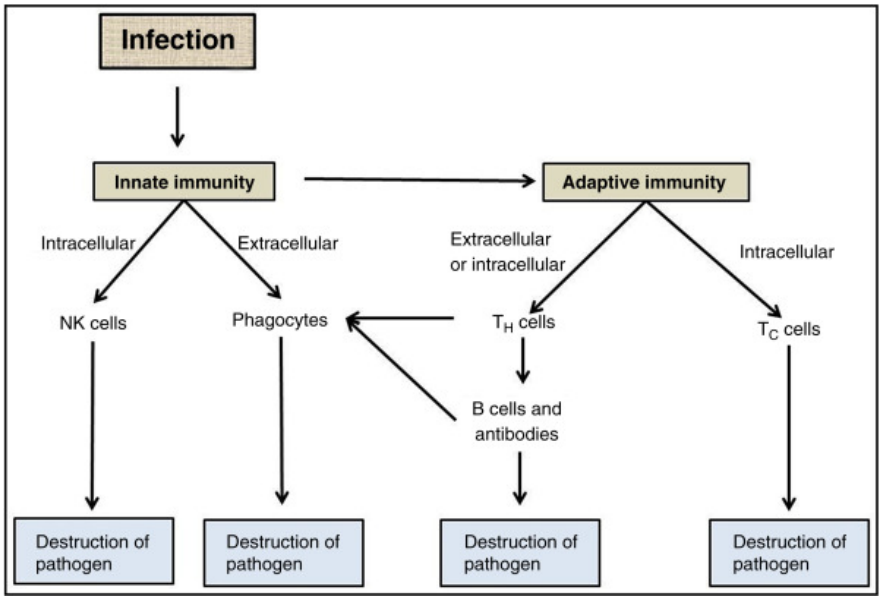


Figure 6.2 source: https://www.sciencedirect.com/topics/agricultural-and-biological-sciences/immune-response

If innate immunity is not enough, and the infection lasts more than a few days, the innate system calls in experts that can deal with the specific nature of each pathogen. This is the **adaptive immune system.**

The adaptive immune system makes its own sensors, to recognize virtually any foreign molecules. It can detect even molecule never seen in nature and synthesized only in the lab. It is called "adaptive" because it builds, refines and amplifies new sensors. It has B-cells that make antibodies that can bind to foreign molecules. In this lecture we will focus on **T-cells**, whose job is to kill cells infected with virus and cancer cells. To do so, T-cells monitor the cells of the body to see if they make proteins that belong to viruses or mutated

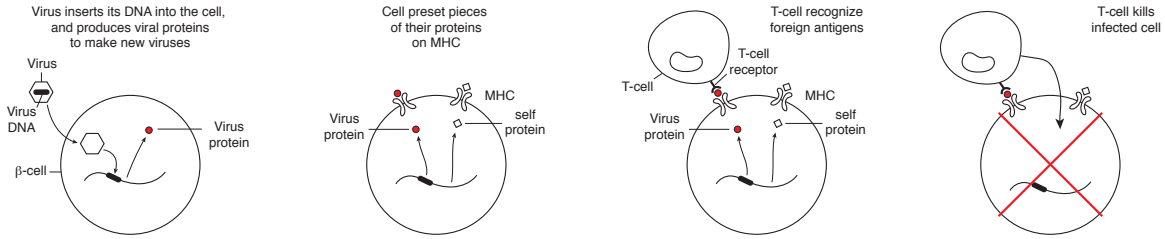


*Figure 6.3*

cancer proteins (Fig 6.3). All cells present parts of their proteins on special molecular "platters" called MHC on the cell surface, where they can be read by T-cells. Each cell has many MHC molecules presenting various pieces of their proteins.

There are billions of types of T-cells in each person. Each T-cell has a unique T-cell receptor that can recognize (bind to) a different protein fragment presented on the MHC. The recognized protein fragment is called the **antigen**. If the T-cell binds to a foreign antigen, it multiples. Now there is an army of T-cells with the same receptor. The T-cell army seeks cells that present the antigen on their MHC and kills them. Thus, T-cells eliminate cells infected with a virus, thanks to the foreign protein antigens produced by the virus inside the cell and presented on the cell surface in the MHC.

Most of the antigens presented on the MCH are fragments of healthy proteins normally made by cells. These are called **self-antigens**. A huge question in immunology is how self-antigens do not lead to immune attack, which would destroy the cells of our healthy tissues. *How can the immune system tell self from non-self?*

The main concept is that **most of the T-cells that react to self-antigens are eliminated**. T-cells are made in bone marrow in an inactive state and then move to an organ near the lungs called the **thymus** (Fig 6.3). Each T-cell has a unique T-cell receptor, and some T-cells can recognize self-antigens. In the thymus, the new T-cells are presented with virtually all types of self-proteins in a safe environment. T-cells that bind self-antigens too tightly kill themselves. Other turn into regulatory T cells, called $T_{regs}$, which will be important in this lecture. These $\boldsymbol{T_{regs}}$ **inhibit killer T-cells**. This process of elimination of self-reactive T-cells is called central tolerance.

B-cells that produce antibodies have a similar selection process against self-reactive cells. It happens in the bone marrow (The "B" in B-cells stands for bone marrow, the "T" in T-cells for thymus).

Since T-cells are dangerous, they are not immediately licensed to kill. When they leave the thymus, T-cells are in a **naïve state**, and cannot function. They need to be activated. Both killer T-cells and $T_{regs}$ are activated by recognizing an antigen with their T-cell receptor (TCR). This activation requires the help of special **antigen presenting cells**. Antigen presenting cells, including macrophages and dendritic cells, collect pieces of proteins from tissue and present them on MHCs. Two steps are required. First the naïve T-cell must recognize the antigen with its TCR, and second a **costimulatory "alarm signal"** is needed. In this alarm signal, the antigen-presenting cell (APC) provides a protein on its surface called CD28 that "shakes hands" with a protein called B7 on the T-cell . This costimulatory signal is provided if there is inflammation: the innate immune system provides the signals for inflammation, and for setting APCs into action. This ensures T-cells are activated only in the context of an infection or problem in the tissue. This activation explains the additional rounds of T-cell selection in the body (called peripheral tolerance, Fig 6.4). If T-cell binds an antigen on an APC without the second "alarm" signal, the T-cell is eliminated (processes called anergy and clonal deletion).
Furthermore, T-cells that get over-stimulated are also eliminated by **activation-induced cell death**. This helps turn off the immune response if it is too strong. It also eliminates T-cells that respond to self-antigens, due to the huge amount of self-antigen in tissues that

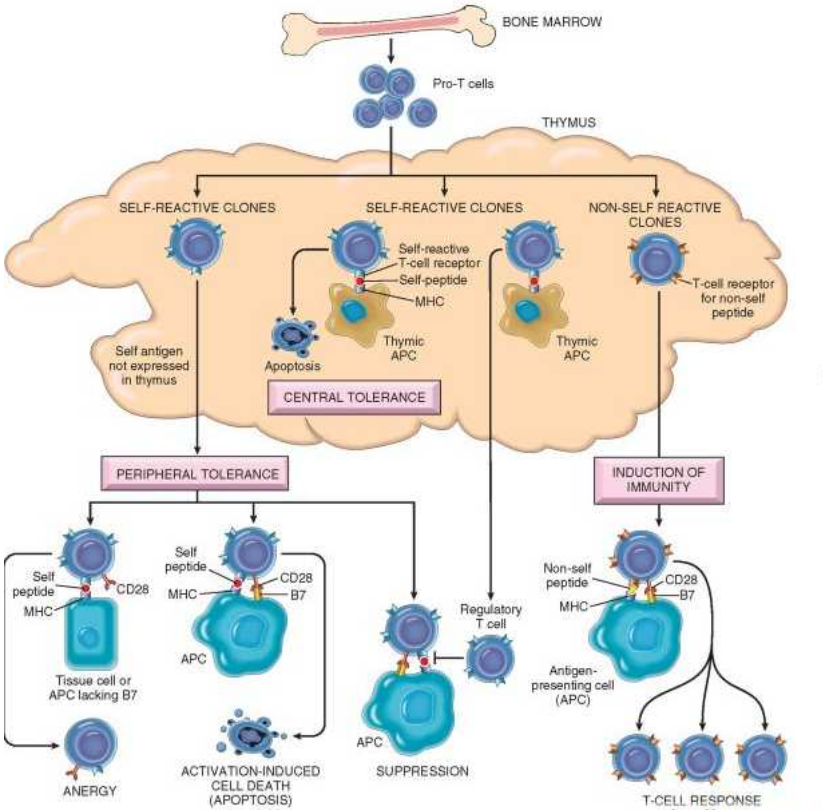


Figure 6.4. Source: https://www.muhadharaty.com/files/lectures/006/file5964.pptx_d/image13.png.jpg

can trigger activation-induced cell death. Thirdly, activation-induced cell death can also an weed-out T-cell mutants that have mutation making them hyper-sensing. These mutants would otherwise turn into killers on the loose. This is a biphasic type of mechanism, against mutants, similar to glucotoxicity of lecture 2.

Thus, elimination of self-reactive cells is done by both comparing to a "library" of the proteins found in our body (central tolerance in the thymus) and by context (peripheral tolerance). Despite these elimination measures, experiments show that healthy people have self-reactive T-cells.

If the T-test passes all of these tests successfully, it is activated when its antigen is presented to it by an APC together with an alarm signal. When activated, the T-cell divides and produces a clone of cells with the same TCR, ready to go to the tissues and kill cells that present the antigen. A small fraction of this clone becomes **memory T-cells** (and similarly, memory B-cells). The memory T-cells respond at once to the pathogen if it returns months or years later. They are the basis for vaccines, in which a weakened version of the pathogen causes memory T-cells to be formed, ready to fight the real pathogen should it appear.

Historically, the way the adaptive immune system works was proposed in a theory paper by Australian physician Frank Macfarlane Burnett (1957). Burnett's theory had four tenants:

- Each adaptive immune cell bears a single type of receptor with a unique specificity.
- Receptor occupation by antigen is required for cell activation.
- Activation makes the cells divide and bear receptors of identical specificity as the parent cell.
- Adaptive immune cells bearing receptors for self-molecules are destroyed at an early stage.

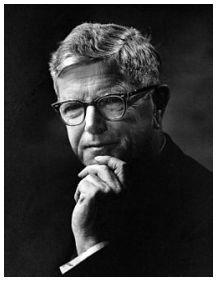

*Figure 6.5*

Experiments soon confirmed this 'clonal expansion' theory, such as experiments by Peter Medawar showing that each immune cell has a single type of receptor. Over the years, theory has had an important role in the development of immunology.

Now that we have the main players, T-cells and $T_{regs}$, we can ask how the immune system can detect exponentially growing threats like pathogens and cancer.

**The Sontag model for T-cells explains how exponential threats are detected.**

The immune system has T-cells that kill, (called **effector cells,** which includes subgroups which we didn't discuss, cytotoxic T-cells and helper T-cells) and regulatory T-cells that inhibit their activation. We will follow an elegant model by Eduardo Sontag (2017). Sontag is a control theorist, and uses control theory terminology of calling the input u, the output y and the internal variable x.
So, we will say that the input is the amount of antigen from a pathogen or tumor, u=a(t). The amount of effector cells is the output, x=T(t). The amount of regulatory cells is an internal variable y=R(t).

The antigen a causes activation of both effector cells T and regulatory cells R. The regulatory cells R inhibit the production of effector cells T.

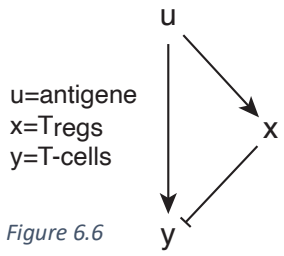

*Figure 6.6*

This results in a regulatory motif that is well-known in systems biology, called the **incoherent feedforward loop** (Fig 6.6). Let's see what this name means. "Feedforward loop" is due to the forward direction of the arrows in a triangle pattern, flowing from input to output in two arms: input u activates both x and y, with x affecting y. The feedforward loop is called "incoherent" because u does a thing and its opposite: (i) activates y and (ii) inactivates y by activating its inhibitor x. There are also coherent feedforward loops in which x activates y. In 2002, Ron Milo, Shai Shen Orr and Shmoolik Mangan, who were PhD students with me, discovered the IFFL when studying gene regulation networks. The IFFL motif appears in the gene regulation networks of all cells studied so far. It has important functions, such as fold change detection, as we will discuss below.

The IFFL equations in a simplified form of Sontag's immune model are based on the following interactions. The antigen a causes activation of both effector cells T and regulatory cells R, at rates $\beta_1 a$ and $\beta_2 a$. The regulatory cells inhibit the production of effector cells, so that T production is $\beta_2 \frac{a}{k+R}$. Here, the $1/(k+R)$ term is a typical Michaelis-Menten description of the reduction in the activation of T-cells caused by $T_{regs}$. This reduction occurs, for example, by cytokines secreted by $T_{regs}$, and by $T_{regs}$ 'drinking' up cytokines required for T-cell proliferation such as IL2. We will generally deal with situations in which $T_{regs}$ are numerous enough to ignore the "k" in the $1/(k+R)$ term, and thus T production term is, to a good approximation, $\beta_2 \frac{a}{R}$. Both T-cells and $T_{regs}$ are removed with lifetimes $1/\alpha_1$ and $1/\alpha_2$ of about 10 days. Thus,

$$(1)\ \frac{dR}{dt} = \beta_1 a - \alpha_1 R$$
$$(2)\ \frac{dT}{dt} = \beta_2 \frac{a}{R} - \alpha_2 T$$

Let's see how this circuit behaves. We will begin with a step of input and then do an exponentially rising input.

**Solved exercise 1: Find the steady-state of the circuit for a strong antigen stimulus**

To find the steady state, we set all time derivatives to zero. The steady state of R, derived by setting $dR/dt = 0$ in Eq. 1, is proportional to antigen.

$$(3)\ R_{st} = \frac{\beta_1}{\alpha_1} a_{st},$$

The steady state of T, derived by setting $dT/dt = 0$ in Eq. 2, is

$$(4)\ T_{st} = \frac{\beta_2 a_{st}}{\alpha_2 R_{st}}$$

Plugging in $u_{st}$ and $R_{st}$ we find a steady state solution that does not depend on input $a_{st}$:

$$(5)\ \ T_{st} = \frac{\beta_2 \alpha_1}{\alpha_2 \beta_1}.$$

Now suppose there is a step-like rise in antigen a(t). As a result of the rise, T is made, but then R is made and shuts off T production. As a result, R(t) first rises and then drops. A step of antigen results in a pulse of effector cells. (Fig. 6.7)

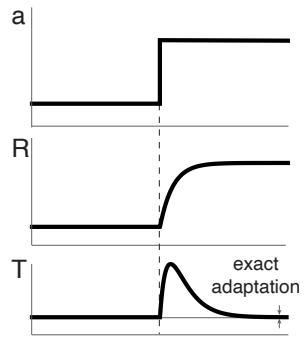

*Figure 6.7*

The pulse actually shows **exact adaptation**, in which T levels return to their original steady-state before the step, despite the continued presence of a. Exact adaptation occurs because $T_{regs}$, R(t), rise in proportion to input u, and normalize it out in the production term of T(t), which goes as $a/R$ when R is large enough. That is why the new steady state $T_{st}$ is the same as the original steady state, because $T_{st}$ does not depend on input.

Thus, **the response to a step of antigen a(t) is a pulse, a rise of T(t) and a drop back to the original steady-state.**

This pulse can be useful to avoid errors of attacking self-tissue. Suppose there is tissue damage causing an ongoing release of self-antigen a(t), like a step function. There is a risk that auto-reactive T-cells respond to it, killing self-cells. The IFFL ensures that the response is only transient.

In fact, this IFFL circuit provides **fold-change detection** (Fig. 6.8). It responds to relative changes in input antigen a(t). To see this, we note that after an input step from 1 to 2, $R_{st}$ is twice as large as before the step. Thus, a new step from 2 to 4, has the initial production of y normalized by R=2, and thus $a/R$ is the same as in the first step.

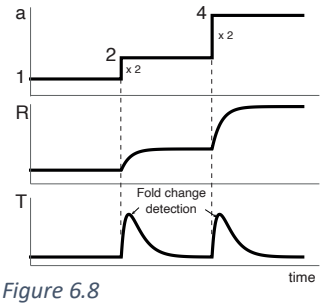

*Figure 6.8*

So far in this course we saw two different motifs that can provide fold-change detection: the two-gland feedback loop of the HPA axis, and the IFFL of T-cells. These are the two main types of FCD motifs found across biology, on the level of gene regulation circuits and sensory systems (reviewed in Adler et al, 2018).

Because of fold-change detection, even a linear rise in antigen with time, $a(t) \sim \alpha\, t$, called a ramp, becomes progressively less potent in activating immune response, and indeed T(t)

adapts to baseline. We say that the **IFFL 'rejects' steps and linear ramps of input**. (Fig. 6.9)

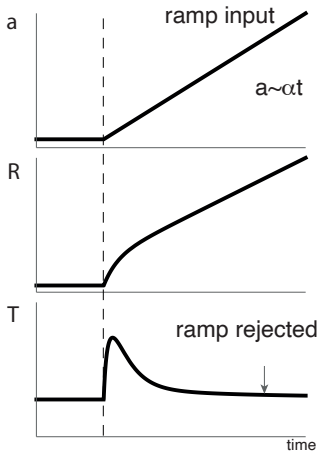

*Figure 6.9*

The only way to get a persistent T-cell response is to keep making *relative* changes in a(t) - in other words, **an exponentially rising antigen level a(t)**. This is prefect for detecting the main threats that the immune system is designed for: pathogens and tumors.

**The immune system can measure the exponential growth rate of pathogens and tumors**

Let's consider a pathogen such as a bacterium or virus, or a tumor. These make non-self antigens. Without the immune system, these pathogen or tumor cells make more of themselves at rate $\alpha$, and thus

$$\frac{da}{dt} = \alpha a$$

whose solution is exponentially rising pathogen with time

$$a(t) = a_0 e^{\alpha t}$$

This rise will kill the host, unless the immune system can respond. Because $a(t)$ rises exponentially, the effector cells T(t) can no longer exactly adapt.

**Solved exercise 2: Show that the IFFL circuit does not adapt to an exponentially rising input (Fig. 6.10)**

To solve with $a(t) = a_0 e^{\alpha t}$, we note that R(t) tracks the input. Thus, we try an exponential solution for R(t), namely $R(t) = R_0 e^{\alpha t}$. Our task is to find $R_0$. From Eq. 1, $\alpha R_0 e^{\alpha t} = \beta_1 a_0 e^{\alpha t} - \alpha_1 R_0 e^{\alpha t}$. We can see that the terms $e^{\alpha t}$ cancel out, so our guess for R(t) was good, and we find

$$(6)\ R_0 = \beta_1 \frac{a_0}{\alpha + \alpha_1}$$

Since both R(t) and u(t) rise with the same exponent $e^{\alpha t}$, they normalize out in the production term in Eq. 2 which goes like a(t)/R(t). This term becomes a constant, $a_o/R_o$. As a result, from Eq. 5, we find that y reaches a steady-state higher than its original steady-state value:

$$(7)\ T_{st}^{exponential\ input}(\alpha) = \beta_2(\alpha + \alpha_1)/\beta_1\alpha_2$$

As a sanity check, note that when the pathogen does not grow at all, $\alpha$ =0, that is when u(t) is constant, we get back Eq. 5.

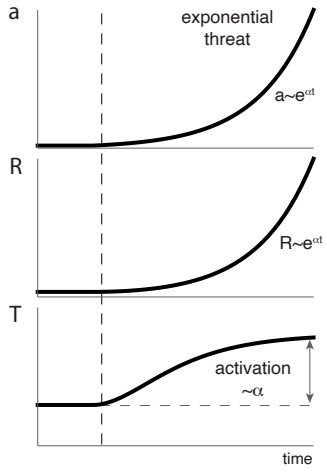

*Figure 6.10*

The difference between $T_{st}$ and its baseline is **proportional to the pathogen/tumor growth rate**

$$T_{st}^{exponential\ input}(\alpha) - T_{st}^{constant\ input} = \beta_2\alpha/\beta_1\alpha_2.$$

Thus, the IFFL circuit is an **estimator of pathogen growth rate.**

Sontag's model provides a mechanism for previous experimental and mathematical work that postulated a dynamical threshold for setting off the immune system (Grossman and Paul (1992), Pradeu et al. (2013)).

So far, we let the pathogen grow exponentially with its natural rate. For clarity, lets denote this natural rate $\alpha_0$. Now we consider how this growth rate is affected by the immune system which kills the pathogen/tumor cells. Effector T-cells kill infected cells and tumor cells, and secrete cytokines that help cells fight the viral replication, and enhance inflammation that kills bacteria. Thus, the growth rate of the pathogen/tumor is reduced by the effector cells (Fig. 6.11). This reduction of the natural growth rate is proportional to the effector cells y, with proportionality constant c:

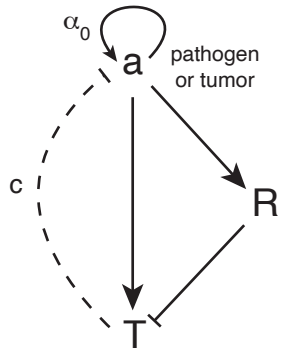

*Figure 6.11*

$$\frac{da}{dt} = (\alpha_0 - c\,T)a$$

Is this enough to kill off the threat? To find out, we write the equation for the pathogen growth rate.

**Solved exercise 3: Find conditions for killing of the pathogen/tumor**

Let's consider the system at steady-state in which the pathogen grows at rate $e^{\alpha t}$, where

$$(7)\ \ c = \alpha_0 - c\,T_{st}$$

This growth rate $\alpha$ takes into account both the natural rate $\alpha_0$ and the reduction due to the immune system. We want $\alpha < 0$ to get rid of the pathogen; if $\alpha > 0$, the pathogen grows exponentially and kills us. The immune response at steady-state, $T_{st}$, is determined by $\alpha$. Plugging in $T_{st}^{exponential\ input}(\alpha)$ from Eq. 6, we find that the pathogen growth rate in Eq. 7 is:

$$\alpha = \alpha_0 - c\frac{\beta_2(\alpha+\alpha_1)}{\beta_1\alpha_2},$$

We can combine the terms with $\alpha$ on both sides to get

$$\alpha\left(1 + c\frac{\beta_2}{\beta_1\alpha_2}\right) = \alpha_0 - c\frac{\beta_2\alpha_1}{\beta_1\alpha_2}$$

For $\alpha$ to be positive, the term on the right needs to be positive. Thus, if the pathogen/tumor has a large enough natural growth rate $\alpha_0$, exceeding a threshold, it escapes

$$\alpha_0 > \alpha_{th} = c\frac{\beta_2\alpha_1}{\beta_1\alpha_2}$$

Otherwise, the pathogen/tumor shrinks and vanishes exponentially.

Thus, **the pathogen or tumor is eliminated if its natural growth rate is below a threshold,** and grows exponentially if its natural growth rate is above the threshold (Fig. 6.12). The threshold is the killing rate of the steady-state immune response to a constant input of Eq.5: $\alpha_{th} = c\frac{\beta_2\alpha_1}{\beta_1\alpha_2} = cT_{st}$. The immune system is better at removing threats the larger this threshold.

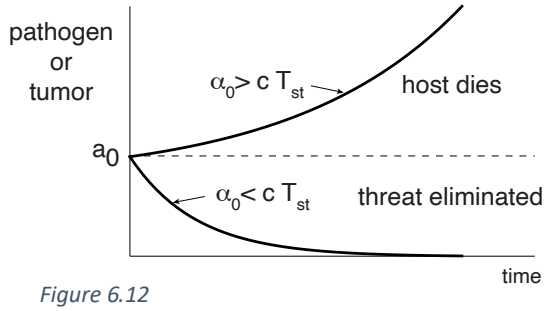

*Figure 6.12*

The threshold increases with the killing parameter c and production parameter of effectors $\beta_2$ and removal rate of regulators $\alpha_1$. It also increases the smaller the production of regulators $\beta_1$ and removal of effectors $\alpha_2$. This all makes simple sense, threshold rises with "pro-killing" and drops with "pro-inhibition" parameters.
People vary in these parameters, and thus a given pathogen can have different effects on different people. Recall that it may not be feasible to enlarge parameters like the killing rate parameter *c* to very high values, because it may set off auto-immune disease. Similarly, the lifetimes of the cells are probably tuned to avoid overly extended or overly brief immune responses.

One may ask how the self-reactive immune cells avoid attacking embryos who grow exponentially. This is achieved by preventing mom's immune cells from crossing the placenta and reaching the embryo. Furthermore, during pregnancy the killer-T-cell arm of the immune system is down-regulated. This is evident in reduction of mom's risk of autoimmune diseases caused by T-cells during pregnancy. These diseases often flare up after giving birth.

After birth, babies' growth rate steadily declines, and reaches a plateau in childhood of about 6cm/year. It grows again during puberty and then declines to zero. The 'fold-change detector' of the immune system thus is most likely to be falsely triggered during puberty. Puberty is indeed a phase with increased onset of autoimmune diseases (Pradeu, 2012).

Pathogens and tumors can evolve ways to deal with the immune system. For example, cancer can fool the immune system to leave it alone. Since cancer cells divide and mutate quite often, they can undergo **evolution inside the body**. Cancer cells that evade immune killing survive and take over the tumor. Thus, cancer evolves several ways to avoid immune surveillance. One way is to increase expression of "don't kill me" signal expressed by healthy cells. One such signal, a protein on the cell surface, binds a receptor on T-cells called PD-1 and inactivates the T-cells. Cancer cells often gains mutations that express a lot of don't-kill-me signals on their surface. These mutations are selected because those cells are spared by the killer T-cells. In the past decade, this finding has been used for therapy. Drugs called **checkpoint inhibitors** that block PD1 or its ligands can cause some cancers to suddenly be attacked by the immune system, and sometimes the cancer is cured. This does not work for all cancers and all patients for reasons that are not fully understood. There are additional ingenious evasion strategies. Cancers can turn T-cells into $T_{regs}$ by secreting signals such as TGF-beta. Some cancers are surrounded with many immune cells

that are inactivated in this way (hot tumors), whereas others have a lack of immune cells altogether (cold tumors). Cancer cell metabolism also helps inhibit the immune system: cancer uses glucose to grow quickly, secreting lactic acid which produces an acidic environment that inhibits the immune system. Cancers sometime also reduce their expression of MHCs, to hide from T-cells. They cannot remove all of their MHCs however, because innate cells called NK cells hunt for cells without MHCs and kill them.

Our work in this lecture can add to this list also a dynamic aspect to immune evasion. Tumors grow exponentially when they are small. If they grow very quickly they can outrun the immune system ($\alpha_0 > \alpha_{th}$) as we just described. Then, they reach the limit where they can no longer get oxygen and nutrients just by diffusion. This happens at about a million cancer cells. Tumor growth then slows down, and cancer cells evolve the ability to call in blood vessels. Tumors thereafter grow quite slowly, sub-exponentially with time. This slow growth may help them stay under the radar of the adaptive immune system.

Similarly, pathogens evolved to exploit every possible chink in the armor of the immune system. Viruses like influenza reshuffle their genomes to change their coat proteins so that last year's antibodies are not effective against this year's strains. Some pathogens do not grow rapidly and thus dynamically hide from the immune system, such as the herpes virus. Such pathogens typically also inhibit the process of presentation on the MHCs. Other pathogens send devious signals which interfere with immune system communications, or even attack immune cells themselves like HIV. Our helpful microbiome also coexists with us and is not destroyed by the immune system, which instead farms it in ways that are a current research frontier. The arms race between pathogens and immune systems is ongoing.

As Eduardo Sontag writes "we proposed a very simple phenomenological model that recapitulates some of the basic features of interactions between the immune systems and tumors (or, more generally at this level of abstraction, other immune challenges). The model leads to interesting conclusions regarding transitions between tolerance and elimination and the role of dynamics in self/non-self-discrimination and makes contact with several theory and experimental papers. Obviously, our model represents a purely phenomenological, macroscopic, and hugely over-simplified view of a highly complex, intricate, and still poorly understood network of interactions between different components of the immune system as well as immune interactions with pathogens and tumors. Paraphrasing the well-known quote, our model is "as simple as possible but not simpler" to illustrate the particular phenomena of interest."

**Appendix 1: A more realistic model of viral response dynamics:**

Data on viral infections show that virus load u(t) and immune cells first rise and then fall over the course of a week or two. Virus falls before the immune cells do (Fig 6.13). The simple IFFL model in this lecture captures only the "falling" phase of the infection. To capture the initial phase, the reactive $T_{regs}$ and T-cells should start from initial conditions of $R(0) = 0$ and $T(0) = 0$. Thus, we need the $T_{regs}$ inhibition term to go as $1/(k + R)$, so things don't diverge when $R = 0$. Second, in order to obtain a realistic response, we need to add two features to the model equations. We need a good delay between the time a virus is formed and the T-cells are activated. This is due in part to the time the antigen is presented on an APC. The presented antigen lasts about the lifetime of an APC, which is several days. If this was all, the immune system can oscillate due to the delays, by responding to the virus of a while ago. To allow the system to firmly kill the virus when it reaches low levels, instead of oscillating back up, we need to model the stochastic killing by the innate immune system and other effects. Each virus particle (virion) has a chance p to be killed or to be defective or to fail to find a host cell. Only when $(1 - q)u \sim 1$ does one virion succeeds on average: the virus stands about a 50% chance of replicating further. For chance of killing of $q = 99.9\%$, for example, u must exceed a minimal dose of about $a_0 = 1/(1 - 0.999) = 1000$ virions. One can model this roughly by letting the natural growth rate $\alpha_0$ be reduced at virus numbers below a half-way dose $u_0$. An example for such a term is $\frac{\alpha_0 a}{a_0 + a}$. Thus, an improved model adds a new variable p(t) for antigen presented on APCs, and has four equations with the above effects:

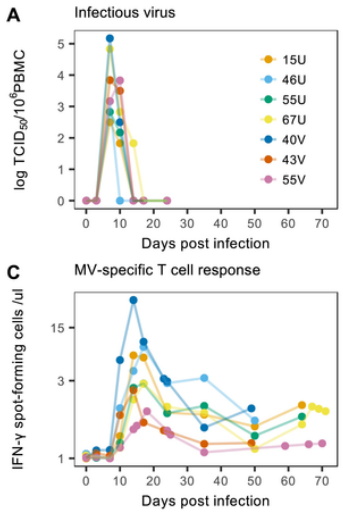


*Figure 6.13, Measles virus, in 7 individual monkeys, from Lin et al 2012*

$$\frac{da}{dt} = \left(\frac{\alpha_0 a}{a_0 + a} - cT\right) a$$

$$\frac{dp}{dt} = a - \alpha_3 p$$

$$\frac{dR}{dt} = \beta_1 p - \alpha_1 R$$

$$\frac{dT}{dt} = \frac{\beta_2 p}{k + R} - \alpha_2 T$$

Where $1/\alpha_3$ is the lifetime of the antigen-presenting APC. Simulating these equations shows that when virus growth rate is below a threshold, the virus and immune cells rise and then fall, as in Fig 6.14.

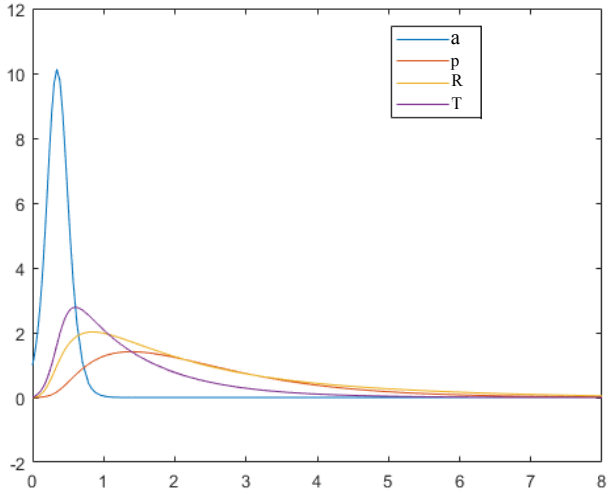


*Figure 6.14*

The parameters in the simulation in the figure are $\alpha_0 = 10; c = 10;\ k = 0.1;\ u0 = 0.01, \alpha_1 = \alpha_2 = \alpha_3 = \beta_1 = \beta_2 = 1$, with initial conditions $a(0) = 1$, and $p(0) = R(0) = T(0) = 0$. With these parameters, each unit of time is about 10 days.

**Appendix 2:**

What about autoimmune disease? If cytotoxic T-cells kill self-cells at rate k, they generate self-antigens, presented by APCs, we have

$$\frac{da}{dt} = k\,T - \alpha_3 a$$

where $\alpha_3$is the rate constant for removal of the APCs that present the antigen. Note that the equation is not auto-catalytic, there is no $k\ y\ u$ term, since here it's not a self-replicating pathogen/tumor, but rather T-cells damaging a vast amount of normal cells. This equation does not have an exponential solution for u(t) and thus the antigen rise is rejected at long times, and $T = T_{st} = \frac{\beta_T\,\alpha_R}{\alpha_T\,\beta_R}$.

Full blown autoimmune disease therefore probably requires a non-linear process of T autocatalysis leading to a locked-on high activity. Another possibility is inactivation of $T_{regs}$ at very high u levels, as in a recent experimental study of thyroiditis in mouse [https://www.pnas.org/content/pnas/116/52/26788.full.pdf].

**References:**

Biology is described in a clear math modelling paper by Kahilae et al 2013. https://www.frontiersin.org/articles/10.3389/fimmu.2013.00474/full

The study of immune systems and their interactions with tumors has long been the focus of theoretical and mathematical immunology (
Jerne, 1974, Bell et al., 1978). Two influential contributions were the paper by Stepanova (1979), in which a set of two ODEs was used to represent tumor and immune system cells, and the paper by

Kuznetsov et al. (1994), in which a similarly simple model was used to provide an explanation for the sneaking-through phenomenon, although with escape of small tumors and with no mechanism for detection of rates of change of the immune challenge. It is impossible here to review the literature in this very active area of research; some reviews and textbooks are Bell et al., 1978, Callard and Yates, 2005, Andrew et al., 2007, Eftimie et al., 2011, Wodarz and Komarova, 2014, de Pillis and Radunskaya, 2014, and Vodovotz et al. (2016).

During the past 30 or so years, a number of authors, most notably Grossman and Berke (1980) and Pradeu (2012), have proposed the necessity of incorporating dynamics of antigen presentation when attempting to understand the body's decision to initiate the immune response. They support this line of reasoning by experimental observations that (1) lymphocytes mount a sustained response only when faced with a sufficiently steep increase in their level of stimulation (for example, acute antigen presentation, proliferation rates of infected cells or tumors, stress signals) and (2) even when a new motif triggers an

immune response, its chronic presence may result in adaptation: downregulation or even complete termination of the inflammatory response. One mathematical formulation was introduced by Grossman and Paul (1992) who postulated the "tunable activation threshold" model for immune responses: effector cells in the innate or adaptive systems should become tolerant to continuously expressed motifs, or even gradually increasing ones, but should induce an effector response when a steep change is detected. Among recent variations upon this theme are the "discontinuity theory" postulated by Pradeu et al. (2013) and the "growth threshold conjecture"Arias et al. (2015)STAR Methods