Nonlinear Dynamics from Physics to Biology

Self-Organization: An Old Paradigm Revisited[1]

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Self-organization has been a hot topic in the second half of last century when physicists and chemists discovered a variety of nonequilibrium phenomena that could be subsumed under a common heading. Self-organizing systems form ordered states in space and time spontaneously and without an external template. The patterns are characterized as dissipative structures because their maintenance requires a flow of energy or matter. After introducing a flow of increasing strength into a system at equilibrium, patterns form instantaneously at certain critical values of the flux. In the language of dynamical systems theory the patterns emerge at bifurcation points corresponding to some critical intensity of the flow. At present we know many well-studied examples of self-organizing systems at many time scales and largely different spatial extensions. Examples are the gigantic red spot on Jupiter, cloud patterns in the atmosphere, the Bénard phenomenon in the coffee cup, the Taylor-Cuvette flow, the Belusov-Zhabotinskii reaction, Liesegang rings, and many other nonlinear phenomena.[2] Recent progress in all fields where self-organization is important confirmed the original concepts and, in addition, gave rise to a new formulation of the old paradigms that allows for a distinction of different forms of self-organizing dynamics in physics, chemistry, and biology. We distinguish here three cases that involve different levels of complexity: self-organization of (i) structure, (ii) function, and (iii) intention or seeming purpose.

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Structural self-organization became a central issue of nonequilibrium dynamics ever since Alan Turing published his seminal work on chemical morphogenesis [1]. Turing suggested a chemical mechanism based on slow diffusion of an activator and fast diffusion of an inhibitor that can lead to spontaneous formation of stable stationary nonequilibrium patterns through diffusion of some key compounds and argued that such a mechanism could be responsible for the formation of biological patterns. It took 20 years before the Turing mechanism was incorporated into a conceptual framework for pattern formation in early embryonic development that results eventually in the patterns we find in adult organisms [2–6]. Activator and inhibitor are thought to represent two "morphogens," leading to short-range activation and long-range inhibition. For a long time no diffusing morphogen was known in developmental biology and, more-

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over, in the 1970s not a single chemical reaction-diffusion system was available that formed stationary patterns spontaneously. The first breakthrough in this problem was achieved by the seminal work of the Bordeaux group in nonlinear reaction kinetics [7]: The diffusion of the activating species is slowed down by the choice of a gel as reaction medium. Based on this principle it became possible to design chemical mechanisms at will that form predefined patterns [8]. The search for evidence of a reaction-diffusion mechanism in embryological pattern formation has been much less successful. Suggestions that early development of the fruit fly *Drosophila* follows a reaction-diffusion mechanism were not supported by experimental data and only very recently the first evidence for a Turing mechanism was found in murine hair development [9, 10]. The spacing of hair follicles is determined by the activity of two gene groups: WNT signaling activates follicle development, whereas the gene products of the DKK group act as inhibitors. Experiments with mice confirmed the predictions of patterns by a reaction-diffusion mechanism more than 50 years after it was suggested.

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Self-assembly of structures optimized by evolution is a central issue of virology. Many examples of "virion"[3] formation have been studied in great detail on the molecular level. The range of complexity is enormous; we mention here only the two extremes: In tobacco mosaic virus (TMV) [11, 12] the carrier of the genetic information, an RNA molecule, is packed into a cavity formed by more than 2134 copies of a single protein molecule, the coat protein, which is encoded by the virus. The coat protein self-assembles into a rod-shaped helix with 16.3 protein molecules per helix turn. In the interior of the helix the RNA is bound to the coat protein, which protects is from degradation by environmental agents. Complex phages like Φ29 [13] or T4 [14] have developed complete molecular machineries for virion assembly making use of scaffolds and preformed parts. Highly specific and sophisticated molecular recognition dominates all cases of virus assembly. It results from optimization of structure, which is brought about by an evolutionary process. The Darwinian mechanism of inheritance, variation, and selection is indeed Nature's tool for optimization.

SELEX experiments[4] with RNA molecules have shown that evolutionary adaptation of structures for binding predefined targets works also very efficiently in vitro [15]. The difference between chemical and biological self-organization boils down to the existence of a carrier for genetic information in the latter case. In the form of an RNA or DNA molecule the biological objects contain an inheritable memory of the past that allows for variation by mutation. At the same time comparison of genetic sequences provides a powerful tool for the reconstruction of previous generations. Modeling evolution in populations by means of chemical reaction kinetics has been suggested and analyzed already in the 1970s [16–19]. Self-organization of populations in sequence space gives rise to stationary mutant distributions called "quasispecies," which are formed at mutation rates below a critical value called the error catastrophe. More recent studies on quasispecies formation identified the error catastrophe with a phase transition in the limit of infinite sequence lengths [20–22]. Inheritance breaks down above the threshold and no stationary population is formed at error rates higher than the error catastrophe. The error threshold concept has been applied, for example, to virus infections [23–25]: When the error rate of viral RNA replication is driven above threshold by means of drugs, no infectious virus particles can be produced, the infection cannot spread in the infected organism, and the disease is cured.

Functional self-organization occurs on two different levels: (i) the weaker condition in the form of optimization of properties in order to match an externally defined function and (ii) the stronger condition of emergence of new functions that are identified a posteriori. The weaker condition is fulfilled by all optimizations of "ribozyme"[5] functions through evolutionary techniques that are described in [15]. The optimization procedure is similar to SELEX; only different tools for selecting the best suited variants are required. A large collection of ribozymes catalyzing a great variety of reactions has been produced so far. The collection of catalysts includes also some for nonnatural organic reactions like the Diels-Alder addition. New functions of protein enzymes can be created and evolved by recombination of genes for enzymes [26]. A direct origin of new function from an already active ribozyme has been described by Schultes and Bartel [27]: An RNA sequence was constructed that folds into two different structures, which are both active as ribozymes but have different catalytic functions. Then, the authors showed that uninterrupted paths involving only single mutations exist, which connect the sequences of the two reference ribozymes. Accordingly populations of RNA molecules can travel through sequence space without loosing their catalytic activity. New catalytic functions can arise when the population hits a point where sequences for both functions exist.

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The most challenging version of self-organization is "intentional self-organization." Seemingly purposeful behavior is thought to evolve from ordinary molecular genetic systems. Goals emerge together and simultaneously with structure and function. Instead of using unclear models or hand-waving arguments, we refer to a well-known example of a two-dimensional cellular automaton called Coway's "game-of-life" [28] (see also John Conway's Game

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of Life Internet documentation and downloads at http://www.bitstorm.org/gameoflife).[6] The game is played on a two-dimensional board of checkboxes. Empty and occupied boxes are distinguished. The simple rules for the development of the automaton are all fixed, and the behavior of the system is completely determined by the choice of initial conditions, which can be easily encoded by a binary string. Some of these initial conditions give rise to seemingly purposeful dynamics. "Gosper glider gun" is an impressive example: Starting from a nonregular initial condition the automaton develops a configuration that shoots packages, called "gliders" in one particular direction. Assuming a population of initial condition and an advantage for shooting automata, we can easily visualize an evolutionary development by mutation and selection operating on the strings encoding initial conditions that eventually leads to the kind of purposeful behavior described above. I am convinced that, sooner or later, molecular biologists will also find an experimental laboratory system that evolves into aggregates, which seem to pursue certain self-defined goals.

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NOTES

1. This essay was inspired by a keynote lecture presented by Henri Atlan on September 26, 2006 in Oxford at the European Conference on Complex Systems (ECCS 06).
2. Nonlinear stands here for a distinction between two common scenarios: (i) The linear world allows for general methods that can be applied to all systems and provide tools for global analysis, whereas (ii) nonlinearities are tantamount to rich repertoires of dynamical behaviors from a wide variety of phenomena that escape analysis by general tools and are commonly local (which means that different behavior can be found in different parts of phase space). This nomenclature comes from a classification of differential equations where the linear equations always fulfill the conditions of linear systems.
3. "Virion" is the common notion for a virus particle that consists of a molecule, RNA or DNA, that carries the genetic information and a coat made from protein molecules or lipids and proteins in case of animal viruses.
4. SELEX stands for "selection by exponential enrichment" and represents a technique that mimics evolution under laboratory conditions. A population of molecules with different properties is created by error-prone reproduction and the best-suited candidates are selected by chromatography. Several cycles involving reproduction, variation, and selection commonly lead to molecules with the desired properties.
5. A ribozyme is an RNA molecule that catalyzes a specific chemical reaction. The name is created from **ribo**(nucleotide en)**zyme**.
6. The interested reader who shares some healthy skepticism with most nonspecialists is invited to download the program from the Web page and to play "gosper glider gun." It is also recommended to make small variations in the initial conditions by adding and removing occupied cells. The result is reminiscent of mutations in nature: (i) Some changes are neutral in the sense that they give rise to the same dynamical pattern, (ii) some modify the pattern, and (iii) some develop quickly into a stationary pattern.

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