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17 A theory for complex systems: reactive animation

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1. SYNAPSES

"Multidisciplinary Approaches to Theory in Medicine" is the name of this book. *Multidisciplinary* is easy to understand; medicine encompasses different academic disciplines that investigate the organism at many scales of enquiry: genetic, molecular, cellular, systemic, pathological, behavioural, social, and historical. The use of the term *multidisciplinary* here, however, refers specifically to the synapse between bio-medical scientists and applied mathematicians and physicists aimed at understanding the complexity of the organism. This multidisciplinarity is characterised by the use of mathematics and computer science to explicate biology. Here, we discuss concepts of theory, complexity, and understanding, and describe a visually dynamic way to represent and study complex biologic data: Reactive Animation (RA).

2. THEORY

What is the meaning of *theory* in medicine? The Oxford English Dictionary provides various definitions of *theory*, including this one:

> *4. a. A scheme or system of ideas or statements held as an explanation or account of a group of facts or phenomena... the general laws, principles, or causes of something known or observed.*

So a *theory* is an explanation based on laws, principles, or causes.

The word *theory*, however, does not derive from law, principle or cause; *theory* is derived from the Greek $\theta\varepsilon\omega\rho\iota\alpha$, which means to *look at* or *view* (Oxford English Dictionary, 1989). The etymology of *theory* makes the point that a theory is basically a way of *looking at* the world. Usually we make theories about things that we cannot actually see with our bare eyes; despite its etymology, a theory usually aims to explain a reality behind appearances. A theory is a way a mind eyes the world. A theory, from this point of view, is a representation of what cannot be seen, but only surmised. (Parenthetically, note that the word *representation*, like the word *theory*, is a paradox; just as a *theory* visualises the invisible, a *representation* presents the absent.)

So, ''Theory in Medicine'' refers to what our view of the organism – in health, disease, and experiment – can teach us about the core laws, principles, or causes that form and animate the organism. *Theory* thus contributes to understanding: We look at a complex piece of the world and our theory expresses the way our minds *understand* the spectacle.

3. COMPLEXITY

A complex system, such as an organism, is a system composed of many different interacting parts. The attribute we call *emergence* distinguishes a complex system from a simple system (Cohen, 2000). The solar system is a simple system because, however complicated, the solar system boils down to the bodies in the system (sun, planets, moons, etc.) and the laws of gravity that connect their masses. For example, knowledge of the masses of the earth and the moon (and the sun too) and the law of gravity is good enough to put a man on the moon (provided you have a proper rocket ship). Understanding the component parts of a simple system is sufficient to understand the system, viewed as a whole system.

Just as the solar system is formed by a fundamental interaction between masses (the laws of gravity and motion), the organism is formed by the fundamental interactions of its component molecules (the laws of chemical reactions). However, the organism is more complex than is the solar system because cataloguing the chemistry of all the individual molecules that make up the body does not suffice for understanding the organism as a whole. We cannot readily see how the component parts of the body generate the behaviour of the organism, so we need *theory*; we need a *representation* of the inside – the microscopic components – of the organism that will account for the emergence of the visible – macroscopic – properties of the organism.

4. PARTS CATALOGUE

An automobile is composed of thousands of parts, many of which move and mutually interact, while they also interact with the road and the driver. But an automobile, compared to a cell, is not really a complex system because a good mechanic can fix one or even build one using the parts and the parts catalogue; quite simply, each part of an automobile has a defined place and a defined function. Your living body differs fundamentally from your automobile in relation to its component parts: body parts, unlike automobile parts, are pleiotropic, redundant, degenerate, and apt to learn new tricks. Many (probably most) biologically important molecules perform more than one function (bio-molecules are *pleiotropic*); different molecules can perform similar functions (important cells and molecules are *redundant*); interacting ligands and receptors are hardly ever exclusively specific (molecular interactions are *degenerate*); and a molecule's structure and function (allosteric effects, post-translational modifications, and the like) are responsive to the environment and the history of past interactions (Cohen, 2000). One cannot predict the behaviour of an organism based on a list of its component molecules and their possible interactions. The structure – function relationship of your automobile has a simple one-to-one arrangement between parts and performance: not so your body.

Consider, for example, the role of interferon gamma (IFNγ) in autoimmune diseases. IFNγ is the prototypic Th1-type cytokine responsible for destructive inflammation in autoimmune diseases, clinically and experimentally (Liblau et al., 1995). Any treatment that down-regulates the expression of IFNγ will turn off the disease (Cohen, 1997; Elias et al., 1997).

So, IFNγ is an undisputedly essential agent in the disease process. But it is very difficult to visualise exactly what IFNγ does that is so essential; IFNγ is a molecule that, among its own many direct activities, activates at least 220 other genes (Boehm et al., 1997); IFNγ is very pleiotropic (but probably not more so than other cytokines). Strangely, some of the effects of IFNγ can be carried out by a molecule called tumor necrosis factor alpha (TNFα) (Sullivan, 2003). Thus IFNγ and TNFα are somewhat redundant. IFNγ is also degenerate; it can interact as a ligand for more than one receptor (Dinarello, 2002).

How frustrating to knock out key genes in a mouse, only to discover that the knock-out mouse manifests an unpredicted phenotype, or no noticeable change in its wild-type phenotype. IFNγ is a frustrating example; mice with their IFNγ gene knocked out still can develop autoimmune diabetes (Serreze et al., 2000) or experimental autoimmune

encephalomyelitis (Glabinski et al., 1999). But remember, treatments that inactivate IFNγ do block these diseases (Liblau et al., 1995; Cohen, 1997; Elias et al., 1997). So how can knocking out the gene itself leave the disease phenotype intact? We may suppose that the mammalian immune system is sufficiently complex to self-organise an effective immune response in the absence of IFNγ by implementing other programmes. Your automobile, unfortunately or not, simply cannot learn to make do.

5. SIMPLICITY BELIED

Classically it was assumed that the organism, however complicated, could be reduced, like an automobile, to a collection of individually simple functional sequences, each sequence characterised by a one-to-one relationship between a gene, its encoded protein, and a specific function (Mayr, 1961). Immunologists, like other biologists, have attempted, and attempt even today, to represent the immune system using the simplest theory imaginable – not without controversy (Efroni and Cohen, 2002; Langman and Cohn, 2002; Cohn, 2003; Efroni and Cohen, 2003). The genome was thought to be the body's blueprint; knowing the genome, it was hoped, would allow us to understand the organism. But now we realise that the genes are not enough (Cohen and Atlan, 2002); we have to catalogue all the proteins too and decipher the proteome. And that too, be assured, will not suffice. Pleiotropism, redundancy, ligand-receptor degeneracy and epigenetic and post-translational modifications of the organism's component molecular and cellular parts thwart understanding (Cohen, 2000). Indeed, the living organism is generated, not by parts, but by process – a dynamic web of interactions generates the system; the component cells and molecules and the laws of chemistry are mere infrastructure. Life *emerges*. The organism and its states of being cannot be reduced to the laws of chemistry and physics in the way that the solar system can be reduced to the laws of chemistry and physics, or the automobile to its parts.

6. UNDERSTANDING COMPLEXITY

Science grounds understanding on observation, measurement, and repeatability. So understanding in biology (and in any science) is not merely a state of mind; biological understanding must be a proficiency, a competence (Cohen, 2000). Understanding the world amounts to dealing well with the world. Understanding is active. Understanding is

manifested by how we *respond* to what we see. Medicine illustrates this well: The degree to which the doctor understands the patient's illness is demonstrated by the ability of the doctor to restore the patient to better health. The patient, in fact, does not care much about the theories the physician might have had in mind when he or she started the treatment; the patient rightfully judges the physician's understanding by the physician's performance: "Am I getting better"?

What specific rules of competence demonstrate scientific understanding? The doctor, for example, understands the illness by making a correct *diagnosis*. The proper diagnosis allows the doctor to predict the patient's clinical course, and so make a *prognosis*. *Diagnosis* and *prognosis* are abstractions, merely words; classifications of illnesses are merely *representations* of reality. Nevertheless, these representations can be translated into significant actions. A diagnosis, for example, rests on a regularity of nature. All cases of type 1 diabetes emerge from a lack of insulin. A diagnosis of type 1 diabetes tells the doctor that the patient needs insulin. Thus, the abstract nosological representation we call diabetes allows the physician to predict the course of the illness, based on professional knowledge. The abstract representations we call diagnosis and prognosis allow the doctor to institute successful *therapy*. Correct therapy makes the patient healthier – changes the world.

Science too measures understanding by performance: A scientist understands his or her field to the degree to which he or she carries out (or teaches others to carry out) productive research. Productive research requires three proficiencies. Similar to *diagnosis, prognosis*, and *therapy* in medicine, scientific understanding is tested by successful *representation*, *prediction*, and *utility*.

7. REPRESENTATION

A complex system is complex precisely because we cannot reduce the data to a simple basic law or single cause that can account for all the details we have learned about the system through observation and experimentation. We are confounded by the limitations of memory and mental computation. In former days, when we had relatively little data, it was easy to formulate theories that included all we knew. At the present state of biology, however, we have learned too much; we suffer from a flood of information. Now only the computer can supplement our weak memories and help us compensate for our limited mental computation. The database is too heavy for the mind alone to bear; we are confounded by the organism's basic pleiotropism, redundancy, degeneracy, and functional adaptation.

Of course, an experimenter does not need a comprehensive and integrated understanding of the field to continue with the reductionist agenda of isolating and characterising each molecule, cell, connection, and process in a system of study. Normal biologic science can go on and on successfully accumulating data about the parts catalogue. But a more comprehensive and integrated understanding of living systems seems to be on the agenda. The present proliferation of ''systems biology'' programmes arises from a general perception that reductionism alone (a completed parts catalogue) will not suffice for understanding. At least some people will have to keep track of the whole system, and inform the rest. Interdisciplinary efforts will be needed to make good biological theory. Thus, the impact of theory on biology and medicine will depend to some degree (probably to a great degree) on how intelligently we use computers to represent in comprehensible format the complexity of biological data. Apt representation is the key to comprehension.

But when is a representation ''apt''? How can we tell an appropriate representation from an inappropriate representation? Is there, in fact, only one true representation of a complex system? A representation, like any idea, can be judged by its performance. As we shall now discuss, a good representation will usefully engage our minds to formulate predictions, think new thoughts, and undertake new experiments. Obviously, then, there is no one true representation of a complex system. Different presentations of the data can suit different purposes. In fact, different presentations of the data constitute different theories about the meaning of the data.

8. PREDICTION

The value of prediction in science needs no elaboration. Science aims to detect and characterise the regularities of nature, and prediction is a functional test of regularity. If you cannot foresee the outcome of the experiment, then your theory might be wrong. Fortunately, even complex systems are predictable. In fact, a living system survives through its ability to predict what its environment has to offer. A living system survives by mining information and energy from its niche in the environment (Cohen, 2000). A theory or a representation of a living system, like the living system itself, survives by the success of its predictions.

9. UTILITY

Clearly, a most important feature of a theory is its usefulness. A theory is manifestly useful when it solves a problem – achieves a goal, provides a

technique, leads to a cure. But, a good theory not only solves a problem; but also should engage minds to think new thoughts and undertake new experiments.

James B. Conant (1951 p.25) has defined science as

> *"an interconnected series of concepts and conceptual schemes that have developed as a result of experimentation and observation and are fruitful of further experimentation and observation".*

Science, according to Conant, is a chain reaction: theory leads to experiments that produce new data, and the new data, in turn, stimulate new theories that trigger new experiments, that generate new data, and on to more useful models of understanding.

10. THEORY FOR COMPLEXITY

The distinction between simple systems and complex systems suggests that each type of system needs its own type of theory. A scientific theory for a simple system boils down to a timeless list of immutable laws or standing principles that explain the workings of the system of interest. As we have discussed above, we can understand the solar system by reducing the system to the unchanging laws of gravity and motion. Discovering a fundamental law that governs the behaviour of a simple system puts one's mind to rest; the problem of understanding the data seems to be solved. The data can be replaced by the fundamental law that accounts for them. The laws behind a simple system supersede the noisy details of the data. The fundamental laws of a simple system represent the system as neatly and as efficiently as possible.

Complex systems, in contrast to simple, can never get away from the noisy details. The noisy details are the essence. Consider two well-studied species: the round worm, *C. elegans* and the human, *H. sapiens*. A physicist would note that both the creatures obey precisely the same basic laws of matter, are composed essentially of the same molecules, and house the same spectrum of chemical reactions. In fact, both creatures realise very similar, if not identical principles of organisation. There is no essential difference between the person and the worm, when we view both with the tools of physical theory. The differences, for the mathematician and physicist, and for the chemist too, between worm and us are in the noisy details. But the noisy details between the species are exactly what we want to understand as biologists, physicians, and citisens. Reduction to fundamental laws fails to explain what we want to understand. Theory

for a complex system cannot do away with the noisy details. A simple theory for a complex system misses the system.

Actually, there is one simple theory that has proved to be of continuous usefulness in biology, and in complexity generally: the theory of evolution. The theory of evolution is the best – perhaps the one-and-only – basic law in biology. The theory of evolution tells us to mind the noisy details; evolution says nothing about any of the particular details that comprise and distinguish species, only that they are likely to be essential.

11. REACTIVE ANIMATION: A PROTOTYPE FOR COMPLEXITY

So, a theory for a complex system must live with the data; the theory does not supersede the data. Complex system theory amounts to organising the data and representing it in a way that engages the mind to see the data anew and undertake new experiments. A theory for a complex system, then, must pass two tests: the theory must simplify and compress the data to the point where the system is rendered comprehensible, but the simplification and compression must not go beyond the point at which the essence of the complexity is lost. This principle sounds simple enough, but it would require a book or two to present a full theory of complexity theory, and we have only this brief chapter. Let us close then by describing *reactive animation* (RA for short), our initial approach to organising the data so as to engage the mind without over-simplifying the system.

12. ORGANISING THE DATA

We have used the visual formalism of Statecharts to capture and model data related to the immune system. The Statecharts language was developed originally as a language for aiding in the design and specification of computerised, man-made systems (Harel, 1987). Statecharts captures the states of a system and the transitions between them. Its most popular version is applied within an object-oriented framework, where the system is described as a collection of interacting objects and each object is provided with a Statechart that captures its behaviour. Statecharts has become widely used in system design in computer science and engineering (Harel and Gery, 1997), and we have only recently begun to apply Statecharts to the immune system. Our first piece of work was a pilot project on the activation of T cells (Kam et al., 2001). Now we have applied Statecharts to the development of T cells in the thymus (Efroni et al., 2003).

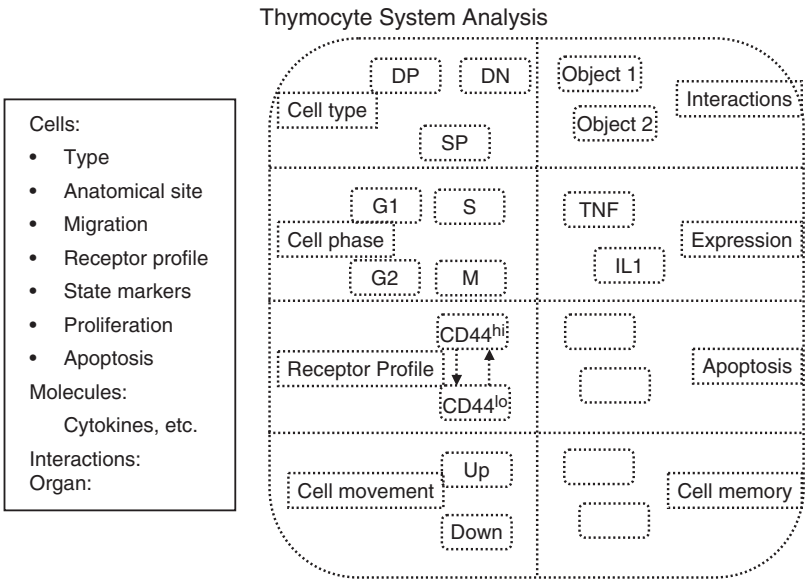

Fig. 1. Thymocyte system analysis. Here is a general overview of the data incorporated into the Statecharts analysis of thymocyte development. Note that the range of data covers scales from molecules to the developing organ.

The objects in the immune system are molecules, cells, and organs, individually and collectively; connections between objects include their relationships and their interactions. The object-oriented version of Statecharts suits biologists because biologists experiment with objects (genes, molecules, cells, organs, organisms, and societies) and study their connections (fig. 1). The visual formalism of Statecharts is also much less daunting than are mathematical equations, and are more convenient for most biologists who are used to representing data visually; open any biological text. Indeed, biologists are no strangers to the notions that objects exist in particular states and that the behaviour of a system may involve the transitions of component objects to new states.

Figure 2 illustrates a Statecharts representation of some aspects of thymocyte development (Efroni et al., 2003). In a Statechart the boxes represent states, and may be nested to capture levels of detail. States can also be related to each other concurrently (depicted by dashed separator lines). The transitions between states are represented by arrows labelled with the triggering event and possible guarding conditions. The Statecharts themselves are used to represent the behaviour of each class of objects. The Statecharts language is described in detail in the literature (Harel, 1987; Harel and Gery, 1997; Harel and Politi, 1998); here we shall only mention its attractive features for biological complexity.

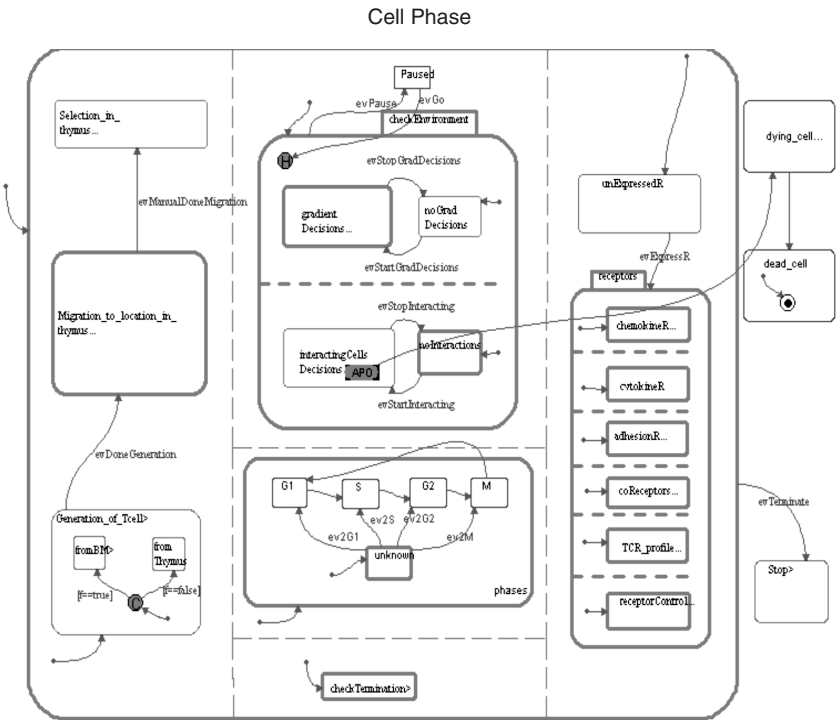

Fig. 2. Thymocyte cell phase. Here is an example of one of many hundreds of charts that comprise the Statecharts analysis.

Detailed data. The details of the database can all be included in the Statechart description. Statecharts makes possible a ''bottom–up'' representation of the data about experimental objects.

Multi-scale. One can zoom out to look at cells and collectives of cells, or zoom in to look at molecules inside cells, or cells inside organs, or at combinations of scales, as long as these scales of the system have been modelled too.

Mathematical precision. The visual formalism of Statecharts is mathematically precise and semantically legible to computers.

Modular. Statecharts easily accommodates new data by allowing the user to add to an existing model new kinds of objects as they are discovered and to specify their behaviour using new Statecharts, or to add to, or modify the Statecharts of existing objects as new facts about behaviour are discovered. One does not have to redo all the equations when one wishes to integrate new information into the representation of the system.

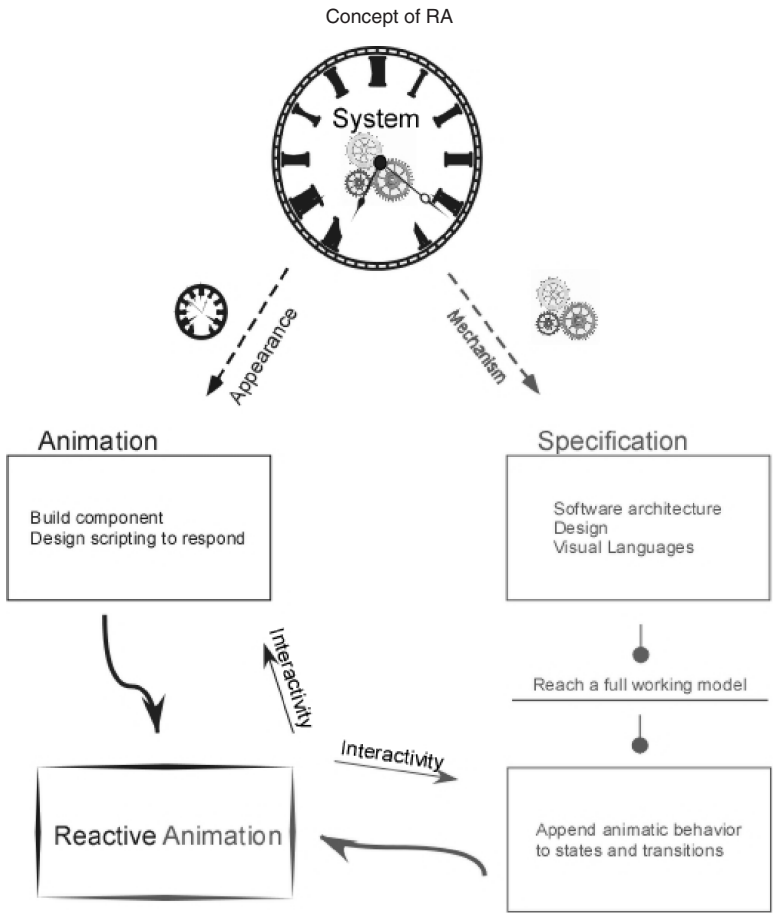

Fig. 3. The concept of reactive animation (RA). RA is based on the general idea that any system has two functional components: the mechanisms that comprise the system and the appearance of the system to our minds. RA separates the precise specifications of the mechanisms that simulate the system from an animation of the simulation that engages our minds. In this way, the data create a semantically precise representation of the system's behaviour that is translated into an interactive, moving representation that reveals emergent properties, excites curiosity, motivates experimentation, fosters creativity and strengthens understanding.

Executable and interactive. Systems represented in a Statecharts format can be ''run'' on computers. Statecharts simulations are feasible and are supported by powerful software tools, and so experiments can be performed *in silico*. The user can see the simulated effects of adding or removing molecules or cells, or of changing or manipulating interactions. Thus, Statecharts makes it possible to experiment with complex systems without simplifying or ignoring the known data. RA uses Statecharts to organise and run the data, but RA adds animation to organisation.

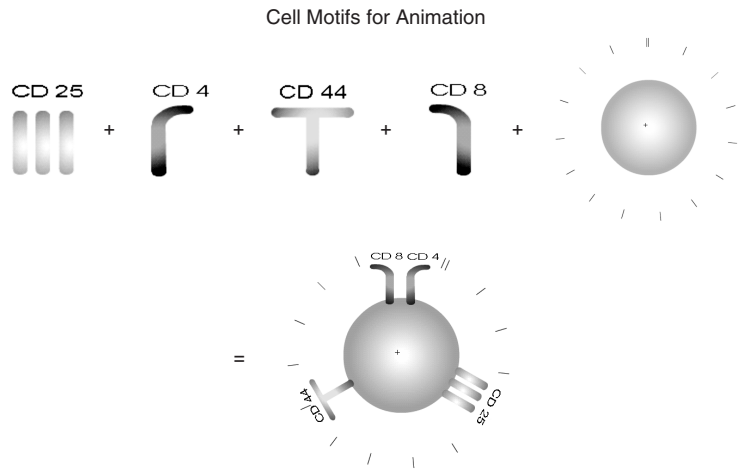

Fig. 4. Motifs for making a T cell. In our present example of RA, we equip Flash with basic components for making T cells, thymic epithelial cells (not shown here), and other motifs, from which the animation is constructed.

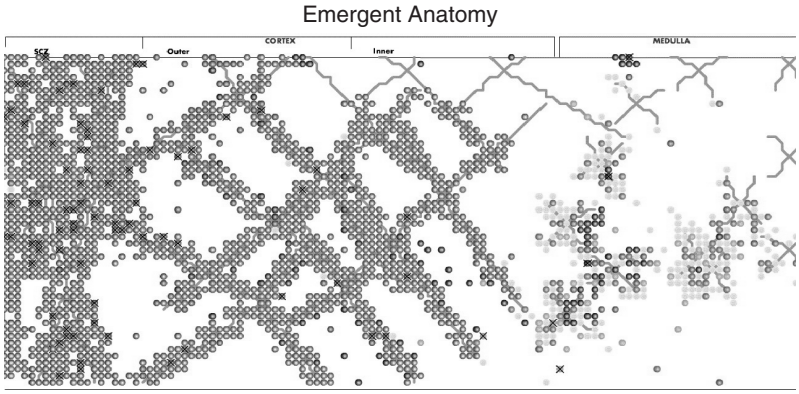

Fig. 5. The emergence of thymus functional anatomy. The figure illustrates that a functioning, anatomically correct thymus can emerge from the entry of a few stem cells and their migration and differentiation according to molecular gradients and cell interactions.

13. ENGAGING THE MIND

A theory for complexity, as we have discussed above, should motivate the mind to make new associations and propose new experiments. Statecharts, with its diagrammatic visual formalism, is not the customary way the minds of biologists (or of humans generally) represent systems.

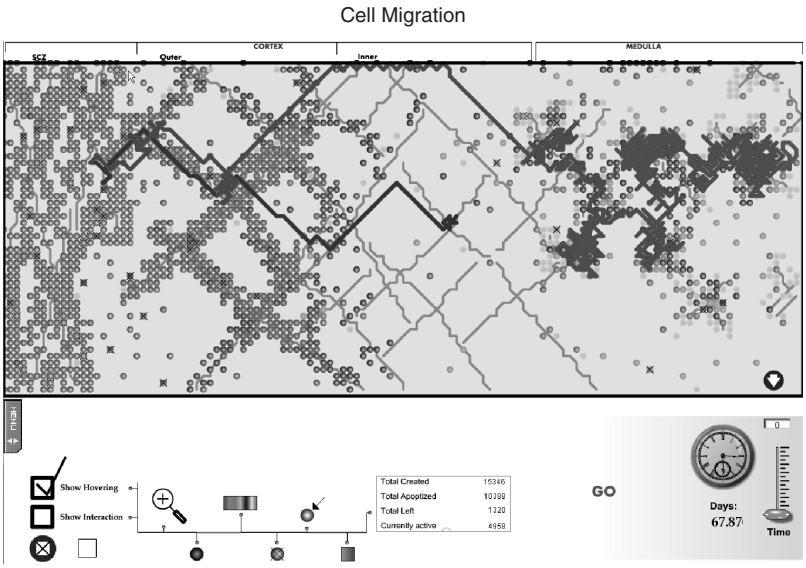

Fig. 6. Migration of a single thymocyte. The blue line traces the cell's migration from its entry to the cortico-medulary junction as a stem cell to the subcortical zone (SCZ). The red line traces the cell's journey of differentiation to the medulla, from which it will exit to serve the immune system outside the thymus. Note the control panel at the foot of the thymus animation.

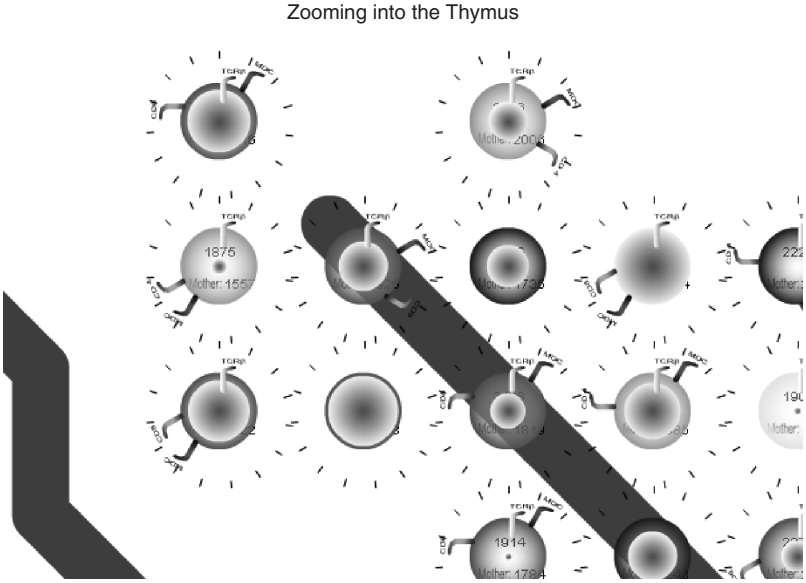

Fig. 7. Zooming into the thymus. The thick blue line represents the extensions of the thymus epithelial cells upon which the thymocytes interact, differentiate, proliferate or die. Thymocytes are coded according to their state and expression profile.

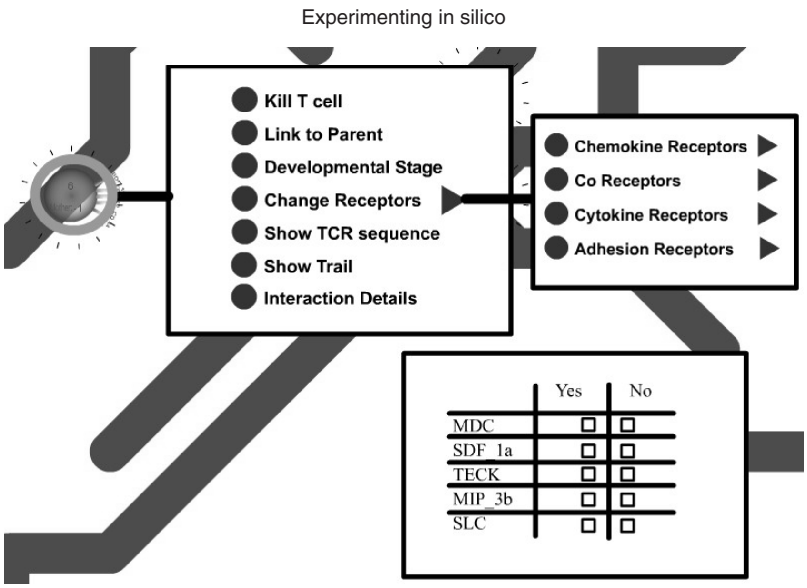

Fig. 8. Experimenting *in silico*. The RA format makes it possible to probe the animation and experiment with various functional components of the system. Here is an example of some of the things one can ask of a thymocyte, and see what happens to the cell.

Humans draw pictures and respond to pictures that ''resemble'' the prototypic objects they like to see, or have learned to see. We need not discuss here the meaning of visual ''resemblance'', or why humans tend to feel at home cognitively with visual objects. But it is clear that we are captivated by visual representations. In fact, we are most responsive to *moving* pictures. The cinema, TV, DVD, the computer screen, the world of advertising, all demonstrate that moving pictures move minds and generate returns. So we have built RA to connect the simulations of Statecharts to traditional (textbook-type) representations of cells and molecules in an animated format.

The RA animation is created by connecting the Statecharts language and its support tool, Rhapsody, to the Flash system, a commonly used software package for programming animation (Efroni et al., 2003). We supply the Flash program with a repertoire of basic motifs representing cells and key molecules. The simulation produced by Statecharts then connects to Flash to create a moving picture of the simulation. Moving pictures of biological systems are not our innovation; turn on any educational TV channel and see moving cells, developing organs, bodies mending. The innovation of RA is that here the moving representation emerges from – indeed is driven by – the precise specification of the data run on Statecharts. The moving pictures seen in RA are generated by the

data themselves, bottom–up, and not by our imagination or preference, top–down. The aim of RA is to represent the data in a way that does not over-simplify its complexity (recording the data and simulating it by Statecharts), but yet engineer the representation (by its connection to Flash) to stimulate the mind with a moving and interactive picture of the show. Seeing the cells move, differentiate, interact, proliferate, kill or die excites curiosity and triggers associations. Thus, the Statecharts arm of RA guarantees mathematical precision; the Flash arm of RA enhances creativity.

RA, in other words, departs from the approaches to biological system modeling developed till now; traditionally, modeling has focused on neat concepts (top–down) rather than on messy data (bottom–up), or has abandoned the data entirely to construct artificial and synthetic computations aimed at "reproducing" *in silico* ersatz genomes, life-like patterns, or evolving biomorphs (see Kumar and Bently, 2003). RA encourages the user to experiment with the system, and not only to see it in action; is that not the aim of any theory for biological complexity?

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