Immune System Computation and the Immunological Homunculus

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Two Questions

Students for the Master of Science degree at the Weizmann Institute of Science are obliged to spend the first year of the two-year program doing three-month rotations through three different laboratories in any of the various faculties at the Institute. In 1998, Na'aman Kam rotated through my laboratory in the Department of Immunology where he did molecular modeling of an antibody (1). His next rotation, he told me, would be with David Harel in the Department of Computer Science and Applied Mathematics. When you get there, said I, tell David Harel about the immune system and ask him two questions:

1. Is the immune system a computer?
2. If a computer scientist would set out to build a computer capable of doing what the immune system does, what kind of computer would it have to be?

Connecting Computer and Biological Sciences

The questions (or to be more accurate, the student who transmitted them) led to a continuing collaboration with David Harel catalyzed by joint Master's, Doctoral and Post-doctoral students who have worked to combine computer science and biological systems: After Na'aman Kam came Sol Efroni (2-4), Naamah Swerdlin (5), Yaki Setty, Hila Amir-Kroll, and Avital Sadot. Students can be a boon to inter-disciplinary research because, being unencumbered by expertise, they fearlessly lead (or carry) their supervisors into unfamiliar territories.

Let us return to the first of the two questions that led me to collaborate with a computer scientist: Is the immune system a computer? Obviously, the immune system differs from the devices made by humans called computers in its construction, operation and use. The more interesting question is whether the immune system is a biologic computing machine, and the most interesting questions are what it computes and how it computes.

A Defense System

Many immunologists, probably most, would not think of the immune system in computational terms. There are two reasons for this: the defense role assigned to the immune system and the clonal selection theory of adaptive immunity.

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It has been taught for about a century, and is still taught, that the defining role of the immune system is to defend the body against foreign invaders (6). To attack an invader, your immune system has to detect and identify the invader as distinctly not belonging to your body. Thus, the immune system exists, it is claimed, to discriminate between one's own self-molecules (ignore them) and molecules foreign to the body (attack them). From this classical point of view, the immune system has evolved to discriminate between self and non-self molecules in the most general sense and concretely between one foreign molecule (antigen) and another (7, 8). (An *antigen* is any molecule that can bind to the antigen receptor of a lymphocyte.) The discriminating agent is proposed to be the individual cell, not the system of cells.

Clonal Selection

The emphasis on clones (single cells and their progeny) is anchored in the clonal selection theory of adaptive immunity, the most widely accepted paradigm of immunology. This theory proposes that each lymphocyte, and its clonal progeny, either responds or does not respond to a given antigen molecule (9). Depending on the specific structure of each lymphocyte's unique antigen receptor, that lymphocyte will either attack the antigen molecule, or ignore it. The classical discourse of immunologists about such discriminations has emphasized the antigen receptors on individual immune cells, paying little attention to computation at the level of the system as a whole.

Maintenance

Experimental facts, however, can depart from classical teachings. It is now clear that the immune is responsible for more than body defense; immune system cells promote, even control, processes such as healing wounds and repairing broken bones, growing new blood vessels, building and pruning scar tissue, disposing of dead cells, killing and removing injured or abnormal cells, clearing effete molecules, advancing regeneration of various body tissues, and the like. The dynamic processes initiated in response to injury are termed inflammation; the aim of inflammation is healing (8). The immune system is the system that commences, orchestrates and resolves inflammation. Immune activities, including restorative inflammation and defense against pathogens, can be generalized under the concept of body maintenance. Indeed, the activity of the immune system is responsible for maintaining a peaceful, ongoing host-parasite relationship with the billions of bacteria, the so-called normal flora, that occupy niches throughout our body in the gut, skin and respiratory tract; even our cells – nervous system cells, immune cells, and others – harbor latent viruses quietly held in check by continuous, unimposing and covert immune maintenance. Normal flora and latent viruses become pathogens only when the immune system has been damaged or weakened, for example, by AIDS, cancer or immunosuppressive medications. We may say that the immune system, by managing inflammation, functions to maintain the body in working order in response to the daily grind of

existence as well as to sporadic episodes of clinical illness due to infection or injury. The immune system acts as a maintenance system; defense is only one aspect of maintenance (9). Actually, Eli Metchnikoff experimented with immune maintenance a century ago, but the discovery of antibodies to infectious agents seduced immunology away from body maintenance and into body defense (10).

(If you ask an immunologist, he or she will admit that immune cells and molecules perform vital maintenance functions; why defense continues to be paradigmatic for mainstream immunology is a matter for sociologists (11), not for computer scientists.)

The task of maintaining the body obviously demands immune computation. Maintenance, including defense, requires the dynamic deployment of varied inflammatory processes based on reliable information about cells in flux. The inflammatory response suited to repair a broken bone, for example, is clearly different from the inflammatory response required to hold one's gut bacteria in check or to cure a bout of influenza – which cells and molecules are to take part in the process, when, where, how, in what order, in which intensity, and with what dynamics? The answers arise from computation. The immune system mines information about the state of the various cells of the body (Is there a problem here? What kind?), integrates the body information into immune system information (antibody repertoires, cell repertoires, cell differentiation and numbers, cell movements and migrations, secreted molecules, and so forth). The modified state of the immune system, expressed locally at the site of injury and to some extent globally, is key to the inflammatory process. Immune inflammation, in turn, triggers a response of body cells in the area of injury leading, usually, to healing and restoration of function. As the process evolves, the immune system updates the inflammatory response to match the particular circumstances that emerge on the way to healing, maintaining and/or defending the body. The general success of physiologic inflammation in keeping us fit is highlighted by the occasional disease caused by pathogenic inflammation – inflammation that is not properly managed by the immune system (9) can cause autoimmune diseases such as multiple sclerosis, degenerative diseases such as Alzheimer's disease, or allergic diseases such as asthma.

At the operational level, it is now clear that clones of lymphocytes do not function in isolation, as taught by the classic clonal selection theory. The immune system works as an integrated, whole system, and can respond potentially in many different, and even contradictory ways when it detects an injury or an antigen. The outcome of any immune response involves a choice between many alternative types of possible response, and many different types of cells take part in the response choice. This immune decision-making process uses strategies similar to those observed in nervous system cognition (9, 12). A cognitive theory of the immune system, in contrast to the clonal selection theory, is computational in spirit and practice.

The Immune System Computes

We can summarize thusly: If we define computation as the transformation of input data into output data, then we should conclude that the immune system computes: the

input to the immune system is the state of the body and the output of the immune system is the healing process (the inflammatory response) that maintains a healthy body. In this sense the immune system is a computation machine that transforms body-state data into immune-system data that, simultaneously, feeds back on the body to modify its state and restore body health. The difference between the physiologically regulated inflammatory response that keeps us healthy and the dysregulated or chronic inflammatory response that can make us ill lies in the dynamics and fidelity of the computations performed by the immune system – the cells and molecules that mediate inflammation, both healthy and noxious inflammation, are exactly the same (13). In other words, the hardware of the immune system is standard for all types of inflammation. The differences between inflammatory responses emerge from the different possible deployments in quantities and timing of a standard set of cells and molecules. Thus, the nature of an inflammatory response depends on a continuous computation based on the collective interactions between immune and body cells. These interactions are required throughout one's lifetime; only upon death does the immune system terminate its computations of the state of the body. The bottom line is that the immune system is a continuously reactive computing system (9, 14).

Living Systems Compute

I have taken the immune system as my text for discourse because I am an immunologist; but all living systems – cells, organisms, communities – can be characterized by the type of computations they execute to maintain life. All living systems transform input from their immediate environment – be it other cells, molecules, organisms, societies, physical variables such as light, sound, pressure and temperature, nutrients, toxins, parasites, diurnal and seasonal rhythms, and so forth – into outputs that make possible survival – or non-survival (9). All living systems must compute to maintain themselves in the world. The way the immune system computes provides an insight into how other living systems compute. So how does the immune system compute?

Immune Computation

First, we should note that immune computation works without the standard features of human computers and human computation:

No external operator or programmer;

No programs, algorithms, or software distinct from the system's hardware – its cells and molecules;
(Parenthetically, let me say that DNA is definitely not a program or set of algorithms (15); DNA is information whose meaning is defined by the way the DNA is used by the whole cell and its component molecules.)

No central processing unit (CPU);

No standard operating system: no two immune systems are identical, even in identical twins (since the maintenance histories of their bodies differ, their immune systems must differ);

No formal, mathematical logic;

No termination criteria; the system does not halt its operations;

No verification procedures.

Secondly, the immune system not only lacks the standard features of human-made computers, it expresses properties that no human computer can match:

Self-assembly: the immune system, like the rest of the individual, develops from a single fertilized egg;

Continuous replication: immune molecules and cells proliferate;

Continuous death: immune molecules and cells undergo death, both physiologically ("programmed death") and by chance, and are constantly replaced without a hitch in function – indeed, the death of immune cells is required for healthy immune computation (9);

Distributed in space: immune cells and molecules roam the body;

Ad hoc organization: immune cells and molecules collect and interact at different sites throughout the body when necessary;

Immune memory is based on the evolution of the immune system in response to accumulating experience, and not on of strings of digital information;

A dismantled system may still operate: immune responses can be made by cells growing in tissue culture and upon transfer of immune cells into naïve recipient animals.

Immune Computation Defined

The computational task of he immune system, as we said, is to translate the state of the body (locally and globally) into the state of the immune system (locally and globally). The computational process of translation is iterative and unending; the immune system and the body continuously respond to and update each other. That is the essence of immune computation. How is it done?

The Data Are the Program

How can the immune system compute if, unlike a human-made computer, it has no programmer, no program, no CPU and no termination rule? The answer is that immune computation does not need them.

No termination rule is needed because the immune system never terminates its computation; it is continuously adjusting its state to the state of the body. The immune system, as we said, is a concurrently reacting system (14).

The immune system computes without programmer, program or CPU because the immune system makes no distinction between program and data or between hardware and software; the data are the program and the hardware is the software. Just as the infinite tape acted upon by a universal Turing machine can be considered as both the input data and the program that dictates the computation, so can the reciprocally responding states of the immune system and of the body be viewed as both data and program. The data, which are cells and molecules and their various states, are also the hardware of the immune system. The equivalence between hardware, data and program is easy to grasp in principle; in practice, as we shall discuss below, the details are enormously complex and pose a grand challenge to computer science.

Immune Parallel Processing

Immune computation emerges from the parallel processing of information – parallel processing in the extreme. Each cell in the immune system is a distinct processor; each cell, by its thousands of receptors, collects input, and each cell, by it secretions and behaviors, translates input into output. The immune system of a human is composed of many millions, hundreds of millions, of individual cells, each of which are an individual processor. The computation emerges from the integration of these processors working in parallel; the integration occurs through networking. The networking is organized by anatomical architecture and by cellular interactions. The architecture of the system brings select immune cells together in discrete space and time, and the interactions between the now adjacent cells create the integrated, dynamic response of the system. The details are the provenance of the field of immunology; you don't have to know them now to grasp the principles or appreciate the wonder.

Anatomic Networking

The cellular processors of the immune system are in a constant state of dynamic flux, but the flow of cells is well organized by the circulatory system (blood and lymph flows), by the variable residence of immune cells in regular lymphoid organs (lymph nodes, spleen, bone marrow, thymus, immune cell collections associated with the gut, the skin, the respiratory tract, and so forth), and by the ad hoc congregation of immune cells at sites where they are needed to deal with ongoing maintenance as well as haphazard injury, infection, and tumors (9). The position of any particular cell is influenced by many factors, including chance and stochastics, but the dynamics of the collective is highly organized at the population level through chemical sensing; each immune cell expresses a variable repertoire of surface receptors that directs its movements and its rest stations. The various cells and tissues of the body and of the

immune system itself produce signal molecules that call particular immune cells to sites of interaction. This anatomical/vascular/chemical architecture ensures that the necessary cellular processors meet and mutually interact.

Cell Diversity and Interaction Networking

Every immune cell is a processor, but they are not all the same type of processor. The exact number of different immune cell types is a parochial matter for immunologists, but there are at least several dozen types that differ in the inputs they receive (they express different receptor molecules) and in the outputs they export (they secrete different molecules and/or behave differently). The key to immune computation is the fact that each cellular processor is strongly influenced by its neighboring cellular processors. Immune cells not only interact with body cells and molecules, immune cells interact with each other.

Integration by Co-respondence: Immune CPU

Each immune cell processes information about the body it patrols and, at the same time, each immune cell processes information about how the other immune cells are processing information about the body at or near that site. I have termed this coordinated response of immune cells to the body *co-respondence* (9, 16). What is co-respondence? Keep in mind the diversity of each immune cell: Each immune cell expresses a particular class of receptors, and some classes of immune cells (T cells and B cells) even express receptors unique to the individual cell (antigen receptors; see below). Therefore, the collective of immune cells at the site of action (injury, infection, tumor, etc.) contains classes of cells and individual cells that respond (by their diverse receptors) to different features of the state of injury, infection, tumor, etc. Each cell sees and responds to only a small piece of body action; no single cell sees the whole show. Nevertheless, each cell, in responding to what it does see, produces molecules and expresses behavior that signify its own state – its own response to what it has seen. The essential mediator of co-respondence is the fact that each immune cell bears receptors that collect as input part of the output of the other immune cells. Thus, each cell sees what it sees of the body's injury while it also sees the effect on other immune cells of their own perceptions of the injury. In fact, there are classes of immune cells – regulatory cells – that specialize in responding, not to the states of body cells but directly to the states of other immune cells. Integration of the resulting inflammatory response takes place because each cell updates its own output in co-response to the output of its fellow cells. In other words, each immune cell participates in the collective regulation of the inflammatory response that maintains the organism.

Keep in mind that each of the co-responding cells continues to maintain its own intrinsic class and individual diversity; the cells do not all do the same thing. But whatever any of them does is strongly influenced by what the other cells see and do. This mutual updating of individual cellular processors leads to a consensus of the

immune cell collective that integrates the totality of input and output of the different parallel processors. Co-respondence is dynamic; changes in the state of body cells lead to an integrated change in the state of the immune cells, as the immune cells interact with the changing states both of the body and the adjacent immune cells.

One might say that the process of co-respondence functions as a central processing unit – the immune CPU. The immune CPU comes into being because the immune system is self-referential; it looks at itself looking at the body. The saving power of self-reference is evident on many scales; a flock of birds succeeds in evading the falcon not because every bird in the flock sees the falcon; it suffices for them each to see what the adjacent birds are doing. Or, to laugh at the right time in the theatre, you need not have understood the joke. Collective behavior is integrated by collective self-reference.

Note that the body, for its part, is not merely a passive subject in co-respondence; the body adjusts its activities in response to the adjustments of the immune cells: scar tissue is formed or dissolved, blood vessels grow or degenerate, tissue cells express different genes, proliferate or die, and so on and so forth on the way to healing or containment (or to inflammatory disease, if the computation goes awry). The body, therefore, looks at the immune system looking at the body (9). This world of changing, reflecting mirrors may seem Cabbalistic, but such is life.

Networking Innate and Adaptive Mechanisms

Now that you have begun to grasp the complexity of immune computation, let me call your attention to an added level of complexity: the receptors of some immune cells are continuously created by random generation during one's lifetime; such cells can receive input unique to them and their descendents (the clone). These uniquely manufactured input receivers are the famous antigen receptors of the lymphocytes – the T cells and the B cells (9). The antigen receptors of B cells can also be secreted by the cells as cell-free antibody molecules. The antigen receptors of B cells and T cells are the products of new genes fashioned by these lymphocytes from raw-material DNA inherited from the individual's ancestors (9). The genetic endowment of the species provides the raw-material DNA for making new receptors, but species evolution cannot dictate any particular antigen receptor. Thus, an individual antigen receptor is the product of an individual's somatic development and not a molecule predetermined by the evolution of the individual's species.

(The creation of new genes by immune cells is just one example that supports the conclusion that DNA cannot function as a controlling program but is only part of the cell's data (15). The de novo generation of antigen receptors by clones of immune cells also explains much of the fascination of mainstream immunology with the clonal selection paradigm.)

Along with somatically generated antigen receptors, all immune cells are quipped with innately inherited receptors for various key molecules that serve to disclose to the immune system the states both of body cells and of immune cells (17). These

innate receptors are part of the genetic endowment of the species. The interplay between innate-receptor input (species-encoded) and clonal antigen-receptor input (individually encoded) provides co-respondence with an unparalleled richness of personalized information for integration and collective immune cell decision-making (9). Indeed, the lymphocytes and their individualized receptors endow the adaptive immune system with an evolving individual memory (9). The details are beyond our present scope, but you can already sense the magnitude of the challenge (and the need) for computer science to help deal with this largess of complexity.

Note that all multi-cellular organisms feature immune systems, but not all immune systems include cells that fashion antigen receptors. In fact, most living creatures (plants, insects, roundworms, squid, etc.) manage to populate the world and deal with their parasites armed with immune cells that express innate receptors only; adaptive, individualized antigen receptors and antibodies characterize only the more complex vertebrates (9). It is conceivable that the more complex tissue structures of vertebrates require a more complex immune system to maintain their more complex body plan.

Scales of Computation

Biological computation takes place across multiple scales, in which systems are embedded one within the other like Russian dolls (9, 18). A single cell is itself a complex computing system: The cell's many thousands of receptors simultaneously gather a large amount of diverse input from both outside and inside the cell. These receptors generate signals within the cell that become integrated by intra-cellular signal-transduction networks, leading to the dynamic activation of genes or to the silencing of genes, changes in the shape and movements of the cell, and the evolution of the cell's state and its output. Each immune cell is only a single computational, reactive system within the cohorts of millions of cells comprising the immune system. The immune system, in turn, is embedded in the greater system we call the organism, and the organism is a single computational element in a species, a society, a nation, a world economy, a biosphere (9). The computational process we are exploring in the immune system repeats itself throughout lower and higher scales of biological reality.

Immunological Homunculus

At this point, we can conclude that immune computation leads to a dynamic representation of the body and its various states encoded within the substance of the immune system. The immune picture of the body, as we discussed, emerges from the fact that the state of the immune system mirrors the state of the body. Note that the immune picture of the body does not contain the whole body; the immune representation of the body is reduced to the body molecules that impinge on immune receptors – both innate receptors and antigen receptors – and to the response of the immune cells to this information. Although the amount of information contained in

the limited number of body molecules perceived by the immune system is far less than the total amount of information contained within the body itself, this limited information would seem to be sufficiently informative for the purposes of immune maintenance. The reduced representation of the body grasps functionally the essence of the body's state. How does the immune system gather and assess essential body-state information?

Much has yet to be learned about the interplay of antigen receptors and innate receptors in immune maintenance, but we already know that the individual's immune system organizes the repertoires of developing T cells and B cells around particular body molecules (9, 19). One's body cannot know ahead of time the exact antigen receptors one's lymphocytes will generate when making new genes during individual development. Order, however, can be imposed on random events. It turns out that, during the somatic development of new antigen receptors, the immune system selects for survival only those T cells and B cells that receive input from particular body molecules (*self-antigens*). This positive selection by self-molecules for cell survival, together with a parallel process of negative selection for cell death, focuses the repertoire of antigen receptors on a particular set of body molecules. In other words, developing lymphocytes live or die depending on how they respond to representative body molecules. It should not be surprising that some of these somatically selected body molecules, such as stress proteins, are key players in body maintenance (17). Evolution too has learned to focus immune attention on particularly informative molecules; the innate receptors of different immune cells detect the concentrations of stress proteins and other state-sensitive molecules (17).

I have termed this immune image of the body the *immunological homunculus* (9. 19). I adopted the term from the neurological homunculus, the functional virtual image of the body encoded by organized sets of neurons (20). Like your brain, your immune system maintains your body by deploying a reduced, virtual image of the body represented in the molecular inputs and outputs of organized immune-system cells. I originally formulated the concept of the immunological homunculus based on the reactivity of antigen receptors of lymphocytes for selected self-antigens (9). Now, however, I would extend the homunculus concept to include the innate receptors that also receive input from body molecules. Some homuncular self-molecules are so important to the immune system that immune cells of different types see these molecules using both innate receptors and adaptive antigen receptors (17).

Three Bodies

We have not discussed here the computations made by the nervous system that maintain the body, but in closing I would like to include the neurological homunculus in a broader picture of the organism. In summary, one might say that each of us gets through life manipulating three bodies: one actual full-size body and two reduced, virtual bodies. The body we live in is the actual body; the neurological homunculus and the immunological homunculus are the virtual bodies that help maintain the actual body on its journey through the world (9). The actual body makes it through

life's changing and often hostile environment by adjusting its neuron-based behavior by way of the neurological homunculus and by adjusting its immune-based inflammatory activity by way of the immunological homunculus. Know that the immune and nervous systems influence each other's activities, but that complex issue is beyond the scope of the present discussion. The point here is that three-body computation is a fact of life.

Evolutionary Programming

A universal characteristic of living systems is that they change over time: the ongoing computational activities of the brain, the immune system and the body lead to evolving, dynamic systems. Evolution thus plays an important role in the development of each of the three bodies at different scales of space and time: the evolutionary scale of the species; the developmental scale of the individual; and the experiential scale of the individual's life history. Evolution is central to our understanding of life's computational machinery (9).

I wrote above that immune computation has no external programmer. Perhaps that statement should be revised; the evolutionary process, indeed, could be viewed as the master programmer of immune computation, along with all the other living computational systems that have evolved. Living systems owe their existence to evolution. But evolution is an exceptional programmer: Human programs characteristically precede their implementation in time; first we plan, then we do. Evolutionary programs, in contrast, come into being only after their implementation. Evolution is not aware of its future. We can see evolution's program only by looking back in time – post-implementation.

Above, I suggested that biological computation succeeds because living systems need make no distinction between program, data, hardware and software. The programmer of the operation, then, it is the evolutionary process itself – the process is programmer.

The Fourth Body

Biology and computer science come together now at the beginning of the 21st Century to create yet a fourth body. This fourth body, like the neurological and immunological homunculi, is a reduced, but functional representation of the organism. Unlike the neurological and immunological homunculi, this fourth body is to be built *in silico*. The *in silico* body, to be useful, must be tailored to include the essential features of the real-life organism, but it also must be sufficiently reduced in its complexity so that we can understand it (4, 21). The fourth body created by the biology-computer science alliance will serve to document, organize, represent, and model aspects of the other three bodies – the real body and the two homunculi – in a way that will make it possible to carry out experiments in silico supportive of new thinking, new hypotheses and new predictions (Figure 1).

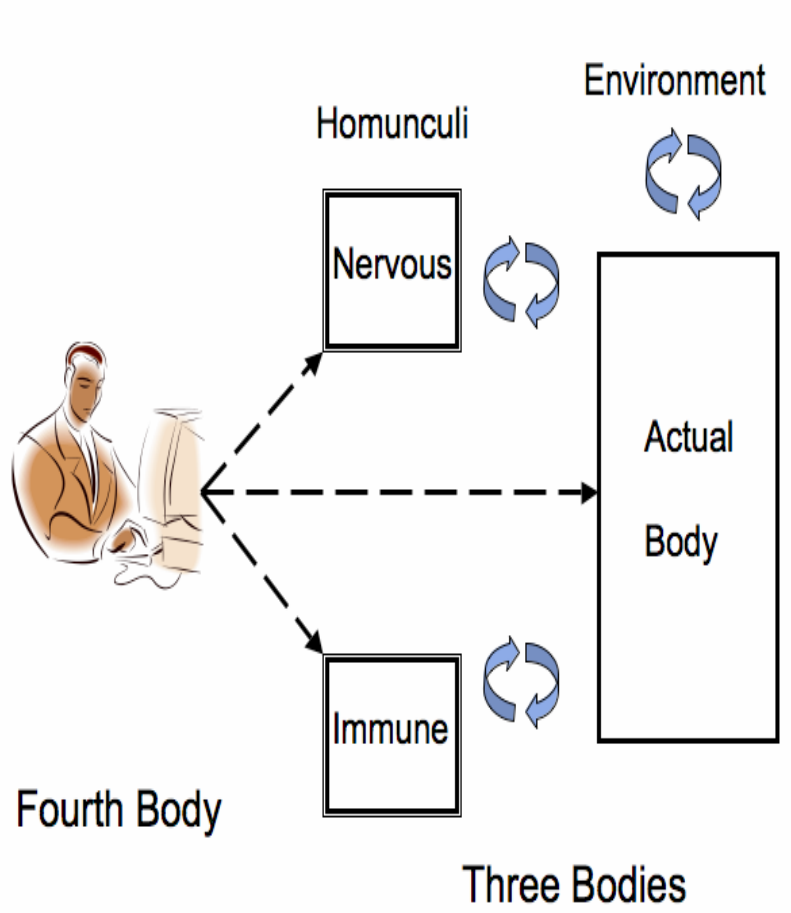

Fig. 1. The four bodies. The actual body, the organism, interacts successfully with the environment with the aid of two internal homuncular bodies – the nervous system homunculus, which manages the organism's behavior, and the immunological homunculus, which deals with body maintenance and protection against invaders. The complexity of these three bodies studied by biology requires, for understanding, an alliance with computer science to create a fourth body, the *in silico* homunculus.

Fourth-Body Challenges Come in Four Sizes

The challenges of developing the *in silico* fourth body will engage biologists and computer scientists productively for a long time to come. The challenges in immunology come in five sizes:

> **Small:** Help immunologists and others organize the masses of experimental data into informative representations (22);

Medium: Simulate limited parts of essential immune interactions to make them better understood (5);

Large: Model immune-cell and other biologic computations and make it possible to do novel *in silico* experimentation (2, 3);

Extra-large: Combine the body state and the immune system state in a detailed, comprehensive and dynamic true-to-life realistic model of body maintenance (23).

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