# New and Notable

## Colliding Dynamical Complex Network Models: Biological Attractors versus Attractors from Material Physics

Avi Ma'ayan*
Department of Pharmacology and Systems Therapeutics, Systems Biology Center New York, Mount Sinai School of Medicine, New York, New York

Creation and innovation do not commonly arise from nothing. Typically, novel entities emerge from the merging of two or more already existing entities, whether these are ideas in our mind or material objects in our world. Some things go together very well, like peanut butter and jelly, but some things can never come together to form a new novel entity. When two complex systems are merged, the result is unpredictable. For example, the merging of two corporations intuitively should work. This is because, theoretically, corporate mergers reduce competition, increase shared knowledge and expertise, increase efficiency, and reduce redundancy. As a result, the newly formed merged company (i.e., the new innovative entity) should have better fitness in the marketplace. However, there are many examples of corporate mergers failing. Sometimes only one side benefits or both sides lose out. This happens because of the intricate interactions that occur within each corporation, and between each company and its suppliers and customers. The two merged companies' cultures, policies, procedures, customers and suppliers collide, and sometimes this works but at other times it does not. The result is unpredictable. The phenomenon of unpredictability when two complex systems merge is general for almost all types of complex systems, including human cells.

In a study published in this issue of *Biophysical Journal*, Koulakov and Lazebnik (1) modeled cell fusion using a simple dynamical systems modeling approach. They created different dynamical model networks, inspired by the continuous Hopfield model using a Lyapunov function, in which the dynamics of each network model settles into defined attractors. Each network is made of 2304 genes that sparsely interact to influence each other's activity. The authors studied the consequences of combining such network models of interacting genes into one system, merging the two dynamical models into one. They observed that sometimes one attractor swallows the other, sometimes the new system settles into a completely different attractor, and sometimes the new merged system becomes unpredictable, generating spurious attractors. The beauty of the study is the visualization of the results on a $48 \times 48$ pixel grid where attractors are displayed as two-color icons such as paper planes, bells, suns, and hearts.

Koulakov and Lazebnik modeled cells as complex dynamical systems with interacting variables that sometimes settle into defined attractors; however, biological complex systems, including cells, are substantially more complex than the Koulakov and Lazebnik model. First, cells are made of many different types of parts that interact in many different ways and on different timescales. The fate of a cell, or the cell's dynamical state, is determined not only by its internal network state but also by the signals that the cell senses from the environment, and the signals the cell sends to the environment. It is not sufficient for a new fused cell to fall into a new stable internal attractor that may enable the cell to stay alive on its own. The new fused cell needs to have an evolutionary advantage to survive among other peer cells over time and through generations. This concept changes the definition of attractors in physics versus attractors in biology. Attractors in many other complex systems, such as technological systems, are similar to biological attractors (2). The attractors in biological complex systems must have an evolutionary fitness advantage to survive and become an attractor. The fused cell must be innovative. In physics, and with the types of attractors modeled by Koulakov and Lazebnik, the only requirement for an attractor is to settle into a stable dynamical state. The system settles into such attractors spontaneously. In classical models of systems from material physics, this is a place where the dynamical system is exerting a minimal amount of energy.

In material physics, energy is used to define a low-energy attractor state; however, cells use energy for almost all of their functions, so a new attractor in biology may actually use more energy than nonattractor neighboring states that use less energy. These biological attractors (e.g., cell types in our body or cancer cells) may become less energetically efficient but will have a better overall evolutionary fitness. This can happen when two cells fuse, but cell fusion is rare in biology. The fusion of the two cells must provide a functional advantage for the cell to keep existing, to become stable. Human cells have the amazing ability to self-reproduce, and proliferate by self-replication. For cells to create exact replicas of themselves, they need to have two copies of each chromosome. Cell fusion can prevent that from happening and thus limits indefinite cellular self-replication.

Although human cells have all the parts needed for cell fusion, there are few physiological examples of successful, functional cell fusion events in human cells. The most obvious cell fusion event is fertilization, when a sperm joins with an ovum to create a new embryo. Another example is the historical merging of the prokaryotic

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*Correspondence: avi.maayan@mssm.edu

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proteobacterium protomitochondrion with a eukaryotic cell. Interestingly, the mitochondria's responsibility in eukaryotic cells is to generate energy. Hence, cell fusion of a eukaryotic cell with a prokaryotic cell, through creation and innovation, enabled biology to further decouple itself from the low energy attractors observed and studied in material physics.

Although multinucleated cells are observed in human biology, and may suggest other functional roles for cell fusion in human physiology, such cells should be viewed carefully. The formation of myotubes from myoblasts (3) indeed requires cell fusion, but between cells of the same type. This is a different kind of cell fusion, defined as self-fusion by Oren-Suissa and Podbilewicz (4). The origins of multinucleated giant cells created from monocytes or macrophages, as well as multinucleated cells that appear in tumors, are not completely clear; however, these cells could result from incomplete cell division and not necessarily cell fusion. Cells within tumors lose cell-cycle control. Thus, a rapid, uncontrolled cell-cycle could lead to incomplete cell division. On the other hand, as suggested by the Koulakov and Lazebnik model, "a large number of abnormal hybrids" resulting from cell fusion could lead to some of those hybrids having some evolutionary advantage that would render them tumorigenic, or biological attractors.

The assumption that cells roll into basins of attraction through the development process is a nice theory that is popular among physicists who build models of dynamical, biological molecular networks. It is an elegant theory because it simplifies and explains the massive complexity of transitions between cell types through development and reprogramming. However, a new definition of attractors in biology is needed because cells are complex systems that have evolved for billions of years, and thus the laws of physics do not exactly govern the higher-order dynamics of these systems. Cells use energy for almost all of their processes and are highly organized structures. Biological natural cells, as well as other agents in other complex systems, act and react, self-repair, self-replicate, switch between pack and individual behavior, and live and die similarly to multicellular organisms (including us). Such agents are not playing a passive role like the collection of variables in the Koulakov and Lazebnik model. Although genes can easily fuse to create new functional gene products through their functional structural- and sequence-based domains, cell fusion is more difficult because cells are more complex, needing to retain their ability to self-replicate and effectively interact with their environment. Cell fusion is also a perturbation that affects all of the variables of a system at once, and may change the system too much compared with a milder evolutionary tinkering such as gene fusion.

Overall, the article by Koulakov and Lazebnik is creative and interesting because it helps us visualize the abstract concept of cell fusion and multiple attractor states for cells in a clear manner. The article opens up discussion about the consequences of modeling entire cells and the interactions between and within cells as a set of attractor states that can be readily visualized. Because the number of cell types in the human body is finite (estimated to be between 200 and 400 cells), transitions that occur between cell types during development and reprogramming, as well as in disease, could be modeled and visualized as attractor networks (5). If such models were more accurate, reflecting real dynamics in human cells, perturbations could be screened computationally, and with appropriate experimental validation, precise perturbations could be designed. Intuitively, such perturbations are already massively utilized with knockdown techniques such as siRNA screening and applications of drugs to human cells followed by some global measure of the system state (e.g., genome-wide mRNA or protein expression). However, our understanding of the wiring of the network is still fuzzy, and dynamical systems that can model entire human cells accurately are still some years away. Such models need to consider not only internal interactions within the cell but also how the new perturbed cell interacts with its environment, and how the perturbations influence the overall function of the cell in the entire tissue and body.

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