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The cell as nexus: Connections between the history, philosophy and science of cell biology

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Abstract

Although the cell is commonly addressed as *the* unit of life, historians and philosophers have devoted relatively little attention to this concept in comparison to other fundamental concepts of biology such as the gene or species. As a partial remedy to this neglect, we introduce the cell as a major point of connection between various disciplinary approaches, epistemic strategies, technological vectors and overarching biological processes such as metabolism, growth, reproduction and evolution. We suggest that the role of the cell as a nexus forms the basis for a new philosophical and historical appreciation of cell biology. This perspective focuses less on the cell as a well-defined, stable object and places more emphasis on its role as a mediator of fundamental biological processes.

1. Introduction

Cells are undoubtedly important biological elements, and many commentators have discussed them as the fundamental unit of life, the basis on which all other living entities are built. The British neurophysiologist Sir Charles Scott Sherrington, for example, characterized the cell as ‘an organized life-system centred upon itself. The cell’, he went on, ‘is a unit-life, and our life, which in its turn is a unitary life consists utterly of the cell lives’ (Sherrington, 1946, p. 73). Such claims, however, are not as straightforward as they may seem. Cells are many things: structural units, physiological factories, developmental agents, and subjects of evolution. They can be understood ontologically as such units, but also epistemologically, as the entities to which biological processes must be related in order for biological knowledge to be gained. It is perhaps no coincidence that it was an outsider to biology who first captured this role of the cell. In the preface to the first edition of *Das Kapital*, Karl Marx claimed that the unit of analysis in the study of ‘bourgeois society’ was ‘the commodity-form of the product of labour’, in analogy to the cell as studied by ‘microscopic anatomy’ (Marx, 1996 [1867], pp. 7–8). He made this suggestion in preference to the individual citizen, which the already popular metaphor of the organism as a cell state would have suggested (cf. Reynolds, 2007). If we invert Marx’s metaphor, the cell as studied by biologists turns out to be a medium of global processes of exchange and reproduction, rather than a well-bounded and stable entity in its own right.

Once this perspective is taken, it becomes less of a surprise that historical analyses of cell concepts show them to have been understood in many very different ways, and that tensions between such concepts have marked the history of cell theory. The multiplicity and ambivalence of how cells are understood makes them analogous to genes and their many

conceptualizations over the last century (Müller-Wille and Rheinberger, 2008). While 'obvious' in many specific and scientific contexts, a more critical retrospective view undermines that very obviousness in the same way it did for genes. At the same time, this very multifacetedness is what makes cells so biologically important and epistemologically plastic. Just as commodities, to build on Marx's metaphor, have taken on a great variety of forms and functions in capitalist societies, so do cells manifest in a plethora of forms and functions in living systems.

Rather than conceive of the cell in any particular way, this special issue therefore proposes a broad primary function for cells and cell concepts — one that encompasses their multivalence over time. The cell, we suggest, is a nexus: a connection point between disciplines, methods, technologies, concepts, structures and processes. Its importance to life, and to the life sciences and beyond, is because of this remarkable position as a nexus, and because of the cell's apparently inexhaustible potential to be found in such connective relationships. The nexuses explored by the papers in this special issue are diverse. An inevitable issue, when talking about cells from any perspective, is that of part-whole relationships. The cell lies at the intersection of molecular and organismal approaches to life, and can be argued to be the natural unit of integration for top-down and bottom-up approaches. Epistemically, therefore, cells are the nexus of decompositional and recompositional methods for understanding life, whether on a molecular, organismic or populational level of analysis.

The cell is also found at the intersection of approaches that seek to provide simplified and highly generalizable accounts of biological processes, and those that are intent upon much more complex but particular explanations. Disciplinarily, the cell mediates not only molecular and whole-organism perspectives, but also much more distant approaches such as physical chemistry and electrochemistry as they connect with cytology and physiology. Biologically, although it is common to think of the cell as a structural unit housing physiological capabilities (e.g., organelles and cytoskeletal elements), it is also the locus of reproduction and evolution, and thus of genetics and evolutionary biology. An evolutionary focus on the cell involves not just its role as the aggregative vehicle enabling population genetics, but also as a basic unit of macroevolution in the transitions between different cell types (prokaryotic to eukaryotic) and from uni- to multicellularity.

This special issue has developed out of an exploration of the philosophy and history of cell biology, and it has led to the re-evaluation of some standard conceptualizations of cells and the rethinking of some traditional epistemologies of cells. The result is this collection of papers that covers at least two centuries of research on cells. Each paper in this issue examines a range of these conjunctions, and in the process, gives philosophers and historians new reasons to reflect on cells and cell biology. As a consequence, we hope, this issue will raise questions and open avenues of inquiry for future historians and philosophers of cell biology to explore.

2. Overview of contributions

William Bechtel's paper outlines how the cell nestles at the junction of two explanatory strategies: one in which it is the *locus* of explanation and another in which it is the *object* of explanation. The first explanatory mode decomposes cell-based mechanisms into their constituent parts and operations. This decomposition begins with the characterization of organelles and biochemical pathways, and progresses to molecular interactions. Such approaches have obviously been highly successful, not only in the era of molecular biology, but throughout the longer history of cell biology. The second mode of explanation involves recomposition, in which to explain certain cellular processes it becomes necessary to understand cells as integrated wholes in relation to their environments. Circadian rhythms, for example, rely on intracellular mechanisms that bring about not only oscillatory effects in the individual cell, but also exogenous effects on the population of cells in multicellular organisms. Bechtel thus offers insights into the cell in a broad and dynamic conjunction of decompositional and recompositional research, which oscillates between the cell as a locus and an object of inquiry in its own right.

Mathias Grote also elaborates on this dialectic in his examination of the multilevel relationships between electrochemical fuel cells and biological cells. He outlines a history of research that draws material and theoretical analogies between these two uses of cell, and he shows how research based on the electrical effects of chemical reactions in containers (fuel cells) influenced understandings of the biological cell. A pivot point for this history is the debate over oxidative phosphorylation — the process by which mitochondria produce energy — in the 1960s and 70s. The key figure in this story is Peter Mitchell, who drew heavily on analogies with fuel cells to present his chemiosmotic model of energy generation via membrane-based processes. The spatialization such analogies enabled allowed cells to be understood as compartments for physiochemical work. Furthermore, subsequent cell biology and bioenergetics followed up on these 'deconstitutional' approaches, based on biochemical and fractionation approaches, with a reconstitutional one in which lipid vesicles are used to construct electrochemical biology. Grote's analysis places the cell at the confluence of several streams of activity: physical chemistry and biology, morphology and electrochemistry, theoretical and material modelling. This capacity to occupy several epistemic niches gave bioenergetic approaches to cells a considerable influence on molecular biology and, more generally, epistemologies of living systems.

Andrew Reynolds begins his paper with an outline of how cell theory cast cells as the fundamental unit of organization and physiology, and how this concept has been challenged since its very inception. A core criticism is that the notion of cellular autonomy has been purchased at the expense of understanding organismal effects on cells. The concept of the cell as already differentiated and autonomous was heavily contested in the late nineteenth century, especially when the focus of attention shifted to the nucleus, and as preformationist conceptions of development reared their heads. Alternative epigenetic perspectives argued that the cell achieves its differentiated state through organismally driven developmental processes. Cells, rather than being primary, become in this perspective secondary vehicles of organismal development. As this debate continued into the twentieth century, a vague consensus formed around the compromise that cells are both autonomous and dependent, in

a similar manner to how genes and environment have to be understood. But this is not the only nexus the cell inhabits in this discussion. Reynolds draws out the consequences for cell theory in epistemological terms. If cell-based 'laws' of life do indeed have exceptions, and if more particularized accounts of cellular phenomena are more viable explanations of living things, then the cell itself has to be perceived as a more plastic sort of entity than classic conceptions allow. This plasticity means, of course, that over-generalized accounts of life are suspect, and that cell theory has to be understood as a pragmatic account that has constructively sown the seeds of its own doubtfulness.

Dan Nicholson's discussion focuses on biological atomism, which he outlines as the tenet that all life is composed of elementary and indivisible vital units. He situates cell theory at the culmination of a long search for 'the' biological atom. Cells became identified as the most basic component of life, with consequences for how the organism is understood. One of the main criticisms of cell theory, therefore (raised also by Reynolds), revolves around the question of the status of organisms qua cells, and the cell's role in the development of the organism. But, says Nicholson, criticisms of cell theory come not only 'from above' (i.e., the organismal perspective), but also from below. Sub-cellular candidates for biological atoms proliferated in the nineteenth century (e.g., bioblasts) and have found further proponents in the twentieth century (e.g., neo-energides). Although these positions play only a minor role in today's cell biology, the continuation of this debate provides further illustration of the intriguing capacities of cells to function as both epistemic and conceptual nexuses, thus focusing multi-level debates about biological entities, as well as the different epistemic strategies that accompany them.

Maureen O'Malley discusses cells not as general units of life, but in the form of the two major cell types known to biology: the prokaryote cell and the eukaryote cell. As soon as such a distinction is made, however, the question in Darwinian biology becomes one of what their evolutionary relationship is, and whether one cell type gave rise to or can be traced back to the other. O'Malley examines the two main models of the origins of eukaryotes. These are the phagotrophy model, which is based on the claim that a protoeukaryote pre-existed the acquisition of the mitochondrion, and the syntrophy model, which posits the engulfment of one prokaryote by another as the primary event in eukaryogenesis. An issue at the heart of the debates about which scenario is more likely is that of autogenous versus xenogenous (exogenous) evolution. In the former, the transition of a cell from pre-eukaryote to proto-eukaryote and finally, to the eukaryote state itself, is achieved autogenously — as an act of 'self-generated' evolution. This model is contrasted against the exogenously driven transition from two prokaryote cells to a eukaryote cell. These metaphysical claims about the eukaryote cell and its evolution structure a number of epistemic tensions: between, for example, molecular and cell-biological approaches, environmentally driven and internally constrained factors, plausibility and uniqueness claims, simplicity and comprehensiveness of explanation, and the irreducibility or continuity of the evolving entities. The evolutionary nexus at which the origins of the eukaryote cell lie thus exemplifies in a range of ways the connectivity of cells in scientific practice.

Staffan Müller-Wille's paper on Darwin, Mendel and cell theory places the cell at centre-stage in a historical drama that interweaves heredity and evolution. In this analysis, the cell

is not only the primary unit of specific physiological reactions, but also the locus of differential reproduction. These general functions of evolving life converge upon the cell, but result in more than a mere increase in cell types. Cells become the units of life-cycles, not life 'out of time' as they are in purely physiological conceptions. Generations of cells can thus be conceived as the medium of biological and evolutionary time: they bring together the ontogenetic and phylogenetic. Moreover, as a nexus for questions of preformation and epigenesis, the cell raises questions that echo the autogeny-xenogeny issues raised above — of whether vitality inheres within cells and confers specific agency to them, or whether cells are mere products of external organizing forces. Darwin took such themes further, when he explicitly placed the cell at the conjunction of not just physiology and generation, but of speciation and macroevolution. In his 'provisional hypothesis of pangenesis' Darwin stated that cells themselves supply the material of heredity — the gemmules — and constitute the organism as a whole. Speciation can thus be focused on the same unit as development: the budding, reproducing cell. This range of processes and inquiries is thus both biologically and theoretically anchored in the cell: the ultimate nexus of life and the life sciences.

3. Conclusions

Despite the considerable biological importance of the cell and cell concept, philosophers have largely ignored all cell biology and its unit of inquiry. We believe this is probably due to philosophers of biology — most of whom are anti-reductionist — being concerned that a focus on the cell is reductive because it decomposes the organism (generally an animal, for philosophy of biology). On the other hand, reduction of organismic phenomena is not as easily criticized from a more holist perspective, because cells — in stark contrast to genes — remain fundamentally alive in most biological analyses based on cytological approaches. The wrongness or rightness of anti-reductionist movements is not our point here; we do think, however, that the papers collected in this issue show how any ontological or epistemological conviction can find ways in which to think with cells, due to the nexus-like properties we outlined above. Even the critical perspectives of cell theory (as outlined in different ways by both Reynolds and Nicholson) show the cell's value as a connection point between bottom-up and top-down perspectives, and as a mediator of autonomous and dependent life. Cells can perform as both contingent particulars and lawful actors on a broad biological stage.

What is critical, however, is not to take anything for granted about cells — from seeing them as strictly physiological units to treating them as entities that require a certain approach. Contemporary research, as the papers above show, is only just beginning to understand cells and their properties, and new understandings arise every day in cell biology and related disciplines. Even the very idea of cells as fundamental to life has fluctuated wildly since the first thoughts of such units, and evolutionary analyses of cell types outline an extraordinary capacity for cells to transform into entirely different entities (i.e., new cell types, new organizations of cells). Some forms of molecular biology, most notably synthetic biology, hope to create life without creating cells, and thus conceive of the cell as having more to do with packaging — a 'chassis' — than it has with the intrinsic machinery of life (Lartigue et al. 2007). Whether this is a successful strategy remains to be seen. In the meantime, the

philosophy and history of cell biology has many avenues of future inquiry open to exploration, and any philosopher or historian concerned with today's cell biology would do well to keep in mind the rich and ambivalent history of cell theory and research practice.

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