CLONING AND STEM CELLS
Volume 7, Number 4, 2005

Opinion Piece

Cell Doctrine in a Complex and Uncertain World: Time for Reappraisal?

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INTRODUCTION

In recent decades, complexity theory has provided profitable new perspectives and analyses in the discourse of many "hard" and social sciences (Johnson, 2001; Lewin, 1999). The oft-quoted remark by Stephen Hawking—"I think the next century will be the century of complexity" (Chui, 2000)—will prove, in the near term, to be either hyperbolic appreciation or prophetic, but the good professor, at least, recognizes that an epochal shift, powered by this paradigmatic approach to analysis of systems of interacting agents, is on the way. While many fields, including many disciplines within the biological sciences, have embraced the analytic approaches of complexity theory, there remains a relative paucity of discussion or debate regarding its potential to shed light on cell or molecular biology.

CELLS SELF-ORGANIZE INTO BODIES

Cells themselves, however, now come under scrutiny by theoreticians interested in this analytic approach (d'Inverno et al., 2005; Hussain and Theise, 2004; Kurakin, 2005a,b; Theise, 2004; Theise and d'Inverno, 2004; Waliszewski and Konarski, 2001). There are four criteria fundamental to agents that comprise a complex adaptive system. These criteria are: that the agents exist in great numbers; that they interact directly with each other and with the environment with homeostatic, negative feedback loops; that they do so responding only to local cues without monitoring the entire system as a whole; and finally, that these interactions have a degree of limited stochasticity, often referred to as "quenched disorder." Any group of interacting individuals fulfilling all these criteria on the micro-scale gives rise to *emergent* phenomena on the macro-scale, phenomena which, for all the world, appear to have been planned (centrally or externally). In other words, the individuals self-organize with an appearance of intelligent design.

Cells fulfill all these criteria (Theise, 2004; Theise and d'Inverno, 2004). Thus, tissues, organs, and bodies, from embryonic and fetal development through post-natal life, are the emergent phenomena arising from cells acting as agents of a complex system.

This perspective is readily in keeping with standard understandings of Cell Doctrine, merely fleshing out, so to speak, how the organization of multicellular organisms can arise without external planning. As we have suggested previously, the implications of this concept may shed light on a variety of phenomena: how seemingly trivial variations within the body, (such as recent low level *in vivo* cell plasticity phenomena) may be physiologically important beyond their apparent scope; how the almost inevitable "mass extinction events" to which complex systems are prone may underlie some idiopathic disease conditions; and how an alternate approach to tissue "engineering", per se, might involve manipulation of start-

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ing conditions to allow for self-organization into tissues rather than careful attempts to architecturally arrange cellular building blocks into preplanned structures (d'Inverno et al., 2005; Hussain and Theise, 2004; Theise, 2004; Theise and d'Inverno, 2004).

The implications however may be still more profound. Indeed, the logical extension of these concepts may actually undermine the primacy of cell doctrine itself. If this is true, then scientific studies of the body may have to re-evaluate previously discarded models for how the body is structured (Theise, 2005).

HIERARCHIES OF COMPLEX SYSTEMS

For the observer of a complex system, the nature of the system depends on the scale of observation (i.e., how close up one gets to it). What appears to be a unified, functional entity on the macroscale is also an extraordinarily dynamic, organizational dance of myriad, separate individuals on the microscale. Employing the oft-used example of the ant colony (Johnson, 2001), we note that, from afar, at a distance in which the individual ants cannot be discerned, the colony appears to be a thing, a shifting, black mass on the ground. But closer inspection reveals that it is not a solid, unified entity at all, but is instead hundreds or thousands of interacting individuals. Thus, the colony may be described as the emergent behavior of the community of ants. However, having described bodies as emergent phenomena arising from cellular interactions, we recognize that if we move in closer still, with our microscopes, then the individual ant as entity also disappears—its discrete, compact, living body being the self-organization of the collective cellular agents.

Therefore, complex systems can exist as hierarchies over wide variations in scale of observation. The emergent characteristics of a complex system can then behave like a single, solitary entity, which can participate in the formation of a higher level complex system, giving rise to higher level emergence. Reversing this, the interacting agent appears solid and solitary on one level of scale, but on a lower scale can be viewed as a community of smaller interacting individuals. Definitions and descriptors thus depend dramatically on selection of scale. Of course, this leads to an obvious question: Does the importance of scale apply to cells themselves? And, if so, what does it mean for cell doctrine?

To consider these questions, it is useful to first consider a little history. Cell Doctrine emerged as the final champion of a more than two millenia debate: is the body comprised of an endlessly divisible fluid or of aggregated, small, indivisible subunits called "atoms" (n.b., physics once was in the habit of borrowing terminology from biology)? Answers had rested on faith and imagination, since technology for evaluation of the body's substructure was unavailable.

With the invention of the microscope, cell membranes and cell walls were visualized for the first time. Cells were so-named because they had the appearance of the cell of a monk or a prisoner: walls, ceiling, floor, scant furniture. Schleiden and Schwann, acknowledging that such empty boxes were clearly indivisible units of substructure, formulated cell doctrine and settled the debate (Harris, 2000). Thus, biological sciences entered the modern age, steadily progressing toward the triumphs of genetics, and cell and molecular biology.

FOR EXAMPLE: THE BODY AS FLUID

With complexity analysis in mind, however, we must consider a still lower scale of observation. Focusing downward, from the micoscopic toward the nanoscopic, the dominant unit of observation is the biomolecule. Like moving in to see the ant colony dissolve into ants, and the ants dissolve into cells, at submicroscopic levels, cells themselves cease to be discreet objects. Instead, we see them as dynamically shifting,interacting biomolecules, which self-organize emergently to create "the cell" at a higher level.

For this analysis to bear weight, we must clarify whether biomolecules and their interactions fulfill all the necessary criteria of agents forming complex systems. Some such aspects, as with cells themselves, are clear: they exist in sufficient quantities to generate emergent phenomena, they interact only on the local level, responding to neighboring molecules and the environment directly, without monitoring the system as a whole, and their interactions involve homeostatic, negative feedback loops. It is less obvious, however, whether their interactions display quenched disorder, a zone somewhere between total randomness and complete rigidity.

Recent nanoscopic observations of individual molecules interacting with each other yields an expanded appreciation for how nanoscale molecular interactions are less like machines than we often imagine (Ishii et al., 2004). Moreover, they lie at the interface of physical phenomena where quantum effects may border on the classically mechanical. Such observations suggest that indeed there is a type of quenched disorder in their interactions.

Dr. Toshio Yanagida, University of Kyoto, provides a good example, with his pioneering observations of single molecules, in particular of actin and myosin sliding (Yanagida et al., 2000). He shows that consumption of ATP does not provide the energy of movement of the myosin arm, bending and sliding the molecule past the neighboring actin filament, as had previously been thought. Instead, the myosin hinge bends, and the molecule moves in response to Brownian motion of water molecules. The energy of the ATP does not result in movement, but instead it constrains the Brownian movement–driven molecules into the physiologically required direction. In other words, ATP hydrolysis provides the energy to constrain, or quench, the disorder of Brownian motion.

Examples of such phenomena have increased in recent years (Calapez et al., 2002): not only movement of molecular motors such as myosin, dynein, and kinesin (Nishiyama et al., 2003), but activation of receptors by ligand binding such as EGF to EGF-receptor (Ichinose et al., 2004), movement of mRNA within the nucleosome (Calapez et al., 2002), enzyme activation, and digestion of macromolecules such as metalloproteinase digestion of collagen fibers (Calapez et al., 2002; Nishiyama et al., 2003; Yokota et al., 2004).

Thus, at the microscale, the body is made up of indivisible, reproducing subunits: the cell. And all cells, "obviously," come from other cells. But it is different at lower levels of scale as the cell entity dissolves into organization of small structures, the characteristics of which give rise to *the appearance* of a discrete cell entity higher up. From this perspective, for example, that defining feature, the cell membrane, has neither an inside nor an outside of any relevance; it is merely three-dimensionally arranged molecules interacting with each other within the watery substance of the body. Up and down, in and out, are terms that are irrelevant to the behavior of the constituent molecules. What matters are their interactions with each other as they float amongst and are bounced around by water molecules. Thus, cells as *things* cease to exist in the same way that the ant colony disappears at the level of the individual ant. The discredited side of the ancient debate, that the body is a fluid continuum, appears also to hold water.

ALTERNATE MODELS OF THE BODY?

This might be dismissed as poetry, but such a misunderstanding may reflect that the above description of self-organizing complex systems takes the form of words, rather than mathematical equations. However, mathematics underlies the basic features and behaviors of these systems. Very few biologists, including this author, have even the most cursory training in, let alone capacity to understand, the mathematical language necessary for their precise and complete description. Nonetheless, such an understanding is not necessary to recognize the import and utility of the mathematics.

Indeed, a description such as presented in this essay reflects the mathematics, much in the way that popular accounts of relativity make the general concepts accessible, even as Einstein's mathematical derivations remain completely opaque. "Emergence" and "complexity" are not fuzzy descriptors, but are the words, more or less poetic depending on the skill and bent of the author, which cloak a deep sophistication and precision of analysis. Thus, there is indeed something of possible use here for the modern (or post-modern) world, including, at last, mathematically rigorous formulations of biological systems, as have been available to physicists for describing the physical world since Newton. For the time being, however, such mathematical or computational biology will likely require close, inter-disciplinary collaborations, until computational biology becomes a discipline in its own right (d'Inverno and Prophet, 2004).

Speaking yet again of physics, this approach to the relationship of cells and the biomolecules which give rise to them also highlights that some other borrowings by biologists back from physicists might also not just be metaphorical. First Potten and Loeffler, based on concepts regarding modeling of stem cell systems, and then we, responding to experimental cell plasticity findings, have suggested that there is cellular uncertainty, akin to Heisenberg's uncertainty (Potten and Loeffler, 1990; Theise, 2002; Theise and Krause, 2001, 2002). This states that examination of a cell necessarily disrupts its microenvironment, and therefore since "the internal and the external codetermine the cell" (Lewontin, 2000), to change the microenvironment necessarily changes the cell, potentially altering its fate. But is there a fundamental uncertainty to cells? Or might it be possible to conceive of a technology that could completely define all aspects of the cells (i.e., the position and behaviors of all of its constituent molecules), a perfect, supersensitive MRI machine, perhaps?

A complexity analysis suggests that the answer to this question is "no." The cell as unit only has observational validity on the level of the microscopic. On a level of scale higher up, they are invisible (which is why the debate between fluid and atoms raged, unanswerable, until the microscope). Lower down, on the level of molecular interactions, the cell also vanishes. The "cell as entity" depends on how one is looking at it. As a magician might say, "Now you see it, now you don't" (Theise, 2005).

So any experimental procedure regarding cell behavior always, necessarily, introduces some aspect of bias into the data collected. The lack of attention to this fact underlies much of the confusion around capabilities of adult stem cells, for example. More conscientious attention to cellular uncertainty should result in fewer polemics and more careful assessments of findings (Theise, 2003).

Another important point raised by a complexity analysis is that it admits the possibility of hypothesis-based investigations about bodily phenomena that are considered largely outside the bounds of "modern" biology because they cannot be explained within the coherent structure of cell doctrine. Accupuncture is perhaps the most obvious example of this potential. The acupuncture points and meridians mediate specific physiologic and therapeutic effects at a distance that are testable and reproducible (Shang, 2000). However, dissection of the tissues beneath the meridians does not reveal an anatomic subunit that actually mediates. In the absence of an anatomic subunit, these effects cannot be explained by the building blocks of that anatomy. With Cell Doctrine, acupuncture is likely to remain only useful, but also utterly resistant to complete explanation.

CONCLUSION

Complexity theory provides explanation of how cells, as interacting individual agents that fulfill certain criteria, self-organize into the tissues of the body. But it also suggests that, as such, cells exist within a laddered hierarchy of systems, each of which, depending on the scale of observation, either appears as a single, unified entity or instead as a dynamic ballet of smaller subunits. At the gross level, bodies are things. At the microscopic level, they are not things, but systems of interacting cells. Likewise, cells appear as things on the microscopic scale, but disappear on the way to the nanoscale as their biomolecular subunits become the target of observation.

Thus, Cell Doctrine is only one model of perhaps many, depending on perspective and scale of observation. If we restrict ourselves to the single perspective at which cells make their appearance, we will leave the study and explication of some bodily phenomena outside the investigatory capacity of modern biology. If we consider rewriting the paradigm without capital letters—"cell doctrine"—we open up the possibility that alternate models of the body, which may be scientifically and pragmatically useful, are available. Perhaps the last field of study to do so, modern biology catches up with the post-modern world.

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