Evelyn Fox Keller

Self-Organization, Self-Assembly, and the Inherent Activity of Matter

THE HANS RAUSING LECTURE 2009
UPPSALA UNIVERSITY

SALVIA SMÅSKRIFTER

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SALVIA SMÅSKRIFTER, NO. 12

Swepografiska, Stockholm 2009
ISBN 978-91-506-2119-8

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This has undoubtedly been the year of Darwin. Indeed, at this very moment, Uppsala is hosting its very own Darwin celebration. But it is often forgotten in all this celebratory enthusiasm that, for all his indisputable achievements, Darwin left a sizeable problem for future generations to solve. Namely, he left the question of how the first "primordial form, into which life was first breathed" from which "all the organic beings which have ever lived on this earth have descended" – that "simple beginning" from which "endless forms most beautiful and most wonderful have been, and are being, evolved" – first came into existence.

In fact, it is surprising how often, or how easily, this conspicuous lacuna in Darwin's argument is overlooked, and not only in the celebratory fervor of his anniversary. It tends especially to be overlooked by advocates of Natural Selection as the universal solvent of life, capable of generating any biological property whatever. For example, let's look at the hallmark of biological systems that goes under the name of function – as in, the function of x is to do y. Over the last decade or so, something of a consensus has emerged among philosophers of science about how to treat this problem. Proper function, as first argued by Ruth Millikan and as now widely asserted, should be understood solely in the context of natural selection – i.e., the function of X is that "which caused the genotype, of which X is the phenotypic expression to be selected by natural selection".[1]

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[1] Neander, K. (1998). "Functions as Selected Effects," *Nature's Purposes: Analyses of Function and Design in Biology* (Eds.: Allen C, Bekoff M & Lauder G), Cambridge MA.: MIT Press, p. 319.

In this way, it is often claimed that the problem of function has been solved. But I disagree. I think rather, that it has been circumvented. It entirely avoids the problem of how function, understood as a property internal to a biological structure, might have first arisen, particularly in the light of recent arguments that it almost certainly emerged prior to the onset of natural selection. That is to say, natural selection, as conventionally understood since the neo-Darwinian synthesis (and I will adhere to the conventional understanding), requires the prior existence of stable, autonomous, and self-reproducing entities. Single celled organisms, e.g., or, simply, stable, autonomous, cells capable of dividing. But of necessity, these first cells needed already to be endowed with numerous sub-cellular entities (or modules) that would endow the primitive cell with the functions minimally required for the cell to sustain itself and reproduce, to be alive. To be sure, these early cells lacked many features of the modern cell. But in order to persist – and to maintain their identity – long enough for natural selection to operate, they had to already have had primitive mechanisms to support metabolism, cell division, etc.; there needed to have already come into being primitive embodiments of function that would work keep the cell going and to protect it from insult.

But perhaps I should say what I mean by function. Let me try to clarify my meaning by taking off from Michael Ruse's argument against the use of the term for inanimate systems, and more specifically against sufficiency of circular causality. Ruse offers the familiar example of the cyclical process by which rain falls on mountains, is carried by rivers to the sea, evaporated by the sun, whereby it forms new rain clouds, which in turn discharge their content as rain. The river is there because it produces or conveys water to form new rain clouds. The rain clouds are a result of the river's being there. But Ruse argues that we would not want to say the function of the river is to produce rain clouds, and he is right. What is missing, he claims, is the means by which "Things are judged useful.” I won’t follow Ruse in his deployment of such worrisomely adaptationist notions as ‘value’ and ‘desire’. Instead, I want to salvage his observation by redescribing what he calls ‘judgement’ as a measurement of some parameter, or if you like, as an evaluation, that is performed by a mechanical sensor and, when exceeding some pre-set limit, is fed back into a controller which is able to restore the proper range of parameter. In other words, I use the term function in the sense that the philosophers Ernst Nagel and Morton Beckner originally did, i.e., in the sense of a simple feedback mechanism. Like a thermostat. Once such a mechanism is added to the rain-cloud-river cycle, (say, a mechanism that triggers a change in evaporation rates when the water level falls too low) we can, in this sense of the term, legitimately speak of function and say, e.g., that the function of such a mechanism is to maintain the water level within a certain range of parameters. But crucially, this device differs from the thermostat in that maintaining the room temperature at comfortable levels does not contribute to the persistence of the home whereas maintaining the water level does contribute to the persistence of the entire cycle; hence it also contributes to the persistence of the mechanism that performs this function. In much the same vein, I suggest that we can refer to the many different cellular mechanisms (proof-reading and repair, chaperones, cell-cycle regulation) that maintain the cellular dynamics necessary to the persistence of the cell (and its progenitors) as mechanisms that have functions. They survive not as a result of natural selection but as a consequence of the internal selection that follows automatically from their contribution to the persistence of the system of which they are part. It is a form of selection that does not depend on reproduction (which might be regarded as one way of ensuring persistence, rather like autocatalysis) but rather, a more general kind selection of which natural selection is a particular example. Indeed, their existence is what lends the cell the stability necessary for natural selection to operate.

The existence of such mechanisms is crucial to what makes a system qualify as biological, just as the properties that characterize these mechanisms are crucial to the science that early 19th century scientists (like Lamarck) deemed sufficiently distinctive to mandate its own designation. The separation of a science of life from the science of non-life was indeed a milestone, for it effectively codified the problem I am talking about. And in doing so, set the stage for the dilemma with which we have struggled ever since. Either the distinction that separates these two sciences is ontological and cannot be bridged, or it is provisional, in which case we are confronted with the difficult task of accounting for how mechanisms that embody such properties might have originally come into being. How might such devices – devices that bear all the marks of design – have arisen naturally, without a designer? In other words, if biology is to be a natural science, we need to explain the emergence of those properties (and here I take function to be a stand in for purpose and agency as well) that led Immanuel Kant to first introduce the term self-organization, i.e., to attribute to the living organism a self with the capacity for its own organization. This is the problem of accounting for the origin of entities capable of persisting long enough for Darwinian selection to operate, entities therefore capable of subsequently evolving into all those "endless forms most beautiful and most wonderful". That is, it is the problem of accounting for the origin of that system "into which life was first breathed," – the primordial cell. In other words, for the origin of life.

The question boils down to this: by what processes (or dynamics) did these early machines come together, and combine to constitute a primitive cell? Clearly, if natural selection is itself is a product of this early evolution, we cannot evoke that process as an answer. What are the alternatives? What, other than intelligent design, can provide the requisite directionality to the random processes of change to which entities in the physical world are subject? Is it in fact possible to account for the emergence of natural design, of a 'self' that can be said to organize – indeed, for the emergence of natural selection itself – from purely physical and chemical processes?

Lamarck and Leduc

Although Darwin did not himself attempt to answer this question, Lamarck did. In fact, one might say that Lamarck saw it as the central problem of evolution. His *Zoological Philosophy* (written in 1809) was, from first to last, "an enquiry into the physical causes which give rise to the phenomena of life".[2] As I've already said, Lamarck was one of those responsible for insisting on a distinct designation for the science of life: "Between crude or inorganic bodies and living bodies", he wrote, "there exists an immense difference, a great hiatus, in short, a radical distinction such that no inorganic body whatever can even be approached by the simplest of living bodies."[3] Nevertheless, he rejected any evocation of extra-natural causes of the origin of life, and he was firm in this conviction. He faulted past thinkers for seeking the "special exciting cause of organic movements" beyond nature: "not having sufficiently studied nature they sought it beyond her, they imagined a vital principle, a perishable soul for animals, and even attributed the same to plants; thus in place of positive knowledge, which they could not attain from want of observations, they created mere words to which are attached only vague and unreal ideas."[4] By contrast, Lamarck sought a purely physical account of the "power of life", of its natural tendency to increased complexity, and of the origin of entities that could be said to self-organize. He was convinced, as he put it, that "Nature has no need for special laws, those which generally control all bodies are perfectly sufficient for the purpose." Nevertheless, "if we wish to arrive at a real

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[2] Jean Baptiste de Lamarck. 1809 [1963]: *Zoological Philosophy: An Exposition with Regard to the Natural History of Animals. translated*, with an introduction by Hugh Elliot Lamarck, New York: Hafner, p. 282.

[3] Ibid., p. 194.

[4] Ibid., pp. 211-212.

knowledge of … what are the causes and laws which control so wonderful a natural phenomenon, and how life itself can originate those numerous and astonishing phenomena exhibited by living bodies, we must above all pay very close attention to the differences existing between inorganic and living bodies".[5]

What then accounts for these differences? What can be said about what life *is*? As Lamarck saw it, "Life is an order and a state of things that permit organic movement there; and these movements, which constitute active life, result from the action of a stimulating cause that excites them."[6]The stimulating, or excitatory cause, which he likened to the spring of a watch, was to be found in "subtle, invisible, uncontainable, incessantly moving fluids" (like caloric and electricity) that came originally from outside, insinuating themselves in the interstices of the soft parts of the body, exciting movement, tension, and increasing organization of that body. Caloric, e.g., was "...an invisible penetrating, expansive everactive fluid that percolates slowly through the supple parts, distending them and making them irritable; and that is constantly being dissipated and renewed and is never entirely absent from any body that possesses life...".[7] He saw caloric as the prime source of what he called orgasm, or irritability, and electricity as the prime source of animal motion. "It is," he wrote, "from the uninterrupted co-operation of these factors and of long periods of time, combined with an infinite variety of environments that all the orders of living bodies have been successively formed."[8] To be sure, the body's power of life initially depends on the external supply of these fluids, but with the increasing complexity of organization, he was convinced that they would, over time, be internalized.[9]

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[5] Lamarck: *Zoological Philosophy*. p. 191.

[6] Ibid., p. 202.

[7] Ibid., p. 218.

[8] Ibid., p. 233.

[9] See Richard W. Burkhardt. 1977 [1995]. *The Spirit of System: Lamarck and Evolutionary Biology*. Cambridge, MA.: Harvard Univ. Press., pp. 150-156, for further discussion

Two centuries later, an obscure French biophysicist from the University of Nantes, Stephane Leduc, sought to revive Lamarck's efforts and to demonstrate empirically (even if not theoretically) the possibility of generating such basic biological capacities as "the productive force of movement", or cell division, out of the interactions of purely inorganic materials. His approach was to seek an understanding of the origin of life incrementally, by the simulation of ever more "life-like" constructions from simple chemical precipitates. Leduc may or may not have coined the term, but his 1912 publication of *La Biologie Synthetique* predated current fashion by almost a century.

The results of his efforts were clearly illustrated – in this as in his other publications – and, at the time, they attracted a great deal of attention. For example, in *The Mechanism of Life* (1911), Leduc published an account of artificial cell division, created out of nothing more than a semi-saturated solution of potassium nitrate and India ink.[10] **(Figure 1)**

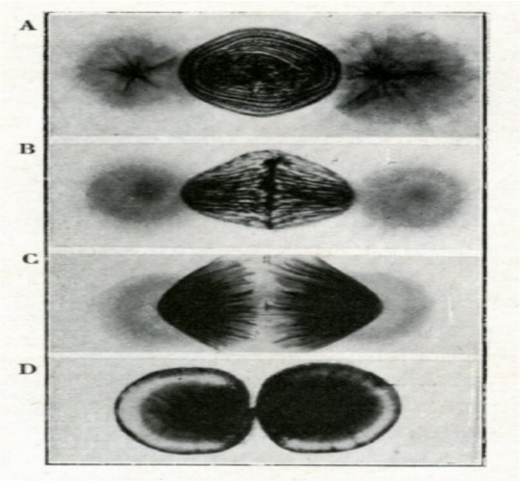

Figure 1. *Pictures of artificial cell division from Leduc's The Mechanism of Life.*

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[10] Stephane Leduc. (1911): *The Mechanism of Life.* translated by W.D. Butcher. New York, p. 32. The same account, and the same figures, had also appeared in Leduc 1910: *Théorie physico-chimique de la vie et générations spontanées*. Paris: A.Poinat.

As he explained,

> We cover a perfectly horizontal glass plate with a semi-saturated solution of potassium nitrate to represent the cytoplasm of the cell. The nucleus in the centre is reproduced by a drop of the same solution coloured by a trace of Indian ink, the solid particles of which will represent the chromatin granules of the nucleus. The addition of the Indian ink will have slightly lowered the concentration of the central drop, and this is in accordance with nature, since the osmotic pressure of the nucleus is somewhat less than that of the plasma. We next place on either side of the drop which represents the nucleus a coloured drop of solution more concentrated than the cytoplasm solution. The particles of Indian ink in the central drop arrange themselves in a long coloured ribbon, having a beaded appearance.[11]

And he concluded, "The resemblance of these successive phenomena to those of natural karyokines is of the closest. The experiment shows that diffusion is quite sufficient to produce organic karyokinesis, and that the only physical force required is that of osmotic pressure."[12]

In similar ways, employing similar techniques, he also succeeded in producing a number of examples of growths that could qualify as artificial or osmotic "organisms":

> When a soluble substance in concentrated solution is immersed in a liquid which forms with it a colloidal precipitate, its surface becomes encased in a thin layer of precipitate which gradually forms an osmotic membrane round it.[13]

Increase in osmotic pressure then gives rise to "osmotic growth". Leduc describes the effect as follows:

> The first cell gives birth to a second cell or vesicle, and this to

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[11] Leduc: *The Mechanism of Life*, p. 93.

[12] Ibid., p. 32.

[13] Ibid., p. 94. As he explains, "Particularly beautiful osmotic cells may be produced by dropping a fragment of fused calcium chloride into a saturated solution of potassium carbonate or tribasic potassium phospate, the calcium chloride becoming surrounded by an osmotic membrane of calcium carbonate or calcium phosphate." (p. 124).

> a third, and so on, so that we finally obtain an association of microscopic cellular cavities, separated by osmotic walls – a structure completely analogous to that which we meet with in a living organism.[14]

Indeed, by employing a variety of metallic salts and alkaline silicates (e.g., ferrocyanide of copper, potash, and sodium phosphate), and adjusting their proportions and the stage of "growth" at which they were added, Leduc was able to produce many truly spectacular effects – inorganic structures exhibiting a quite dramatic similitude to the growth and form of ordinary vegetable and marine life. **(Figure 2)**

Figure 2. *Picture of ozmotic growth from Leduc's The Mechanism of Life.*

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[14] Leduc: *The Mechanism of Life*, p. 124.

By "appropriate means," it proved possible to produce "terminal organs resembling flowers and seed-capsules," "corral-like forms," shell forms, and "remarkable fungus-like forms. …. With salts of manganese, the chloride, citrate or sulphate, the stages of evolution of the growth are distinguished not only by diversities of form, but also by modifications of colour. …. Very beautiful growths may be obtained by sowing calcium chloride in a solution of potassium carbonate, with the addition of 2 percent of a saturated solution of tribasic potassium phosphate. This will give capsules with figured belts, vertical lines at regular intervals, or transverse stripes composed of projecting dots such as may be seen in many sea-urchins." **(Figure 3)** Some of Leduc's osmotic "organisms" also exhibited an apparent capacity for both "free-swimming" and reproduction: "Frequently a single seed or stock will give rise to a whole series of osmotic growths. A vesicle is first produced, and then a contraction appears around the vesicle, and this contraction increases till a portion of the vesicle is cut off and

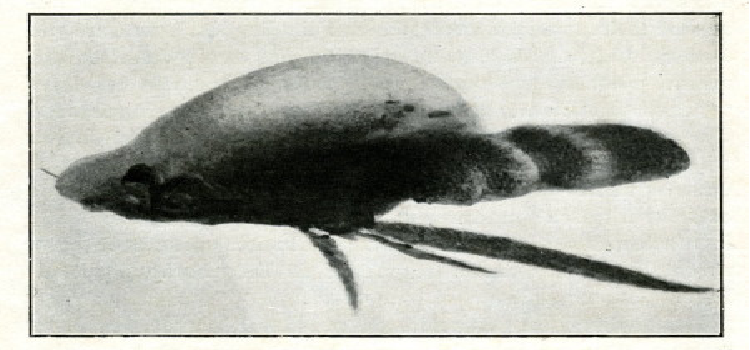

Figure 3. *Picture of nageoires from Leduc's The Mechanism of Life.*

swims away free like an amoeba."[15]

Leduc's efforts were not well received in France; Pasteur's legacy had seemed effectively to foreclose the issue of how living matter arose might arise from the non-living. He had hoped for a better reception in Darwin's home country, and indeed, his work did elicit a somewhat better reception both in the U.K. and the U.S.). As Bashford Dean from Columbia University wrote,

> Leduc's book is interesting and it deserves to be carefully read. We need not admit that it *is* biology; but we must admit that the inorganic conditions which here are given detailed consideration have occurred and are occurring constantly in organisms. And we shall be apt to admit that the synthetic method promises results which will prove of great value. Leduc would be the first to agree that living substance may not be synthesized for ages, if at all. But each advance brings the goal nearer….[16]

But even among Anglo-American readers, not all were persuaded. Another review appearing that same year in *Nature* (p. 410, May 25, 1911) was scathing: "With a little ink and water one can conjure up all sorts of phantasms, … [but] is this sort of thing useful?" Almost four decades later, in *Doctor Faustus*, Thomas Mann felt obliged to "leave it to the reader's judgment whether that sort of thing is matter for laughter or tears."[17]

So what was, or is, the point in these exercises? The contemporary biologist would scarcely know what to make of Leduc's efforts. Leduc's aim was to demonstrate the continuity between living and non-living matter, and in his own words, to do so incrementally. Obviously, these were not living organisms. Yet they did bridge the gap with living systems in one dimension: They looked like organisms. In other words, Leduc had demonstrated that structures

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[15] Leduc: *The Mechanism of Life*. pp. 131, 133, 136-7, 139, 140.

[16] Bashford Dean. (1911):"Scientific Books. Leduc's *Théorie physico-chimique de la vie et générations spontanées*," *Science* 843 (33, February 24), p. 311.

[17] Thomas Mann. (1948): *Doctor Faustus; the Life of the German Composer*, Adrian Leverkuhn, New York: A. A. Knopf., pp. 19-20.

resembling living organisms in their outward morphology and in some aspects of their behavior *could* spontaneously arise from brute matter, without help from either a designing deity or a vital force.[18]

Contemporary Accounts

Lamarck's terms and categories are alien to us, and his account hardly seems like an explanation at all. We are far more likely to be satisfied by explanations couched in our own contemporary terms and categories. Here is one such account that has become popular in recent years, and for many, the principle – perhaps even the only possible – scientific alternative to evolution by natural selection. I refer to the view of the origin of life as an example of the spontaneous emergence of order, of the kind associated with the process of self-organization as that process has come to be understood in the physical sciences over the last several decades – the kind of self-organization that can be seen in a nonlinear dynamical systems that can "mold itself," as Paul Davies put it, "into thunderstorms, people and umbrellas". Many workers in this field have drawn inspiration from Statistical Mechanics, aiming to describe the emergence of organized structured systems out of blind random physical processes. Self-organization becomes a kind of phase transition. Or as Stuart Kauffman writes, "metabolic networks need not be built one component at a time; they can spring full-grown from a primordial soup. Order for free, I call it."[19]

Kauffman is correct. Many complex structures – including networks – can and do arise spontaneously. Indeed, we can find examples of order-for-free all around us. The problem is that such structures do not yet have function, agency, or purpose. They are

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[18] For further discussion, see Evelyn Fox Keller. (2002). *Making Sense of Life*. Cambridge, MA: Harvard University Press, Chapter One..

[19] Stuart Kauffman. (1995): *At Home in the Universe*. New York: Oxford University Press. p. 45.

not yet alive. Self-organization, as mathematicians and physicists use the term, may indeed be necessary for the emergence of biological forms of organization, but as I have argued on a number of occasions, and as Stuart Kauffman now acknowledges, for understanding living processes, it is not enough. The gap between living and non-living persists.

Despite all our efforts, the critical properties of function, agency, and purpose continue to mark organisms (even if not machines) apart from thunderstorms – indeed, apart from all the emergent phenomena of nonlinear dynamical systems, remaining conspicuously absent from the kinds of systems with which physics deals. An account of how properties of this sort might emerge from the dynamics of effectively homogeneous systems of simple elements, however complex the dynamics of their interaction might be, continues to elude us. Such properties seem clearly to require an order of complexity that goes beyond that which spontaneously emerges from complex interactions among simple elements – a form of complexity that control engineers have been struggling to characterize ever since the 1940s, and that Warren Weaver, Herbert Simon, and now John Mattick and John Doyle have dubbed organized complexity.

For Weaver (1948), the domain of problems characterized by organized complexity lay in sharp contrast to the problems of statistical mechanics that made up the domain of disorganized complexity. For Simon, organized complexity was complexity with an architecture, and in particular the architecture of hierarchical composition (or modularity) whereby a system "is composed of interrelated subsystems, each of the latter being in turn hierarchic in structure until we reach some lowest level of elementary subsystem".[20] For Mattick, the organization of complexity is mandated by the meaninglessness of the structures generated by

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[20] Simon, Herbert. (1969): "The Architecture of Complexity," *Proceedings of the American Philosophical Society* 106 (6), p. 468.

sheer combinatorics of complex interactions: "[B]oth development and evolution," he writes, "have to navigate a course through these possibilities to find those that are sensible and competitive".[21] Yet none of these authors quite grapple with the question of just what kind of organization would warrant the attribution of the properties of agency or function, would turn a structure or pattern into a self.

Cybernetics, and its emphasis on the relation between feedback and function characteristic of homeostatic devices, offered one clue; I believe that Herbert Simon offered us another. In fact, it is sobering to go back and read Simon's 1962 essay on 'The Architecture of Complexity'. Here Simon introduces a crucial if much neglected argument for a form of evolution that is alternative both to natural selection and to emergent self-organization: evolution by composition. The idea is this: If stable heterogeneous systems, initially quite simple, merge into composite systems that are themselves (mechanically, thermodynamically, chemically) stable, such composite systems in turn can provide the building blocks for further construction. Through repetition, the process gives rise to a hierarchical and modular structure that Simon claims to be the signature of systems with organized complexity. "Direction," he explains, "is provided to the scheme by the stability of the complex forms, once these come into existence. But this is nothing more than survival of the fittest – that is, of the stable."[22]

We need to be a bit careful here about what we mean by stability – we are not interested in the stability of rocks, and perhaps not even of the limit cycles of dynamical systems closed to informational or material input. Rather, we are interested in the stability of nonequilibrium systems that are by definition open to the outside world, not only thermodynamically but also materially. Perhaps a better word would be robustness. The systems that endure are

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[21] J. Mattick. (2004): "RNA Regulation: A New Genetics?" *Nature Reviews Genetics* 5, p. 317.

[22] Simon: "The Architecture of Complexity," p. 191.

those that are robust with respect to the kinds of perturbations that are likely to be encountered. The critical questions then become, first, how do new ways of persisting – new stable modes of organization – come about, and second, how are they integrated into existing forms?

In neo-Darwinian theory, novelty arises through chance mutations in the genetic material and integrated into existing population by selection for the increased relative fitness such mutations might provide. In the picture Simon evokes, novelty arises through composition (or combination), is further elaborated by the new interactions that the proximity of parts bring into play, and, finally, integrated into the changing population by selection for increased relative stability. Of particular importance is the stability of the composite acquired with the passage of sufficient time "to undergo a process of mutual co-adaptive changes under the optimizing forces of selection".[23] Symbiosis provides what is probably the best example of all three aspects of the process, and perhaps especially of the ways in which the net effect is to bring into being entirely new kinds of entities that would persist by virtue of their enhanced robustness.

But over the long history preceding the arrival of the first cell, a different kind of composition was required – not composition of existing life forms, but composition of complex molecular structures (like proteins, e.g., or nucleic acids, or complexes of these macromolecules). Molecular composition rather than symbiosis. (Or perhaps simply what Jean Marie Lehn refers to as supra-molecular chemistry).

A crucial question is: how do such molecular or supra-molecular composites come about? Random collisions are undoubtedly a big part of the picture. As is heterogeneity as well. Perhaps even more important are the cumulative effects of stabilizing selection operating on the products of random collisions over the course

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[23] Simon: (1974, p. 76). No reference to title in bibliography.

of time. Molecules, and especially large molecules like proteins, are not simple billiard balls. They are sticky, they have binding sites. They have hooks that actively engage other molecules and invite the formation of larger complexes through the formation of covalent and non-covalent bonds. I submit that there is a kind of primitive activity already inherent in such collections of molecules, perhaps bearing some resemblance to what Lamarck sought in his imponderable fluids. Unlike the proto-organisms in Lamarck's fluids, however, these elements, arriving on the scene long before the complexities of animal movement could evolve, have an activity that is already internalized. The springs of activity are built into the very structure of many macromolecular complexes, amounting to a kind of agency that comes directly out of molecular structure. Drawing energy from their interactions with their neighbors and the larger environment, these are molecular entities that act; indeed, they perform the work that is required for the survival of living systems. Often, they depend on thermal noise, converting non-directional Brownian motion into mechanical or chemical work. We might speak of chemical forces and free energies rather than of caloric and electricity in describing these activities, but the idea seems to me to have distinct echoes in Lamarck's earlier vision.

In any case, there is a still further point about one feature of molecular composition that I want to make, and it is one that, for the purposes of understanding vital activity, may be the most important yet. The formation of the covalent and non-covalent bonds that hold such molecular complexes together can also sometimes change the structure of the components with which the process started. In so doing, they can also induce changes in the rules of engagement, thereby creating the possibility for new interactions, new binding sites, new hooks. The new binding sites are not simply the consequence of the new proximities created by molecular binding, but more interestingly, of the changes that have been triggered in the ways in which the component parts can interact. They might be thought of as Brownian motors in evolutionary space, feeding on chance events to build ever more complex configurations. Macromolecules like proteins are thus not only not billiard balls; they are also not simply sticky balls. They are sticky balls that actively respond to getting stuck, composite structures that might even be said to embody a link between rudimentary forms of perception and action. This is an especially provocative claim, and I need to explain.

The phenomenon I am trying to describe rests on two basic facts: first, that many complex macromolecular structures are capable of stabilizing in a variety of distinctive shapes or forms, and second, that the binding of new molecules can trigger a shift from one conformation to another, thereby exposing new binding sites, and new possibilities for subsequent composition. The claim that this process can be thought of as a link between perception and action requires only that we characterize the binding site to which the new molecule binds as a kind of sensory receptor, and the change in behavior induced in the larger complex induced by the actual binding of that new molecule as a kind of action.

Prions provide a particularly simple example of what I am talking about. Prions are proteins that are also infectious agents. They are proteins that have become infectious agents as a result of a particular change in folding – a change in folding that has the peculiar effect that it endows the molecule with the capacity to transmit its new state (conformation) to other (normally folded) proteins with which it comes into contact. The infectious nature of prions has only recently been discovered, but in fact it is an instance of a far more general process in which changes in conformation induce new properties in properties – a process widely referred to as *allostery* in molecular biology. The term was originally introduced in 1961 by Monod and Changeaux to describe the fact that some proteins (hemoglobin, e.g.) can exist in more than one state, with different properties associated with each state. Allostery has since been recognized as a fairly common property of macromolecules (like proteins), and I suggest that it adds a new dimension of particular importance for evolution –especially for evolution under the pressure for increased stability. Prion infection results from a single allosteric change, but cumulative changes are also possible, and the possibility of cumulative changes turns allostery into a mechanism for exploring new evolutionary spaces and for accelerating the formation of ever more complex structures. It seems to me not unreasonable to expect that some of these structures would have the capacity to respond to perturbations in ways that would enhance the stability of the system in which they were embedded – i.e., they would be functional in the sense that I defined above.

By virtue of their generativity, processes of this sort would seem to be especially pertinent to the evolution of cellularity. Biological cells are replete with devices for ensuring survival, stability, robustness. Think, for example, of the structures (devices) that have arisen to regulate cell division, ensuring that cell division is not triggered too early (when the cell is too small) or does not wait too long (when the cell has gotten too big). Or of the vastly complex kinds of machinery for guaranteeing fidelity in DNA replication, the accuracy of translation, or the proper folding of proteins. Each of these processes – or functions – could presumably have evolved by virtue of the enhanced stability/persistence that the structures on which they depend lend to the system of which they are part.

Because each such mechanism transforms the available options, and pathways, for subsequent evolution, its arrival might be said to demarcate a distinctive evolutionary epoch. In fact, the history of pre-Darwinian evolution is replete with such demarcations. Think, for example, of the advent of nucleic acid molecules, appearing on the scene long before the existence of anything like a primitive cell. Nucleic acids introduced a major advance over mechanisms of autocatalysis for making more because it made possible the replication of molecules with arbitrary sequences. The subsequent formation of a translation mechanism between nucleic acid sequences and peptide chains required the combination of already existing nucleic acid molecules and already existing protein structures, and the innovation of a translation mechanism – in effect, the advent of genes – ushered in an entirely new order of evolutionary dynamics dominated, according to Carl Woese, by horizontal gene transfer. Woese argues that cellular evolution, precisely because it needed so much componentry, "can occur only in a context wherein a variety of other cell designs are simultaneously evolving". He writes, "The componentry of primitive cells needs to be cosmopolitan in nature, for only by passing through a number of diverse cellular environments can it be significantly altered and refined. Early cellular organization was necessarily modular and malleable."[24] Indeed, only with the sealing off of these composite structures and the maintenance of their identity through growth and replication – i.e., after a few hundred million years of extremely rapid evolution – did individual lineages become possible. As Freeman Dyson puts it, "one evil day, a cell resembling a primitive bacterium happened to find itself one jump ahead of its neighbors in efficiency. That cell separated itself from the community and refused to share. Its offspring became the first species. With its superior efficiency, it continued to prosper and to evolve separately."[25] The rest, as they say, is history – i.e., the history of Darwinian evolution.

But much more than nucleic acids and genetic codes needed to be built up before a (more or less) autonomous cell could survive – i.e., to survive long enough for natural selection to kick in. Long before the advent of that cell, long before anything like a system with such distinctly biological properties as function became possible, other molecular discontinuities would surely also have been needed, and if we are to understand the evolution of those aspects of cellular machinery responsible for pushing the cell over the threshold of the living, these too will need to be identified.

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[24] Carl Woese. (2002): "On the Evolution of Cells," *Proceedings of the National Academy of Sciences* 99 (13), p. 8742.

[25] Freeman Dyson. (2007): "Our Biotech Future," *The New York Review of Books* 54 (12, July 19).

I am arguing that one transition (or discontinuity) of particular importance was the emergence of what I might call "smart matter," or rather, smart molecules. Smart molecules are molecules that can both register (sense) signals in their environment and respond by changing their rules of engagement – e.g., allosteric molecules. I suggest that such molecules came on the scene somewhere over the course of the evolution of macro-molecules like DNA and proteins, and further, that their appearance was crucial to the subsequent evolution of living systems. Ray Kurzweil, undoubtedly employing a somewhat different notion of 'smart', has written that "once matter evolves into smart matter…it can manipulate matter and energy to do whatever it wants".[26] I wouldn't go quite that far, but I would suggest that once matter evolves into smart matter, the range of what it can do becomes enormously expanded.

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[26] Ray Kurzweil. (2005): *The Singularity is Near: When Humans Transcend Biology.* New York: Viking Penguin, p. 364.

Author's biographical sketch

Evelyn Fox Keller received her B.A. from Brandeis University (Physics, 1957) and her Ph.D. from Harvard University (Physics, 1963). She came to MIT from the University of California, Berkeley, where she was Professor in the Departments of Rhetoric, History, and Women's Studies (1988-1992). Professor Keller has taught at Northeastern University, S.U.N.Y. at Purchase, and New York University. She has been awarded numerous academic and professional honors, including most recently the Blaise Pascal Research Chair by the Préfecture de la Région D'Ile-de-France for 2005–07, which she spent in Paris, and elected membership in the American Philosophical Society and the American Academy of Arts and Science. In addition, Professor Keller serves on the editorial boards of various journals including the *Journal of the History of Biology and Biology and Philosophy*.

Keller's research focuses on the history and philosophy of modern biology and on gender and science. She is the author of several books, including *A Feeling for the Organism: The Life and Work of Barbara McClintock* (1983), *Reflections on Gender and Science* (1985), *The Century of the Gene* (2000), and *Making Sense of Life: Explaining Biological Development with Models, Metaphors and Machines* (2002). Her most recent book, *The Mirage of a Space Between Nature and Nuture*, is now in press.

SALVIA SMÅSKRIFTER

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In 2002 the Hans Rausing Professor of History and Science Tore Frängsmyr took the initiative to inaugurate a publication series *Salvia Småskrifter* with the aim to publish lectures arranged by the Office for History of Science at Uppsala University. The coinage *Salvia* is meant in memoriam of Sweden's first scientific book printer *Lars Salvius* (1706-1773) as well as that it refers to a wild growing Swedish plant, *Salvia pratensis*.

Salvia Småskrifter no. 1-9 had been published under the auspices of Tore Frängsmyr. In 2007 the newly installed Hans Rausing Professor at Uppsala University, H. Otto Sibum, took over the editorship.

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