

How does the immune system see to it that it is doing a good job

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In his essay Yaron Cohen asks How does the immune system *know* when it is making the right response, when it is doing the right thing? My own answer follows.

Feedback toward multiple goals. My first point is that there are many “right things”. Because the term is usefully evocative I call these right things *goals*, indeed “in a metaphorical sense” (Cohen). The goals are numerous, somewhat ill-defined or “dispersed”, overlapping, and often even contradictory. For example, the immune system “tries” to kill dangerous pathogens and to avoid harm to the self. These goals are in partial conflict, because inflammation harms self (for example to kill intracellular pathogens the immune system kills cells of the host). As Cohen stresses, many other goals of the immune system involve maintenance tasks ranging from assisting in wound healing to helping control tissue regeneration.

Cohen holds that the immune system “aim(s) at representing a part of the world” and it uses the resulting internal images to learn and adjust various reaction programs, each of which “amounts to a functional image of a stimulus that elicits a response”. True, I think, but not the whole truth. A fuller truth takes into account more explicitly the way the immune system copes with uncertainty by a generalized feedback, “beyond set points”. This feedback aims not to optimize immune response, but rather to improve it in real time with the aid of suitable sensory input.

Dispersed feedback copes with the unpredictable. Much of immune challenge and response is effectively unpredictable. Consider for example the matter of the generation of dominant epitopes by antigen presentation. This involves numerous fluctuating molecular level processes such as interaction with chaperones to protect the MHC, directed intracellular traffic, cleavage by restriction enzymes, selection of peptides to bind to the MHC and removal of degradation products from the MHC groove. The result is that the “choice of the favored determinant is essentially aleatory... and requires empirical test...”

[14]. Other unpredictable matters include the chance gene rearrangements that yield the operational spectrum at any given time of antibodies and T-cell receptors, the random choice of host genotype, the shifting spectrum of pathogen mutations, the function-altering polymorphisms in cytokine genes [9] and the impingement of unforeseeable environmental fluctuations. Even macroscopic organ systems might well provide a degree of uncertainty. The general possibility of chaos in complex dynamics is now well-accepted. More concretely, evidence has been obtained that features of fractal-like dynamics underly aspects of the complex variability in the healthy human heartbeat [5] and also in human gait [3]. Further, certain forms of life-threatening pathology, such as heart failure, are associated with a breakdown of these multiscale fluctuations and the emergence of excessively periodic and highly predictable behavior [1].

Engineers know how to deal with uncertainty, by *feedback*. The rotating-weight governor on steam engines is an old example of monitoring performance and reacting to the monitoring to reduce deviation from some set-point; if the engine rotates too fast then the swinging out of the weights partially opens a valve and thus decreases the steam pressure. Too slow rotation is countered analogously. More sophisticated engineering feedback came quite late, in the cybernetic age of the mid-twentieth century.

As a rule biology is way ahead of engineers, and the rule holds for feedback too. Indeed, Cohen mentions several examples of physiological feedback where sophisticated adjustments reduce deviations from evolutionarily established set points.

If evolution can establish *classical feedbacks* toward set points, then the ubiquity in biology of redundancy and variability lead one to expect that evolution can handle systems where set-point “goals” are ill-defined, numerous and contradictory. I believe that this expectation is indeed confirmed by the presence of a complex control system that employs what one can term *dispersed feedback*. Dispersed feedback uses information from a variety of sensors to improve in some sense the performance of the system with respect to its collection of goals. There is no optimization.

Dispersed feedback in metabolism. Chemotaxis provides an example of dispersed feedback [10]. Metabolism provides an even better example. To see this consider just the single instance provided by the glycolytic enzyme PFK, which has at least five regulatory sites. There is upregulation of PFK activity by AMP and (indirectly) by glucose as well as inhibition by ATP, H^+ , and citrate. Biochemistry textbooks explain the functional advantages of the multiple regulation [15]. (i) Upregulation of energy is promoted by a combination of a high level of the ATP precursor AMP and a low level of ATP itself. (ii) Glycolysis supplies precursors such as citrate for reactions that synthesize enzymes, signalling chemicals and structural elements. High levels of citrate signal abundant precursors. (iii) Via excessive production of lactate, glycolysis can bring about a harmful drop in blood pH (acidosis) — hence the down regulation by H^+ .

Conflicting overlapping goals for metabolism are evident: supply energy;

provide enzymes, signalling chemicals and structural elements in suitable quantities; avoid pH extremes. It is also evident that these goals overlap and conflict, and that the degree of “effort” invested in achieving one goal will effect the amount of resources that can be allocated to another goal. It seems quite clear that evolution has honed the ramified regulation of the metabolic machinery in such a way as to allow metabolism to respond appropriately to unpredictably shifting demands on the structure and function of the organism. In general, the multiple conflicting goals of physiological systems reflect the multiple conflicting influences on the complex organism’s survival that are exerted by the physical and biological environment.

Immunology: feedback exploits information to improve on an initial broad spectrum response. Here is how I believe that dispersed feedback works to improve performance of immune system goals. When the immune system is faced by a challenge, it first replies rather reflexively with a broad spectrum response — for example with a mixture of antibodies, with Th1 *and* Th2. How this response is triggered will not concern us here; suffice it to say that the trigger can be one or a combination of factors such as detecting conserved microbial constituents [6], exceeding a tunable activation threshold [2], sensing danger [8] or sensing tissue destruction [4].

Feedback modifies the immune response in the light of *information* that the immune system collects on how well it is performing, and on the general physiological state of the organism. Of central relevance here is what Orosz [9] apply termed *immunoinformatics*: how the immune system generates, posts, processes, and stores information. Aspects of immunoinformatics appear in a number of the following paragraphs.

Information molecules indicate progress toward goals. The primary sources of information for dispersed feedback are molecules that can indicate progress of the system toward its various goals. Two categories of such molecules are *kill chemicals* and *harm chemicals*. A kill chemical K provides strong evidence that a pathogen has been destroyed. A harm chemical H indicates that damage is being done to the host. But is the host damage being done by the pathogens, in which case the immune response should be elevated? Or is the host damage being done by the immune system, in which case the immune response should be damped? What might be termed the *principle of association* distinguishes between these two alternatives. If a cell’s receptors simultaneously sense high levels of the pathogen P and of the harm chemical H then it is likely that there is considerable harm H_p due to the pathogens. If H is high and P is low then the inference should be that H_I , the harm due to the immune system, is high while H_p is relatively low. In another use of this idea of “guilt by association” extensive killing of dangerous pathogens (large K_{DP}) can be signalled by the simultaneous sensing of considerable pathogen killing (large K) and considerable pathogen damage (large H_p). In brief, $K_{DP} = KH_p$.

A general harm chemical H must be generated by host damage. Epitopes of host hsp would be good candidates. A chemical that provides evidence of host harm, and indeed downgrades inflammation, is a trisulfated disaccharide

fragment from the inflammation-induced cleavage of extracellular matrix by heparanase [7].

Is there evidence for the presence of kill chemical K ? A kill chemical K can be identified if it fulfills the following requirements. (i) It is far more prevalent in pathogens than hosts. (ii) It is an intracellular molecule (for then its presence indicates that the host has been destroyed). (iii) It is essential to the pathogen (otherwise pathogen mutation will replace the molecule in question). (iv) There is evidence that the presence of the molecule modifies the immune response, presumably via a suitable receptor. Candidates for K include N-formyl peptides, palindromic DNA sequences, endotoxins, and mycolic acid [11]. Note the important difference between mycolic acid, a intracellular constituent of cell walls in gram negative bacteria, and LPS, an extracellular constituent of the same cell walls. The information content of ligation of LPS by the LPS receptor is “potential damage is present, from gram negative bacteria”. Ligation of CD1 by mycolic acid should propagate the message “gram negative bacteria are being destroyed”.

How information is used to improve performance. The title of this essay asks how the immune system “sees to it” that it is doing the right thing. Implicit here is the assertion that the immune system “sees”, or, more generally, “senses”, which it certainly does. It senses many things, and processes the information. But it is not enough to “know” what is right; for survival the system must “see to it” that the information it has is used to improve performance. The immune system can employ dispersed feedback to do this in at least two ways. Dispersed feedback can select appropriate effectors among the varied options available to it and it can utilize information to improve the performance of a given effector.

Let us consider (briefly) the possibility of using feedback to improve effector performance. (See [12] for a discussion of effector selection.) How can the system be driven toward better performance of the twin, conflicting, goals of enhancing K_{DP} (killing dangerous pathogens) and avoiding H_I (harm by the immune system to the self)? A simple possibility is that the system can operate according to the following prescription (where a , b , and c are constants):

$$\text{Cellular action} = \frac{aK_{DP}}{1 + bH_I + cK_{DP}} . \quad (1)$$

All other things being equal (H_I fixed), cellular action will be more intense the more the it leads to killing dangerous pathogens. (Cellular action increases when K_{DP} increases, in just the same saturating way that increasing substrate concentration increases the velocity of a Michaellean reaction.) All other things being equal (K_{DP} fixed) cellular action will be more and more strongly damped the more it damages self (cellular action decreases when H_I increases, in just the same way as increasing inhibitor concentration damps the velocity of a Michaellean reaction).

Cellular actions include proliferation, motion (both random and chemotactic), signalling, and effector functions. Formula (1) gives an example of how

these actions can be affected by information on how the system is doing. It is to be expected that a piece of information such as H_i will not act directly on cellular action, but rather indirectly, via cytokines. (For example binding of the kill chemical CpG to intracellular receptors in macrophage upregulates the secretion of Th1 cytokines [16, 17].) The functional message is translated into a cytokine profile. A cardinal immunoinformatic principle is that the same information differently affects different actions of different cells, for example knowledge that gram negative bacteria are in the vicinity should enhance the production of complement and down-regulate cytotoxicity. In (1) this would mean that the “constants” a , b , and c in fact depend on cytokine levels, in different ways for different cell types, and in different ways for different actions of the same cell type (for example in different ways for inducing B cells respectively to proliferate and to secrete antibody).

The classical view of cytokines is that they form a *command network* (for example, IL-6 commands a switch from IgM to IgG). I believe that it is more profitable to regard cytokines as forming an *informational network* (for example TGF- β , PGE-2 and PAF are secreted when scavenger receptors are ligated, giving the message “apoptosis is occurring”). The focus on cytokines as providing information renders understandable the initially puzzling findings that each immune function is effected by a variety of cytokines (the immune system is simultaneously pursuing a variety of goals) and that a given cytokine has many functions (the same information differently effects different cells and different cellular functions). Viewing cytokines as an informational network means that there should be more research emphasis on determining what receptor ligations lead to cytokine secretions.

Remarks on graft rejection. Here are two connections between the picture I have been trying to develop and ideas of Orosz [9] on graft rejection. (i) The notion that immune response is initially broad-spectrum and later honed according to performance effectiveness is consistent with findings that there are multiple mechanisms of acute allograft rejection and with the suggestion that immune resources are stockpiled at an inflammatory site, such as a graft site, for possible later use. (ii) Acute allograft rejection displays different patterns in different tissues — reflecting the different homeostatic agendas of the different tissues. The “competing network agendas” of the tissues and the immune system can be regarded as an instance of multiple conflicting goals.

In his essay, Cohen suggests that an allograft “looks like an aberrant self-tissue in need of maintenance”. Our view of cytokines as an informational network suggests the broad strategy of using cytokines not with the “command goal” of directly countering “harmful maintenance” but rather with the “informational goal” of somehow changing the internal image of the allograft from aberrant to normal self-tissue.

Final remarks. In my view, it is desirable to employ the term *feedback* not, as is common, in the broad sense of “interaction” but rather in the more focussed sense of *reaction to information concerning progress* toward set points (classical feedback) or toward improved performance with respect to a set of

overlapping and conflicting goals (dispersed feedback).

“Goals”, “dispersed feedback” and “progress sensing” via sensors are intimately interrelated. If a biological system has a sensor then it is probably worthwhile to regard the sensor as having evolved to sense progress toward one or more goals, or to sense useful general information on the state of the system. Via intracellular processing, dispersed biological feedback integrates information from membranal sensors to promote fitness by enhancing fulfillment of the overlapping and contradictory goals. “Promoting fitness” is too lofty an aim to be sensed. But it is inherent in my definition of physiological goals that progress toward promoting a given goal can be sensed by a cell. Indeed, “the individual cells and molecules... do not know... when each is doing the right thing” (Cohen). But the cells can know from their sensors when they are doing a better thing or a worse thing and they can modify their behavior in light of this knowledge. Furthermore a given cell can provide information to other cells on its own action and on its reading of the general state of the system; the cell collective can employ this information to select cell subsets that more appropriately help promote the ever-shifting spectrum of goals. Thus the cells’ reaction to their sensors’ information is responsible for the fact that not “the right thing” but a somewhat better thing usually “emerges from a collective and dynamic interaction” (Cohen).

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