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Modeling complexity in biology

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Abstract

Biological systems, unlike physical or chemical systems, are characterized by the very inhomogeneous distribution of their components. The immune system, in particular, is notable for self-organizing its structure. Classically, the dynamics of natural systems have been described using differential equations. But, differential equation models fail to account for the emergence of large-scale inhomogeneities and for the influence of inhomogeneity on the overall dynamics of biological systems. Here, we show that a microscopic simulation methodology enables us to model the emergence of large-scale objects and to extend the scope of mathematical modeling in biology. We take a simple example from immunology and illustrate that the methods of classical differential equations and microscopic simulation generate contradictory results. Microscopic simulations generate a more faithful approximation of the reality of the immune system. © 2001 Elsevier Science B.V. All rights reserved.

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1. Explanations

Science seeks explanations that work. Immunologists, for example, would like to understand the immune system in a way that would allow medicine to turn on effective

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immune responses against infectious agents and cancer cells and turn off damaging immune responses to foreign transplants or to self-targets in autoimmune diseases. What constitutes a useful explanation?

For the past century, the agenda of immunology has been, for the most part, reductionist; it has sought to explain macroscopic immune behavior by characterizing the component cells and molecules that comprise the hardware of the immune system. The reductionist agenda has been successful to a great degree, and immunology now knows all of the system's cells and probably most of its genes and molecules. This microscopic knowledge, according to the reductionists, should have sufficed to enable the macroscopic control of disease. But, unfortunately, the nearer one approaches a goal, the closer one comes to its shortcomings. It is now clear that further reduction of the system to yet more microscopic chemical information will not satisfy our need to understand the macroscopic physiology of the system—the dynamic web of interactions that generates the clinical behavior of the system. How, we ask, does overt immune behavior emerge from immune chemicals? The gap between immune chemistry and immune physiology, it is thought, can be bridged most quickly and effectively by mathematical modeling, computer assisted [1]. The question we wish to raise here is fundamental to the modeling enterprise: what type of modeling is best able to explain the emergence of immune complexity out of chemical simplicity?

2. Differential equations

Physics and chemistry have progressed on the wings of the calculus invented by Newton and Leibniz. Differential equations [2] and related methodologies are a way of explaining quantitatively and with mathematical precision the interactions of a system as they evolve over time [3]. Intrinsic to differential equations is the smoothness and continuity of the analysis. Individual differences between discrete elements in a system are neutralized by their being lumped into average characteristics of interest. The power of differential equations is in their assumption that the local “average” embodies more truth than does the collective of individual microscopic differences, which are always susceptible to chance sampling errors. Differential equations have revealed their power in physics and chemistry, and so biology has seen fit to use the language of the differential equation to try and understand the complexities of living systems. The problem is that the differential equation is not merely a convenient tool; it is a way of thinking that imposes its own preconceptions.

Here, we introduce a microscopic simulation (MS) methodology [4] that we will show is more suited to explaining the realities of the immune system (and other biological systems too) than is classical differential equation modeling. Indeed, the MS approach can generate outcomes that are the very opposite of those predicted by differential equation models. The discrepancies are important because they embody differences in thinking about the origins of the complexities of real life.

3. Lymphocyte proliferation

To illustrate some of the differences between our MS model and traditional differential equations, we shall model the proliferation of a population of receptor-bearing lymphocytes in response to given concentrations of a specific antigen. The proliferation of clones of lymphocytes in response to an antigen, clonal expansion, is the fundamental event in the initiation of the immune response, at least according to the classical view of the clonal selection theory of acquired immunity [5]. A proliferating lymphocyte can be described as an agent (L) that has a probability of τ of duplicating whenever it meets a stimulating antigen A [6]. The lymphocyte cell has a natural death rate d_L . The response of the lymphocyte can be described as a two reaction system. First, whenever the lymphocyte (L) meets its antigen (A), the lymphocyte divides to create a new lymphocyte, identical to the first, with a probability of τ . We will denote this as



The second reaction is the death of the lymphocyte with a constant probability of dying, d_L . This can be written as



The dynamic of the antigen can be described as entry into the system with a rate of λ and death with a rate of d_A . This dynamic can be denoted in a way similar to that of the lymphocyte as follows:



The antigen and lymphocyte reactions are schematically represented in Fig. 1.

The description of this system using differential equations assumes that the distribution of lymphocytes and antigens is uniform. Both the lymphocytes and the antigen can

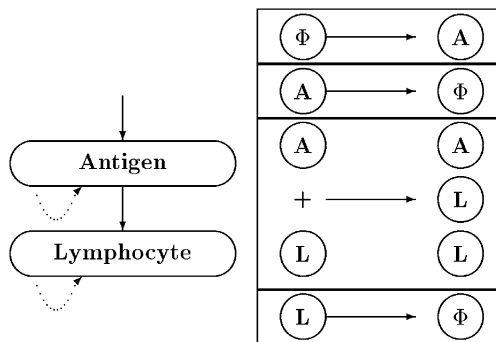


Fig. 1. The lymphocyte–antigen interaction. Antigens enter the system and are destroyed; lymphocytes proliferate and die.

slowly diffuse, but this diffusion is unimportant if we assume homogeneity. Moreover even if the original distribution was non-homogeneous, diffusion tends to homogenize the system. The proliferation of the lymphocytes in response to the antigen signal yields a growth rate proportional to the average antigen density multiplied by τ . Thus the number of new lymphocytes produced in a time interval Δt is

$$\Delta L = \tau A L \Delta t . \quad (5)$$

Natural lymphocyte death yields a decay rate proportional to the death rate multiplied by the lymphocyte concentration:

$$\Delta L = d_L L \Delta t . \quad (6)$$

Thus the total change in L is

$$\Delta L = (\tau A - d_L) L \Delta t . \quad (7)$$

This equation becomes an ordinary differential equation (ODE) when we take the limit

$$\Delta t \rightarrow 0 . \quad (8)$$

Analysis of the antigen reactions is similar to those of the lymphocytes. The ODE approximation in the continuum limit for these reactions is

$$\dot{L} = \tau A L - d_L L , \quad (9)$$

$$\dot{A} = \lambda - d_A A . \quad (10)$$

After a time of the order of magnitude of $1/d_A$, A will stabilize to a value of $\langle A \rangle = \lambda/d_A$. The solution of the ODE for the lymphocytes would then be [7]

$$L = \exp(\langle A \rangle \tau - d_L) t . \quad (11)$$

The behavior of this solution yields three types of behavior: (a) If the average lymphocyte growth rate is higher than the decay rate, $\langle A \rangle \tau - d_L > 0$, the L concentration grows with an exponential growth rate of $\langle A \rangle \tau - d_L$. This exponential growth will end when other controlling mechanisms become active, but we shall ignore them for now. The rise in L is represented by the rising line in Fig. 2. (b) If the average growth rate is lower than the decay rate, $\langle A \rangle \tau - d_L < 0$, the L concentration decays to 0. This decay is represented by the descending line in Fig. 2. (c) If the average growth rate is equal to the decay rate, $\langle A \rangle \tau - d_L = 0$, the L concentration remains constant over time.

The ODE model outlined above suits the classical clonal selection paradigm because it confirms that an immune response may be controlled by the concentrations of antigen impinging on clones of receptor-bearing lymphocytes [5]. It may be said that the clonal selection paradigm views the immune response as if it were a chemical reaction: the concentration of the reactants controls the reaction. The receptor-bearing lymphocytes are seen as inactive until a sufficient concentration of specific antigen enters the system, usually carried by an invading infectious agent. The lymphocytes with receptors for the antigen then respond by proliferating, as we have modeled it above,

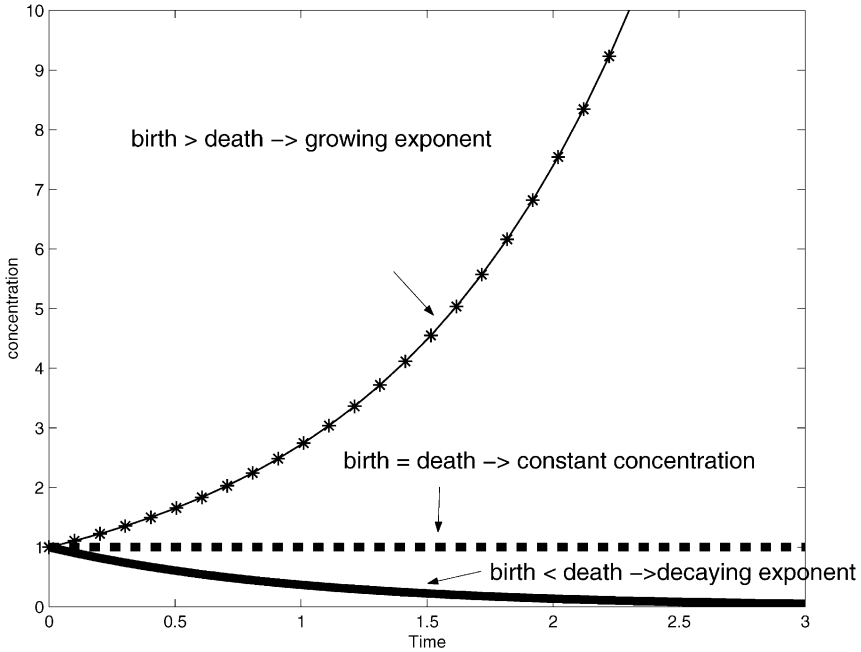


Fig. 2. The different solutions for Eq. (3)— $dy/dt = Cy$ for different values of C : a decaying solution (full line), a growing solution (asterisk) and a constant solution (broken line).

and secrete antibodies or other effector molecules (which we have not modeled here) that neutralize the antigen (kill the infectious invader). And the removal of the antigen puts an end to the expansion of the responding lymphocytes. Memory lymphocytes are assumed to persist, and any further contact with the antigen is met with an accelerated and vigorous secondary response [8] (which, for the sake of simplicity, we also have not modeled here). If the immune response really acts like a homogeneous chemical reaction, then explaining the immune system is best served by an ODE-like approach. The problem with the ODE approach, however, is that the immune system is far from being homogeneous.

4. Non-homogeneity

The ODE solution, and the clonal selection paradigm too, does not take into account the non-homogeneous distribution of antigens. Immunologists have discovered that lymphocytes, particularly the T cells, do not respond to antigen alone. T cells, and probably B cells too, respond best to antigens presented by specialized antigen presenting cells (APC) [9]. The antigens in a real system are not distributed uniformly; they are concentrated in space at discrete points in the system by APC. In other words, the proliferation rate of lymphocytes varies from one point to another according to the

non-homogeneous distribution of APC. Regions with a high concentration of APC will have a high lymphocyte proliferation rate, while regions with a low APC concentration will have a low lymphocyte proliferation rate.

Parenthetically, one may look at the immune strategy of spatial discreteness (of which the APC are only one example) thus: If the concentrations of antigens and lymphocytes really were to control the immune response, then mice and elephants, with their vastly different volumes, would need vastly different doses of antigen to induce an effective immune response. And this is not the case. Each species irrespective of its size has to make a living in a world populated with standard-sized infectious agents.

In the ODE, we assumed that the effective proliferation rate is equal to the average proliferation rate over the system as a whole $\langle A \rangle \tau - d_L$. This assumption, in most cases, is simply wrong. Indeed, the interactions between L and A are mediated by APC and, hence, they are local. Thus the local dynamic of L and A at each location i , A_i , is

$$\dot{L}_i = \tau A_i L_i - d_L L_i - \mu_L \nabla^2 L, \quad (12)$$

$$\dot{A}_i = \lambda - d_A A_i - \mu_A \nabla^2 A. \quad (13)$$

The last term in each equation represents the diffusion of lymphocytes and antigens. The averaging of Eqs. (12) and (13) yields

$$\dot{L} = \tau \langle AL \rangle - d_L L. \quad (14)$$

$$\dot{A} = \lambda - d_A A, \quad (15)$$

where A is the average over all the lattice points of A_i , L is the average of L_i , and $\langle AL \rangle$ is the average of $A_i L_i$. The diffusion term average is 0. If A and L were independent variables, that is if the number of lymphocytes at a point would not depend on the local number of antigens, this equation would be equal to the ODE presented in Eqs. (9) and (10). However, the assumption of the independence of the lymphocyte and antigen concentrations in this case is wrong, since the lymphocyte concentration is high precisely at the points where the antigen concentration is high.

The non-homogeneity problem has led us to adopt the MS formalism.

5. The microscopic–macroscopic world

In the MS formulation, we compute each discrete event separately. This is the fundamental divergence of the MS from the ODE and related formalisms.

In the following discussion, we shall discretize both the location of reactants (A and L) and their number. Note, however, that only the discretization of the number of reactants is essential to the analysis. The discretization of the localization on a square lattice is used only to simplify the simulation; it is not essential to the MS method.

At each lattice point in the MS system space, we compute the probability of each reaction, and then perform reactions randomly according to these probabilities. We

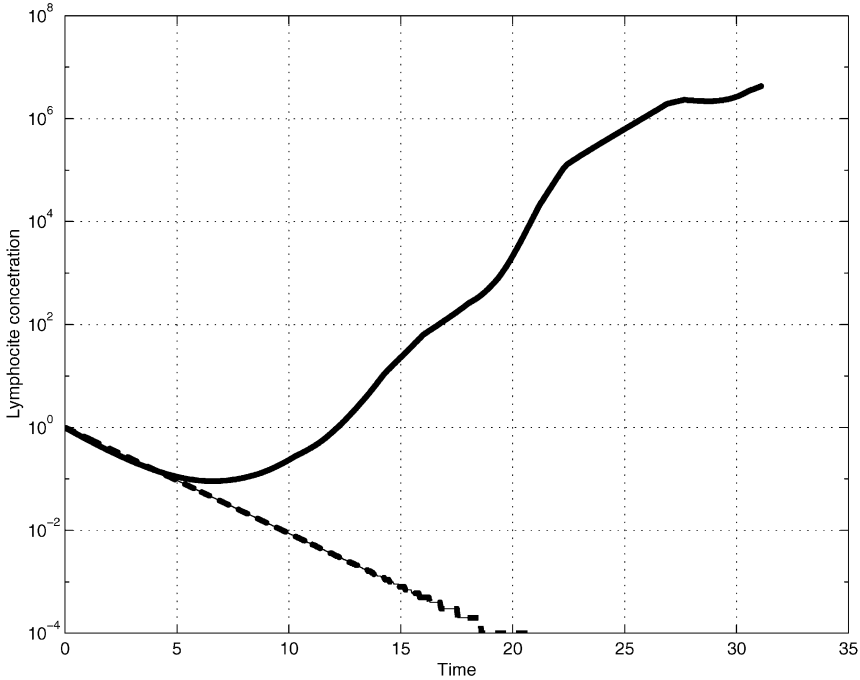


Fig. 3. Comparison between the MS and ODE descriptions of a system of proliferating cells. The graph represents the log of the average of the lymphocyte concentration in the MS (full line) and in the ODE (dashed line).

shall use the same two reactants (A and L) as we used in the ODE formulation and in the reactions described in Fig. 1.

If we take account of the fact that the signaling agent (antigen A presented by APC) has a discrete distribution, the results of the MS are very different from those obtained using the ODE. True, the antigen can be viewed as a random discrete agent with a low local concentration; from this point of view, the antigen distribution is uniform over *large* scales. The point is that *locally* the concentration of antigen shows granularity. Note that this granularity is the origin of large-scale differences between the results computed by the ODE and the MS models.

For example, when $\langle A \rangle \tau - d_L < 0$ (the average proliferation rate is lower than the average death rate), the ODE computation yields a decaying population; but the MS computation yields, in many cases, an exponential growth of lymphocytes, as can be seen in Fig. 3. The origin of this growth is the granularity of the signaling agent, the antigen-APC. Quite simply, each point in immune space contains a different concentration of signaling antigen. For some points $A_i \tau - d_L < 0$, and so the local concentration of specific lymphocytes decays to zero. For other points in immune space, $A_i \tau - d_L > 0$, and so the concentration of lymphocytes will grow at an exponential rate. Indeed, after a short time, the contribution of the points with decaying lymphocyte populations will

be negligible and only the local points with an exponential growth of lymphocytes will contribute to the average concentration of specific lymphocytes in the immune system. The average specific behavior of the system will then be characterized by exponential growth. The number of cells involved in exponential growth becomes macroscopic. The system, as a whole, can be seen to express the microscopic granularity of the APC-antigen apparatus.

The polar difference between the MS and the ODE world descriptions is not generated by the special details of the distribution of the antigen, for example on APC. A polar difference between the ODE and the MS descriptions of the world occurs for all distributions produced by a random process. Once a reaction starts, only the points with the highest growth rate (the highest antigen concentration) will dominate the system average; the concentration at other points, although possibly growing, will be relatively negligible. Thus the average concentration of cells will grow exponentially, but the growth rate is proportional to the peaks of the local concentration of antigen, and not to the average concentration throughout the system. So the elephants need not envy the mice. Note, however, that there are special cases in which the size of the system is important. The MS description enables us to define these cases.

6. Spatial structure

The fate of the system in the ODE is determined only by $\lambda\tau/d_A - d_L$. In the MS description, the fate of the system is controlled by parameters that cannot even be taken into account in the ODE description: the diffusion rate of the lymphocytes and the antigens, and the ratio between them and their proliferation rate (λ).

When the production (λ) and death rate (d_A) are low, the amount of antigen at each region does not change abruptly. Antigens are discrete, so that although their large scale distribution is uniform, their granularity will lead to the creation of local “hot spots”. At these points, the average lymphocyte proliferation rate will be higher than the death rate. Thus, at these points the lymphocyte population will grow. If the lymphocytes diffuse, the antigen hot spot will generate an island of lymphocytes around it to form a germinal center [10].

The analysis of the system now becomes an analysis of the centers of activity rather than the direct analysis of the lymphocytes. The centers of activity grow on antigen hot spots, and they disappear when the local concentration of the antigen drops below a certain threshold. Thus these centers of activity have a typical lifespan determined by antigen entry and diffusion.

The collective behavior of the centers of activity determines the fate of the system. Each center is defined by its location (the A hot spot), its size and its lifespan. The size of the center of activity is determined by the lymphocyte diffusion rate. Three typical scenarios are possible: (a) The lymphocyte diffusion rate is so high that by the time a center disappears the tail of its distribution will span new hot spots which generate

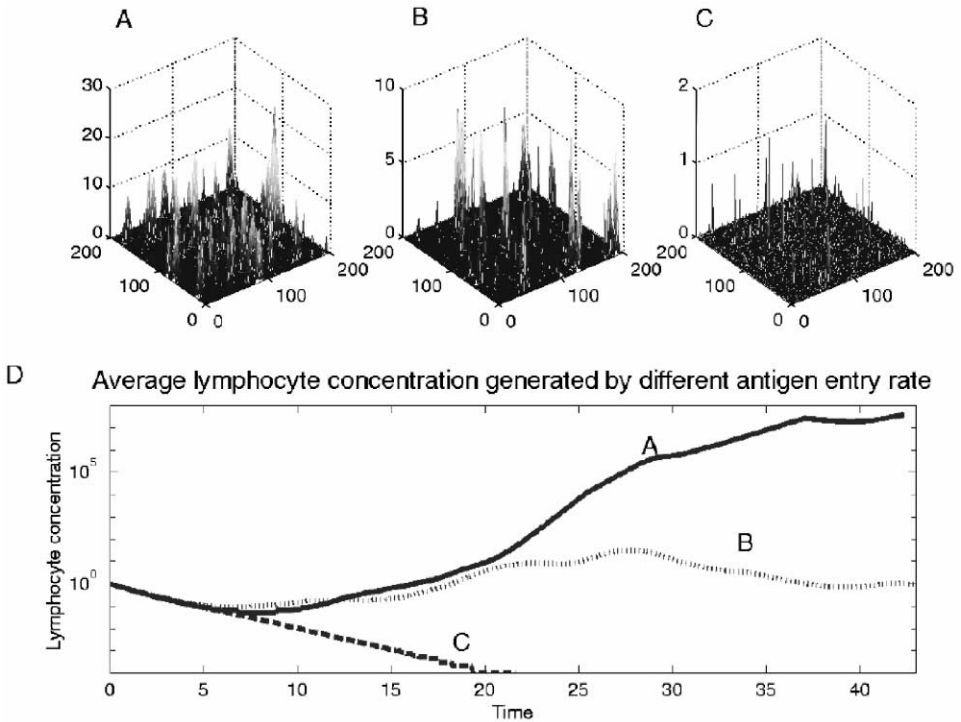


Fig. 4. Different lymphocyte behaviors in response to different rates of antigen entry. (A–C) show the log of the local concentration in three scenarios containing the same global parameters. $\lambda/D_A = 0.7$, $n_A = 0.7$, $\tau = 0.5$, and $d_L = 1.0$. Note that the change in color of particular peaks represents merely the height of the peak. The difference between the simulations is the antigen entry rate. In graph A, the antigen entry rate is equal to the lymphocyte diffusion rate; in graph B, the antigen entry rate is twice the lymphocyte diffusion rate; and in graph C, it is 10 times the lymphocyte diffusion rate. Graph D shows the average lymphocyte concentration for each scenario. It should be noted that the log representation in (A–C) hides the very steep gradient of the lymphocyte concentration. Thus most of the concentration of each islet is in its center, but the global behavior of the system is determined by the islet tail size.

new centers. In this case the lymphocyte concentration will grow until limited by some active control (Fig. 4A). (b) The lymphocyte diffusion rate is so low that the centers die while they are yet small. In this case, the average lymphocyte concentration will oscillate and slowly decrease to 0 (Fig. 4C). (c) The most interesting outcome occurs when the diffusion rate of the lymphocytes is approximately similar to the lifespan of the centers of activity. In this case, the system will generate large semi-periodic oscillations. These oscillations will continue for a very long time, until a large enough oscillation decreases the total concentration of lymphocytes to zero. In this case the fate of the system is sensitive to its size. The bigger it is, the less is its probability of disappearing (Fig. 4B) .

7. General conclusions

In summary, the basic assumption of the MS is that nature puts each cell (or any responsive agent) in a spatial location. In the present treatment, we represent the position by a lattice point. We can assume that whenever two cellular agents are within a non-zero distance r of each other, they have some probability of interaction. This interaction radius thus describes functionally the distance between natural lattice points. Cells separated by a distance greater than r will not interact, unless they move. Cellular agents that are within the radius r are assumed to be on the same lattice point, and have a finite probability for interaction. Although a signaling agent, a cell or molecule, may be distributed in a random way, so that its average concentration is constant everywhere, each lattice point will contain a different number of signaling agents. It is this intrinsic microscopic granularity of nature that creates the macroscopic reality of biologic systems. Macroscopic emergence is inherent in microscopic non-homogeneity, but ODE models are blind to it. Thus the traditional ODE and partial differential equation models are less true to the nature of the immune system than is our MS model. Unlike the traditional differential equation models, the MS approach explains how macroscopic structures, such as lymph nodes and germinal centers, can emerge from the fundamental discreteness of cells and molecules.

Conflicts between models are not trivial; modeling is important for understanding. Indeed, one's choice of modeling strategy implies a world view; the model, in effect, may implant the mind of the observer with certain expectations even before he or she actually uses the particular model to test reality. The chosen model itself surreptitiously bears biases that can influence the viewers interpretation of nature's facts.

The clonal selection theory of the immune system, with its satisfying chemical paradigm of the L - A interaction, was caught off guard by the discoveries of APC processing and presenting functions, the MHC, cytokines, cellular help and suppression, the major impact of innate immunity on adaptive immune decisions, the discrete structuring of natural autoimmunity and much else of what is now being studied by immunologists [11]. We do not mean to imply that the MS model would have foreseen these elements. In fact, the MS model needs a significant amount of work to accommodate these discoveries.

The point is that the chemical simplicity of the classical clonal selection theory and the ODE are in such harmony that, in principle, one might believe that the major problems have been solved, and that immunology only need mop up the details. On the contrary, immunology is only now beginning to think about the transition from analysis to synthesis. The question is how to explain (and control) the emergence of macroscopic immune physiology from unit cells and molecules that are distributed, discrete and autonomous. The question of emergence is not limited to immunology; all of modern biology is concerned with emergence: signal transduction, the growth and development of an individual from a fertilized egg, the self-organization of the brain and behavior, the evolution of species, and so forth.

The processes of physics and chemistry, like those of life, do involve discrete elements. However there is a basic uniformity of physical and chemical processes over wide scales of their expression. Biology, in contrast, employs widely different processes at the various scales of interaction in living systems: from genes to proteins, to cells, to organs, to organisms, to species, to ecosystems. Biologic systems thus require discretization at each scale. Life exploits the inhomogeneity of matter to amplify complexity. How life carries out this program now needs to be explained in detail. A continuing program of molecular reduction, by itself, will not explain the emergence of macroscopic complexity. We need appropriate modeling.

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