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Biological atomism and cell theory

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A B S T R A C T

Biological atomism postulates that all life is composed of elementary and indivisible vital units. The activity of a living organism is thus conceived as the result of the activities and interactions of its elementary constituents, each of which individually already exhibits all the attributes proper to life. This paper surveys some of the key episodes in the history of biological atomism, and situates cell theory within this tradition. The atomistic foundations of cell theory are subsequently dissected and discussed, together with the theory's conceptual development and eventual consolidation. This paper then examines the major criticisms that have been waged against cell theory, and argues that these too can be interpreted through the prism of biological atomism as attempts to relocate the true biological atom away from the cell to a level of organization above or below it. Overall, biological atomism provides a useful perspective through which to examine the history and philosophy of cell theory, and it also opens up a new way of thinking about the epistemic decomposition of living organisms that significantly departs from the physicochemical reductionism of mechanistic biology.

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1. Introduction

Cell theory is generally regarded as one of the central unifying ideas in biology. It is widely acclaimed in textbooks as a cornerstone of biological science (for example, Sharp, 1921, p. 9; Harold, 2001, p. 17) and, alongside Charles Darwin's theory of evolution, the most important generalization in biology (for example, Wilson, 1900, p. 1; Webster, 2003, p. 9). However, cell theory is far from being an obvious, self-evident truth that is universally accepted among biologists. In fact, ever since it was formally enunciated by Matthias Schleiden and Theodor Schwann in 1838 and 1839 (Baker, 1948), the extent of its applicability, and even its internal coherence, have remained the subject of controversy in biology. The main aim of this paper will be to uncover the rationale underlying the major objections that have been waged against cell theory since its formulation to the present day. To do so, it will be necessary to identify the philosophical foundations upon which cell theory rests. In turn, this will require going beyond the 'official history' of cell theory, on the grounds that there is, philosophically speaking, no direct path connecting Robert Hooke's first microscopical observations of cells in 1665 with Schleiden's and Schwann's articulation of cell theory 175 years later.

Rather than enumerating the successive recorded observations of cells from Hooke to Schleiden and Schwann, it may be instructive to consider the genesis of cell theory by examining the epistemological motivations that led to its formulation, as these can help situate the subsequent criticisms of the theory in an appropriate philosophical context. Of course, there is no single way of accomplishing this. E. S. Russell (1916), for instance, explained the development of cell theory and the subsequent challenges to it as an expression of the fundamental biological dispute over the causal primacy of form or of function. Georges Canguilhem (2008 [1965]), on the other hand, interpreted the history of cell theory as a dialectical battle between two opposing representations of the anatomical constitution of organisms: one emphasizing continuity, and the other emphasizing discontinuity. And Timothy Lenoir (1982) traced the steps that led to Schleiden's and Schwann's enunciation of cell theory as part of a broader 'teleomechanical' research programme in biology, which he argued arose out of a materialistic interpretation of Immanuel Kant's teleological conception of the organism advanced in his third Critique.

In this paper, the perspective adopted to make philosophical sense of past and present disputes over the legitimacy of cell

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theory is one I call *biological atomism*. I characterise biological atomism as the doctrine which postulates a basic indivisible unit of life and seeks to explain the morphological constitution and physiological operation of all living beings in terms of these fundamental units. The activity of a living organism is thus conceived as the result of the activities and interactions of its elementary constituents, each of which individually already exhibits all the attributes proper to life. It is important to distinguish from the outset what I call biological atomism from mechanistic[1] efforts to reduce biological entities (e.g., organisms) to physicochemical ones (e.g., genes), given that in theories of biological atomism the final units of analysis are still living beings in their own right.

By looking at cell theory through the prism of biological atomism, I want to suggest that we can reach a better understanding of the ideas which led to its formulation, and a fuller appreciation of the rationale underlying the major objections that continue to be waged against it. I begin by surveying the major incarnations of biological atomism prior to cell theory, and by illustrating the philosophical continuity between them. I will then consider the conceptual development of cell theory itself and highlight its atomistic foundations. Following this, I will examine the main criticisms of cell theory, categorizing them according to whether they represent efforts to locate the true indivisible unit of life above or below the level of the cell. I will conclude by reflecting more generally on the philosophical value of biological atomism and on the consequences of this perspective for biology.

2. Biological atomism before cell theory

The roots of biological atomism can be traced back to the popularization of corpuscular theories of matter and light by Sir Isaac Newton in the late seventeenth and early eighteenth centuries. In the rare instances when Newton theorized about life, he referred to chemical transformations, especially fermentation, which he explained in corpuscular terms (Hall, 1969, p. 18). One of the chief exponents of Newtonian natural philosophy in eighteenth-century France was Georges-Louis Leclerc de Buffon, and it is to him that we owe the first explicit formulation of an atomistic theory of life. Though originally trained in physics and mathematics (he published a French translation of Newton's *Method of fluxions* in 1740), Buffon made his most important contributions in biology. As a true Newtonian, Buffon endorsed the corpuscular conceptions of matter and light, and argued by inference that living matter must likewise be corpuscular in nature. In the second volume of his *Histoire naturelle* (published in 1749), Buffon presented his theory of 'organic molecules', which stated that organisms are compound assemblages of elementary living particles. These biological atoms, common to animals and plants, are primary and unalterable, such that the generation and destruction of organisms is in reality the result of the association and dissociation of these elementary living beings:

> The life of the animal or vegetal appears to be nothing more than the result of all the actions, all the particular little lives (if I may be allowed to express myself in this way) of each one of these active molecules, whose life is primitive and appears to be indestructible: we have found these living molecules in all living or vegetating beings: we are certain that all these organic molecules are also proper to nutrition and by consequence to the reproduction of animals and plants. It is thus not difficult to conceive that, when a certain number of these molecules are united, they form a living being: life being in each of the parts, it can be in a whole, in any assemblage whatsoever of these parts. (Buffon, quoted in Canguilhem, 2008, p. 37)

To explain the confinement of the aggregation of organic molecules in the organism, as well as the stable organization of the organic molecules in three-dimensional space, Buffon introduced the concept of 'inner mould' as a sort of principle of morphological constancy. With his theory of organic molecules, Buffon was able to account for a number of fundamental biological processes, including heredity, reproduction, and development.[2] Buffon's friend, the geophysicist and mathematician Pierre-Louis Moreau de Maupertuis, published a similar atomistic theory in his *Vénus physique* (published in 1745), though the elementary particles of his theory were not just alive but were also endowed with psychic properties, such as desire, aversion, and memory (Hall, 1969, pp. 18–28). In any event, the idea that living particles are the basic building blocks of plants and animals was widely discussed and even generally accepted during much of the eighteenth century. For instance, the article on 'animal economy' in Diderot's *Encyclopédie* described the constituents of plants and animals as 'living atoms or organic molecules' (Diderot, quoted in Grene & Depew, 2004, p. 88).

One of Buffon's contemporaries, the Swiss physiologist Albrecht von Haller, advanced a rather different atomistic theory of the organism—one that persisted in various forms well into the nineteenth century: the fibre theory. Building on earlier ideas expounded by Francis Glisson, Nehemiah Grew, and James Keill, Haller postulated that the fibre is the elementary unit of all living bodies, famously asserting in his *Elementa physiologiae corporis humani* (published in 1757) that the 'fibre is for the physiologist what the line is for the geometer' (Haller, quoted in Toulmin & Goodfield, 1962, p. 391). According to Haller, there is only one kind of fibre to form all organs. It is the manner in which the fibres are arranged, the texture of the network they form, and the quantity of liquid retained by the mesh, that gives each organ its distinctive characteristics. Haller conceived fibres as the fundamental units of life, arguing that sensibility and irritability, the two sources of all vital activity, are themselves properties of the constituent fibres of the body.

At the end of the eighteenth century, the French anatomist Xavier Bichat distanced himself from Haller's fibre theory, and in so doing developed an atomistic theory of his own. Like Haller, Bichat identified sensibility and contractility (i.e., irritability) as the basic vital properties, but unlike Haller, he located these in the tissues rather than in the constituent fibres. Thus for Bichat, each individual tissue has individual life. As Claude Bernard would remark years later, 'Bichat decentralized life and incarnated it in the tissues' (Hall, 1969, p. 129). A distinctive feature of Bichat's tissue theory in relation to previous forms of biological atomism is that the elementary units of his theory are heterogeneous rather than homogeneous. Bichat distinguished twenty-one different kinds of tissues, and asserted that the particular attributes of an organism are the direct result of the different combinations of these tissues. In an explicit recognition of the atomistic nature of his theory, in the *Anatomie générale* (published in 1801) Bichat compared his twenty-one 'biological elements' to the thirty-three chemical elements Antoine Lavoisier had described in his *Traité élémentaire de chimie* of 1789 (Haigh, 1984, p. 118). Nevertheless, later anato-

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[1] I am using the term 'mechanistic' in the sense in which it has traditionally been used in biology, namely to describe the longstanding research programme which conceives living organisms as machines and seeks to explain them in terms of their physicochemical constituents. It should not be confused with the new usage of this term in relation to recent philosophical discussions concerning the epistemic role played by explanatory mechanisms in contemporary scientific practice. For analysis of the various biological senses of 'mechanism', see Nicholson (2009).

[2] For example, with regards to heredity, the theory of organic molecules appeared to overcome the limitations of the two rival unilateral preformationist theories of animal generation of the time—ovism and animalculism—by proposing a bilateral conception of heredity that accounted for the phenomenon of hybridization.

mists, such as Karl Friedrich Heusinger (who coined the term 'histology' in 1822), and Philipp Franz von Walther, attempted to further reduce the variety of tissues described by Bichat to a single elementary one from which all others derived. In 1807 Walther declared that the difference between Bichat's tissues was only one of degree given that 'all tissues contained in the texture of the organs of the animal body are formed by the metamorphosis of one and the same original tissue', which he identified as 'cellular tissue' (Walther, quoted in Jacyna, 1990, p. 165).

References to cellular tissue can already be found in the writings of Haller and other eighteenth century physiologists like Théophile de Bordeu and Johann Friedrich Blumenbach, but these authors conceived it as the gelatinous material resulting from the association of the body's constituent fibres, and *not* as an elementary unit of life in its own right (Wilson, 1944, pp. 169–170). In contrast, most of the early nineteenth-century biologists who theorized about cellular tissue did in fact view it as the primary component of all living matter. Jean-Baptiste Lamarck devoted an entire chapter to cellular tissue in the second volume of his *Philosophie zoologique* (published in 1809), in which he wrote:

> It has been recognized for a long time that the membranes that form the envelopes of the brain, of nerves, or vessels of all kinds, of glands, of viscera, of muscles and their fibres, and even of the skin of the body are in general the productions of *cellular tissue*. However, it does not appear that anyone has seen in this multitude of harmonizing facts anything but the facts themselves; and no one, so far as I know, has yet perceived that cellular tissue is the general matrix of all organization, and that without this tissue no living body would be able to exist nor could have been formed. (Lamarck, quoted in Conklin, 1939, p. 541)

Given assertions like this one, some commentators have argued that Lamarck deserves to be credited as one of the forefathers of cell theory (for example, Conklin, 1939; Sapp, 2003). However, this assessment is only correct in as much as Lamarck asserted that there is a fundamental indivisible unit of life which forms all organisms. But for Lamarck, this elementary unit was *not* the cell but cellular tissue. Consequently, Lamarck is only as much of a precursor of cell theory as the other proponents of biological atomism I have considered in this section. One must move forward a number of years after Lamarck to find the first attempts to conceptually reduce tissues to cells as the basic units of life. One of the earliest to do so was the botanist P. J. F. Turpin, who in 1826 published a paper with such a long and complete title that it can serve as a concise abstract of the novel claims contained within it:

> Observations on the origin and first formation of cellular tissue, on the vesicles composing this tissue, considered as distinct individualities having their own vital center of vegetation and propagation and destined to form by agglomeration the composite individuality of all those plants whose organization is composed of more than one vesicle. (Turpin, quoted in Conklin, 1939, p. 541)

Before proceeding to examine the cell theory, it is necessary to consider one more expression of biological atomism that preceded it, the globule theory, which despite having been the product of flawed microscopical observations nonetheless reflects the same atomistic thinking as the other theories I have discussed. Recorded observations of 'globules' can be traced all the way back to the two seventeenth century Dutch pioneers of the microscope, Antonie van Leeuwenhoek and Jan Swammerdam (Baker, 1948, pp. 115–116), yet it is only with the physiologist Caspar Friedrich Wolff in the eighteenth century that we encounter the first formulation of the globule theory. In his *Theoria generationis* of 1759, Wolff noted that the 'constituent particles of which all parts of the animal body are composed at their first beginnings, are globules (*globuli*), which always yield to a moderately good microscope' (Wolff, quoted in Baker, 1948, p. 116). Johann Friedrich Meckel was probably the first to discuss the globule theory in a textbook of anatomy, published in 1815. In it, Meckel argued that all living matter is essentially an agglomeration of elementary globules embedded in a coagulated matrix. Still, the most notorious account of the globule theory was the one expounded by the French zoologist Henri Milne-Edwards, who in 1823 carried out a systematic examination of a wide range of animal organs from different species, and concluded that they were *all* made up of globules 1/300 millimetres in diameter (Toulmin & Goodfield, 1962, p. 392). However, what is important for our purposes is the fact that during the 1810s and 1820s the globule theory represented a serious theoretical model of tissue structure and formation which exerted considerable influence in France and Germany (see Pickstone, 1973). Ultimately, the development of the microscope and the accumulation of conflicting accounts of globular structure led to the widespread rejection of the globule theory. Nevertheless, as Jutta Schickore (2009) has recently argued, the globule theory should not be regarded as a misguided conception irrelevant to the history of cell biology, but rather as a preliminary and tentative atomistic account of living matter whose influence and eventual rejection contributed to the consolidation of cell theory in the second third of the nineteenth century.

3. The atomistic foundations of cell theory

So far I have reviewed the major episodes in the evolution of atomistic thinking in biology up to the first decades of the nineteenth century. I will now show how the formulation and conceptual development of cell theory in many ways represented the culmination of the search for the biological atom. The cell, just like the organic molecule, fibre, tissue, and globule before it, is a notion tailored for the analysis of living matter that is meant to capture the ultimate, indivisible unit of life. But whereas previous theories of biological atomism had been tentative first approximations to the analytic understanding of living structures, cell theory appeared to successfully identify the actual minimal units of life and to root all major biological processes in the activities and interactions of these units.

I have already mentioned Turpin's remarkable 1826 paper, which sketched what was probably the first atomistic conception of the cell in plants.[3] This same notion was reiterated even more clearly and forcefully by the German botanist Franz Meyen in 1830:

> Plant cells occur either singly, so that each forms a single individual, as in the case of some algae and fungi, or they are united together to form greater or smaller masses, to constitute a more highly organized plant. Even in this case each cell forms an independent, isolated whole; it nourishes itself, it builds itself up, and elaborates the raw nutrient materials which it takes up, into very different substances and structures. (Meyen, quoted in Hall, 1969, p. 188)

Meyen elsewhere referred to plant cells as 'little plants inside larger ones' and as 'essential elementary organs of assimilation and construction' (Meyen, quoted in Conklin 1939, pp. 541–542). Matthias Schleiden, the co-founder of cell theory, did little more than restate in different words Turpin's and Meyen's atomistic conceptions of

[3] Around the same time, another Frenchman, Henri Dutrochet, published similar atomistic assertions regarding animal cells. However, Dutrochet's contribution to cell theory is difficult to assess as many of his observations of what he called 'cells' were most probably of globules (see Wilson, 1947; Baker, 1948; Pickstone, 1973).

plant cells when he asserted, in the oft-quoted passage of his *Beiträge zur Phytogenesis* of 1838, that:

> Each cell leads a double life: an independent one, pertaining to its own development alone; and another incidental, in so far as it has become an integral part of a plant. It is, however, apparent that the vital process of the individual cell must form the very first, absolutely indispensible fundamental basis of vegetable physiology and comparative physiology. (Schleiden, quoted in Conklin, 1939, p. 543)

The atomistic nature of Schleiden's conception of plant cells is evident. For Schleiden, each constituent cell in a plant is first and foremost an autonomous living being. The activity of a plant is conceived as the result of the individual activities of each of its constituent cells. In 1837 Schleiden conveyed these ideas to his colleague Theodor Schwann, who at once extended them to the animal kingdom. Each cell, wrote Schwann, 'contains an independent power, a life of its own'. The totality of the multicellular organism, plant or animal, 'subsists only by means of the reciprocal action of the single elementary parts' (Schwann, quoted in Wilson, 1900, p. 58). In 1839, acknowledging his indebtedness to Schleiden, Schwann formulated the cell theory, grounding it on three fundamental principles (Hall, 1969, pp. 189–192):

1. All parts of plants and animals are cellular either in organization or in derivation.
2. Cells are autonomous living units, and although each cell is influenced by its neighbours, the life of the whole organism is the product, not the cause, of the life of its cellular elements.
3. Cells arise inside or near other cells by differentiation of a homogeneous primary substance called the *cytoblastema* in a process analogous to crystallization.

The first principle was promptly corroborated through extensive microscopical studies of a wide range of tissues from different species. The second principle, which stressed the atomistic nature of the theory, acquired widespread currency and was further articulated in the second half of the nineteenth century, as I will show in a moment. The third principle, in contrast, was immediately challenged by Schleiden's and Schwann's contemporaries. For one thing, observations of cell division had already been reported by a number of authors before them, including Turpin (in 1826), B. C. J. Dumortier (in 1832), Hugo von Mohl (in 1837), and Meyen (in 1838). In the 1840s and 1850s, more detailed investigations, particularly those carried out by Robert Remak on the early developmental stages of the chick embryo, ultimately confirmed that cell division is not just the main, but the *only* way in which new cells are formed. This led to the rejection of Schleiden's and Schwann's conception of free cell formation, which Remak deemed 'just as improbable as the spontaneous generation of organisms' (Remak, quoted in Mendelsohn, 2003, p. 16).

The new principle of cell formation was further generalized by the pathologist Rudolf Virchow, who in 1855 proclaimed that just as an animal can only proceed from an animal and a plant from a plant, wherever a cell may originate another cell must pre-exist to give rise to it, immortalizing this assertion with the Latin dictum '*omnis cellula e cellula*'—that is, every cell from a cell (Virchow, quoted in Baker, 1952, p. 436). A few years later, Virchow published his seminal *Die Cellularpathologie* based on a series of lectures delivered at the University of Berlin, in which he updated Schleiden's and Schwann's cell theory and gave it a formulation which remained highly influential in subsequent decades (Sapp, 2003, p. 78). With Virchow, the atomistic connotations of cell theory became even more conspicuous. Cells are not just the minimal indivisible units of physiological activity, but they are also the seats of *disease*. The disciplines of physiology and pathology in the hands of Virchow became unified by the cell as their common elementary unit (Coleman, 1977, pp. 32–33).

By the end of the nineteenth century, the atomistic dimension of cell theory had become its single most distinctive feature. In 1893, the German zoologist Oscar Hertwig provided the following characterization of cell theory:

> Animals and plants, so diverse in their external appearance, agree in the fundamental nature of their anatomical construction; for both are composed of similar *elementary units*, which are generally only perceptible under the microscope. Through the influence of an old theory, now discarded, these units are called cells, and thus the doctrine that animals and plants are composed in an accordant manner of very small particles of this kind is called the *cell-theory* ... The common life-process of a composite organism appears to be nothing else than the exceedingly complicated result of its numerous and diversely-functioning cells. (Hertwig, quoted in Baker, 1948, p. 105)

Two years later, the English anatomist G. C. Bourne offered a similar account of cell theory: 'The multicellular organism is an aggregate of elementary parts, viz. cells. The elementary parts are independent life units. The harmonious interaction of the independent life units constitutes the organism. Therefore the multicellular organism is a colony' (Bourne, quoted in Reynolds, 2007, p. 83). The twentieth century brought enormous empirical advances in every area of cell biology, but the fundamental understanding of cell theory has remained largely unchanged. Indeed, through the decades one finds that cell theory has been periodically rearticulated by different authors in the same atomistic terms. For example, the Austrian theoretical biologist Ludwig von Bertalanffy asserted in 1952 that cell theory has morphological, embryological, and physiological meanings, and each of them emphasizes the theory's atomistic connotations in its own way:

> *Morphologically*, it means that the cell is the sole building element of the living world, and that multicellular elements are aggregates of cells. *Embryologically*, the development of the multicellular organism is resolved into the actions of the individual cells in the embryo. *Physiologically*, the cell is considered to be the elementary unit of function. (Bertalanffy, 1952, p. 35)

To sum up, cell theory tells us that the cell is the basic constituent of living matter; it is the fundamental unit of structure, function, and disease; it is the primary agent of organization; and it is the locus of all major organismic processes, including metabolism, development, reproduction, and heredity. In short, the cell, as the American zoologist Charles Otis Whitman so perceptively noted, 'has come to signify in the organic world what the atom and molecule signify in the physical world' (Whitman, 1893, p. 639).

Having completed my survey of the conceptual development of cell theory through the perspective of biological atomism, I will now employ this very same perspective to make philosophical sense of the major objections that have been waged against cell theory. I will show that all major criticisms of this theory can be understood as attempts to relocate the true biological atom away from the cell to a level of organization either above or below it. The next two sections will examine each of these two kinds of critique in turn.

4. The cell as the biological atom: challenges from above

One of the most salient consequences of cell theory's atomistic conception of the cell is that 'organism' becomes a biological category possessing little ontological weight of its own. According to cell theory the organism is the product of its cellular units. It is, in effect, a 'state' of autonomous living units which operate collectively to constitute it (see Reynolds, 2007). The common point of departure for all the challenges to cell theory I will consider in this section is a fundamental dissatisfaction with this understanding of the organism. In fact, they can all be classified under what Whitman (1893) called the 'organismal standpoint', which later became known as the 'organismal theory' (Ritter, 1919). Organismal theory postulates that it is the whole organism, rather than its cells, that represents the primary unit of life and thus the true biological atom. The organism is considered to be the cause, not the product, of its cellular constitution. Of course, cells are still regarded as important, but without an organismal-level perspective, questions of structure, function, and organization cannot be adequately addressed. In brief, organismal theory maintains that the biology of the organism is not reducible to the biology of its cellular constituents. In what follows, I will consider the three main criticisms of cell theory that have been advanced by proponents of the organismal theory.

4.1. Criticisms

4.1.1. Criticism one: 'The organism is not an aggregate of independent living units, but a genuine biological individual in its own right'

The fact that the organism is cellular in constitution is not contested by the organismal theory. What is disputed is the idea that the organism represents an aggregation of autonomous living units. Organismal theorists point out that physiology offers ample evidence that the organism functions as a fully integrated whole, and not as a collection of individual unities. The harmonious organization existing at the organismal level cannot be easily explained in terms of the sum of the individual activities of the component cells. One can certainly study biological phenomena at the cellular level, but one must ultimately interpret the findings of these studies from the perspective of the whole organism to fully appreciate their biological significance. Therefore, the fact that the organism can be analytically decomposed into its constituent parts does not imply that the organism is ontologically reducible to a collection of autonomous entities. Even if the organism is constituted of cellular subunits, organismal theory maintains that the organism as a whole remains the true individual unit of life.

Given the history of biological atomism prior to cell theory, it is probably not that surprising to find that this critique of the conception of the organism as an aggregate of individuals actually predates the formulation of cell theory by Schleiden and Schwann. What is perhaps more surprising is the fact that one of the authors who most clearly expressed this criticism, the Romantic biologist Lorenz Oken, is sometimes referred to as one of the forefathers of cell theory (for example, Singer, 1959, p. 33). In his *Die Zeugung* (published in 1805), Oken objected to the idea that multicellularity entails multi-individuality:

> The association of primitive animals in the form of flesh should not be thought of as a mechanical joining of one animal to the other, like a pile of sand in which there is no other association than an accumulation of numerous grains. No. Just as oxygen and hydrogen disappear into water, mercury and sulfur into cinnabar, what occurs here is a veritable interpenetration, an interlacing and a unification of all the animalcula. From this moment on, they no longer lead their own lives. They are put to the service of the more elevated organism; they work in view of a unique and common function; or rather, they carry this function out in realizing themselves. No individuality is spared here; individuality is quite simply ruined. But this language is inappropriate: the individualities brought together form another individuality; the former are destroyed and the latter only appears by their destruction. (Oken, quoted in Canguilhem, 2008, pp. 40–41)

Like many of the biological atomists I have considered, Oken compares the cells in an organism to the atoms in a chemical compound; but what is interesting about this passage is how Oken uses this analogy to draw the opposite conclusions. Just as the atoms of oxygen and hydrogen lose their independent identities when they combine to form a molecule of water, living cells fuse their separate individualities when they collectively constitute an organism. For Oken, as for all the organismal theorists ever since, the organism cannot be regarded as a 'cell republic' (as cell theorists like Virchow claimed) given that it is already the minimal individual unit of life. Its constituent cells should be regarded not as autonomous individuals, but as '*organs* of the organism just as muscles and glands and hearts and eyes and feet are so regarded' (Ritter, 1919, p. 191).

4.1.2. Criticism two: 'A unicellular organism is physiologically analogous and phylogenetically homologous to a multicellular organism, not to one of its constituent cells'

Cell theory has important consequences for microbiology, particularly for the study of protists (or 'protozoa', as they used to be called). Since multicellular organisms are conceived as colonies of single-celled individuals which have undergone a physiological division of labour, cell theory suggests a direct evolutionary link between unicellular beings like protists and multicellular ones like higher plants and animals. Specifically, the 'cell state' of a multicellular plant or animal is considered to be the evolutionary product of the colonial association of single-celled protists. The implication of this view, as noted by Max Verworn and Oscar Hertwig at the turn of the twentieth century, is that studying protists provides important insights for understanding the cells of multicellular organisms, since the former are essentially homologous with the latter (Richmond, 1989).

The organismal criticism of this viewpoint is grounded on the recognition that since multicellular organisms are individuals, rather than communities of individuals, their evolutionary origin must be rooted not in the association of many protists but in a single polynucleated protist whose parts subsequently evolved specialized functions, gradually forming the various tissues and organs of multicellular organisms (Sedgwick, 1896). Protists cannot be homologized with somatic cells of multicellular organisms because they are already autonomous individuals in their own right. Instead, the protist must be morphologically and physiologically compared with the multicellular organism *as a whole*. Indeed, both are individuals with specialized internal regions, and both are capable of independent locomotion, feeding, growth, reproduction, and regeneration.

One of the most vigorous exponents of this organismal critique was the English protistologist Clifford Dobell. Being so convinced of the fundamental and irreconcilable differences between protists and the individual cells of plants and animals, Dobell refused to accept even the designation 'unicellular' to describe protists. He argued that these should be referred to as 'acellular' organisms (Dobell, 1911). This acellular conception of protists exerted a considerable degree of influence during the first half of the twentieth century, but it has become largely marginal in the present day (see Corliss, 1989).[4]

[4] The reason for this seems to be that Dobell's objection to use the term 'cell' in relation to protists was based on the problematic assumption that a cell by definition is always a *part* of an organism and never a whole organism. This understanding of 'cell' stems from the fact that this concept was first used in relation to the component cells of higher plants and animals, and that consequently when it began to be used in relation to protists, it carried with it inappropriate connotations of parthood which obscured the protists' individuality as autonomous organisms. However, it is difficult to think of a good reason why the concept of 'cell' should be restricted in its usage in the manner that Dobell prescribed, which is probably why the term 'acellular' gradually lost its currency (see Reynolds, 2010).

4.1.3. Criticism three: 'Multicellularity is the product, not the cause, of the organism's development'

In no area of biological inquiry have the atomistic presuppositions of cell theory been more hotly contested than in developmental biology. The implications of cell theory for the understanding of embryological development have spawned a wide array of dissenting voices. The disagreements again centre on the problematic relationship between cell and organism. According to cell theory, cells assemble the organism from the bottom up. In the words of Schwann, 'the individual cells so operate together in a manner unknown to us as to produce a harmonious whole' (Schwann, quoted in Weiss, 1940, p. 38). As the multicellular organism is a community of interacting and mutually dependent individuals, development consists of a sequential multiplication of individualities resulting from the successive cell divisions of a primordial individual, the egg.

The point of departure for the organismal critique of this viewpoint is the contention that the process of development has no effect on an organism's individuality. Before cellular segmentation, the egg is a whole organism; after segmentation, it is the same whole organism, only more differentiated. The egg is an integrated whole within which parts gradually arise through cell division. At no time do the cells constitute independent units, since from the very beginning they are subordinated to the growth of the organism as a whole. From the perspective of organismal theory, multicellularity is not achieved by the coordinated aggregation of cells but by the secondary chambering of the organism into cellular subunits. This understanding of the attainment of multicellularity has important ramifications, as it implies that cells, far from being the elementary individuals described by cell theory, are effectively nothing more than internal subdivisions within the organism. In the course of the organism's development, cells are fashioned according to their context within the developing whole. The generation of biological form (i.e., morphogenesis) operates above the level of individual cells, and is thus a strictly organismal phenomenon.

Many of these ideas were brought together and further developed in Whitman's classic paper, 'The inadequacy of the cell-theory of development'. Arguing from the organismal standpoint, Whitman asserted that the growth and differentiation of the developing embryo occurs 'regardless of the way it is cut up into cells' (Whitman, 1893, p. 644). Whether as a single-celled egg or as a multicellular adult, the organism maintains its individuality independently of the number of cells present. This argument represents an important challenge to the atomistic assumptions of cell theory, as the number of cells composing an organism is deemed to be largely irrelevant for the understanding of the organism's form and organization.

A number of developmental studies conducted in the twentieth century provided further support for Whitman's criticisms. In the 1940s Gerhard Frankhauser experimented with the effects of ploidy on newt development (Frankhauser, 1945), and he found that polyploid embryos, generated by suppressing early cleavages, had fewer but larger cells. The number and size of cells differed in haploid, diploid, and pentaploid embryos, but the whole embryo remained the same size in all cases, enforcing the organismal hypothesis that development is more appropriately understood as resulting from the internal partitioning of an individual rather than from the agglomeration of a community of cooperating individuals, as implied by cell theory.

Contemporary research on plant morphogenesis has also helped to substantiate these views. Donald Kaplan and Wolfgang Hagemann (1991) reviewed evidence accrued during the preceding thirty years from a broad range of botanical studies and concluded that multicellularity in plants is better described by the organismal than by the cell theory. If plant cells were responsible for organismal form, one would expect there to be a strict correlation between the pattern of plant cell division and the zones of plant growth. However, what one actually finds is that the processes of cell division and growth are causally independent in plants. Overall, the constitution of plants seems to demand that considerations of growth, differentiation, and morphogenesis at the cellular level be placed in the context of the plant as a whole.

4.2. Cell theory versus organismal theory: the nature of the dispute

With the examination of the three main organismal critiques of cell theory now complete, what can be concluded regarding the nature of the dispute between cell theory and organismal theory? Are the two theories incompatible and mutually exclusive? Or do they constitute complementary viewpoints? Can the two theories be integrated? Finally, is the underlying conflict between the two theories representative of a more fundamental philosophical dispute? In relation to this last question, the Austrian embryologist Paul Weiss suggested in 1940 that the conflict in developmental biology between what he called the 'egg-equals-cell' theory (i.e., cell theory) and the 'egg-equals-organism' theory (i.e., organismal theory) constitutes a modern expression of the age-old antithesis between epigenesis and preformation.[5] Weiss argued that both viewpoints are correct since ontogeny is to a certain extent epigenetic and to a certain extent preformed. The process of development reveals the cell 'partly as an active worker and partly as a passive subordinate to powers which lie outside of its own competence and control, i.e. supra-cellular powers' (Weiss, 1940, p. 45). In an attempt to integrate the two theories, Weiss concluded that Virchow's dictum of cell theory, '*omnis cellula e cellula*', should be complemented by its organismal theory counterpart, '*omnis organisatio ex organisatione*' (ibid., p. 46).

More recently, Kaplan (1992) has rejected the possibility of reconciliation between cell theory and organismal theory on the grounds that they entail opposite causal understandings of the constitution and development of the organism. For Kaplan, 'there is no compromise between these two theories' (ibid., p. S29). Deciding upon one of them will determine our epistemic priorities and dictate how we approach the study of the organism. If cell theory is correct, then we only need to focus on the behaviour of individual cells, not the organism as a whole. Conversely, if the organismal theory is correct, the study of the properties of the organism becomes more significant than a focus on individual cells. Peter Sitte (1992), however, disagrees. In his view, there is no real conflict between the two theories, as both sides have convincing arguments in their favour that nowhere contradict each other directly. Provided that neither of the two viewpoints is overstated, the two theories may be regarded as the result of different starting positions, or different methodological preferences, with defenders of cell theory favouring the analytical and experimental approaches of cell and molecular biology, and advocates of organismal theory generally preferring the more holistic approaches of morphology and embryology. If this is the case, it is no longer necessary to view the two theories as contradicting or mutually exclusive.

It would appear that current research in plant morphogenesis is advancing steadily towards the epistemic integration of cell theory and organismal theory (see Fleming, 2006). The botanist Hirokazu Tsukaya (2003) has indicated that both viewpoints need to be

[5] Cell theory is epigenetic insofar as it claims that the organism's organization is arrived at through the sequential accumulation of cells, whereas organismal theory is preformationist insofar as it considers the organism's organization to be already present in the egg (see Müller-Wille, 2010).

combined in a Weissian manner in order to make sense of plant development. He shows that the shape and size of indeterminate organs, such as roots and stems, is directly correlated with the shape and size of the cells in these organs, as predicted by cell theory, whereas in determinate organs, such as leaves, the number of cells does not reflect organ shape or size but is rather determined by the plant as a whole, as predicted by organismal theory. In an attempt to bring the two theories together, Tsukaya has formulated what he calls the 'Neo-Cell Theory', which postulates that even though cells are the units of morphogenesis, each cell is also controlled by organismal-level compensatory systems that govern the morphogenesis of the organ of which the cells are a part.

5. The cell as the biological atom: challenges from below

In addition to the organismal critiques, challenges to the atomism of cell theory have also been advanced from the other direction. There are biologists for whom cell theory is problematic not because it is excessively atomistic (as argued by the organismal theorists), but rather because it is not sufficiently atomistic. For them, the biological atoms are located below the cell at a more basic level of organization. Cells in this view do not represent the minimal units of life as they can be conceptually reduced to even more elementary vital units.

This kind of critique has a long and colourful history. Shortly after Schleiden's and Schwann's formulation of cell theory, some biologists began to express doubts that cells really represented the ultimate indivisible units of life. Already in 1841 the German anatomist F. G. J. Henle had suggested that the cell might be composed of more fundamental biological units (Wilson, 1900, p. 289). In the second half of the nineteenth century, this idea was taken up by a large number of biologists, and a wide variety of theories were proposed that sought to identify *within* the cell more fundamental multi-molecular systems exhibiting the basic attributes of life. Many of the suggested vital units were deemed to be beyond the resolution of the microscope, and were hypothesized in order to account for the particular phenomena biologists were interested in explaining (e.g., nutrition, heredity, growth, differentiation, etc.). (In this respect, these theories are not that different from some of the earlier expressions of biological atomism I discussed in Section 2, such as Buffon's theory of 'organic molecules'.) Examples of this class of biological atoms include Herbert Spencer's 'physiological units', Charles Darwin's 'gemmules', Ernst Haeckel's 'plastidules', Karl Nägeli's 'micellae', Julius Weisner's 'plasomes', Theodor Engelmann's 'inotagmata', August Weismann's 'biophores', Hugo de Vries' 'pangenes', Oscar Hertwig's 'idioblasts', and Charles Whitman's 'idiosomes' (see Hall, 1969, pp. 313–354).

With the development of biochemistry at the turn of the twentieth century, many of these atomistic theories were abandoned. However, some of them were reinterpreted as genetic determinants following the rediscovery of Mendel's laws of heredity in 1900. In fact, one can find numerous references to genes as the atoms of biology in the literature on genetics between 1901 and 1930 (see Allen, 2007, pp. 146–152). Many early geneticists, such as William Bateson, H. S. Jennings, C. B. Davenport, and W. E. Castle, appealed to the analogy between genes and atoms in their work. Castle, for instance, asserted that genes 'are supposed to be to heredity what atoms are to chemistry, the ultimate, indivisible units, which constitute gametes much as atoms in combination constitute compounds' (Castle, quoted ibid., p. 147). However, this atomistic conception of genes does not quite fit the tradition of biological atomism I have been considering in this paper, as the vast majority of atomistic geneticists did not conceive genes as *living units* in their own right. Rather, the assimilation of genes to atoms was based on their ability to combine in different ways to produce different phenotypic effects (just as atoms combine in different ways to produce different molecules), and on the fact that genes, like atoms, arise out of each association unchanged in their fundamental properties. Consequently, it may be more appropriate to refer to this mode of thinking in early twentieth-century genetics as *genetic atomism* in order to distinguish it from biological atomism. In biological atomism the atoms are the units of *life*, whereas in genetic atomism the atoms are the units of *heredity*.

Interestingly, Richard Dawkins's famous concept of the 'selfish gene' (Dawkins, 2006 [1976]) appears to stand somewhere in between genetic atomism and biological atomism. It is a form of genetic atomism in the sense that Dawkins's atoms are physicochemical replicators, which act both as the units of heredity and the units of selection. However, Dawkins's conception of organisms as passive receptacles for genes, built and blindly programmed by them in order to secure their own preservation, presupposes an attribution of agency to genes that is usually associated with living beings. In this respect, Dawkins's concept of the selfish gene bears the hallmarks of a theory of biological atomism, and can therefore be regarded as a contemporary challenge to the atomism of cell theory from below. In fact, Dawkins is quite explicit concerning his atomistic reduction of cells to genes: 'Some people use the metaphor of a colony, describing a body as a colony of cells. I prefer to think of the body as a colony of *genes*, and of the cell as a convenient working unit for the chemical industries of genes' (ibid., p. 46). As a theory of biological atomism, however, many biologists today find the idea of selfish genes rather objectionable given that the view that genes are the primary causal agents of all the phenomena of organismic life is not well supported by the findings of contemporary biology (see Keller, 2000; Morange, 2001; Moss, 2003).

Leaving genes aside, there are a number of other subcellular theories of biological atomism that deserve attention. Returning to the wide array of atomistic theories formulated at the end of the nineteenth century, it should be noted that not all of the proposed biological atoms were inferred; some actually referred to subcellular structures that could be observed through the microscope. One of the most notable theories of this kind was formulated by Richard Altmann in 1890. Altmann suggested that the small granular bodies visible in the cytoplasm of cells, which he called 'bioblasts', are actually elementary organisms capable of nutrition, growth, and division. He argued that all major structural features of the cell—nucleus, cytoskeleton, secretion vesicles—are either aggregations of bioblasts or products of bioblasts. Altmann was convinced that he had found in the bioblast the true atom of life, declaring that it 'forms the long-sought morphological unit from which all biological considerations originally proceed' (Altmann, quoted in Hall, 1969, p. 340). Conceiving cells themselves as colonies of bioblasts, Altmann even reduced Virchow's dictum '*omnis cellula e cellula*' to its bioblastic equivalent '*omne granulum e granulo*'.

From a modern perspective, Altmann's theory is not as far-fetched as it may seem. The granular bodies that Altmann identified as bioblasts were renamed 'mitochondria' by Carl Benda in 1898 (Sapp, 2003, p. 90), and today it is generally accepted that mitochondria were originally free-living unicellular organisms that at some point in their evolutionary history were engulfed within another unicellular organism (see O'Malley, 2010). This means that Altmann's conception of bioblasts as subcellular 'elementary organisms' is quite compatible with our current understanding. In turn, the contemporary feasibility of Altmann's basic conception presents a further challenge to cell theory's view of the cell as the minimal structural unit capable of displaying the attributes proper to life, even if it is true that a mitochondrion needs to be contained within a cellular host in order to exhibit the characteristics of a living system.

A further difficulty faced by cell theory that I have not yet considered is the fact that many organisms are not cellular but are actually *supracellular* in constitution. There are numerous examples throughout the eukaryotic domain of giant multinucleated cells known as *coenocytes* (formed by the uncoupling of mitosis from cytokinesis) and *syncytia* (formed by cells fusing together). In order to account for these phenomena, cell biologists are faced with the following dilemma: they can either shift their attention to the whole supracellular body and turn to the organismal theory, or they can assume, alongside the theorists I have considered in this section, that the cell is itself a composite entity and argue that the real minimal unit of life resides in some smaller structure within it.

The first biologist to be prompted to reject cell theory and postulate a subcellular biological atom in light of the evidence for the coenocytic and syncytial constitution of organisms was the German botanist Julius von Sachs. In 1892, upon examination of coenocytic algae, Sachs concluded that a nucleus always organizes the area of cytoplasmic space that surrounds it, regardless of whether or not it is enclosed by a cell membrane. Sachs called this subcellular system the 'energide', and postulated that it constitutes the minimal autonomous unit bearing the basic characteristics of life. He suggested that single-nucleated cells are 'monoenergidic', whereas multinucleated coenocytes are 'polyenergidic'. For Sachs, the cell is of secondary significance, as it is essentially a chamber which may contain one or more energides:

> [The] Energide is represented by a nucleus associated with its protoplasm in such a way that the nucleus and surrounding protoplasm form an organic unit, both from the morphological and physiological perspectives ... The term Energide does not encompass the cell skin; the case is more that each individual Energide is able to enclose itself by a cell skin, or that several Energides together can enclose themselves within one single cell skin. (Sachs, quoted in Baluška et al., 2006, p. 5)

After Sachs, the energide theory was all but forgotten for a hundred years. However, in 2004 the cell biologists Frantisek Baluška, Dieter Volkmann, and Peter Barlow published a paper entitled 'Eukaryotic cells and their *cell bodies*: Cell theory revised', which has effectively revived Sachs's energide theory. These authors have proposed the concept of the 'cell body' as 'the smallest unit of life that is capable of self-organization, self-reproduction, and of responsiveness to diverse external stimuli' (Baluška et al., 2004a, p. 12). The cell body is characterized as an autonomous subcellular structure consisting of a nucleus and a set of perinuclear radiating microtubules. It is complemented by the 'cell periphery apparatus', which comprises the plasma membrane and the actin cytoskeleton, and which encases the cell body and protects it from the external environment.

Baluška et al.'s contention is that the endosymbiotic theory of the evolutionary origin of mitochondria and chloroplasts in eukaryotic cells needs to be extended to the nucleus as well. They thus suggest that the cell body represents the vestige of a tubulin-based 'guest' proto-cell, which after penetrating an actin-based 'host' proto-cell became specialized for transcribing, storing and partitioning DNA molecules via the organization of microtubules. Similarly, they regard the cell periphery apparatus as the vestige of an actin-based 'host' proto-cell which became specialized for cell body protection, motility, and actin-mediated intercellular signalling. Given these assumptions, the 'cell body versus cell periphery apparatus' distinction can explain the striking duality of eukaryotic cells at the level of genomic organization (eubacterial versus archaebacterial features), cytoskeleton (actin versus tubulin), membrane flow (exocytosis versus endocytosis), and division (mitosis versus cytokinesis). Moreover, the cell body theory can explain the fact that the nucleus–microtubule complex often divides independently of the cell in which it resides, resulting in the coenocytes found in eukaryotes. Likewise, syncytia can also be accounted for by assuming that nuclei are vestiges of originally free-living cells.

Overall, the similarities between cell body theory and Sachs's energide theory are obvious. The authors explicitly recognize this in a more recent paper (Baluška et al., 2006), in which they go as far as to drop their notion of cell body altogether in favour of Sachs's concept of energide, recognizing that 'the term Energide better invokes the unique properties of this universal unit of supracellular living matter endowed with the vital energy' (ibid., p. 1). Baluška et al. confidently predict that their 'neo-energide theory' will ultimately displace cell theory and that the energide 'will take over from the cell as the fundamental unit of eukaryotic structure', and as the 'propagule of life itself' (Baluška et al., 2004b, p. 371).

How plausible are these estimations? In considering this question it is important to bear in mind that the neo-energide theory largely rests on the assumption that eukaryotic cells originated from the endosymbiotic coupling of a 'guest' and a 'host' cell. The problem is that there is at present no consensus regarding the origin of the eukaryotic nucleus. Some cell biologists do support the endosymbiotic hypothesis that the neo-energide theory requires, but others argue that the nucleus was generated autogenously by a single prokaryote through the invagination of its plasma membrane, while a third group maintain that viruses were the main catalyzers of the initial formation of the eukaryotic nucleus (see Pennisi, 2004; Zimmer, 2009; O'Malley, 2010). Consequently, the extent to which the neo-energide theory can legitimately be claimed to threaten the tenability of cell theory hinges on its ability to validate a particular hypothesis regarding the evolutionary origin of the eukaryotic nucleus that is yet to be accepted by the cell biology community as a whole.

6. Conclusions

In this paper I have proposed the perspective of biological atomism to make sense of the nature of cell theory, trace its philosophical antecedents and historical developments, and understand the rationale underlying the major criticisms of it. I have shown that the idea of biological atomism can be applied in the context of many different biological theories. What implications does this have for our understanding of the 'biological atom'? What exactly does this notion refer to? Is it a *real thing*, a *theoretical abstraction*, or a *heuristic device*? These questions are of no little importance, as their answer may help clarify the conditions that need to be met in order to resolve ongoing disputes between rival atomistic theories. Indeed, if biological atoms are real things, then we can expect that the accumulation of empirical evidence will eventually settle the exact level of organization at which the biological atoms are actually located. This seems to be the case in the current dispute between cell theory and the neo-energide theory. However, if biological atoms are theoretical abstractions, then it is unlikely that proponents of a theory can be persuaded to abandon it in favour of another solely on the weight of empirical evidence. In this case, we need to view atomistic theories of life more as rationalizations of the beliefs of their authors regarding the question of whether or not an organism, or a cell, *should* consist of more elementary vital units. Buffon's theory of organic molecules, Dobell's organismal rejection of cell theory in protistology, and some of the theories of subcellular atoms of the late nineteenth century appear to fit this characterization. Finally, if biological atoms are heuristic devices, then it is no longer necessary to regard rival theories as mutually exclusive, but simply as having different epistemic emphases. If this is the case, complementary theories can be integrated to produce more inclusive viewpoints. Tsukaya's proposal of a synthetic neo-cell theory in response to the conflict between cell theory and organismal theory in plant morphology seems to be a good example of this strategy. On the whole, it appears that each of these answers is correct under different provisions, in which case we may conclude that the actual nature of biological atoms can only be determined in relation to the explanatory contexts in which they are formulated.

Does the context-dependent nature of biological atoms entail that the meaning of biological atomism is itself dependent on the context in which it is applied? I do not believe it does. The commitment to biological atomism always implies a very specific expectation guiding biological research, namely the view that a particular element within the organism can be singled out as an independent, functional, reproducible, 'serial' unit. Of course, these units need not be homogeneous. We saw that in the case of Bichat's tissue theory the heterogeneous nature of his biological atoms was a fundamental aspect of his conception of them. Similarly, the appeal to atomistic thinking in modern cell biology does not imply an epistemic commitment to flattening the differences between types of cells. What it *does* imply is an understanding of the organism as a community of individuals making up a higher-level individual in which the cells display both the autonomous properties of wholes and the dependent properties of parts. In this way, the perspective of biological atomism provides a way out of the longstanding dichotomy between the conception of organisms as sums of their parts and the conception of organisms as fully integrated wholes. Biological atoms assert both their individuality as semi-autonomous sub-wholes, and their function as parts which collectively associate to produce the greater organismal whole.

The philosophical value of biological atomism can be fleshed out even further by contrasting it with other ways of analytically decomposing living organisms for the purposes of explanation. The mechanistic approach to the study of organisms has been one of the most influential research programmes in biology since it was first proposed by René Descartes in the seventeenth century. Guided by an ontological conception of organisms as complex machines which can in principle be disassembled and thereby explained, the mechanistic biologist proceeds by reducing living organisms to their molecular components and their interactions. Although biological atomism shares with mechanistic biology the commitment to explaining organisms by analytically decomposing them into their component parts, the final units of its analysis (i.e., the biological atoms) are always living beings in their own right. Thus, when the two are taken together as complementary perspectives they capitalize on each other's epistemic limitations and thereby provide a more inclusive understanding of the morphological constitution and physiological operation of living organisms.

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