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Understanding cell lineages as complex adaptive systems

Neil D. Theise[a,*] and Mark d'Inverno[b]

[a] *Division of Digestive Diseases, Departments of Medicine and Pathology, The Milton and Carroll Petrie Division of Beth Israel Medical Center, New York, NY 10003, USA*
[b] *Center for Agent Technology, Cavendish School of Computer Science, University of Westminster, W1M 8JS London, UK*

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Abstract

Stem cells may be considered complex reactive systems because of their vast number in a living system, their reactive nature, and the influence of local environmental factors (such as the state of neighboring cells, tissue matrix, stem cell physiological processes) on their behavior. In such systems, emergent global behavior arises through the multitude of local interactions among the cell agents. Approaching hematopoietic and other stem cell lineages from this perspective have critical ramifications on current thinking relating to the plasticity of these lineage systems, the modeling of stem cell systems, and the interpretation of clinical data regarding many diseases within such models.

Keywords: Stem cells; Lineage system; Reactive systems

Introduction

As young children, many of us as were fascinated by the line of ants stretching from food source to anthill we found in our gardens. On closer inspection, what looked like a simple straight line was in fact hundreds of industrious individual agents each seemingly exhibiting energetic and directed behavior. However, it is difficult to interpret the behavior of an individual ant as being purposeful unless you take it in the context of the entire group; it is only by observing the emergent global behavior of the system can we understand its overall goal. In such systems, individual ants may get lost, or die, or become separated from the party without any great loss of the efficiency and effectiveness of the system itself. Somehow, the local interactions between the individuals can respond to local or global environmental changes to maintain some kind of stable system.

The system of ants is one of the best-known examples of *complex adaptive systems* (sometimes called *reactive systems* [1,2]). There are many other systems that exhibit the same kind of emergent self-organization. Examples include the stock market, social systems (human or animal), embryologic development, growth of cities, the rise and extinction of species, and the diversity of immune system responses. Some argue that perhaps even consciousness can arise from the complex system comprising neurons and the networks between them. The key factor that is common to all these systems is that there is an *emergent* self-organization arising on the macro-scale from micro-scale interactions of the individuals constituting the system. (If there were not, then the global system behavior would be at best chaotic.) In our view, adult stem cell processes and the cell lineages that arise for each cell, and thus the numbers and quantities of each type of cell within a lineage, are complex reactive systems with sophisticated and emergent self-organization to maintain appropriate levels of certain types of cell.

It was in discussions with Jane Prophet, a new media artist at the same university as the second author, who has a history of work looking at the modeling of biological systems, that we became aware that adult stem cell processes or, more precisely, the cell lineages that arise from them, can also be thought of as complex reactive systems. It was also clear that modeling stem cell lineages in this way has critical ramifications for the current thinking on the nature

* Corresponding author. Division of Digestive Diseases, Departments of Medicine and Pathology, The Milton and Carroll Petrie Division of Beth Israel Medical Center, 1st Avenue at 16th Street, New York, NY 10003. Fax: +1-212-263-4373.
E-mail addresses: ntheise@chpnet.org (N.D. Theise), dinverm@wmin.ac.uk (M. d'Inverno).

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of the *plasticity* of these lineage systems as well as on interpretation of clinical data regarding many diseases within the context of this complex system model.

In this short paper, our intention is to give an overview of the key defining characteristics of complex systems, review the importance of developing mathematical models of cell lineages and the role they play in building computational simulations of stem cell systems, outline some clinical implications of complexity in cell dynamics, and discuss the implications this view has on the current thinking relating to the "robustness" of stem cell plasticity events.

Complex adaptive systems

In the book *Emergence* [2], four common defining traits of complex adaptive systems are introduced and we describe them below.

- A few individuals or agents will not make a sustainable complex system, only when the number of agents reaches a certain critical threshold will the system exhibit global, meaningful behavior.
- A single agent within the system cannot know the state and current behavior of every other agent, and as a result cannot determine its behavior based on such complete global system information. Instead, the behaviors of agents are governed by simple reactive rules based on local environmental factors. The agents in the system are not in anyway deliberative. Such rules are typically of the form of if "condition" then fire "action." For example, a possible rule for a partially determined cell might be "if there's a space next to me then move into it." Another example for a stem cell might be "if I have no neighbor that is a stem cell then any division will produce two stem cells and no daughter cells." The individuals are not aware either of the larger organization, goals, or needs of the system. The complexity arises through interactions at the micro-level.
- Some degree of nondeterministic behavior is required for a system to be described as a complex one. Again, we give a very simple example where there are just two choices. We may decide that a cell at a certain point in the lineage, with all other environmental factors equal, has a probability p of producing a daughter cell along one lineage, and probability q of producing a cell along an entirely different lineage. Because we cannot say for certain what will happen—that sometimes one action will happen and, in exactly the same situation, sometimes something else might happen—we introduce randomness or, more formally speaking, nondeterminism into the system. Some degree of nondeterminism (though, as it turns out, not very much), is needed for a system to be a complex adaptive one. Self-organization fails to emerge in completely determined systems (the movement of planets and moons in our solar system, the movement of snooker balls using the appropriate equations of motion) and completely random ones (molecules in a gas). It is only with a distinct low-level randomness (*quenched disorder*), that local interactions give rise to system complexity.
- Interactions between the individual agents and between individual agents and their environments form homeostatic, negative feedback loops. These loops lead to adaptation and response. In our simple example, planets do not form communities, as the behavior of each is governed by the current global state of the entire system. On the other hand, people in a club do, and the reason is that the behavior of each participant is essentially governed by the behavior of neighboring clubbers.

Clinical implications

In our work, we are attempting to model cell lineages that demonstrate the above traits to cause a global complex system of cells. First, stem cells and their progeny have no information of the entire state of the system. It is not feasible that they have either the access to information relating to the entire organism, or the processing power to respond to that information if they could. Rather, they respond to locally detected cytokines, chemokines, adhesion factors, and other signaling molecules, from other cells, and from the matrix in the immediate micro-environment. It is in this manner that stem cells and their progeny, which comprise all the cells in the human body, respond to neighbors and local environments through elaborate, yet finite, feedback loops.

Clearly, the fact that the body can maintain itself from day to day, with internal injuries and under extreme environmental conditions (as we write, this the illusionist David Blaine is currently suspending himself in a box for 44 days under Tower Bridge!), necessitates the adaptive nature of stem cells and progeny and the emergent organization that arises from them. Undoubtedly, if these systems were not homeostatically adaptive, we survive past the earliest stages of embryonic development. The issue to understand first is not why the system fails us in old age or terminal illness, but rather how it works so effectively in general.

Mathematical modeling and computer simulation

To this end, our first goal is to build a formal model of cells as reactive agents responding to local environmental factors that can maintain some balance of cells under various conditions. Once we have this kind of stability, we can then consider the effects of disease and life-threatening environments. The reason for building a formal model is to cage our model in a cohesive, precise, and structured framework, understanding unambiguously the state and behavior of the elements in our system. In addition, this is a relatively new area of investigation and so it is important to subsume existing concepts and terminology where pos-

sible so that new ideas about state or process can be clearly delineated. One essential motivation we have is to build a model which gives precise and clear meaning to words, structures, and processes so that we can move towards a common conceptual framework where scientists (and in the case of our project, also artists) have the same base from which to discuss and develop new ideas whether formally or otherwise.

In addition, we can use the formal model of our stem cell complex system to build a computer simulation of a large system of stem cells and progeny. Indeed, computer simulations have been very successful in showing how emergent, global, self-organizing properties can arise through very simple descriptions of individual behavior. For example, it is possible to simulate the simple feedback loops of ants' behavior to produce the food line that we described earlier. However, the computational demands required to model large systems are enormous, even given the massive technological advances in grid computing, hardware, parallel processing, and so on. The mathematical modeling and simulation of large complex systems is a major research topic in itself, and is one which we have drawn on in our development of the model and simulation of stem cell lineage.

As we have already stated, our belief is that the mathematical modeling of stem cell lineage systems is critical [3,4] for the development of an integrated attempt to develop ideas in a systematic manner, although it has not been a research area that has received a huge amount of attention. One notable exception is the work of Roeder and Loeffler [5] at the University of Leipzig, who model hematopoietic stem cells using various (but limited) parameters including representing both the growth environment within the marrow (the "stem cell niche") and the cycling status of the cell. Also included is a stochastic model of the ability of cells to both escape and reenter the niche and to move between high- and low-niche affinities (called "within-tissue plasticity"). The validity of their model is demonstrated by the fact that the model produces results in the global behavior of the system that exactly match experimental laboratory observations. The point is that the larger patterns of system organization emerge from these few simple rules governing variations in niche affinity and coordinated changes in cell cycle.

Equilibrium states and instability

Complex adaptive systems typically have multiple equilibrium states where, for example, the number of agents of a particular kind may be kept constant. An equilibrium can be more or less stable; a very stable equilibrium needs massive events (either internal or internal) to affect it while a nonstable one can be triggered by relatively small events. These less stable equilibrium are more dangerous for the safety of the systems as a tiny event may lead to massive system change and even to total system collapse. Commonly cited examples are mass extinctions of species, collapse of stock markets, and the demise of cultures and civilizations. It is often changes in the interactions or behavior at the micro-level which affect phenomena such as mass extinctions.

Analogously, the failure of stem cell systems is sometimes not merely due to the size of the internal or external change, it may be simply a necessary result of the generally high durability and sustainability, but complexity, of the cell system. Aplastic anemia, for example, a complete failure of the hematopoiesis system, may not have a specific precipitating event. Likewise, acute hepatitis A is usually benign and self-limited, but a very few infected people suffer massive hepatic necrosis leading to death or transplant. The unpredictability of these events may relate to our limited understanding of pathogenesis, but it might instead be inherent in the fact that the stem cell system is a complex one.

The formal specification of the model currently being developed can be used to construct a computer simulation (and using logic we can prove that the simulation implements the model completely). This means that observed events produced by running the simulation can be carefully interpreted within the semantic context of the formal structured model. Careful statistical analysis of our simulated clinical events may shed a new and very different light on these dire occurrences. One intention, for example, is to show how a tiny perturbation in system-state may give rise to observable events that are recognized as specific clinical conditions.

Ramifications for our current thinking

Conceptualizing cell lineages as complex adaptive systems gives us a new perspective from which to debate some of the key contested issues of adult stem cell research. One example is the longstanding debate as to whether stem cell lineages are determined or stochastic processes [6]. The work of Loeffler et al. is significant because it includes stochastic elements to get the required observable results. Indeed, the increasing number of articles on the reversibility of gene restriction makes the stochasticity of lineage fate unavoidable in conceptualizing issues of cell plasticity [7,8]. Also, in considering the results of both clinical studies [9] and single cell culture and gene expression experiments [10,11], a greater variability of gene expression pathways is revealed than would be expected from a completely determined model.

In this paper, we do not go into detailed discussion of these findings but wish to make it clear that the evidence is now strongly indicating a nondeterministic view. Crucially, this is necessary for our complex system interpretation to be appropriate: if we conceive of cell lineages as complex and adaptive, then stochasticity is implicit because fluctuations

are necessary for self-organizing systems to explore new possibilities.

Another current controversy concerning adult stem cell lineages relates to data that indicates low levels of engraftment from bone marrow into other system organs: often less than 5%, sometimes less than 1%, in the absence of overt, severe injury [12,13]. Some have argued that even if bone marrow plasticity can be demonstrated, such low levels of engraftment from the blood are physiologically trivial, insufficiently "robust" to be of relevance to tissue maintenance [14].

However, if we consider these alternate lineage phenomena as parts of a complex adaptive system, it reveals to us that that the converse is more likely to be true. The documented low level of apparently random fluctuation, this quenched disorder that we mentioned earlier, is precisely what allows the system to be adaptive. Going back to our ants example, it is only through the small percentage of ants which stray from the main path that enables the formation of new paths to food if the current line becomes interrupted or the food source runs out. From the complex system point of view, the low-level engraftment fluctuations are critical; without them, robust responses to injury might not be so efficient or even possible.

In conclusion then, it is precisely this intermediate level of stochastic variation, somewhere between a fully determined system (where all events can be predicted; the behavior of each element is simply a function of the current state of the whole system) and a totally nondetermined system where any event can happen at any time (called "chaos" in both mathematics and in nonformal literature) that makes cell lineage systems, and therefore our own bodies, complex, adaptive, and alive. We are currently developing a formal model of this theory using techniques from multi-agent systems [15] from which to build a simulation with a view to validating some of the ideas in this paper.

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