Now you see it, now you don't

Cell doctrine: modern biology and medicine see the cell as the fundamental building block of living organisms, but this concept breaks down at different perspectives and scales.

Neil D. Theise

Complexity theory, which describes emergent self-organization of complex adaptive systems, has gained a prominent position in many sciences. One powerful aspect of emergent self-organization is that scale matters. What appears to be a dynamic, ever changing organizational panoply at the scale of the interacting agents that comprise it, looks to be a single, functional entity from a higher scale. Ant colonies are a good example: from afar, the colony appears to be a solid, shifting, dark mass against the earth. But up close, one can discern individual ants and describe the colony as the emergent self-organization of these scurrying individuals. Moving in still closer, the individual ants dissolve into myriad cells.

Cells fulfill all the criteria necessary to be considered agents within a complex system: they exist in great numbers; their interactions involve homeostatic, negative feedback loops; and they respond to local environmental cues with limited stochasticity ('quenched disorder'). Like any group of interacting individuals fulfilling these criteria, they self-organize without external planning. What emerges is the structure and function of our tissues, organs and bodies.

This view is in keeping with cell doctrine — the fundamental paradigm of modern biology and medicine whereby cells are the fundamental building blocks of all living organisms. Before cell doctrine emerged, other possibilities were explored. The ancient Greeks debated whether the body's substance was an endlessly divisible fluid or a sum of ultimately indivisible subunits. But when the microscopes of Theodor Schwann and Matthias Schleiden revealed cell membranes, the debate was settled. The body's substance is not a fluid, but an indivisible box-like cell: the magnificently successful cell doctrine was born.

But a complexity analysis presses for consideration of a level of observation at a lower scale. At the nanoscale, one might suggest that cells are not discreet objects; rather, they are dynamically shifting, adaptive systems of uncountable biomolecules.

Do biomolecules fulfill the necessary criteria for agents forming complex systems? They obviously exist in sufficient quantities to generate emergent phenomena; they interact only on the local level, without monitoring the whole system; and many homeostatic feedback loops govern these local interactions. But do their interactions display quenched disorder; that is, are they somewhere between being completely random and rigidly determined?

Analyses of individual interacting molecules and the recognition that at the nanoscale, quantum effects may have a measurable impact, suggest that the answer is yes. In particular, the behaviours of increasing numbers of biomolecular 'machines' are seen to rely on brownian motion of the watery milieu in which they are suspended. Previously it was thought that binding of adenosine triphosphate (ATP) and hydrolysis releases the energy that drives these tiny machines. Now, it seems that this energy is too small to move the molecular machine mechanically, but is large enough to constrain the brownian-driven mechanics to achieve the required movement. This constrained movement is neither completely stochastic (that is, brownian), nor rigidly determined (by structure or by consumption of ATP). Examples of such phenomena include actin/myosin sliding, the activation of receptors by ligand binding, and the transcription of DNA to messenger RNA.

So, at the nanoscale, cells cease to exist, in the same way that the ant colony vanishes at the perceptual level of an ant. On one level, cells are indivisible things; on another they dissolve into a frenzied, self-organizing dance of smaller components. The substance of the body becomes self-organized fluid-borne molecules, which know nothing of such delineating concepts as 'intracellular' and 'extracellular'. The other side of the ancient argument seems to hold: the body is a fluid continuum.

Is this merely poetic description? I suggest not. The fragility of the cell as the fundamental unit has been described before as 'cellular uncertainty', akin to the Heisenberg uncertainty principle: any attempt to examine a cell, inevitably disrupts its microenvironment, thereby changing the state of the cell. But are cells fundamentally 'uncertain' or is it possible to conceive of a technology — a perfect MRI machine, if you will — that could collect the data to describe a cell completely without altering it?

D. SCOTT/CORBIS

Scale up: hundreds of individual ants form a superorganism.

Complexity analysis suggests that no machine could ever achieve this. The cell as a definable unit exists only on a particular level of scale. Higher up, the cell has no observational validity. Lower down, the cell as an entity vanishes, having no independent existence. The cell as a thing depends on perspective and scale: "now you see it, now you don't," as a magician might say.

This analysis also allows for hypothesis-based investigations of phenomena considered outside the bounds of 'traditional' biology. A prime example is acupuncture, wherein application of stimuli to special points (meridians) on the body accomplishes remote physiological effects. The meridians do not correspond to identifiable anatomical subunits. So acupuncture, although testable and useful, cannot be explained by cell doctrine and conventional anatomy.

The validity of cell doctrine depends on the scale at which the body is observed. To limit ourselves to the perspective of this model may mean that explications of some bodily phenomena remain outside the capacity of modern biology. It is perhaps time to dethrone the doctrine of the cell, to allow alternative models of the body for study and exploitation in this new, post-modern era of biological investigation. ■

Neil D. Theise is at the Division of Digestive Diseases, Beth Israel Medical Center, First Avenue at 16th Street, New York New York 10003, USA.

FURTHER READING
Theise N. D. & d'Inverno, M. *Blood Cells Mol. Dis.* **32,** 17–20 (2004).
Theise N. D. & Krause D. S. *Leukemia* **16,** 542–548 (2002).
Kurakin A. *Dev. Genes Evol.* **215,** 46–52 (2005).

CONCEPTS