Beyond Cell Doctrine

Complexity Theory Informs Alternate Models of the Body for Cross-Cultural Dialogue

Neil D. Theise

Departments of Pathology and of Medicine, Beth Israel Medical Center of Albert Einstein College of Medicine New York, New York, USA

Cell doctrine is the foundational paradigm of Euro-American medicine and biology. Even without stepping outside that tradition, one may imagine alternate models of the body such as a fluid model in which cells do not exist or a model wherein cells are described as overlapping fields of molecular organization in space and time. With a complexity analysis of cell biology, we find that the existence of cells as unitary entities, as things, is contingent on the level of scale at which the body is observed. Therefore, alternate models of the body may be conceived that are specific and appropriate to other levels of scale. These ideas suggest that some bodily phenomena, particularly from Asian traditions, which have previously resisted explanation from within the cell-based Euro-American tradition (e.g., acupuncture) may be productively investigated with one or more of these other models. Additionally, the seemingly metaphorical concepts from Tibetan medicine of the coarse, energy, and subtle bodies may represent precise, though somewhat poetically expressed representations of the body at different levels of scale.

Key words: **complexity; emergence; coarse body; energy body; subtle body; cell doctrine; acupuncture**

Cell theory is the foundational doctrine of "Western," i.e., the Euro-American tradition of medicine and biology. While it seems almost self-evident that the body is made up of very small, indivisible subunits, until the invention of the microscope biologically curious scientists and philosophers only had their creative imaginations to explore its substructure. So, going back to the Ancient Greeks, there had actually been a debate as to the nature of the substance of the human body: on the one hand it might be comprised of such indivisible subunits, but on the other hand it could also be imagined as an endlessly divisible fluid.[1]

With the invention of the microscope and the visualization of the box-like cell, the debate was definitively settled, since such a box could not be further subdivided. That this answer appeared to be definitive, accounts for the lack of competition for the cell doctrine in Western biology. This lack of competition has not, however, drawn attention to itself because the dramatic success of this view still continues in terms of investigative science, therapeutics, and industrial applications. But cracks in this unitary view are starting to form, some of them from the encounters between our customary approaches and those of other, "non-Western" traditions of medicine and biology, but also because of interdisciplinary challenges from within the Western scientific realm.

My colleagues and I have recently argued, in particular, that a complexity theory analysis of cell and molecular biology indicates that cell theory is incomplete and that any model of the body is scale and perspective dependent and therefore also incomplete.[2–5] Thus, other

Address for correspondence: Neil D. Theise, M.D., Division of Digestive Diseases, Beth Israel Medical Center, First Avenue at 16th Street, New York, NY 10003. Voice: 212-420-4254; fax: 212-420-4373. ntheise@chpnet.org; www.neiltheise.com

Longevity, Regeneration, and Optimal Health: Ann. N.Y. Acad. Sci. 1172: 263–269 (2009).
doi: 10.1111/j.1749-6632.2009.04410.x

models of the body may be useful for understanding some bodily phenomena which so far have resisted explanation by our Western approaches. I would further suggest that models derived from alternate scales and perspectives may serve as a means to investigate and understand non-Western approaches.

One Alternative: Body as Fluid Continuum

Even without resorting to a complexity analysis, imagining possible alternate histories immediately tells us that cell theory is not the exclusive final stage of biological understanding. When the cell walls and cell membranes were first observed with the new microscopes, the word "cell" was applied because it looked like the cell of a monk or of a prisoner: floor, ceiling, four walls, but no furniture. It was empty. With the passage of twenty years or so histochemical stains were developed and substructures within the cell were visualized, beginning with the nucleus. Bit by bit, the details of cell structure were revealed.[1]

What if the technology had been different? What if the first structures visible with the new technology had been the nuclei, not cell walls or membranes? Then, a very different answer to the ancient debate would have been conceived. The body would indeed look like an endlessly divisible fluid, only with small little globes suspended in it. Twenty years later, with the advent of histochemical staining to demonstrate cell membranes, the fluid theory of the body would not have been jettisoned; rather, the new structures perhaps would have been described as semi permeable partitioning of the fluid continuum.

Thus, the nature of the body, the solution to the ancient debate, is dependent on point of view and technological means. If the perspective is that of the cell membrane, the body is made of indivisible subunits. If the perspective is of the nucleus, the body is an endlessly divisible fluid, albeit with semi permeable partitioning. Dependence on point of view for our theoretical modeling of the body suggests something of a post-modern stance and, indeed, this is the background for my recent introduction of the phrase "post-modern biology."[4,5]

Enter Complexity Theory

Imaginative, alternate histories are not, however, a terribly convincing way to dislodge a doctrine as profoundly embedded in our thinking as cell theory. A more rigorous approach, though, is provided by the mathematics of complexity theory. In brief, complexity describes how systems of interacting individuals, whose interactions fulfill certain criteria, will self-organize into larger, adaptive, *emergent* structures or behaviors. These are known as *complex adaptive systems*.[6,7] The four criteria are:

(1) There must be large numbers of individuals. (Moreover, different numbers of individuals will yield different emergent behaviors).
(2) Interactions must have an overall balance of negative feedback loops over positive feedback loops.
(3) No individual is sensing the global status of the system as a whole; instead, each individual is only reacting to local characteristics and events.
(4) There must be some limited level of randomness, so called "*quenched disorder.*" Too much randomness and the system will be chaotic or completely disordered. Too little randomness and the system is rigidly determined and therefore cannot adapt to a changing environment.

Ant colonies are a frequent, easily accessible example of a complex adaptive system. They are comprised of large numbers of interacting individuals which respond to a finite number of signals from other ants as well as from the local environment. Their interactions are governed by a balance of negative over positive feedback loops. No ant is monitoring the status

or behavior of the colony as a whole. As for quenched disorder, all one has to do is bend down to closely examine a seemingly straight food line of ants and one will see that some small number of ants are not following the food line, but instead are diverging from this straight path.[7]

This limited randomness, which at first glance may seem a wasteful expenditure of colony energies, is vital to the adaptation and survival of the colony. It is these divergent ants that are the rapid response members to find a way around your foot if you step into the food line, interrupting it, or to find a new food source if the current one runs out. Computer modeling of the interactions of individual ants confirms the importance of this limited randomness. Indeed, the computer modeling of quenched disorder is fundamental, for example, to the apparently seamless maintenance of land line telecommunications: while signals are interrupted from time to time through inherent random fluctuations in the system, virtual divergent "ants" so quickly find a route to reestablish the line that one does not even notice that an interruption occurred.[7]

Furthermore, computer modeling of individual behaviors of the members of any complex system will generate virtual emergent structures similar to those in the real world. Thus, we can demonstrate that these often very complex, adaptive organizational structures, while appearing planned from the top down, are truly not planned, but arise spontaneously from the bottom up. (Of course this immediately calls to mind the contemporary American attacks from biblical fundamentalists proposing a "science" of intelligent design–that the appearance of design implies an intelligent creator–on the teaching of evolution.[8])

We have suggested that cells fulfill all these criteria and therefore comprise a complex adaptive system, the emergent behaviors and structures of which are our bodies: the processes of embryonic, fetal, and post natal development and maintenance, the very structures of our tissues and organs, in health and disease.[9–12] Indeed, our bodies, in themselves, are therefore nothing more than emergent self-organization. The implications of this lie in the many corollaries of the principles of complexity, including the inevitably of mass extinction events and the unpredictability of the precise details of emergence. But these topics have been covered more fully elsewhere and are not germane to the central arguments of this essay.[9–12]

The most important corollary for this essay, however, is that complex systems can exist in hierarchies. For example, the ant colony is comprised of scurrying ants and the ants are comprised of cells. This view now provides a strange insight: while from a distance the ant colony appears as a unitary object or thing, up close it is disclosed to not be a thing at all, but instead a phenomenon, the self-organization of smaller things. Likewise, the ants, at the everyday level of scale appear like things, i.e., bodies, but at the microscopic level the ant body as thing disappears (as does your body!) and is instead the dynamic organization of their cells. So "thingness" depends on scale of observation. (To touch on an Asian perspective at this point, the Buddhist concept of *shunyata*, often translated as "emptiness" of inherent existence, might be another, earlier way of describing this scale dependent nature of things.[13])

Now what about the cells? Are they the definitive object that underlies the life of multicellular organisms? Or at a lower scale would they too disappear? This depends on whether they can arise from smaller units as an expression of self-organization. And, of course, this is the case, as cells arise from the interactions of biomolecules which fulfill all the same criteria: biomolecules are vast in number, they are governed by a balance of negative feedback loops, there is no global sensing, and there is quenched disorder in the system. At this scale, however, the quenched disorder is particularly interesting.

An example I have used elsewhere, from the work of Toshio Yanagida, is illustrative.[14,15] Dr. Yanagida and colleagues study interacting biomolecules at the single molecule level. For

example, taking a single actin filament and a single myosin filament, he has been able to study the nature of their precise interactions which underlie the aggregate contraction of muscle fibers. Surprisingly, he found that the hydrolysis of ATP did not cause the bending of the myosin hinge that results in movement as had been commonly assumed. Instead, the myosin filament was found to move quite randomly in response to Brownian motion from the watery milieu in which it is suspended, *ex vivo* and *in vivo*.

The addition of ATP did not cause the forward movement of the molecule along the actin filament; rather, it provided the energy to constrain the random movements into directional action. A biophysical analysis confirms that the energy of the ATP is, in fact, too small to cause movement, but is sufficient to constrain movement derived from the higher energy Brownian motion.[15] Many other types of biomolecular pairings have been studied in like manner with similar findings (more detailed review elsewhere[15–17]).

And so, we find that the cell has no inherent existence, but is also scale dependent as were the ant colonies and, in turn, the ants themselves, or, more close to home, like our cities (nations, cultures, civilizations) and the people that populate them. Each appears to exist as an entity only at one level of scale, but this appearance dissolves at scales lower down. This bears on a principle we and others have stated elsewhere, referred to as "cellular uncertainty."[18–21] In our formulation, this principle states that any attempt to observe a cell alters that cell by changing its microenvironment and potentially alters its gene expression profile, functioning, and differentiative fate.

When we first proposed this principle, the reference to Heisenberg ("cellular *uncertainty*") was intended to be more metaphorical than real. However, we now see that, as with elementary particles, "cellular uncertainty" is not an artifact, a limitation of our incomplete technological abilities to study the cell. Rather, a cell's existence is contingent on the level of scale at which the body is observed. Without inherent, scale-independent existence the cell is by definition "uncertain" precisely in the meaning of Heisenberg: by examining the cell we change the cell.

Some Alternate Models of the Body

With the loss of the cell as a scale- and perspective-independent entity, cell doctrine can itself be understood to be contingent on perspective and scale. It becomes only one model for the body out of many (perhaps infinite) possible models. I have already suggested one alternate model, a fluid model, based on the old debate from the Ancient Greeks.

Another model is generated when one takes the genome as the point of view. The night I first observed an hepatocyte derived from bone marrow with Diane Krause, I grappled with the implications of the observation.[22] Trying to emulate Einstein's thought experiment technique, instead of saddling up to ride on a beam of light I tried to imagine traveling on the bone marrow-derived cell from the marrow to its hepatic site of engraftment. Neither I nor any of my colleagues would have had trouble saying that the cell in the marrow had become the cell of the liver, despite the fact that most, if not all of the phenotypic and molecular aspects of the cell had changed in the process of engraftment. The only way in which we could say it was "the same cell" was by marking the genome, for example with a Y-chromosome in a male to female transplantation experiment or by insertion of a transgene producing a detectable protein (e.g., green fluorescent protein or beta-galactosidase). In other words, the cell was defined in such transplantation experiments by its genome and the proteins encoded by it.

If the cell is defined by the genome and the proteins produced by its transcription, then the cell becomes a somewhat different entity than traditionally described by cell doctrine. Take an hepatocyte: albumin is produced by transcription of the gene for albumin. But albumin from the cell is not limited to the spatial region

contained by the cell membrane; it is exported by the cell and moves freely through the entire vascular space of the body. Thus, the borders of the cell when defined by transcriptional products of its genome extend far beyond the cell membrane, to encompass at least the entire vascular space of the body. All the neighboring hepatocytes are defined in the same way and thus they overlap in space and time.

With the genome as the point of view, then, the cell becomes defined not as a structurally bounded box, but as a field of molecular organization in space and time which may overlap with other cellular fields of organization. Moreover, since the body respires, secretes, and sheds into the surrounding environment, a genomic view of the body suggests that the skin is not the actual boundary of the body. The outer boundary becomes indistinct as bodily products suffuse the environment beyond its epidermal limit.

So we can see that observational method and point of view even within the same level of scale can give rise to alternate models of the body which are as potentially self-consistent as cell doctrine, yet also independent of cell doctrine. Changing scale will also yield other possible models. A nanoscopic view of the body is quite different than a microscopic view. Cells cease to exist at that finer scale level; indeed the body itself ceases to be apparent. The body's functions become dominated by quantum effects very different from effects seen at higher scale, some of which even clearly manifest at higher levels. Examples of biologically relevant quantum effects include the importance of quantum tunneling for the energy requirements of some enzymatic action[23,24] and the above described role of Brownian motion in providing energy of movement for interacting single molecules as described above.

Alternate Models and Asian Systems of Medicine

Cracking the dominance of cell doctrine may then allow for appraisal of therapeutically useful systems such as those of Asia. Given its hegemony in 20th century Euro-American scientific thought, it is difficult to find coherent models from within that system to challenge it. But when its limitations are recognized, reproducibly testable phenomena from these other traditions, that have remained unexplained by the cell model, submit to the possibility of productive analysis.

A prime example of such phenomena is found in Chinese medicine, specifically in the practice of acupuncture.[25] It is quite clear that the stimulation of acupuncture points by insertion of needles or application of pressure or electricity achieves biological effects that are not explained simply by, for example, a release of endogenous opiates. Application of the stimulating procedure to random locations on the body, while sometimes producing measurable effects, do not yield the scale of effect achieved when they are applied directly to the appropriate anatomic points in the meridian system. Something particular happens at those points that happens nowhere else. Yet how the effects take place remains unexplained despite decades of Western style investigation.

There is of course a social reason for the inability of Western science to explain acupuncture: until recently, it was generally seen as outside of our scientific tradition so to study it in an organized academic sense was professionally difficult, if not academically risky. But it is more than prejudice that keeps development of hypothesis based investigation of acupuncture from proceeding at an appropriately rapid pace. To explain it in Western terms, we must identify what is going on structurally at the acupuncture points. Yet if one dissects these areas, one does not find an underlying anatomic structure that is readily described by our standard categories: there are no nerves, lymphovascular structures, tendons, fascial planes, or muscle fibers at these points or along the meridians. If they cannot be described in terms of our standard gross anatomy, they cannot be described by cells, the building blocks of that anatomy. Thus, it appears that the model of

cell doctrine is, at least to date, inherently incapable of explaining acupuncture. While it is a consistent model and thus successfully produces hypotheses concerning many observable bodily phenomena, which can be tested and refined, it is also an incomplete model.

Presenting these ideas at this "Longevity, Regeneration, and Health" conference also allowed for their appraisal in light of some terminologic aspects of Tibetan medicine which had previously been opaque to me, but now, perhaps might be somewhat more accessible. Tibetan medicine speaks of different "bodies" which co-exist within our single body: a coarse body, a subtle body, and an energy body.[26] Previously, these phrases always conjured in my imagination overlapping, superimposed "bodies" that were independent of each other and probably only metaphorical (my typically Western bias).

However, when discussing how the body might function or appear at different levels of scale in small groups of American and Tibetan doctors and scientists, the possibility that there was more substance to these terms became apparent. Is it possible that "other bodies" of the Tibetan and other systems actually correspond to our bodies at different levels of scale? If so, can we appreciate medical philosophy and science of other cultural systems, such as the Tibetan system, not as naïve metaphor, but as poetically expressed, yet still precise approaches to considering how the body is put together and might be repaired if injured?

This might be somewhat analogous to how we might look at repair of a broken arm by the placement of a splint or cast at the macroscale as being similar, yet different from administration of a drug that functions to change some receptor binding at a molecular level. They are both therapeutic, but in the former we ignore the molecular nature of the body and in the latter we remain unconcerned about the gross structure of the body.

In conclusion, we see that cell doctrine while obviously hugely successful in terms of investigative science, diagnosis of disease, and therapeutics, is not a complete model of the body. Various changes in perspective and scale of observation lead to alternate possible models–also incomplete but possibly also of great use–that may reveal the accuracy of some Asian models, despite the seemingly metaphorical terminology employed in those systems (from a Euro-American perspective). Limiting ourselves to cell doctrine means that some bodily phenomena may remain resistant to cell-based hypothesis formation and testing. Alternate models may also expand the opportunities for scientists and physicians from varied traditions to productively compare and contrast their concepts and practices, resulting in fruitful cross-cultural dialogue.

Conflicts of Interest

The author declares no conflicts of interest.

References

1. Harris, H. 2000. *The Birth of the Cell*. Yale University Press. New Haven, CT.
2. Theise, N.D. 2005. Now you see it, now you don't. *Nature* **435:** 1165.
3. Theise, N.D. 2005. Cell doctrine in a complex and uncertain world: time for a reappraisal? *Cloning Stem Cells* **7:** 209–213.
4. Theise, N.D & R. Harris. 2006. Postmodern biology: (adult) (stem) cells are plastic, stochastic, complex, and uncertain. *Handb. Exp. Pharmacol.* **174:** 389–408.
5. Theise, N.D. 2006. Implications of 'Post-Modern Biology' for pathology: the cell doctrine. *Lab. Invest.* **86:** 335–344.
6. Lewin, R. 2002. *Complexity: Life at the Edge of Chaos*, 2nd edition. University of Chicago Press. Chicago, IL.
7. Johnson, S. 2001. *Emergence*. Scribner. New York, NY.
8. Scott, E.C. & N.J. Matzke. 2007. Biological design in science classrooms. *Proc. Natl. Acad. Sci. USA* **104**(Suppl 1): 8669–8676.
9. Theise, N.D. 2004. Stem cells react! Cell lineages as complex reactive systems. *Exp. Hematol.* **32:** 25–27.
10. Theise, N.D. & M. D'Inverno. 2004. Understanding cell lineages as complex adaptive systems. *Blood Cells Molec. Dis.* **32:** 17–20.
11. D'Inverno, M., N.D. Theise & J. Prophet. 2006. Mathematical modelling of stem cells: a complexity

primer for the stem cell biologist. In: C. Potten, J. Wilson, R. Clarke & A. Renahan, (eds.). *Tissue Stem Cells: Biology and Applications*, 2nd edition. pp.1-15. Marcell Dekker Inc. New York, NY.

12. Hussain, M.A. & N.D. Theise. 2004. Post-natal stem cells as participants in complex systems and the emergence of tissue integrity and function. *Pediatr. Diab.* **5**(Suppl 2):75–78.
13. Theise, N.D. 2006. From the bottom up: complexity, emergence and Buddhist metaphysics. *Tricycle: Buddhist Rev.* **15:** 24–26.
14. Yanagida, T., K. Kitamura, H. Tanaka, *et al*. 2000. Single molecule analysis of the actomyosin motor. *Curr. Opin. Cell Biol.* **12:** 20–25.
15. Ishii, Y., M. Nishiyama & T. Yanagida. 2004. Mechano-chemical coupling of molecular motors revealed by single molecule measurements. *Curr. Protein Peptide Sci.* **5:** 81–87.
16. Kurakin, A. 2005. Self-organization versus watchmaker: stochastic dynamics of cellular organization. *Biol. Chem.* **386:** 247–254.
17. Kurakin, A. 2006. Self-organization versus watchmaker: molecular motors and protein translocation. *Biosystems* **84:** 15–23.
18. Potten, C.S. & M. Loeffler. 1990. Stem cells: attributes, cycles, spirals, pitfalls and uncertainties. Lessons for and from the crypt. *Development* **110:** 1001–1020.
19. Theise, N.D. & D.S. Krause. 2001. Suggestions for a new paradigm of cell differentiative potential. *Blood Cells Molec. Dis.* **27:** 625–631.
20. Theise, N.D. & D.S. Krause. 2002. Toward a new paradigm of cell differentation capacity. *Leukemia* **16:** 542–548.
21. Theise, N.D. 2003. New principles of cell plasticity. *C. R. Biol.* **325:** 1039–1043.
22. Theise, N.D., S. Badve, R. Saxena, *et al*. 2000. Derivation of hepatocytes from bone marrow cells in mice after radiation-induced myeloablation. *Hepatology* **31:** 235–240
23. Truhlar, D.G., J. Gao, C. Alhambra, *et al*. 2002. The incorporation of quantum effects in enzyme kinetics modeling. *Acc. Chem. Res.* **35:** 341–349.
24. Marcus, R.A. 2006. Enzymatic catalysis and transfers in solution. I. Theory and computations, a unified view. *J. Chem. Phys.* **125:** 194504.
25. Shang, C. 2000. *The Past, Present, and Future of Meridian System Research*. Springer. Berlin.
26. Clifford, T. 1984. *Tibetan Buddhist Medicine and Psychiatry*. Samuel Weiser, Inc. York Beach, ME.