OPINION

Real and artificial immune systems: computing the state of the body

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Abstract | Here I present the idea that the immune system uses a computational strategy to carry out its many functions in protecting and maintaining the body. Along the way, I define the concepts of computation, Turing machines and system states. I attempt to show that reframing our view of the immune system in computational terms is worth our while.

The field of artificial immune systems (AIS) was developed by a group of computer and informatic scientists and mathematicians who hoped to solve computer science and engineering problems using immune system strategies that have developed through evolution to protect an organism[1–4]. In general, we can say that AIS scientists have approached the processes of the immune system both literally and metaphorically. AIS scientists of the literal school attempt to construct algorithmic systems *in silico* that can do what real immune systems do *in vivo*: protect computers, for example, from computer viruses by deploying algorithms designed to mimic receptors that discriminate between self and non-self, neutralize viruses with antibody-like agents, and so forth. AIS scientists of the metaphorical school, who comprise most of the AIS community, look to the immune system for inspiration; they do not try to mimic or simulate algorithm-like systems designed by evolution, but they aim to design new algorithms with the immune system in mind. However, there is yet a third group of AIS scientists, who instead of exploiting the immune system to solve the challenges posed by computer sciences, aim to better understand immunity by developing computer models of an organism's immune system[5,6]. It remains to be seen to what extent AIS research will succeed in advancing the field of computer science[7]; real immune-system modelling by AIS scientists is just beginning to define its goals.

The question for us as immunologists, however, is not what we can do for AIS scientists, but what AIS scientists can do for us. One might think that surely because AIS scientists observe immunology from outside the field they cannot teach us immunology. Why, then, should immunologists bother thinking about AIS? The answer is that AIS research holds a mirror, as it were, to the face of immunology; an AIS reflection can cast a new computational light on our thinking about the immune system. Quite simply, AIS research can help us reframe our current perceptions of immune-system behaviour. And reframing is usually refreshing and enlightening.

Basic computation

First, what is computation (see Glossary)? In a technical sense, computation can be defined as the process of obtaining a solution to a problem from given inputs by means of an algorithm[8,9]. The conceptual progenitor of computation is the Turing machine, a theoretical machine for transforming a sequence of digits inscribed on an infinite (input) tape into another sequence of digits on another (output) tape according to a particular recipe, or algorithm, executed by the machine[8]. Transcribing digits from one tape to another may seem trivial to a biologist but, according to the Church–Turing thesis, any form of algorithmic computation — anything a computer can do — can be reduced to the transcriptional activity of a Turing machine[8] (FIG. 1).

How might immunologists consider immune computation? First, note that the concept of computation takes us beyond particular molecules, cells and interactions. When referring to immune computation the view is synthetic rather than analytical; we look to the end behaviour of the system and not at its component parts. The computational question is not which cellular and molecular interactions comprise the immune system, but, what, if anything, might the immune system be computing. Moreover, reframing the immune system in computational terms shifts our attention from the proposed goals of immunity (defence against pathogens, self versus non-self or danger discrimination and so forth) to the 'state of the immune system'.

What is meant by the state of the immune system? The term 'state' can relate, in general, to any entity's functional organization. Physicists deal with states of matter, psychologists with states of mind, governments with states of nations and computer scientists with the states of information systems, in other words the configurations of information in a program or algorithm. The state of the immune system refers to the information inherent in its organization and the way the system responds to defined inputs. The AIS mirror therefore diverts us from teleology (the evolutionary advantage of the immune system) to instrumentality (the state of the immune system).

Guided by the concepts of computation and system state, we can ask two questions

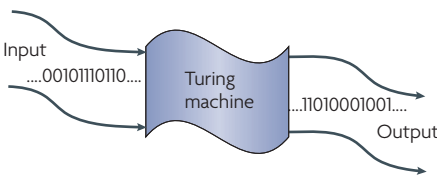

Figure 1 | **The universal Turing machine defines computation.** According to the Church–Turing hypothesis, computation of any kind can be reduced to the activity of a Turing machine that transforms input (represented as a sequence of information on an infinite tape) into output (another sequence of information) according to a set of rules[8,9].

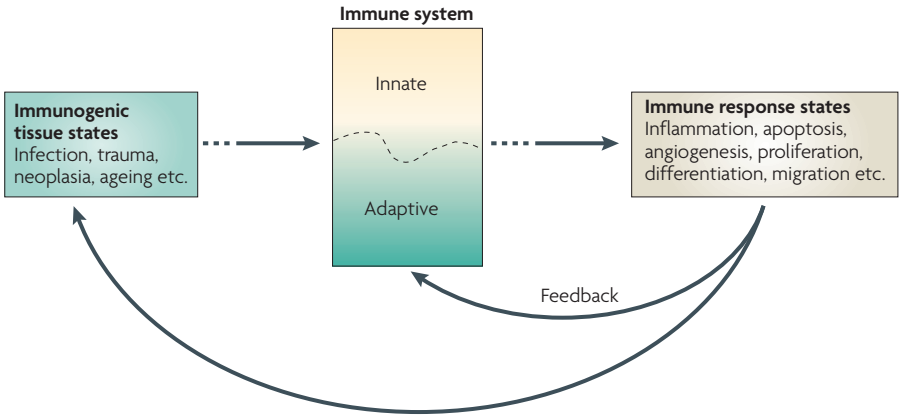

Figure 2 | **Immune computation.** The immune system, which includes both innate and adaptive immune receptors and effectors, functions to compute the state of the body. The input into the immune system is immunogenic tissue states (the state of the body) — molecular signals indicating, for example, infection, trauma, malignant transformation or senescence — and the output from the immune system is the particular immune response state and the inflammatory process it produces, which can induce cell death, proliferation, differentiation, movement, blood-vessel development and other effects. A remarkable feature of immune computation is that the molecular and cellular output is fed back to the tissues to induce healing (or disease) while the output also feeds back to the immune system itself to modify the structure and future behaviour of both its adaptive and innate arms. Thus, the program that dictates the immune response is formulated a posteriori by the immune system in response to the cumulative experience of the immune system in dealing with the body (the self) and with the world (the foreign).

inspired by AIS research: does the immune system compute, and what might we gain from thinking about immune computation?

Computing the state of the organism?

Immune cells and molecules exert many different effects on the body in which they work. If one happens to become infected by a bacterium or a virus, the immune system clears or contains the infection in various ways depending on the nature of the infectious agent, whether it is confined to a particular niche (is it, for example, limited to the gut or has it invaded the blood?) and whether the host has experienced the agent in the past (by way of vaccination or recovery from a previous infection). An appropriate immune response to gut bacteria can make sure these bacteria persist as normal flora[10]; an inappropriate response to the same bacteria can lead to inflammatory bowel disease[11] or even to death from septic shock[12].

In addition to defending the body against pathogens, immune cells and molecules, for example, also help repair cuts, bruises and broken bones[13,14]; activate cell proliferation, differentiation and regeneration[15,16]; stimulate or arrest angiogenesis[17,18]; kill senescent or abnormal cells[19]; and dispose of molecular and cellular debris[20]. These processes have been termed beneficial inflammation — they result in body maintenance[21,22]. In other words, each type of infection, cell transformation or tissue damage, each configuration of the body at any given time or site can stimulate a particular type of inflammatory response mediated by immune cells and molecules, both locally and systemically. The inflammatory process is complex and requires regulation; well-regulated inflammation leads to healing, whereas dysregulated inflammation can lead to inflammatory disease, autoimmune disease or allergies.

We can refer to all the conditions and molecular signals of the body that affect or stimulate the immune system and classify them as the 'immunogenic states' of the body. These states are the molecular configurations that activate particular types of immune activity, innate as well as adaptive. Note that the use of the term immunogenic in reference to body states is much broader than the traditional concept of immunogenicity. In considering immune computation, the immunogenic states of the body encompass all states that induce an immune response, including those states that induce covert, low-level and even tolerant types of immune response as well as the overt, high-level, regulatory and effector responses usually induced experimentally by immunologists.

Likewise, we can refer to all the varied responses of the immune system to changing body states as the response states of the immune system. Irrespective of the molecular and cellular details of these immunogenic and response states (although such details are at the heart of experimental immunology), we can say that the immune system adjusts its own response states to the changing immunogenic states of the body. In other words, the immune system transforms what it senses locally and globally about the states of the body (the input) into various response options, which in effect are different immune-system response states (the output).

Now, if computation (FIG. 1) is defined, by some rule or principle, as the transformation of one configuration of information into another configuration of information[8,9], then we could conclude that, in initiating and adjusting the innate and adaptive arms of the inflammatory process to the needs of the body[21,22], the immune system effectively computes the immunogenic state of the body (FIG. 2). Note that immune computation here refers to computation of the state of the body by the immune system; many immunologists and system modellers have used computational approaches to study the immune system without necessarily implying that the immune system itself can compute information.

Bear in mind that the body's need for different types of inflammation covers a wide range of very different situations that include containment or eradication of infectious agents and body-maintenance functions, such as wound healing, angiogenesis, tissue remodelling and so on. To transform these diverse needs into suitable inflammatory processes, the computational capabilities of the immune system must be great indeed. This conclusion is valid irrespective of the mechanism of the immune response and of our knowledge of how it works. Obviously, there are important differences between a human-made computer and the immune system, such as their hardware (logic chips versus cell networks), software (algorithms versus gene activation), power-supply (electricity versus metabolism), top-down programming versus bottom-up self-organization, chemical connections with the body and other features[23].

Note that the activities of the immune system feed back to modify the immune system itself, as well as the body's tissues (FIG. 2). This feedback highlights a fundamental difference between the computations performed by the immune system and those done by a computer. A Turing machine is not modified by either its input or its output; it simply functions according to a preset program. The immune system of every individual, in contrast to a Turing machine, is self-organizing[22]; it learns from experience; it has memory; and its

molecular and cellular structures and its behaviour evolve in one's lifetime under the influence of antigenic input and inflammatory output. An immune system deprived of stimulation, like a brain deprived of stimulation, fails to develop[22,24]. It may therefore be said that the immune system creates and modifies its own program as it goes. It would be difficult at present, if not impossible, to fashion a human-made computer with such self-organizing capability. The immune system, like the brain, is unmatched in self-organization. Nevertheless, the immune system satisfies the general definition of a computational system. What should this conclusion mean to immunologists? Does this reframing of immune behaviour make any difference? It could. Let us consider briefly two points that might benefit from a computational reframing: understanding the data in hand and formulating new experiments.

Reframing the data

The results of any experiment require interpretation, especially when the data relate to systems as complex as living organisms[25]. To be meaningful, the data have to fit within the family of ideas, principles or paradigms recognized by the field. Immune data are most easily interpretable, for example, when they fit the expectations of immunologists; data that don't fit these expectations often get ignored[26,27]. Therefore, a computational reframing of immune behaviour will benefit immunology if it allows immunologists to incorporate into the field heretofore-unexpected or ill-fitting observations. The following are some examples.

Natural immune reactivity to self-antigens. It is usually taught that the healthy immune system is not able to respond to self molecules, mostly due to the negative selection of T cells[28] and receptor editing of B cells[29]. Self-reactive lymphocytes that 'happen' to escape deletion or editing are silenced in the periphery by regulatory T cells[30]. There is little tolerance in mainstream immunology for the idea that natural autoimmunity could serve some useful purpose.

The computational view of the immune system, however, sees natural autoimmunity as a physiological mechanism for detecting and responding to the states of body cells and tissues[22,23]. Indeed, the idea of immune computation of body state fits well with the concept of the immunological homunculus — the finding that the immune system features receptors that recognize 'normal' body molecules[22,31–34]. The homunculus theory proposes that the autoimmune T-cell and B-cell repertoires and the innate receptors that respond to self epitopes create a functional immune image of key body molecules[22]. Indeed, a microarray analysis of global autoantibody repertoires in cord and maternal sera[35] provides strong evidence that humans are born with IgM and IgA autoantibodies, produced *in utero*, to common sets of key self molecules[36,37]. Such homuncular autoreactivities could be imagined to outfit a human with an immune system sensitive to the state of body tissues from birth (FIG. 3). The immune recognition of stress proteins is a telling case.

Assessing states of stress. Reframing immune-system behaviour in computational terms could also account for the otherwise-unexplained focus of the immune system on stress proteins[38]. The healthy immune system, for example, is populated with T cells[39] and B cells[35] that can recognize self HSP60 (heat-shock protein 60) as an antigen; in addition, innate immune cells[38,40], along with T cells[41] and B cells[42], respond to HSP60 as a ligand for some of their Toll-like receptors. Even peptides of HSP60 can function both as self antigens and as ligands for innate immune receptors[41]. A peptide of self HSP60 can endow poorly immunogenic bacterial capsular polysaccharide antigens with strong immunogenicity[43]. It would seem, in short, that both the innate and adaptive cells of the immune system are equipped to detect self stress proteins and their cleavage products in various ways[44]. Moreover, the different ways the immune system detects various amounts of HSP60 can determine whether the inflammatory output is upregulated[40,43] or is downregulated[41,42]. One could propose a number of reasons to account for the unprecedented focus, innate and adaptive, of the immune system on stress-protein epitopes, but reframing the data in computational terms suggests a relatively simple explanation: the different ways that stress proteins, whole or fragmented, might be expressed by the tissues can provide the various cells of the immune system with crucial information about the local state (stressed or un-stressed) of the tissues. Therefore, stress-protein epitopes can be viewed functionally as 'biomarkers' for computation of the body state by the immune system (FIG. 3).

Natural killer (NK) cells are a class of immune cells outfitted with many different innate immune receptors for various ligand molecules[45]. Cells (including immune cells) that express certain patterns or combinations of NK-cell ligands can activate responding NK cells to kill them; the expression of other combinations of NK-cell ligands will inhibit this NK-cell-mediated killing[45]. Prominent among the NK-cell receptors that activate killing is the NKG2D (NK group 2, member D) receptor. A ligand for NKG2D is the non-classical MHC-class-I-polypeptide-related sequence A (MICA) molecule, which is upregulated on many tumour cells and on cells infected by viruses[45,46]. Ligands for the NKG2D receptor are also upregulated in cells that have suffered damage to their DNA; thus, NK cells can be alerted to kill potentially dangerous body cells according to the stressed state of their DNA[47]. Conversely, healthy body cells that express suitable MHC class I molecules can inhibit NK cells from killing them; thus, damaged, infected or transformed body cells that are 'missing' such inhibitory self molecules will not be able to prevent NK cells from killing them[45].

To summarize, the various states of cells can be sensed by T cells and B cells using arrays of both antigen receptors and innate

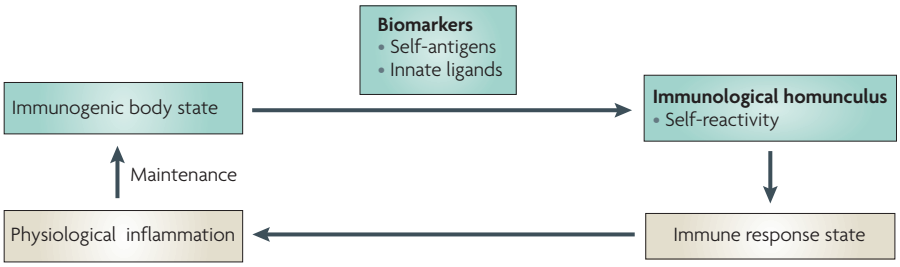

Figure 3 | **Natural autoimmunity serves body maintenance.** The immunogenic state of body cells is expressed by self epitopes (biomarkers) detected by natural autoimmune T-cell and B-cell antigen receptors and by innate immune receptors. These immune receptors constitute the immunological homunculus — the immune system's internal image of informative body molecules[31–37]. The response state of the immune system to the immunogenic state of the body produces the physiological inflammation required to maintain the body. Poorly regulated inflammation can lead to inflammatory and autoimmune diseases.

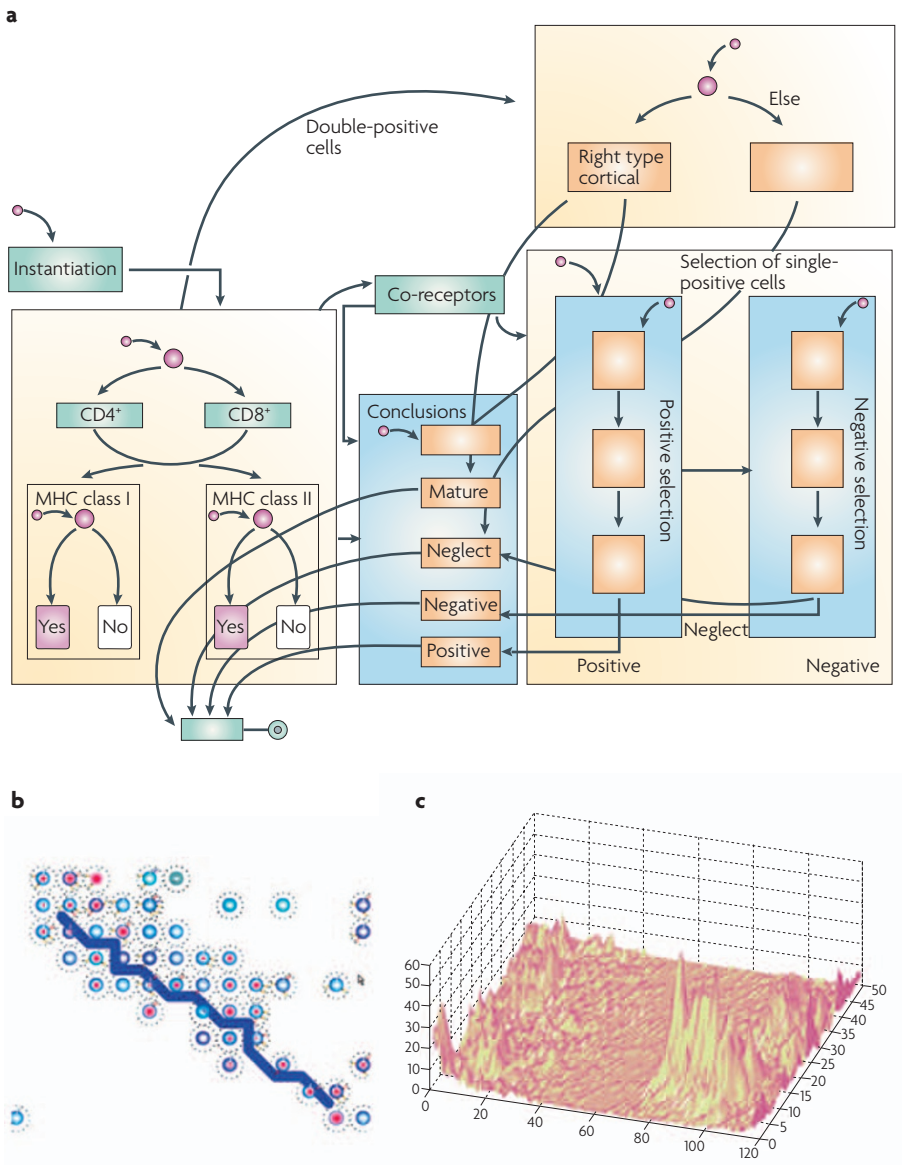

Figure 4 | **Reactive animation.** Reactive animation exemplifies a state-based, visual modelling language. In reactive animation, the system under study is described by cataloguing and defining all the objects that comprise the system (types of cell and types of molecule, for example) and all their possible states (resting, activation, differentiation, secretion, production and proliferation, death and so forth) together with their anatomical locations and all the events and interactions that may influence these objects and their transitions from one state to another. All this basic information about the system and its multiplicity of component parts are represented by a series of visual diagrams, which are described in a mathematically precise notation legible to computers. **a** | A tiny piece of such a representation, depicting a small part of the data about T-cell maturation in the thymus, in the language of Statecharts[70]. Transcribing experimental data (and relevant theories) into the language of Statecharts makes it possible for the computer to run a dynamic simulation of the behaviour of the system based on the individual behaviours of the multiplicity of its component parts (cells, molecules, anatomical environment, etc.). Reactive animation then uses the Statecharts simulation to construct a moving animation of the interacting cells and molecules in formats legible (perceived as realistic) to the human eye and mind[70]. **b** | A still picture of a dynamic reactive-animation simulation of differentiating thymocytes interacting with an extension of a thymic epithelial cell[70]. Reactive animation features an interactive front end that allows the operator to intervene in the simulation to add or knock out cells or molecules, manipulate their numbers and interactions and so on. This simulation tool makes it possible to carry out experiments *in silico* and test hypotheses. It is also possible for the observer to zoom into a single cell or zoom out to the collective behaviour and emerging properties of tens of thousands of cells. Reactive animation also allows the experimenter to extract statistical and local information from the running simulation. **c** | A visual extraction of data regarding apoptosis in the various areas of the thymus[70].

immune receptors; NK cells do the job through innate immune receptor signalling alone. The immune system, during millions of years of co-evolution with the multi-cellular body, has learned to exploit particular self antigens, stress proteins and MHC epitopes as biomarkers that are informative of body state. The immune system seems to have completed its proteomic analysis of body states long before our brains thought to do it.

Treatments with stress proteins modify immune responses. Besides serving as a component in conjugate vaccines against infection[43], HSP60, or its peptides, can be exploited to downregulate the inflammation responsible for various autoimmune diseases, experimental[48] and clinical[49]; even DNA vaccination with HSP genes is effective at modulating inflammatory processes[50]. Stress proteins have also been shown to induce effective immune responses to tumours[51]. The medicinal application of stress proteins for both upregulation and downregulation of immune responses, in fact, can be seen as a test of concept: if the immune regulation of inflammation is responsive to the administration of stress-protein molecules by immunologists, then it is not unlikely that the immune system is also responsive to the expression of these molecules by cells and tissues *in situ*[44,52].

Anti-ergotypic regulation. Not only does the immune system respond to the state of the tissues, some T cells actually respond to the state of activation of other T cells. T cells that recognize and respond to other activated T cells are called anti-ergotypic T cells. Ergotopes are molecules that mark the state of activation of T cells[53]. Ergotopes, such as CD25 (REF. 54) and HSP60 (REF. 55), are expressed by activated T cells; the ergotopes are not expressed by the same T cells in a resting state. Ergotopes are important because anti-ergotypic T cells regulate the cytokines produced by the activated T cells that express ergotopes and so influence the inflammatory process[53]. Moreover, it has recently been discovered that autoantibodies binding to ergotope molecules of activated T cells are also able to downregulate the state of activation of the effector T cells that express the ergotopes[56]. Anti-ergotypic T cells are detectable in newborn and adult rats and in humans[57,58], and they recognize their target ergotopes as peptides in association with MHC class I or class II

molecules expressed by the effector T cells. Anti-ergotypic regulatory cells therefore obtain information about the activation states of other immune cells; the anti-ergotypic response to T-cell activation provides a way for the immune system to monitor itself in the course of an immune response. NK cells, for their part, modulate the states of dendritic cells and immune cells[45,46]. This feedback information about immune-cell state could help the immune system fine-tune its management of inflammation (FIG. 3).

New experimental questions

Reframing our understanding of the way the immune system responds to the body can indicate new questions for the field of systems immunology[59]. Some examples might include asking how a mobile mass of individual immune cells can create a coordinated, self-regulating network that manifests computational skills? What are the cellular and molecular interactions that lead to immune computation[23]? What are the nature and function of the autoimmune repertoires shared in common by groups of individuals? Are there distinct autoimmune repertoires that mark the evolution of immune individuality[31–37]? Do autoimmune repertoires create characteristic signatures useful for individualized medicine, such as early diagnosis, prediction and monitoring of responses to treatment, and prediction of disease susceptibilities[60,61]? What induces a transition of healthy self recognition into autoimmune disease[22], and which self molecules, stress proteins and other molecules are most effective in modulating specific inflammatory processes in different disease states — autoimmune diseases, chronic inflammation, graft rejection, graft-versus-host disease and other disorders of immune reactivity[52]?

Another important question is how the state of a developing tumour might influence the state of the tissues. A transformed cell will not be able to grow into a clinically significant tumour unless its progeny succeed in attracting a blood supply and in forming productive interactions with local inflammatory cells, stromal cells and connective tissues; successful tumours seem to induce adjacent body cells[62,63] and infiltrating immune cells to provide a supportive environment[64,65,66]. A successful tumour evolves to manipulate immune computation to its own advantage, at least for the short run; how does it do this? How can we therapeutically induce the immune system to see the tumour as an abnormal tissue state[46,51]?

Conclusions

Immunologists, like other biologists, have come to appreciate the need to enlist computational scientists to help us organize, study and manipulate the enormous amounts of data we have obtained by experimenting with living systems[59]. If, however, the immune system is a computational entity, then we shall have to interact with computational scientists, not merely for their technological services in data crunching, but as intellectual partners in the quest for understanding immune computation in molecular terms[23].

Note that the concept of immune computation of body state should influence the technologies used by immunologists and other informatic scientists to model the immune system. Most successful models of immune-system behaviour have, until recently, been based on mathematical formulations, usually involving differential equations[67,68]. However, state-based modelling languages that simulate dynamic changes in the organizational states of discrete molecules, cells, organisms and species across the scales of life[69] could well fit a computational view of the immune system. Indeed, experimentalists are likely to feel more at home with modelling languages that are visual and intuitively realistic rather than mathematically abstract. A detailed description of state-based modelling languages tailored to immunology and other complex living systems[70] is beyond the scope of this article, but a glimpse of such an approach can be viewed in FIG. 4. The point here is that a computational view of the immune system will influence our choice of computational tools for the new field of systems immunology.

Glossary

Algorithm
A 'recipe' for carrying out a computation.

Computation
The process of obtaining a solution to a problem from given inputs by means of an algorithm.

Immunogenic state of the body
The conditions and molecular signals of the body that affect or stimulate the immune system.

Immunological homunculus concept
The concept that the adaptive and innate repertoires of the healthy immune system include receptors that recognize a defined set of body molecules. These self-recognizing receptors combine to encode a functional immune image of key body molecules. The immunological homunculus reads the immunogenic state of the body.

Response state of the immune system
The responses of the immune system to the immunogenic states of the cells and tissues of the body.

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doi:10.1038/nri2102
Published online 11 June 2007

1. *Lecture Notes in Computer Science 4163. Artificial Immune Systems. 5th International Conference, ICARIS 2006*. (eds Bersini, H. & Carneiro) (Springer-Verlag, Berlin, 2006).
2. Stepney, S. *et al.* Conceptual frameworks for artificial immune systems. *Int. J. Unconventional Computing.* **1**, 315–338 (2005).
3. Hofmeyr, S. A. & Forrest, S. Architecture for an artificial immune system. *Evol. Comput.* **8**, 443–73 (2000).
4. Timmis, J., Neal, M. & Hunt, J. An artificial immune system for data analysis. *Biosystems* **55**, 143–150 (2000).
5. Bersini, H. & Carneiro, J. in *Lecture Notes in Computer Science 4163. Artificial Immune Systems. 5th International Conference, ICARIS 2006*. (eds Bersini H and Carneiro J) Preface (Springer-Verlag, Berlin, 2006).
6. Perelson, A. S. Modelling viral and immune system dynamics. *Nature Rev. Immunol.* **2**, 28–36 (2002).
7. Garrett, S. How do we evaluate artificial immune systems? *Evol. Comput.* **13**, 145–178 (2005).
8. Harel, D. *Computers Ltd.: What They Really Can't Do*, Revised paperback edition (Oxford Univ. Press, USA, 2003).
9. Harel, D. & Feldman, Y. *Algorithmics: The Spirit of Computing* 3rd edn (Addison-Wesley, 2004).
10. Ivanov, I. I., Diehl, G. E. & Littman, D. R. Lymphoid tissue inducer cells in intestinal immunity. *Curr. Top. Microbiol. Immunol.* **308**, 59–82 (2006).
11. Sepehri, S., Kotlowski, R. Bernstein, C. N. & Krause, D. O. Microbial diversity of inflamed and noninflamed gut biopsy tissues in inflammatory bowel disease. *Inflamm. Bowel Dis.* **13**, 675–683 (2007).
12. Rozenfeld, R. A., Liu, X., DePlaen, I. & Hsueh, W. Role of gut flora on intestinal group II phospholipase A2 activity and intestinal injury in shock. *Am. J. Physiol. Gastrointest. Liver Physiol.* **281**, G957–G963 (2001).
13. Schaffer, M., Bongartz, M., Hoffmann, W. & Viebahn, R. MHC-class-II-deficiency impairs wound healing. *J. Surg. Res.* **138**, 100–105 (2007).
14. Gillitzer, R. & Goebeler, M. Chemokines in cutaneous wound healing. *J. Leukoc. Biol.* **69**, 513–521 (2001).
15. Ziv, Y., Avidan, H., Pluchino, S., Martino, G. & Schwartz, M. Synergy between immune cells and adult neural stem/progenitor cells promotes functional recovery from spinal cord injury. *Proc. Natl Acad. Sci. USA* **103**, 13174–13179 (2006).
16. Zhang, Z. & Schluesener, H. J. Mammalian Toll-like receptors: from endogenous ligands to tissue regeneration. *Cell. Mol. Life Sci.* **63**, 2901–2907 (2006).
17. Cursiefen, C. Immune privilege and angiogenic privilege of the cornea. *Chem. Immunol. Allergy* **92**, 50–57 (2007).
18. Tettamanti, G. *et al.* Growth factors and chemokines: a comparative functional approach between invertebrates and vertebrates. *Curr. Med. Chem.* **13**, 2737–2750 (2006).
19. Savill, J. Apoptosis in resolution of inflammation. *J. Leukoc. Biol.* **61**, 375–380 (1997).
20. Krysko, D. V., D'Herde, K. & Vandenabeele, P. Clearance of apoptotic and necrotic cells and its immunological consequences. *Apoptosis* **11**, 1709–1726 (2006).
21. Cohen, I. R. Discrimination and dialogue in the immune system. *Semin. Immunol.* **12**, 215–9; 321–323 (2000).
22. Cohen, I. R. *Tending Adam's Garden: Evolving the Cognitive Immune Self* (Academic Press, London, UK 2000).
23. Cohen, I. R. in *Lecture Notes in Computer Science 4199 MoDELS 2006,* (eds O. Niestrasz et al.) 499–512 (Springer-Verlag, Berlin, 2006).

24. Mazmanian, S. K., Liu, C. H., Tzianabos, A. O. & Kasper, D. L. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* **122**, 107–118 (2005).
25. Cohen, I. R. *Regen und Auferstehung: Talmud und Naturwissenschaft im Dialog mit der Welt*. (Vandenhoek & Ruprecht, Göttingen, Germany 2005).
26. Kuhn, T. *The Structure of Scientific Revolutions*, 2nd edn (Univ. Chicago Press, 1970).
27. Fleck, L. *Genesis and Development of a Scientific Fact* (Univ. Chicago Press, 1979).
28. Nobori, S. et al. Thymic rejuvenation and the induction of tolerance by adult thymic grafts. *Proc. Natl Acad. Sci. USA* **103**, 19081–19086 (2006).
29. Li, Y., Louzoun, Y. & Weigert, M. Editing anti-DNA B cells by Vlambdax. *J. Exp. Med.* **199**, 337–346 (2004).
30. Cabbage, S. E. et al. Regulatory T cells maintain long-term tolerance to myelin basic protein by inducing a novel, dynamic state of T cell tolerance. *J. Immunol.* **178**, 887–896 (2007).
31. Cohen, I. R. The cognitive paradigm and the immunological homunculus. *Immunol. Today* **13**, 490–494 (1992).
32. Nobrega, A. *et al.* Global analysis of antibody repertoires. II. Evidence for specificity, self-selection and the immunological 'homunculus' of antibodies in normal serum. *Eur. J. Immunol.* **23**, 2851–2859 (1993).
33. Poletaev, A. B. The immunological homunculus (immunculus) in normal state and pathology. *Biochemistry Mosc.* **67**, 600–608 (2002).
34. Avrameas, S. Natural autoantibodies: from 'horror autotoxicus' to 'gnothi seauton'. *Immunol. Today* **12**, 154–159 (1991).
35. Merbl, Y., Zucker-Toledano, M., Quintana, F. J. & Cohen, I. R. Newborn humans manifest autoantibodies to defined self-molecules detected by antigen microarray informatics. *J. Clin. Invest* **117**, 712–718 (2007).
36. Mouthon, L. *et al.* Invariance and restriction toward a limited set of self-antigens characterize neonatal IgM antibody repertoires and prevail in autoreactive repertoires of healthy adults. *Proc. Natl Acad. Sci. USA* **92**, 3839–3843 (1995).
37. Mirilas, P., Fesel, C., Guilbert, B., Beratis, N. G. & Avrameas, S. Natural antibodies in childhood: development, individual stability, and injury effect indicate a contribution to immune memory. *J. Clin. Immunol.* **19**, 109–115 (1999).
38. Srivastava, P. Roles of heat-shock proteins in innate and adaptive immunity. *Nature Rev. Immunol.* **2**, 185–194 (2002).
39. Abulafia-Lapid, R. *et al.* T cell proliferative responses of type 1 diabetes patients and healthy individuals to human HSP60 and its peptides. *J. Autoimmun.* **12**, 121–129 (1999).
40. Flohe, S. B. *et al.* Human heat shock protein 60 induces maturation of dendritic cells versus a Th1-promoting phenotype. *J. Immunol.* **170**, 2340–2348 (2003).
41. Zanin-Zhorov, A. *et al.* Heat shock protein 60 enhances $CD4^+CD25^+$ regulatory T cell function via innate TLR2 signaling. *J. Clin. Invest.* **116**, 2022–2032 (2006).
42. Cohen-Sfady, M. *et al.* Heat shock protein 60 activates B cells via the TLR4–MyD88 Pathway. *J. Immunol.* **175**, 3594–3602 (2005).
43. Amir-Kroll, H. *et al.* A conjugate vaccine composed of a heat shock protein 60 T-cell epitope peptide (p458) and *Neisseria meningitidis* type B capsular polysaccharide. *Vaccine* **24**, 6555–6563 (2006).
44. Quintana, F. J. & Cohen, I. R. Heat shock proteins as endogenous adjuvants in sterile and septic inflammation. *J. Immunol.* **175**, 2777–2782 (2005).
45. Kirwan, S. E. & Burshtyn, D. N. Regulation of natural killer cell activity. *Curr. Opin. Immunol.* **19,** 46–54 (2007).
46. Zwirner, N. W., Fuertes, M. B., Girart, M. V., Domaica, C. I. & Rossi, L. E. Cytokine-driven regulation of NK cell functions in tumor immunity: Role of the MICA–NKG2D system. *Cytokine Growth Factor Rev.* **18,** 159–170 (2007).
47. Gasser, S., Orsulic, S., Brown, E. J. & Raulet, D. H. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature* **436,** 1186–1190 (2005).
48. Quintana, F. J., Carmi, P., Mor, F. & Cohen, I. R. DNA fragments of the human 60-kDa heat shock protein (HSP60) vaccinate against adjuvant arthritis: identification of a regulatory HSP60 peptide. *J. Immunol.* **171**, 3533–3541 (2003).
49. Cohen, I. R. Peptide therapy for Type I diabetes: the immunological homunculus and the rationale for vaccination. *Diabetologia* **45**, 1468–1474 (2002).
50. Quintana, F. J., Carmi, P., Mor, F. & Cohen, I. R. Inhibition of adjuvant-induced arthritis by DNA vaccination with the 70-kd or the 90-kd human heat-shock protein immune cross-regulation with the 60-kd heat-shock protein. *Arthritis Rheum.* **50**, 3712–3720 (2004).
51. Oki, Y. et al. Experience with heat shock protein-peptide complex 96 vaccine therapy in patients with indolent non-Hodgkin lymphoma. *Cancer* **109**, 77–83 (2007).
52. van Eden. W., van der Zee, R. & Prakken, B. Heat-shock proteins induce T-cell regulation of chronic inflammation. *Nature Rev. Immunol.* **5**, 318–330 (2005).
53. Lohse, A. W., Mor, F., Karin, N. & Cohen, I. R. Control of experimental autoimmune encephalomyelitis by T cells responding to activated T cells. *Science* **244**, 820–822 (1989).
54. Mimran, A. *et al.* DNA vaccination with CD25 protects rats from adjuvant arthritis and induces an antiergotypic response. *J. Clin. Invest.* **113**, 924–932 (2004).
55. Cohen, I. R., Quintana, F. J. & Mimran, A. Tregs in T cell vaccination: exploring the regulation of regulation. *J. Clin. Invest.* **114**, 1227–1232 (2004).
56. Zhang, X. Y., Liu, X. G., Wand, W., Wang, W. C. & Gao, X. M. Anti-T-cell humoral and cellular responses in healthy BALB/c mice following immunization with ovalbumin or ovalbumin-specific T cells. *Immunol.* **108**, 465–473 (2003).
57. Quintana, F. J. & Cohen, I. R. Anti-ergotypic immunoregulation. *Scand. J. Immunol.* **64**, 205–210 (2006).
58. Correale, J., Rojany, M. & Weiner, L. P. Human $CD8^+$ TCR-$\alpha\beta^+$ and TCR-$\gamma\delta^+$ cells modulate autologous autoreactive neuroantigen-specific $CD4^+$ T-cells by different mechanisms. *J. Neuroimmunol.* **80**, 47–64 (1997).
59. Heinemann, M. & Panke, S. Synthetic biology—putting engineering into biology. *Bioinformatics* **22**, 2790–2799 (2006).
60. Quintana, F. J. *et al.* Functional immunomics: microarray analysis of IgG autoantibody repertoires predicts the future response of mice to induced diabetes. *Proc. Natl Acad. Sci. USA* **101** (Suppl. 2), 14615–14621 (2004).
61. Quintana, J. F., Merbl, Y., Sahar, E., Domany, E. & Cohen, I. R. Antigen-chip technology for accessing global information about the state of the body. *Lupus* **15**, 428–430 (2006).
62. Orimo, A. & Weinberg, R. A. Stromal fibroblasts in cancer: a novel tumor-promoting cell type. *Cell Cycle* **5**, 1597–1601 (2006).
63. Witz, I. P. Tumor-microenvironment interactions: the selectin–selectin ligand axis in tumor-endothelium cross talk. *Cancer Treat. Res.* **130**, 125–140 (2006).
64. Whiteside, T. L. The role of immune cells in the tumor microenvironment. *Cancer Treat. Res*. **130**, 103–124 (2006).
65. Tan, T. T. & Coussens, L. M. Humoral immunity, inflammation and cancer. *Curr. Opin. Immunol*. **19,** 209–216 (2007).
66. Elaraj, D. M. et al. The role of interleukin 1 in growth and metastasis of human cancer xenografts. *Clin. Cancer Res.* **12**, 1088–1096 (2006).
67. Bergmann, C., van Hemmen. J. L. & Segel, L. A. How instruction and feedback can select the appropriate T helper response. *Bull. Math. Biol.* **64**, 425–446 (2002).
68. Meier-Schellersheim M., Xu X., Angermann B., Kunkel E. J., Jin T., Germain R.N. Key role of local regulation in chemosensing revealed by a new molecular interaction-based modeling method. *PLoS Comput. Biol*. **2**, e82 (2006).
69. Cohen, I. R. & Harel, D. Explaining a complex living system: dynamics, multi-scaling and emergence. *J. R. Soc. Interface* **4**, 175–182 (2007).
70. Efroni, S., Harel, D. & Cohen, I. R. Emergent dynamics of thymocyte development and lineage determination. *PLoS Comput. Biol.* **3**, e13 (2007).

Acknowledgements:
I thank my students and colleagues for teaching me about computation and for their stimulating discussions: H. Amir-Kroll, H. Atlan, E. Ben Jacob, H. Bersini, A. Coutinho, E. Domany, S. Efroni, Z. Grossman, D. Harel, Y. Louzoun, M. Meier-Schellersheim, Y. Merbl, F. J. Quintana, A. Sadot, E. Sahar and S. Solomon. The late L. Segel made a unique contribution to my thinking. I thank S. Efroni for helping me prepare figure 4.

Competing interests statement
The author declares no competing financial interests.

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