Progress in Biophysics and Molecular Biology xxx (2017) 1–15

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Cellular intelligence: Microphenomenology and the realities of being

Brian J. Ford

Gonville & Caius College, Trinity Street, Cambridge University, CB2 1TA, United Kingdom

ARTICLE INFO

Article history:
Received 11 July 2017
Accepted 24 August 2017
Available online xxx

Keywords:
Microphenomenology
Cellular intelligence
Computation
Decision-making
Evolution
Regeneration

ABSTRACT

Traditions of Eastern thought conceptualised life in a holistic sense, emphasising the processes of maintaining health and conquering sickness as manifestations of an essentially spiritual principle that was of overriding importance in the conduct of living. Western science, which drove the overriding and partial eclipse of Eastern traditions, became founded on a reductionist quest for ultimate realities which, in the modern scientific world, has embraced the notion that every living process can be successfully modelled by a digital computer system. It is argued here that the essential processes of cognition, response and decision-making inherent in living cells transcend conventional modelling, and microscopic studies of organisms like the shell-building amoebae and the rhodophyte alga *Antithamnion* reveal a level of cellular intelligence that is unrecognized by science and is not amenable to computer analysis.

Contents

1. Introduction

Post-Cartesian reductionism became an alluring aspiration for Western science, and for cell biology it has matured into an inescapable imperative. Investigators are driven inexorably towards ever smaller entities and tinier processes until the context in which phenomena occur, their purpose, and the motivational constraints by which they are governed, are transcended by the sense of achieving the most minute insights into the grandest of realities. It is as though we are peering closely at particles of pigment, analysing their constituents, resolving their chemical constitution and the precise alignment of their molecules, without noticing that these specimens are actually printer's ink from a book of Shakespearean sonnets. We are fixated by analysing the minutiae of the manuscript, rather than relishing the prose. As Noble (2016) has so ingeniously pointed out in his recent book, which is rich in resonances of his previous pioneering publication (Noble, 2006) the beauty of the cell is its way of interpreting its genetic and epigenetic information to produce the coordinated intricacy of physiology, much as an orchestra creates a symphony from the crisp terseness of a musical score. After centuries of reductionism, Noble is championing the cause of systems biology, where the discrete mechanisms of cell chemistry are united into processes that define

E-mail address: brianjford@cardiff.ac.uk.

http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012
0079-6107/

how an organism functions. The term remains vaguely defined, and tends to draw our attention away from the hidden complexity inherent in living organisms (Nurse and Hayles, 2011).

Now is the time when we need to thrust forward to a further discipline – whole cell biology – for this is where the true significance of our findings finds its most enduring relevance. Studying how cells behave and interact as discrete individuals is highly revealing, and this approach leads us to the inexorable conclusion that the living cell exhibits ingenuity, and perhaps even intelligence (Ford, 2009). Although there is a thrust towards the computer-simulation of biological phenomena, the intricacies of life may not be amenable to digital modelling. Living cells, and the organisms that they comprise, are more complex than current science recognizes. I am reminded by Professor Michael Levin of Tufts University of a quest for the basis of biology summarized by Szent-Györgyi, who was awarded the 1937 Nobel Prize in Physiology or Medicine for his discovery of the action of ascorbic acid:

> "In my hunt for the secret of life, I started research in histology. Unsatisfied by the information that cellular morphology could give me about life, I turned to physiology. Finding physiology too complex I took up pharmacology. Still finding the situation too complicated I turned to bacteriology. But bacteria were even too complex, so I descended to the molecular level, studying chemistry and physical chemistry. After twenty years' work, I was led to conclude that to understand life we have to descend to the electronic level, and to the world of wave mechanics. But electrons are just electrons, and have no life at all. Evidently, on the way I lost life; it had run out between my fingers." (Wallace, 1990)

Physics, construed by many as the "queen of sciences", can account for gross phenomena that relate chemistry to measurable physical parameters such as temperature or concentration (Hauptman and Bang, 2016) but is unable to reconcile the meticulously choreographed complexity of what we observe in living cells to the constraints of mathematical orthodoxies. Conventional physics will not explain the phenomenology of the living cell, though one powerful path to understanding biological complexity is to focus on the individuality and autonomous intelligence of single cells.

2. Eastern traditions of thought

Ancient philosophers from the Asian nations did not pursue the mechanistic views of science and medicine that evolved in the West. Indeed, the German philosopher Martin Heidegger insisted that philosophy is a semantic construct and can only be pursued through Western languages such as German and Greek. The notion of philosophy, he concluded, was anathema to Asian traditions (Sheehan, 1981). In truth, even if we imbue our notion of philosophy with rigid constraints, there are abundant early writings from Asia that show true philosophical interpretations of humanity, our place in the world and universe, and the nature of life itself. The Indian traditions of Ayurveda date back more than 2000 years and embraced many advanced procedures. For example, an ancient Indian physician, Maharishi Sushruta, described a surgical procedure for the treatment of cataract in his medical treatise *Sushruta Samhita, Uttar Tantra*, dating from 800 B.C. It involved displacing the opaque lens inwards by using the thorn of an *Acacia* tree (Magner, 2002), a method explained to me by a traditional Indian practitioner in New Delhi in 1978.

Medical conditions including tonsillitis, rhinoplasty and lithotomy were addressed through surgery for centuries before the British arrived, and Western surgeons adopted many of the techniques observed in India. Yet during the Victorian era of occupation, Ayurvedic medicine was ignored by British colonialists, even though Western medicine had learnt much from it. Early Hindu schools of thought, in existence for 2000 years, included Samkhya (Larson, 2011) which was one of the six āstika schools of Hindu instruction. It emphasised an enumerationist approach founded on the need for criteria by which to assess, or prove, objective reality. This was a clear move towards rational argument and decision-making, much in line with later Western thought. The essential dualism of this school of philosophy comes close to present-day notions of mind and matter. Kanada (कणाद), an Indian sage who lived several centuries B.C. and founded the Vaisheshika school of thought, developed atomistic naturalism, and was thus a pioneer of an atomic concept of nature. He followed a now familiar line of discussion, arguing that all matter can be subdivided, though subdivision cannot proceed indefinitely, and thus there must be ultimately minute entities (*paramanu*) that cannot be divided and are eternal. Democritus (and his mentor Leucippus) similarly envisaged ultimate particles of matter about 400 BCE as atoms. The study of disease had similarly ancient origins, dating back to around 300 BCE in the Charaka (Caraka) Samhita चरक which long predates Sushruta Samhita according to Ayurvedic Tradition.

Charaka's section on infectious diseases is divided into two sections, the first of which lists what we might now recognise as exclusively bacterial diseases, and the second treats of exclusively viral diseases. It names two kinds of infectious agents, to which it gives different names. The basis for the distinction was both clinical and epidemiological, and has clear resonances with present-day interpretations of infectious pathologies. The notion of minuscule entities in living systems arose in Western thought six centuries ago, and were written about by Veronese poet Girolamo Fracastoro (1483–1553) as infectious *seminaria*. Fracastoro (1546) coined the term syphilis, wrote of "foments" that would cause disease, and intuitively conceived seminaria as germs (Wright, 1930).

Thus, before the dawning of the modern era of Western science, there were intimations of invisible living entities from both Eastern and Western traditions. It was only the development of optical instruments in Europe during the sixteenth century that would allow us to perceive minute realities, and this would lead us towards the microscopic investigation of life – and to the realization that great universes of incalculable ingenious microorganisms surround us and inhabit us (see Fig. 1).

3. Microscopical revelation and the spread of reductionism

This global history of philosophy became focussed through the lenses of Robert Hooke, when in April 1663 he first coined the term "cell" (Hooke, 1665). This seminal work has just been reprinted in folio form by Folio Editions, who unfortunately publish the wrong date (1565) for the original work published in 1665. Hooke had observed the dead cell walls of cork, which he compared to the walls of a of a monk's cell, though the date accepted for this universally accepted "discovery" of cells is not actually the first observation. Hooke's depiction of cork cells – in fact, the dead cell walls of cortex – was made at the Royal Society meeting of April 13, 1663; whereas I have shown (Ford, 1998) that a week earlier Hooke had demonstrated the wall screw moss *Funaria hygrometrica*, in which his portrayal of the leaflets clearly showed cells – and these were living cells, not the dried cell-walls of the cork sections. Hooke's studies of moss are a crucial observation and have been elsewhere ignored by historians of science. It fell to the Dutch amateur enthusiast, Antony van Leeuwenhoek, to discern the world of microscopical organisms for the first time. His abiding fascination remained the beauty and meaning of the microbial realm, and his sheer delight in observing microscopical life endured throughout his life (Ford, 1982).

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

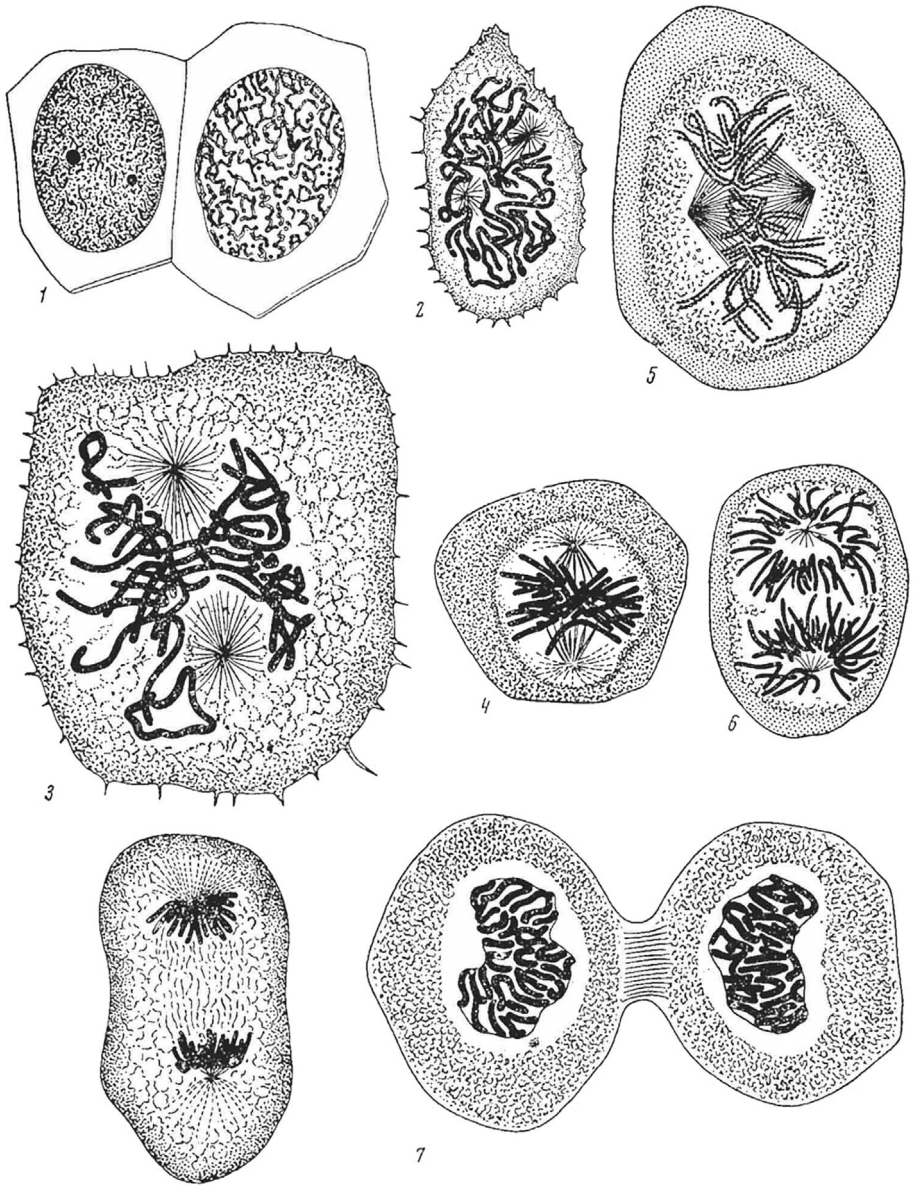

Fig. 1. German microscopist Walther Flemming studied mitosis in salamander cells and published these illuminating figures of cell division in 1882 in *Zellsubstanz, Kern und Zelltheilung*, Leipzig: Verlag von F. C. W. Vogel. Flemming was one of the first to use aniline dyes to stain chromosomes, and his studies vividly portray the sense of vital complexity within the living cell that modern CGI images omit.

Leeuwenhoek's descriptions of protozoa, from his letter of September 1674, told of his excitement at his revelations of whole living cells: "The motion of most of these animalcules in the water was so swift, and so various upwards, downwards and round about that it was wonderful to see." His descriptions are so precise that we can easily reconcile his descriptions with the species that he observed. Thus *Giardia*, which he describes as scurrying along "like a woodlouse," is instantly recognisable to present-day protozoologists (Ford, 2007). Leeuwenhoek had something of the atomist about him, for he often alluded to life as being composed of globular substructures. The suggestion that there were substructures that define larger living entities is discernible as long ago as 1687 when Leeuwenhoek studied erythrocytes and yeast. He wrote of observing minute globules within erythrocytes, and in 1680 he also wrote: "I have made several observations concerning yeast and seen throughout that the aforesaid consisted of globules … in addition I saw clearly that every globule of yeast in turn consisted of six distinct globules." He was not only concerned with observing microscopical life, but wished to seek what lay within it (Leeuwenhoek, 1678).

Similar delight in microscopic life was recorded by other workers, including Abraham Trembley, who carried out extensive experiments with the freshwater polyp *Hydra*, observing its positive phototropism and including eversion, grafting, dissection and dividing in two. These observers were driven to observe, rather than to probe obsessively for hidden microscopical principles (Trembley, 1774). It was the published views of René Descartes that proposed the mechanistic interpretation of life with which present-day science remains preoccupied. At the time of those publications, Robert Hooke in England was using his low-power microscope to unveil structures that lay beyond human sight. Hooke's quest (Ford, 2015) was for revelation of detail in familiar specimens (lice and fleas, pollen and seeds). Robert Hooke's aim was to enthral the reader with the majestic hidden visions that a microscope could

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

reveal which celebrated the mysteries of life; Descartes was advocating the opposite by demystifying existence and encapsulating its propensities in the emergent principles of physics. Wrote Descartes (1664):

> "The [human] body is nothing else but a statue or earthen machine, that God has willed to form entire … we see clocks, artificial fountains, mills, and other similar machines, which, being only made by men, nevertheless do not lack the force to move themselves in several diverse means … the bones, nerves, muscles, veins, arteries, stomach, liver, spleen, heart and brain, nor all the other diverse parts of which this statue must be comprised [are] entirely similar to the parts of our body which bear the same name, and that could be shown to us by some learned anatomist, at least those large enough to be seen, if you do not already know them sufficiently from yourselves … which on account of their minuteness are invisible." He added: "These functions (including passion, memory, and imagination) follow from the mere arrangement of the machine's organs every bit as naturally as the movements of a clock or other automaton follow from the arrangement of its counter-weights and wheels."

Biologists became transfixed by this notional need to delve ever deeper within, seeking for some unattainable ultimate reality, while ignoring the incalculable benefits that would derive from observing life in the round. As we languish under this burden of unwarranted reductionism, the more recent retreat towards systems biology – which Noble enthusiastically espouses – is a timely trend. Once we embrace studies of the functioning of the whole cell we will at last find an application for these various approaches in a conceptual whole. I believe that our recognition of the ingenuity of the living cell, and its capacity even for intelligence, await our investigation as the next phase of research.

4. A reductionist legacy

A conspicuous consequence of the Cartesian movement was the concept advanced by Gottfried Leibniz, whose theory of monads became a key contribution to metaphysical philosophy. This was biological atomism; the monads of Leibnitz were elementary particles with indistinct perceptions of one another, which derived from the corpuscles of the mechanical philosophy of Descartes and others. Monads, Leibnitz posited, were the atoms of the living universe that were seen as eternal, non-decomposable and individually distinct, subject to their own laws that were founded on their non-interactive propensities (Leibniz, 1714). Monads, he claimed, were centres of energy. Substance was comprised of force, while space, matter, and motion were mere phenomena (Köhler, 1720).

From this quest for the ultimately small arose much of the impetus for investigation as microscopes increased in resolution during the Victorian era. From the structure of cells arose a preoccupation with the origin of their complexity, and in 1898 Benda, working in Berlin, recognised mitochondria as organelles within a cell, though was unaware of their origins.

In 1905 (with a more robust account appearing in 1910), Konstantin Mereschkowsky, a Russian cell biologist, ingeniously deduced that many of these cytoplasmic structures within the eukaryote cell – including chloroplasts, as well as the mitochondria –had evolved through the expedient acquisition of smaller organisms by those that were larger. Thus, mitochondria had once been free-living bacteria; chloroplasts began as minute chlorophyte algae (Martin and Kowallik, 1999). This insightful revelation was later expanded upon by my late friend Lynne Margulis, and the resonances of these investigations are with us today. The structure of chloroplasts is indeed that of green algae, and the DNA in mitochondria is now routinely used in medical and genetic diagnosis. This was, originally, bacterial DNA. Although mitochondria are written about in our mechanistic language as energy-generating "factories" they retain a certain autonomy. They travel about inside the cell, change position and proportionality, and seem to seek out areas within the cell that they wish to inhabit. Mitochondria remain as active, dynamic living entities, and are not mere functional subunits that function like transistors or microscopic nanorobots (Margulis and Fester, 1991).

While the Victorian biologists set about studying the wonders of cytostructure and the intricacies of cell division, many microscopists were being consumed by a need to perceive ever smaller structures. The race for resolution was launched. It meant that diatom frustules – inert, non-living silica networks with strict periodicity – were studied while the living microorganisms that produce them were largely ignored. Discerning the fine structure of diatoms including *Amphipleura pellucida, Surirella gemma* and *Nitzschia sigma*[1] became the aim, with microscopists vying with each other to resolve the finest structures. Diatoms were envisaged as geometrical constructs, and they were often arranged in exquisitely complex patterns on a slide. I have spoken to microscopists and explained that, in life, diatoms move along proportionately at the same speed as a human swimmer, only to be greeted with incredulity – the only diatoms they had ever seen were the dead, dried frustules rather than the exquisite living cell. Today, the arranging of diatom frustules to make aesthetically-pleasing microscope slides is still practiced, though it is a dying art.

The quest for ever-increasing magnification continued throughout the twentieth century after the electron microscope emerged in 1931 and again when Abbe's diffraction limit was breached in 1989 (permitting single-molecule resolution with a light microscope). Both were invaluable developments that won their developers Nobel prizes. However, the fashionable enthusiasm for each development diverted attention from research at lower magnification on the behavioural attributes of entire cells. Similarly, x-ray diffraction allowed the structure of DNA to be determined and its helical structure soon became an icon of biological research in an era when living cells remained unfamiliar. In a leading article for *Nature* (Ford, 1975) I pointed out that "our orthodoxy has done a disservice to micro-organisms" and, more than forty years later, that remains the case. Accounts of the structure of living cells have occasionally been highly literate and engaging, and an authoritative summary of the contemporaneous concept of the cell was published by my distinguished late colleague Christian de Duve (1984). It retells much of the early investigations into the microstructure of cells, with revealing illustrations throughout, yet reminds us of the rudimentary extent of our understanding of how living cells behave.

5. Cell resurgence

A major development in the study of entire cells was the recognition of the role of stem cells pioneered by my respected friend Sir Martin Evans at Cambridge who reasoned that cell lines must extend from undifferentiated cells within the somatic matrix, and substantiated the argument by demonstrating 'non-tumourigenetic' cell lines produced *in vitro* from mouse teratomas (Evans, 1972). Even so, the whole cell itself remained largely neglected in

[1] Klaus Kemp at www.diatoms.co.uk is the most prominent in the field of arranged diatoms, who routinely produces resolution slides with *Amphipleura pellucida, Frustulia rhomboides, Pleurosigma angulatum, Surirella gemma, Nitzshia sigma, Stauroneis phoenicenteron, Navicula lyra* and *Gyrosigma balticum*, 2017.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

other areas of biology, and even stem cells as a rule were studied *en masse* while their individual proclivities were ignored. Following the impetus generated by this new line of enquiry, large numbers of regulatory mechanisms that govern the behaviour of cells were identified. One of the first regulatory proteins was described just three years later (Goldstein et al., 1975). Its role was found to be the targeting of proteins for disassembly and degradation, ready for subsequent recycling by the proteasome, and was identified in such a wide range of living cells that it was given the appropriate name *ubiquitin*. We now know of a rapidly-expanding range of factors that are concerned with transcriptional, post-transcriptional and epigenetic regulation. This is more than mere reductionist analysis, for it may reveal fundamental triggers for addictive behaviour (Robison and Nestler, 2011).

Cell renewal and differentiation have been shown to be highly influenced by microRNA which acts as a regulator by the inhibition of the translation of selected mRNAs, notably in stem cells. This has already been demonstrated in stem cell lines from embryonic and germline cultures and in somatic stem cells and this offers us new approaches to the study of gene regulation in stem cells (Kuppusamy et al., 2013). Many of these discoveries have subsequently proved to have wide-ranging implications. Chemokines and cytokines have been shown to be crucial in regulating cell proliferation and myogenesis, and cytokines are now known to mediate appetite, the development (and atrophy) of striated muscle, glucose and lipid metabolism, and sensitivity to insulin sensitivity (Peake et al., 2015). Scant attention was paid to the subtle ways in which single cells communicate, until my postulations forty years ago attracted interest whereupon researchers began to initiate research that might further elucidate these mechanisms (Ford, 1976). Increased attention is currently being paid to bioelectrical signalling between living cells, and the transcription factors now known to be important for cell differentiation and intercellular signalling are being causally related to embryological development (Basson, 2012).

This field of research is rapidly expanding; for example, receptor tyrosine kinases (RTKs) have been shown to initiate the phosphorylation of tyrosine residues, and 20 families comprising 58 distinct RTKs were soon recognised (Lemmon and Schlessinger, 2010). Principles are emerging that reveal how disparate phenomena apply across the realm of living things. The occurrence of genes in the nuclei of plants that code for myosin shows that the systems that are currently being investigated in animals also occur throughout plant cells and our understanding of the choreographed biochemical pathways that create the phenomenon of living is revealing mechanisms that are common to all phyla (Citovskya and Liub, 2017). Now we are encountering reports of interaction between non-living and natural living cells. Simple artificial cells have been assembled that contain genetic complexes which code for quorum responsive transcriptional activators (or repressors) together with the necessary accessory factors. A transcriptional regulator binding site has been inserted upstream of a gene coding a fluorescent protein, so that the *in vitro* transcription/translation reactions could be observed in these synthesised cells by fluorescence microscopy. A report in ResearchGate publishes a conclusion by Mansy: “It is absolutely possible to make artificial cells that can chemically communicate with bacteria. Artificial cells can sense the molecules that are naturally secreted from bacteria and in response synthesize and release chemical signals back.” Mansy (see Lentini et al., 2017) also stated: “Such artificial cells do a reasonably good job of mimicking natural cellular life and can be engineered to mediate communication paths between organisms that do not naturally speak with each other.” This is heady stuff, and is attracting interest. The concept of communication with artificially created life-forms is enticing when thus expressed, but in a more familiar world it is easy to create an anthropic robot that emits a pre-ordained signal, and initiates a response from a human. Traffic lights perform this in our daily lives without eliciting excitement. Siri on your Apple computer (or Cortana for Microsoft Windows) will enthusiastically chat to you, though we would not ascribe to them the functionality of living. Alexa will play music if a command is received, much as a bell will ring if its button is pressed. Voice recognition is a neat trick, but is neither a magical transformation nor an intimation of the hidden secrets of life. The concept of mimicry of intelligent behaviour is a central problem in Artificial Intelligence and Philosophy of Mind. Some in AI will claim that machine-based functional intelligence already exists. One example is the Alphabet Incorporated DeepMind team who constructed AlphaGo, which in 2015 was the first computer to beat a human champion at the board-game Go; and Watson, built by IBM's Deep QA project which won the Jeopardy TV competition in 2011, together self-driving cars, etc.. The public are left with an impression that game-playing computers and anthropomorphic robots are now close to replicating living intelligence. To equate such data-rich digital operations with the infinite subtlety of life is absurd. Organisms – including subsets such as brain functions, the phenomenon of mind, together with the complex responses of single-celled life-forms – can set their loci of control at criticality. Those functions operate on informational input that is essentially Gestalt and not digital. They can construct conceptual structures out of non-digital interactions rather than the obligatory digitized processes to which binary information computing is confined.

6. Whole cell biology

Hyperbole perpetuates the mystique of mechanistic cell biology in the quest for funding, and this reductionist imperative is diverting attention away from more immediate challenges. Knowing how the intricate mechanisms within the cell perform tells us nothing of the entire cell, just as studying the hormone fluctuations and changes of blood pressure in a human subject would reveal little of why they were late for work in the first place. Central to these unacknowledged areas of interest is how cells decide what to do, and what decisions they must individually take to optimize their milieu. It is clearly crucial to understand the nature of signalling systems that living cells can utilize, though more fundamentally important to understand what it is they are communicating, why they are doing so, and what they intend to achieve. It is as though we have clamoured for the most intimate insights into the minutest workings of the telephone exchange, while disregarding the subscribers – who they are, why they choose to speak, or what they are saying.

Denis Noble (2010) has emphasised the importance of stochastic processes in living cells in elegant prose and argues convincingly against the simplistic notion of a “selfish gene” as the ultimate resource of inheritable information (Dawkins, 1976). Noble has explained how research workers have demonstrated the ability of a cell facultatively to adapt its genome to prevailing circumstances. Research into epigenetics by Jack et al. (2015) now reveals the way in which a cell regulates its ribosomes in response to adverse external stimuli. Noble presciently asks: how does the cell communicate to the genome when it is under stress? Crucial that may be, but I wish to pose deeper questions: how does the cell perceive that it is being stressed? What organelles recognise stress and interpret it constructively? What – to a living cell – *is* stress? Research is eliciting initiators of response, although know little of the organelles that embody systems of data-acquisition.

It is apparent that the cell's ability to police its own destiny is not exclusively mediated by its genetic constitution. Experiential changes encountered during the lifetime of a cell may impose

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

aberrations at many scales, ranging from individualised intracellular processes to radical alterations in the environmental *milieu* of an organism and the combined input of so many variables cannot represent events that have been encountered during the evolutionary development of an organism. Stress is a systems property of the whole organism and it is invisible at the molecular level. The genetic status of the cell, at this level, is immaterial (Soen et al., 2015). Similarly, we are now recognizing the regulation of embryogenesis by physiological inputs and this is providing exciting insights into the control of developmental patterning (Sullivan et al., 2016). There are also electro-physiological processes that orchestrate individual cells in favour of the requirements of a whole organism which have been shown to be regulated by spatio-temporal patterns of resting potentials among non-excitable cells. They provide cues in embryogenesis regeneration, and when challenged may result in cancer and the processes of aging (Levin, 2014). These matters address signalling to cells, though the behaviour of the individual cells, and how they respond, remains beyond emulation. There is here a mechanism here that might account for the demonstrated successes of acupuncture, and may offer a rational explanation for the Qi form of "life force".

Although we now recognise that experiential input can bring about epigenetic modification of the cell nucleus, there must be undivined mechanisms that relate the experiences of the entire multicellular organism back to the cell. Evolution must surely be directed; species pass through intermediate stages of specialisation in which they may be, in the Darwinian sense, unfit (partially-formed wings before a creature is capable of flight; lungs prior to their functioning for gas-exchange) and we could postulate a mechanism for evolutionary momentum through these alternative pathways.

7. An illusion of simplicity

The simplicity of single cells has been widely emphasised, though it is merely a convenient illusion. Biological systems are non-linear systems that are not amenable to digital modelling. As Hankey (2015) has reminded us, many are founded on unfathomable complexity. Neither systems science nor conventional concepts of complexity theory can usefully address what we observe in the laboratory. Digital modelling may demonstrate how the heart rate is controlled, but cannot replicate how we fall in love, or why some individuals evince hatred. Single cells truly can consider their options, and modify their responses in the light of contingency. Under the microscope, we can observe a predatory single-celled ciliated microorganism as it inspect its prey from a distance. The ciliate can then select a specific microbial cell, pause, and then swoop upon its prey and capture it within a second. The coordination of this activity is similar to watching a cat catch a sparrow on the lawn, yet it is done within the confines of a single cell. Living cells are smart: the ciliate *Spirostomum* has been shown to possess memory (Beck, 1975). It can be trained. The Chlorophyte alga *Spirogyra* detects an adjacent filament of cells (we do not know how) and produces a connecting canal (utilizing complex procedures we cannot understand) prior to conjugation. Coccolithophores extrude protective scales from an apical pore, and – if they are inappropriately orientated – the cell will invert them to ensure that they fit correctly. For none of the mechanisms of these phenomena have we elicited rational explanations.

The essential autonomy of human cells can be observed in processes of wound healing. These phenomena are invisible to the central nervous system and are an irrelevance to regulation imposed by circulating hormones. The reinstatement of traumatised tissues that the cells accomplish is predicated upon their acting in constructive response to the circumstances in which they find themselves. Similarly, a single polymorphonuclear granulocyte in the circulating bloodstream will seek out and destroy an invading pathogen without external mediation. Our simplistic recognition of quorum sensing does not apply here, for the cells ordinarily act as individuals. This requires them to seek out and identify a pathogen; to recognise the need to inactivate it; to become motivated to move towards the pathogen and, if necessary, alter conventional behaviour to pursue it; and then to maintain pursuit relentlessly until the organism is consumed and eliminated. This is self-regulated, volitional behaviour by a single cell. A polymorph pursuing and ingesting cocci in a human blood preparation was first captured as a 16-mm micrographic movie made around 1958 by David Rogers at Vanderbilt University and it has become a classic. The sequence clearly shows the unwavering and single-minded purpose of the polymorph in pursuit of its prey as the bacteria are wafted along by microscopical currents. It is known that the interaction of antibodies with complement in the blood serum produces putative chemoattractants, such as fragment C5a, and substances such as this or bacterial N-formyl peptides may surface-mark the bacteria for the attention of the polymorph. The movie by Rogers shows the hyaline anterior lamella that is distinct from the granular cytoplasm; in some instances, the moving cell seems to nudge erythrocytes aside. After the target bacteria have been engulfed, the behaviour of the cell reverts to normal. It has been suggested that protruberances visible on the cell surface resemble the blebs that develop on M2 melanoma cells that lack the actin filament crosslinking protein filamin-1 (ABP-280), which may reveal something of the mechanism of membrane protrusion. However, these rudimentary considerations cannot divert attention from the fact that the polymorph single-mindedly pursues its prey and will not cease until its mission has been accomplished. The human polymorph is an amoeba, although a constituent part of our bodies. This is a cell with a mind of its own. Conceptualising the human body as a cooperative community of essentially autonomous entities gives us a more reasonable understanding than our modern models, which see the body as a collection of mechanical organs enclosed in skin.

In lectures at Cambridge, I have spoken of the unadmitted complexity that we see in freshwater amoebae, universally acknowledged as one of the "simplest forms of life." I have explained that (Ford, 2008a,b) an amoeba seems so simple in that it comprises a cell with no prescribed outline, featuring little more than a central oval nucleus (Ford, 2010a,b). Yet *Amoeba proteus* is morphologically distinguishable from other amoebae because of its dimensions, the constraints on its morphology and the patterns of its pseudopodia. Although never the same shape twice, it is always morphologically distinct from disparate species. Even though its shape is infinitely variable, it is recognisably characteristic. *Amoeba* also exhibits head and tail polarity, and its intracellular granules move around if it is constrained and wishes to turn back (Goldacre, 1957). In an extemporised Cambridge presentation in 1992 I had said:

> "Let an amoeba crawl along a groove in a glass plate, a cul-de-sac, and at the far end it will stop. Then, as you can see from the movement of the granules within it, the cell turns around and comes out head first. You have been told how terribly simple it is. Simple? Why, an amoeba can do many of the things that humans can do, in terms of metabolism and activity, sensation and excretion, feeding and motility. All these various attributes that we have, an amoeba has too. But it can also carry out a number of actions which humans cannot do; such as exactly regulating its rate of reproduction to the available food supply, and building a protective capsule around itself, so that

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

when the environment which it needs to sustain life disappears, the amoeba can survive until it returns."

An amoeba is principally comprised of water-soluble constituents yet takes in particulates for food and excretes wastes through vacuole pores without diffusing away into its surroundings. It is immensely complex and many species perform acts of impressive ingenuity that, were we to consider them academically, would challenge our conventional understanding (Ford, 1999). No computer model comes close to emulating the mechanisms manifested by an amoeba, as it seeks its way ahead, selects which food substances are suitable for ingestion, modifies its cell membrane to accommodate the situation and moves on in a direction it has motivationally selected. A team based at Sapporo, Japan, have even shown that amoebae have memory for events (Saigusa et al., 2008). This takes us deeper into the realities of living cells than current conceptions of memory as the propensity only of cell aggregates. Single cells can take decisions; single cells can plan responses; single cells contain memory. A sceptic may attempt to consider this an indigestible over-statement; however, the testate amoebae are a group of the rhizopods that elevate the discussion to a higher level, for these species display ingenuity of a high order of sophistication. They were first described some 130 years ago by Max Verworn, who observed how they produced vase-like shells from silica grains the amoebae collected from their substrate. Verworn cultured the cells in dishes with coloured glass particles, observing how they were collected and cemented together to form a protective testa (Verworn, 1888). These testate amoebae were painstakingly studied by the Victorian anatomist Joseph Leidy. Like many of his time, Leidy was a polymath. He is famed for naming the genus *Hadrosaurus* after discovering a fossilised skeleton of this dinosaur – the first virtually complete dinosaur skeleton yet unearthed – at Haddonfield, New Jersey. As a microscopist, Leidy is best-known for research into *Trichinella spiralis*,[2] the causative nematode of trichinosis, which spreads to the human host chiefly from uncooked pork.

In his fifties, Leidy began to study the testate amoebae observing how they lived in shells constructed from sand grains or diatom frustules. He produced detailed microscopical studies of these peculiar protozoa, but then continued meticulously to observe them over a period of time as whole living cells. Leidy (1879) studied how these amoebae gathered the raw materials from which their testa were constructed and how these particles were allocated during mitosis. Like Verworn, he meticulously recorded how they collected quartz sand-grains and methodically assembled them into symmetrical capsules that served to protect the occupant. During mitosis, Leidy observed how one of the daughter-cells retained the existing shell, while the other retained within its cytoplasm a similar number of quartz fragments from which it soon constructed a shell of its own. The use of high-resolution microscopy and computer analysis has allowed these to be studied in detail. It should be emphasised that the entire organism is itself no larger than a sand-grain; it is utilizing >1000 microscopic particles to construct its shell, many of bacterial dimensions (du Châtelet et al., 2013). For all their diminutive dimensions, the use of quartz and soluble silica by these microorganisms has significant ecological impact and research has revealed that they are key components in the recycling of elemental silicon through the ecosphere (Puppe et al., 2014). Some 2000 taxa of testate amoebae have been intensively studied, and now we can comment on their origin and distribution. They are known from the Mesozoic and the microfossils of putative ancestors have been dated to the Neoproterozoic 500–1000 million years ago (Smith et al., 2008). We now understand how these amoebae, typically ≈500 μm in size, are comprised. They are being identified, their environmental impact quantified, their paleoecology studied, their morphology recorded. Yet consider: little attention is being paid to how they perform. Testate diatoms select specific components to construct their shells; some (like *Difflugia*) choose to restrict themselves to fragments of quartz, whilst others (e.g. *Arcella*) may select diatom frustules. These cells seek and identify the components they need and we have no concept of the way they achieve this. They collect them, though we do not know how. They assemble them in position, through systems we cannot understand; they cement them in place utilizing mechanisms that elude us. The resulting testa are recognisable to species level, though we cannot conceive wherein the cell's template might lie (Ford, 1976). The meticulous construction of these silica shells, in some species complete with a functionless apical projection and in others decorated with symmetrical spines, is testimony to the ingenuity that living cells embody.

Everywhere we can observe this proclivity for ingenuity. When a surgical suture is secured with staples, the resulting repair is conspicuous and crude. Within weeks, the scar is healed, smooth, and scarcely visible. The cells at the site of the incision have identified the nature of the surgical trauma and have initiated manoeuvres to restore it. Capillaries re-form so that the microcirculation is restored, innervation is reinstated, and the many epidermal layers are properly reconstituted. None of this we understand. These complex processes are invisible to the brain, and are not controlled by cerebral activity, neither are they subject to regulatory intervention by circulating hormones. The cells are the decision-makers. We rely on this unadmitted ingenuity by living cells to survive, as do all of nature's varied organisms (Ford, 2006) (see Figs. 2–4).

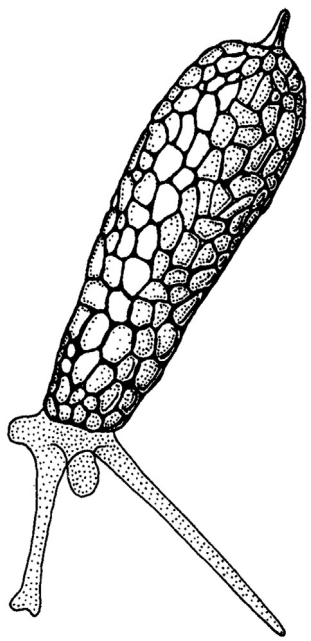

Fig. 2. Drawing of *Difflugia acuminata* to show the proportionality between the occupying cell and the mineral testa that it creates. This illustration was published in 1976 in the author's book *Microbe Power, Tomorrow's Revolution*, London: Macdonald and Jane's; 1977, New York: Stein & Day; 1979, Tokyo: Kodan Sha. The amoeba shows intense activity within the pseudopodia, the cytoplasm swirling like smoke.

[2] The parasitic nematode *Trichinella spiralis* had first been depicted in 1835 by Richard Owen, the British anatomist, also a leading investigator of dinosaurs, who in 1842 coined the term *dinosauria*.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

Fig. 3. Micrograph of a testa of *Difflugia acuminata*. Though this shell is reminiscent of one constructed by a Trichopteran caddis-fly larva, we must remember that insects utilize brains, eyes and a complex nervous system, intricate muscle arrays, jointed limbs and discrete cement glands, none of which occur within a single cell of an amoeba. The mechanisms that allow a single cell to identify and organise silica granules are unknown.

We know so much about what lies within the living cell, and how it is constructed, but very little about why it chooses to do what it does or how it carries out the astonishing activity that we can – in whole cells – so easily observe (Ford, 2010a,b). Wound healing depends upon microscopic plumbing of a nature that we do not understand, and similar phenomena exist in the world of vascular plants. When the mistletoe *Viscum album* or the dodder *Cuscuta europea* parasitize a host plant, the xylem vessels of the invading haustoria unite seamlessly with those of the host. The phloem of parasite and host plant unite, though we cannot understand how. There have been detailed appraisals of the anatomy of the process (Vaughan, 2006) probing the immunological stimuli that initiate conversion of indiscriminate hyphae from the invading parasite into vessel initials. Yet these processes are consequent upon decisions taken by individual cells; we do not understand the precise mechanisms by which they interrogate their surroundings and duly respond.

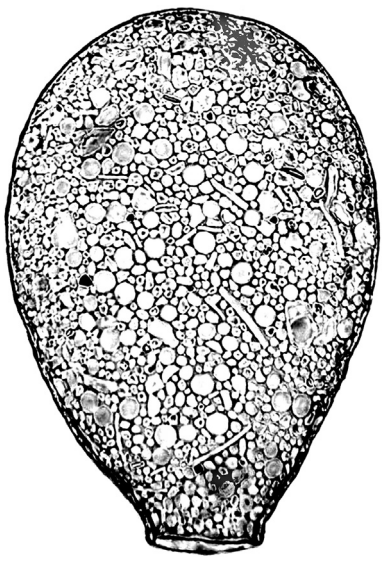

Fig. 4. *Nebela collaris*, named by Ehrenberg in 1848 and here modified from the arcella.nl website, consumes euglyphid testate amoebae and produces shells that incorporate fragments from those amoebae, together with diatom frustules. The cell identifies the requisite components through senses we do not understand, selects those of suitable size, and orients them to produce this characteristic vase-like shell with its distinctive collar.

Living cells are essentially autonomous. They exhibit considerable ingenuity. As Noble and others have shown, cells undertake epigenetic modification when necessary, using as yet unrecognized sensory and diagnostic facilities. They respond, rather than merely reacting, for cells act through volition rather than instinct. None of this do we understand, and little of it is under investigation.

8. Intelligent manifestations of living cells

We may finally explore a further dimension: the intelligence of cells. This is not a novel preoccupation. In a book on 'cell intelligence' published during World War I, Quevli suggested that intelligence in living cells was a driver of evolutionary development. His seemingly prescient publication, however, does not anticipate the present postulations. To Quevli (1916) the intelligence he postulated is a property exterior to the organism. He states (p 165): "Living structures are made to move in air, earth or water or to remain stationary on the earth. In the same manner, we build structures to move through air, over the earth and water. It requires intelligence in the builder to produce these structures." Herein lies Quevli's philosophical dilemma: our devices certainly require an intelligent person to design and construct them, whereas the "living structure" Quevli describes relies on no such external agency. It creates itself in response to its experiences and habitat from raw materials that it alone assembles and reorders. Closer to the concept of an intelligent cell were the precocious observations of Alfred Binet (1888) who believed that protoplasm (=cytoplasm) embodied vitalistic energies that manifested themselves in psychical terms. Binet wrote that phenomena such as the seizing of food particles by the intestinal cells of cold-blooded animals in the course of ingestion was an "essentially psychological" property. He added (and here he is entirely congruent with my views) that "it is plainly impossible to explain these facts by the introduction of physico-chemical forces." He continues that: "they are the essential phenomena of life," with which we would concur, adding with perhaps less authority that they "are the exclusive appurtenance of living protoplasm." We cannot be sure what is here implied; Binet does not propose alterative explanations, such as some form of 'systems thinking' in which we would utilize concepts as self-organization and emergence (mechanisms that would not themselves negate the role of physico-chemical forces) or a role for as yet unidentified forces, even a form of vitalism.

Binet reports that the distinguished psychiatric pioneer Paul Julius Möbius recognizes that "psychological life begins with living protoplasm, and he considers it to be the highest aim of zoology to demonstrate the psychical unity of all animals." Both investigated the study of human intelligence, Binet (1905) bequeathing to us an intelligence scale which, as the Stanford-Binet Intelligence Scale, a modern revision of which by Lewis M. Terman is still in use today. Jennings, in a book first published in 1905, speculated that the behaviour of the microbes, particularly *Paramecium* but also including bacteria, could reveal much of the behaviour of the higher [i.e. vertebrate] species (Jennings, 1905). In 1908, M. F. Washburn opened his discussion of comparative psychology with a brief discussion of amoeba. Much interest was evinced by the publication of

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

a volume that considered microorganisms in a range of guises, and which emphasised both the capacity of single cells, and their relevance to a wide-ranging understanding of life (Ford, 1976). Cells can exhibit *compliance*, in that they ordinarily accede to the constraints of their predicament; they can be *autonomous*, and respond as individuals when a situation requires a departure from the norm, even to the extent of rewriting their genetic database; they can be *ingenious*, by utilizing features from their habitat to benefit themselves – as do the testate amoebae – and *volitional*, adapting their behaviour to solve a contingent problem, as in the restitution of a wound or the invasive acquisition of a host's capacity by a parasite. There remains one fundamental attribute we should properly address: can we show that cells manifest *intelligence*? Disparate definitions of this crucial concept are abundant. In humans, since the time of Binet, there has been a quest for a single identifying datum that can define the intelligence of a person. Binet's 1905 definition was "the ability to learn or understand or to deal with new or trying situations" and in 1958 Wechsler, whose IQ test became widely used, defined intelligence as the "capacity of the individual to act purposefully, to think rationally and to deal effectively with the environment." It seemed sensible to recognise that there are clear categories of intelligent behaviour (Ford, 1978). Fifteen years later, Howard Gardner (1993) devoted an entire book to the subject and raised the definition of intelligence as "the ability to resolve genuine problems or difficulties that he or she encounters." Popular reference works adopted similar definitions. The Merriam-Webster Dictionary (2008) gave "the ability to learn or understand or to deal with new or trying situations." To emphasise the extent of conflicting definitions, one current educator's web site (teachers.sduhsd.net, 2017) summarises an oft-repeated mantra:

> "Whenever scientists are asked to define intelligence in terms of what causes it or what it actually is, almost every scientist comes up with a different definition. For example, in 1921 an academic journal asked 14 prominent psychologists and educators to define intelligence. The journal received 14 different definitions, although many experts emphasized the ability to learn from experience and the ability to adapt to one's environment. In 1986 researchers repeated the experiment by asking 25 experts for their definition of intelligence. The researchers received many different definitions: general adaptability to new problems in life; ability to engage in abstract thinking; adjustment to the environment; capacity for knowledge and knowledge possessed; general capacity for independence, originality, and productiveness in thinking; capacity to acquire capacity; apprehension of relevant relationships; ability to judge, to understand, and to reason; deduction of relationships; and innate, general cognitive ability."

Within those different definitions of intelligence there is one concept on which all seem to focus: the ability to deal constructively with the unforeseen. If we are to identify intelligent behaviour within a living cell, we need recourse to specific situational constrains. Responses that are conditional upon adverse stimuli that may have been encountered, and to which conventional evolutionary mechanisms may have allowed the cell to adapt, may reveal themselves as ingenious but are not in themselves evidence of intelligence.

For example, the slime mould *Physarum polycephalum* has been shown to calculate the shortest route to a source of food, and was said to be able to 'solve' mazes. An inoculum of *P. polycephalum* was introduced into a simple maze with two portals through which food particles could be accessed. The plasmodium of the organism spread out widely through the maze, and once the nearest food source was ascertained, it concentrated its efforts in this single direction. This was taken as some form of "primitive cognition" and the authors devised a mathematical model for the behaviour through a coupled system of differential equations. Yet this is not intelligence; here we have a simple response to chemotropism. There is no problem-solving, and an unforeseeable predicament is not involved. It is a simple matter of concentration gradient and response (Becchetti et al., 2013). The definitive demonstration of intelligence, must observe the cell encountering a situation which it cannot have previously experienced; it needs to demonstrate abnormal behaviour specifically in response; and the cell must act remedially to restore normality to its abnormal predicament. The microscopy of whole cells can provide examples, of which we may briefly review cell repair in the marine Rhodophyte alga *Antithamnion* as an example. When intercalary cells are damaged, adjacent cells bring about reinstatement of the wound (Cole and Sheath, 1990). A hormone-like glycoprotein 14–17.5 kDa, named rhodomorphin, has been shown to influence the growth of repairing cells though its origin remained unclear and it was uncertain where it might be localized during the healing process (Waaland, 1975). Subsequent research revealed that a signal glycoprotein with α-D-mannosyl residues was central to the healing process in *Antithamnion*. Fluorescent-tagged lectins were secreted from the tips of cells involved in repair (Kim et al., 1995). The growth bands identified by fluorescence microscopy were subsequently studied by transmission electron microscopy of fine longitudinal sections of the cell filaments (Mine et al., 2011).

Here we are witnessing the enduring eagerness for reductionism. To me, these minutiae are irrelevant to our understanding of what occurs. The rhodophyte algae are a curious group; although they are aquatic algae they lack flagella, the cells possess no centriole, and they are conventionally regarded as primitive. Yet they display remarkable abilities for repair. I have analysed a time-lapse 16 mm film of repair in *Antithamnion* that has been captured in Melbourne by my friend Jeremy Pickett-Heaps. He and his colleagues first obtained time-lapse micrographs of reproductive behaviour in rhodophyte algae (Pickett-Heaps et al., 2001). Subsequently they obtained sequences of cell repair in *Antithamnion*. The experiment was simple: a filament of cells was established in culture under the microscope. With a steel needle, one of the cells was transected and the cell wall cut across so that the cell contents lysed out. The resulting filament had been severed, the remaining portion of the cellulose cell wall being empty and in juxtaposition much as two halves of an empty egg-shell. Over the following 36 h, the adjacent cells responded to the damage, extending cytoplasm into the empty cell-walls and then re-aligning and reconstituting the intact cell wall. One nucleus of a "dominant" neighbouring cell undergoes mitosis to restore full functionality to the healed cell. At the conclusion, the irretrievably damaged cell has been restored to full function (Pickett-Heaps and Pickett-Heaps, 2000). There is no foreseeable situation in the natural environment in which a severed cell can remain with its broken extremities in proximity. These are marine algae, and should a filament become detached it would be swept away within seconds; the only conceivable situation in which the cell walls could remain in juxtaposition is upon the microscopist's slide. Here is a phenomenon which is not part of the experiential litany of the alga and thus cannot be an evolutionary adaptation (see Figs. 5–11).

This behaviour is the modification of behaviour to meet an unforeseen contingency. It is intelligent behaviour. Three adjacent cells are connected to the damaged cell; we can observe that each responds to the incident, though only one undertakes the repair. The results transcend current preoccupation with labelled lectins and the activity of regulatory mechanisms; they reveal an ability to diagnose a situation and promptly to respond with appropriate action to resolve an unheralded eventuality. The cell musters

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

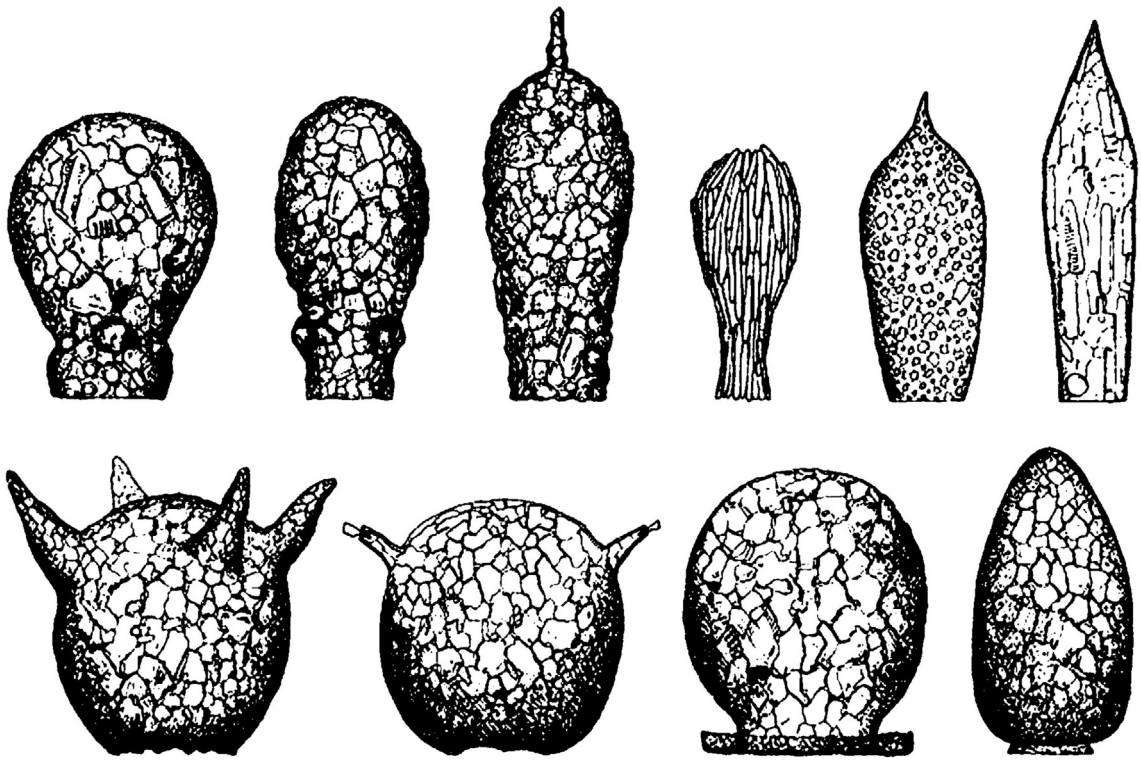

Fig. 5. The range of protective shells produced by species of *Difflugia* is considerable, yet each is characteristic of a given species. These are (modified) from the arcella.nl website and show, top row: *Difflugia capreolata, D. oblonga, D. acuminata, D. bacillifera, D. praestans, D. smilion;* second row: *D. corona, D. lithoplithes, D, arceolata, D. amphora.* The extent of the ingenuity utilized by these amoebae cannot be modelled.

changes in a vast range of systems, ranging from sensation and biosynthesis to regeneration and restitution. Evolutionary specialisation cannot account for these processes, since this is a unique event. They result from the recognition of an unusual, traumatic situation (through senses we do not understand) and the restoration of normality through appropriate remedial action (which requires meticulously coordinated responses of a kind we are unable to fathom) (see Figs. 12a–12g).

These are the criteria by which we diagnose intelligent behaviour. When bacterial or microbial intelligence is conventionally discussed, it devolves on the ability of individual microbial cells to act in concert, as when bacteria cooperate to create biofilms (Niu and Wang, 2012). The emergent concept of swarm intelligence perpetuates the view that cells can manifest crude signs of intelligence only when they work in concert. In my view, our conviction that these phenomena become manifest only through cell communities is a fundamental misconception. Ingenious, perceptive and intelligent behaviour is apparent in a single living cell.

9. The discrete neuron

If a single cell within a rhodophyte filament can manifest intelligent behaviour, it cannot be the case that the most specialised living cell we know, the human neuron, acts a mere “go” or “no-go” binary gate. The functioning of neurons was advanced significantly by pioneering research by my ingenious friend Sir Andrew Huxley and his colleagues before World War II. Recognizing the diminutive dimensions of most neurons, they turned instead to those of the squid *Loligo* (now *Doryteuthis*) *pealeii* in which the axons can be 0.5–1.0 mm in diameter, a curious property first recognised by J. Z. Young (1938). The greater diameter of the giant axon reduces its internal resistance, being inversely proportional to the cross-sectional area, thus increasing the space constant which leads to rapid local depolarization and a faster action potential (Hodgkin and Huxley, 1939). We have since relied upon an understanding of the neuron that is based upon the action potential and the polarizing changes that accompany it, and the biochemistry of the brain. The role of serotonin, for instance, is throwing new light on motivation and mood (Correia et al., 2017). However, the mood is that of the organism; we know little of the neurons. The study of neuronal networks underpins current investigations into the brain. The latest major review article assures us that “organizational principles of neuronal networks at the cellular scale, or micro-connectomics, is a key challenge of modern neuroscience.” (Schröter et al., 2017). One of many challenges it may be, but greater by far is the crucial question of what happens within each neuron. Just as the single cells of *Antithamnion* diagnose problems, take decisions, act to rectify an unforeseen situation and adapt as necessary to problem-solve, so I believe it is the intraneuronal processing giving rise to intercellular signalling that is now the key conundrum. Neurons emit electrical pulses at a frequency of around 40 Hz, known as neuron spikes, recordings of which are familiar in neuroscience. Neuron spike timing is now recognised as important. I became intrigued by envisaging the spikes, not as rapidly repeated signals, but as discrete impulses bearing encoded information. By modifying the time-base of recordings it was possible to replay the processed recordings as audio files, and to perceive the variations between each separate spike. In this way, one could readily detect alterations between each impulse and we were therefore able to eavesdrop on the utterances of neurons. Lecture demonstrations were given at a series of venues.

- Brian J. Ford, 2003, *The thinking microbe*, lecture to Inter/Micro 03, Chicago: McCrone Research Institute, 13:30–14:00, 9 July.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

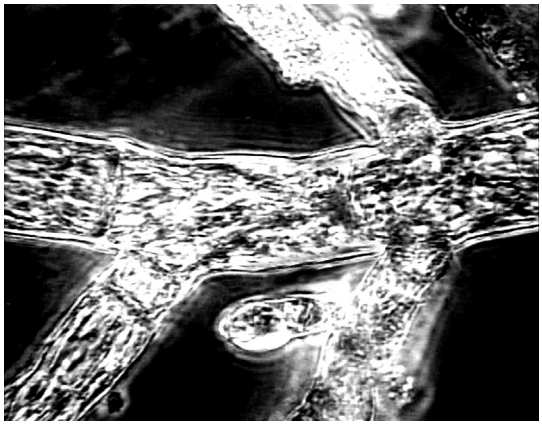

Fig. 6. The rhodophyte alga *Antithamnion* grows to form branching colonies of cells, each approximately 50 μm in width and about 130 μm long. The genus is found in warm marine environments and it possesses a remarkable capacity to heal damaged cells and to regenerate after trauma. These phenomena have been described by Kathleen Cole and Robert Sheath, (1990), *Biology of the red algae*, Cambridge: University Press.

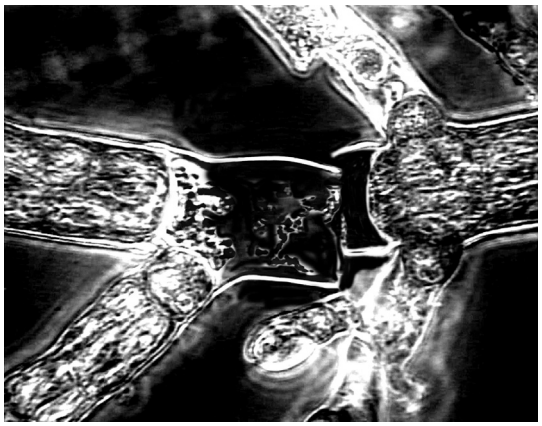

Fig. 7. In a filmed observation, Jeremy Pickett-Heaps at Melbourne has transected a cell using a steel dissecting needle. The cell wall is now separated in two, and the cytoplasmic contents have leached out into the surroundings. In nature, there is no conceivable situation in which this could occur; a ruptured filament would find the cut ends widely separated. Only on the slide can they remain in close proximity.

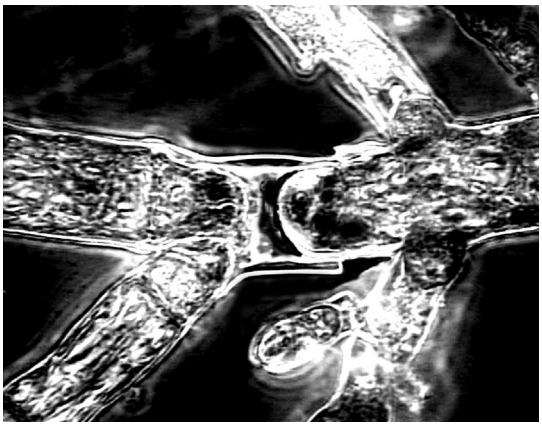

Fig. 8. Within ten hours, the adjacent cell (right) has detected the damage to its neighbour. The transverse septum separating the cells has been removed, allowing the cell body to increase in volume and commence migration into the previously empty cell space. Although the other two adjacent cells (left and lower left) have begun to encroach upon the void, only one cell (right) has commenced completion of the task.

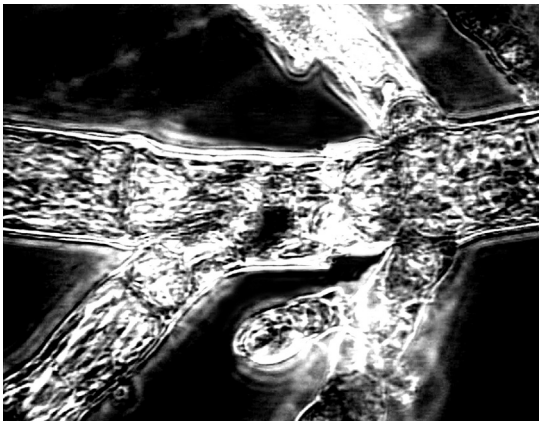

Fig. 9. After some fifteen hours, the transected cell wall is close to its original alignment. The void left in the emptied cell walls has now been re-occupied, and the cell's original configuration is beginning to be re-established. Some workers have shown that lectins bind to wounded sites and that a signal glycoprotein with α-D-mannosyl residues is involved in the process of cell repair.

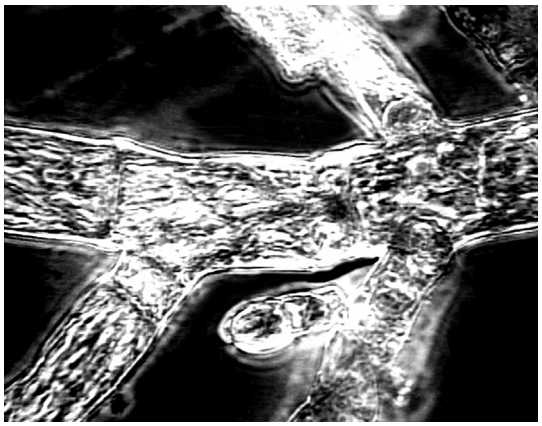

Fig. 10. Approximately twenty hours after the experimental intervention, the damaged *Antithamnion* cell has been largely restored. The cell has been reconfigured and the damaged wall has been sealed. Hydrodynamic pressure has played a part in realigning the cell wall, though the sensing of the initial damage and the initiation of an appropriate repair response are due to mechanisms which elude us.

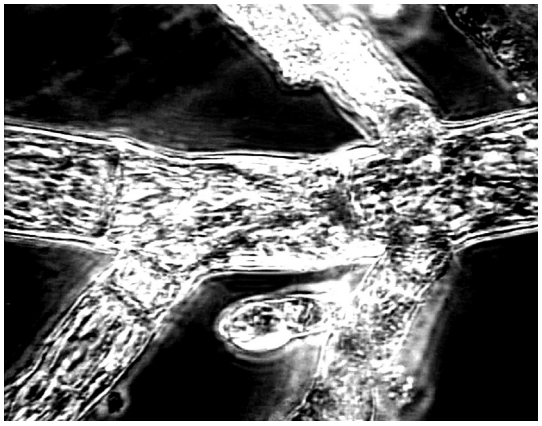

Fig. 11. Within thirty hours, the damaged cell has been restored in its entirety and is functioning as before. Since this is an unprecedented eventuality for which the cells invoke remedial action, it has clear connotations of intelligent behaviour. We cannot conceive of the senses that initiate the process or the mechanisms that regulate it. Such contingent behaviour is inimitable by digital modelling.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

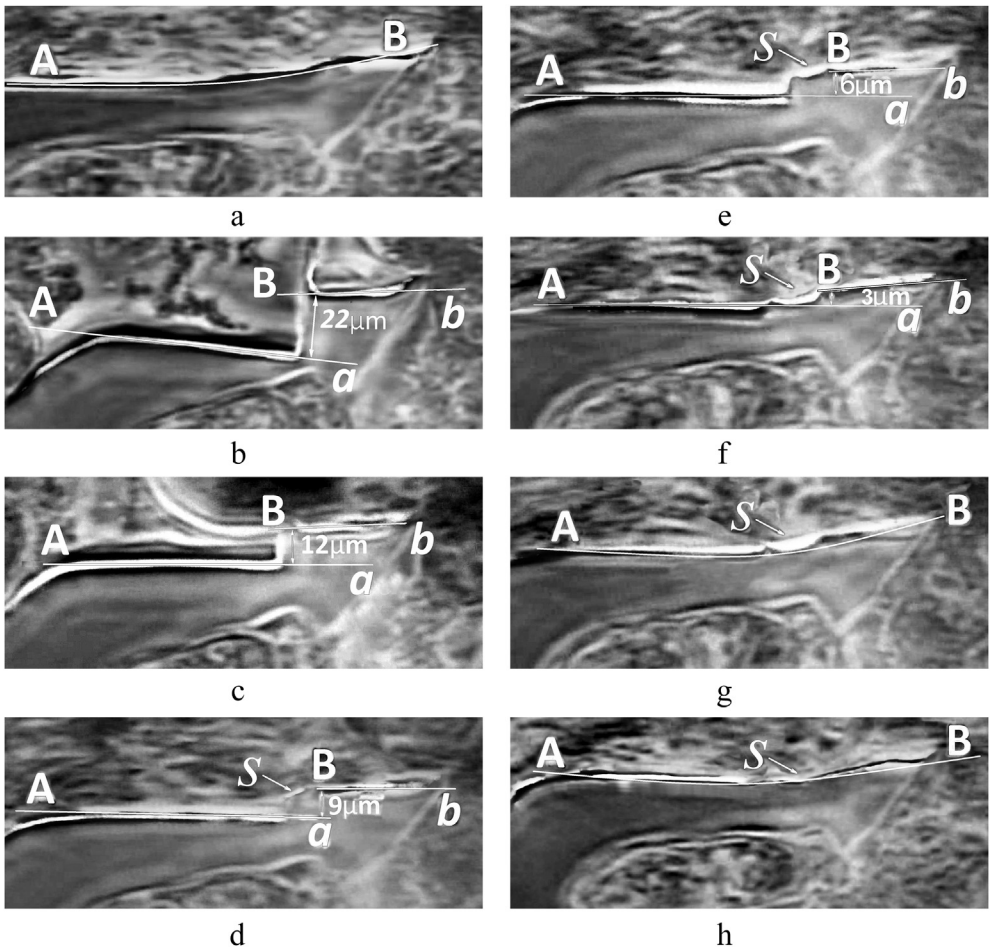

Fig. 12. a: The cell prior to resection (below centre in Fig. 6) shows a curved contour **AB** typical of filamentous rhodophytes. 12b: After resection by steel needle, the cell contents have dispersed and the broken cell wall is 22 μm out of alignment. 12c: The disparity has been reduced to 12 μm after ten hours. Cytoplasmic intrusion is visible as the cell is regenerated. 12d: Within fifteen hours, the cells are only 9 μm misaligned. At ***S*** we may observe the secretion of cell wall substance. 12e: Eighteen hours after resection, realignment is close to completion and the secretion of new cell wall material (***S***) has sealed the gap. 12f: By twenty hours, the sealing cell secretion (***S***) has moved into its final position and the configuration of the cell is largely restored. 12g: The curved alignment **AB** has been restored within thirty hours after transection, with a scar (***S***) visible where the cell wall has been healed.

- Brian J. Ford, 2004, *Clever creatures and ingenious cells - communication in nature and a new view of the neuron*, Cambridge Society for the Application of Research, Churchill College, Cambridge University, 1900:2100, 11 October.
- Brian J. Ford, 2005, *Demonstration of neuronal signalling*, London: exhibition by National Endowment for Science, Technology and the Arts, National Design Centre, 25 January.
- Brian J. Ford, 2005, *Ingenuity of the Single Cell*, illustrated lecture, Singapore: Biopolis, 08:00–09:00, 25 May.
- Brian J. Ford, 2005, *Are Cells Ingenious?* Students' lecture, Singapore: Science Centre, 15:00–16:00 h, 26 May.
- Brian J. Ford, 2005, *The Intelligent Microbe - Ingenuity in animals, plants and micro-organisms and a new look at the brain*, lecture to the Linnean Society of London, Burlington house, London, 18:00–19:00, 9 June.
- Brian J. Ford, 2005, *The Intelligent Microbe*, lecture to the Scientific and Medical Network, Guildford Institute, Guildford: University of Surrey, 18:00–19:00, 6 July.

There have been many lectures given since. In those early presentations, it was shown that the brain functioned as a community of intelligent modules, rather than as a single intelligent entity itself predicated upon unintelligent dipoles. In reality, intelligence and consciousness reside within each neuron, and the essence of being is a property of individual cells. Although the cohort community of cells potentiates these proclivities, they are inherent in a single living cell. Aur and Mandar point out that: “From a neurophysiological point of view, current doctrine remains focused within a spike timing paradigm” and they utilized my alternative approach in elaborating a neurodynamic model of brain function (Aur and Jog, 2010).

Meanwhile, neuroscience regards the brain as the sole controller of all human behaviour. It is conventionally stated that the brain rules every aspect of the body; as one writer put it: “Everything from the beating of the heart, the pulsing of the gut, the production of new blood cells, right down to the raising of individual hairs on our arm when we get a fright, all is controlled by the nervous system and ultimately the brain.” (McCrone, 2002). This view can now be supplanted. I postulate that the brain exists only because animals move; the brain regulates discerned appetites for nourishment and sex, and collates sensory input and negotiates interpersonal activity ranging from socialisation to movement; but it is invisible to most of the somatic cell population that comprise the entire human. The production of blood cells, digestion and metabolic processing of food, orientation of the fibrocytes within the connective tissues and elsewhere, regulation of cell renewal in

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

the skin, the liver, the intestines; the homeostasis of the capillary blood circulation, the parallel circulation of lymph, the coordination of the immune response, growth of bone at the epiphyses, secretion of keratin and production of sebum, regulation of metabolism through the liver … these and a billion other ongoing phenomena are not the concern of the brain nor are they regulated by it. When the gum heals after a tooth extraction it does so, not because of the overriding influence of the brain, but due to the ingenuity and adaptability of the single cells themselves (Ford, 2004). There is no doubt that conscious inputs to the brain modify some responses in the body, but the essential running of the entire metabolic system is irrelevant to the brain's functioning. To the cells in the body, performing their complex daily tasks, the brain is ordinarily an irrelevance. We can monitor intelligent behaviour by observing entire living cells over time (Ford, 2008a,b). An individual's brain is not necessary for life. In individuals in which brain activity is absent, bodily function – if food and water are supplied – continues. Even in individuals with a lack of significant cerebellum a lengthy lifespan is reported. The rare condition cerebellar agenesis results in the absence of cerebellum, though minute remnants may be found *post-mortem*. These individuals lack the normal ability to control voluntary musculature and have poorly developed non-motor functions such as memory and language, but are somatically unimpaired. Several cases are recorded by Eugen Boltshauser (2017) for the National Organization for Rare Disorders.

Notable cases in which persons with extensive brain damage have continued to survive are exemplified by that of Terri Schiavo, whose fate was argued extensively in the courts before she was caused to die in 2005 after food and drink were withheld (Shepherd, 2009). The brain, for most of the body, is an irrelevance.

10. Conclusions

We will never understand the brain purely by mapping synapses; nor can we measure its motivations by analysing the biochemical constituents of its metabolic processes. There are many attempts to emulate the brain by digital modelling. For example, the Blue Brain project[3] in Switzerland is attempting to create a digital emulation of the entire mammalian brain by reverse-engineering brain circuitry. This modelling the mind through digital data cannot succeed, since the neuron is not a simple digital device. A single neuron would be more than enough for us to tackle, and even that is probably not amenable to our primitive methodologies.

For centuries, we have been led to envision life as machinery. The simplistic belief that the brain is a computer, and can be analysed through electrochemical means, is no longer sustainable. Integral biomathics, for all its value in determining gross effects and quantifying environmental parameters that may act as signals to a cell, cannot usefully address the ceaseless hunting of mitochondria or the purposive reorientation of chromosomes in a mitotic cell. Believing that the genes alone mediate the workings of a cell simply as a blueprint cannot be supported. Denis Noble has advocated a broader approach, looking at the living cell as almost infinitely adaptable and able to negotiate its own destiny. Following this momentum, now we need to raise our sights yet further. Studying the living cell as volitional, and appreciating its individual ability to analyse data and take decisions, is our hope for the future. Notions like "artificial intelligence" are self-defeating; robots are mere machines with little comparison to living organisms, and modelling brains with current computer software cannot succeed. The unfathomable complexity of a living cell is not generally appreciated; even a simulation of the way a mitochondrion moves would be beyond our current conventions. Emulating fragments of our trivial understanding does not explain their intricacy for cells are intelligent, and they live lives that we have hardly begun to address.

There is little substance in claims that a computer designed to emulate the circuitry of the brain can undertake tasks that humans cannot: so too can a pair of scissors; so can an office stapler. Similarly, the widespread notion that AI may supplant human intelligence is groundless. Even a calculator can perform tasks beyond them mental abilities of a human, and AI, though undeniably artificial, can never manifest intelligence comparable to that of a single cell. Scholars quote the words of Ernest Rutherford, Baron of Nelson: "Physics is the only real science. The rest are just stamp collecting." (Birks, 1963). This naïve comment reveals nothing of the nature of science, only the profound ignorance of Rutherford for areas beyond his specific competence. Physics cannot account for the living cell and current research into the cell communities that regulate embryogenesis reminds us how little we know of the minutiae of the process at the level of the cell (Zhimin and Shang, 2017). Studying the behaviour of a single living cell and its community of fellows may reveal something of how acupuncture operates, for example; and it can surely throw light on the sense of living that so many philosophers have sought to address for thousands of years. When we observe within a living cell behaviour including the continual and carefully choreographed machinations of mitochondria, the endless migration of granules and voiding of vacuoles, the conduction of discrete particles in two-way streams of cytoplasm like traffic on a highway, the meticulous changes of position of the nucleus in diatoms during division, and the cautious inspection of prey by a predatory ciliate, then we can conceive that the cell may be a billion, or even a trillion times more complex than anyone has understood. Our failure to appreciate the majesty of the cell is astonishing, and our sublime confidence that we are close to an understanding it is an embarrassment. We have raised our sights better to comprehend the extent of our ignorance, and now we should apply our own native intelligence to attempting to unravel from whence it came. The entire living cell is an incomprehensible miracle, and its multi-faceted ability to communicate, to take decisions, and to respond to unforeseeable situations with a degree of intelligence can account for many observed phenomena that are otherwise unexplained. Forget reductionism: the whole living cell, as an entity, now commands our attention as never before.

[3] The Blue Brain Project, 2017, Brain and Mind Institute, *École Polytechnique Fédérale de Lausanne*, Switzerland.

References

Aur, Dorian, & Mandar, S. Jog, 2010, cite Ford, Brian J., [in] *Neuroelectrodynamics, Understanding the Brain language*: pages 7, 21, 208, 231. Amsterdam and Washington DC: IOS Press, February.

Basson, M.A., 2012. Signaling in cell differentiation and morphogenesis. Cold Spring Harb. Perspect. Biol. 4 (6), a008151. http://dx.doi.org/10.1101/cshperspect.a008151 PMCID: PMC3367549.

Becchetti, Luca, Bonifaci, Vincenzo, Dirnberger, Michael, Karrenbauer, Andreas, Mehlhorn, Kurt, 2013. *Physarum* Can Compute Shortest Paths: Convergence Proofs and Complexity Bounds, International Colloquium on Automata, Languages, and Programming ICALP 2013: Automata, Languages, and Programming, pp. 472–483. http://dx.doi.org/10.1007/978-3-642-39212-2_42.

Beck, Hall Pugh, 1975. Parametric Studies of the Response of a Protozoan, Spirostomum Ambiguum, to Repetitive Stimulation. East Carolina University Press.

Benda, Carl, 1898. Über die Spermatogenese der Vertebraten und höherer Evertebraten, II. Theil: die Histiogenese der Spermien. Arch. für Anat. Physiol. 73, 393–398.

Binet, Alfred, 1888. The Psychic Life of Micro-organisms. Open Court, Chicago.

Binet, Alfred, 1905. The development of the Binet-Simon scale, new methods for the diagnosis of the intellectual level of subnormals. In: Readings in the History of Psychology. Appleton-Century-Crofts, New York.

Birks, J.B., 1963. Rutherford at Manchester. London: Heywood, New York: Benjamin.

Boltshauser, Eugen, 2017, https://rarediseases.org/rare-diseases/cerebellar-agenesis/.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

Châtelet, E. A. du, Noiriel, C., Delaine, M., 2013. Three-dimensional morphological and mineralogical characterization of testate amebae. Microsc. Microanal. 19 (6), 1511–1522. http://dx.doi.org/10.1017/S1431927613013226.
Citovskya, V., Liub, B., 2017. Myosin-driven transport network in plants is functionally robust and distinctive. Proc. Natl. Acad. Sci. http://dx.doi.org/10.1073/pnas.1700184114. PubMed ID28179563.
Cole, Kathleen, Sheath, Robert, 1990. Biology of the Red Algae. University Press, Cambridge.
Correia, Patrícia A., Lottem, Eran, Banerjee, Dhruba, Machado, Ana S., Carey, Megan R., Mainen, Zachary F., 2017. Transient inhibition and long-term facilitation of locomotion by phasic optogenetic activation of serotonin neurons. eLife. http://dx.doi.org/10.7554/eLife.20975.
Dawkins, Richard, 1976. The Selfish Gene. University Press, Oxford.
Descartes, René, 1664. De l'homme et de la formation du foetus. Claude Clerselier, Paris.
de Duve, Christian, 1984. A Guided Tour of the Living Cell. Scientific American Books, New York.
Evans, Martin J., 1972. The isolation and properties of a clonal tissue strain of pluripotent mouse teratoma cells. J. Embryol. Exp. Morphol. 28 (1), 163–176. PMID: 467257.
Ford, Brian J., 1975. Microscopic blind spots. Nature 258, 469.
Ford, Brian J., 1976. Microbe Power, Tomorrow's Revolution. London: Macdonald & Jane's; 1977, New York: Stein & Day; 1979, Tokyo: Kodan Sha.
Ford, Brian J., 1978. Intelligence quotient or intelligence type? Nature 271 (5640), 7–8.
Ford, Brian J., 1982. Revelation and the single lens. Br. Med. J. 285, 1822–1824. December.
Ford, Brian J., 1998. Introduction to Robert Hooke's Micrographia of 1665, Facsimile Edition on CD-ROM. ISBN 1891788027. Octavo Editions, Palo Alto.
Ford, Brian J., 1999. Genes, the Fight for Life. Cassells, London.
Ford, Brian J., 2004. Are cells ingenious? Microscope 52 (3/4), 135–144.
Ford, Brian J., 2006. Revealing the ingenuity of the living cell. Biologist 53 (4), 221–224.
Ford, Brian J., 2007. Antony van Leeuwenhoek's microscope and the discovery of Giardia. Microsc. Analysis 21 (4), 5–7.
Ford, Brian J., 2008a. Intelligence and the Living Cell, Presidential Lecture to Cambridge Society for the Application of Research. Churchill College, University of Cambridge, pp. 1900–2130h, 20 October.
Ford, Brian J., 2008b. Microscopical substantiation of intelligence in living cells. InFocus 12, 4–21.
Ford, Brian J., 2009. On intelligence in cells, the case for whole cell biology. Interdiscip. Sci. Rev. 34 (4), 350–365 doi: 030801809X12529269201282.
Ford, Brian J., 2010a. A new era for whole cell biology. Biologist 57 (1), 9–11.
Ford, Brian J., 2010b. Concerning the Abilities of Living Cells, Lecture to Mensa at Cambridge. Sidney Sussex College, University of Cambridge, 22 August.
Ford, Brian J., 2015. The incredible, invisible world of Robert Hooke. Microscope 63 (1), 23–34.
Fracastoro, Girolamo, 1546, De Contagione et Contagiosis Morbis, [in] W. C. Wright, 1930, Hieronymii Fracastorii De Contagione, Libri III, Translation and notes. New York & London: G. P. Putnam's sons.
Gardner, Howard, 1993. Frames of Mind: the Theory of Multiple Intelligences. Basic Books, New York.
Goldacre, R.J., 1957. How amoebae move. New Sci. 3 (57), 23–25.
Goldstein, G., Scheid, M., Hammerling, U., Schlesinger, D.H., Niall, H.D., Boyse, E.A., 1975. Isolation of a polypeptide that has lymphocyte-differentiating properties and is probably represented universally in living cells. Proc. Natl. Acad. Sci. U. S. A. 72 (1), 11–15. http://dx.doi.org/10.1073/pnas.72.1.11. PMC 432229. PMID 1078892.
Hankey, Alex, 2015. Complexity basis for phenomenology: how information states at criticality offer a new approach to understanding experience of self, being and time. Progress Biophys. Mol. Biol. 119 (3), 119 (3), 288–302.
Hauptman, John, Bang, EunJin, 2016. Children Doing Physics: How to Foster the Natural Scientific Instincts in Children. Cognella Academic Publishing, San Diego CA.
Hodgkin, A.L., Huxley, A.F., 1939. Action potentials recorded from inside a nerve fibre. Nature 144 (3651), 710–711. http://dx.doi.org/10.1038/144710a0.
Hooke, Robert, 1665. Micrographia: or Some Physiological Descriptions of Minute Bodies Made by Magnifying Glasses. With Observations and Inquiries Thereupon. Martyn & Allestry, London.
Jack, C.V., Cruz, C., Hull, R.M., Keller, M.A., Ralser, M., Houseley, J., 2015. Regulation of ribosomal DNA amplification by the TOR pathway. Proc. Natl. Acad. Sci. 112 (31), 9674–9679. http://dx.doi.org/10.1073/pnas.1505015112.
Jennings, H.S., 1905. Behavior of the Lower Organisms. Indiana University Press, Bloomington.
Kim, Gwang Hoon, Lee, I.K., Fritz, Lawrence, 1995. The wound-healing responses of *Antithamnion nipponicum* and *Griffithsia pacifica* (Ceramiales, Rhodophyta) monitored by lectins. Phycol. Res. 43 (3), 161–166. http://dx.doi.org/10.1111/j.1440-1835.1995.tb00020.x 1995.
Köhler, Heinrich, 1720. Lehrsätze über die Monadologie. Johann Meyer, Frankfurt and Leipzig.
Kuppusamy, K.T., Sperber, H., Ruohola-Baker, H., 2013. MicroRNA regulation and role in stem cell maintenance, cardiac differentiation and hypertrophy. Current Mol. Med. 13 (5), 757–764. PMCID: PMC 3898432 NIHMSID: NIHMS543450.
Larson, Gerald James, 2011. Classical Sāṃkhya: an Interpretation of its History and Meaning, Motilal Banarsidass. ISBN 978–8120805033. Motilal Banarsidass Publications, New Delhi.
Leeuwenhoek, Antony van, 1678, Letter on blood to The Royal Society, November 28, 1687 [also] letter on yeast to Thomas Gale Esq, June 14, 1680 [and] letter on microorganisms to Henry Oldenburg, September 7, 1674 [and] letter on *Giardia* to Robert Hooke, November 4, 1681 [in] *Collected Letters*, 1964, Amsterdam: Swets & Zeitlinger. See also Ford, Brian J., *The Leeuwenhoek Legacy*, 1991, London: Biopress and Bristol: Farrand Press.
Leibniz, Gottfried, 1714. La Monadologie. The account was hand-written in French for his philosopher correspondent Nicolas-François Rémond and was first published as *Lehrsätze über die Monadologie* by Heinrich Köhler in 1720, Hannover.
Leidy, Joseph, 1879. Freshwater Rhizopods of North America. Government Printing Office, Washington.
Lemmon, M.A., Schlessinger, J., 2010. Cell signaling by receptor tyrosine kinases. Cell 141, 1117–1134.
Lentini, Roberta, Martín, Noël Yeh, Forlin, Michele, Belmonte, Luca, Fontana, Jason, Cornella, Michele, Martini, Laura, Tamburini, Sabrina, Bentley, William E., Jousson, Olivier, Mansy, Sheref S., 2017. Two-way chemical communication between artificial and natural cells. ACS Central Sci. 3 (2), 117–123.
Levin, Michael, 2014. Endogenous bioelectrical networks store non-genetic patterning information during development and regeneration. J. Physiol. 592, 2295–2305. http://dx.doi.org/10.1113/jphysiol.2014.271940.
Magner, Lois N., 2002. A History of the Life Sciences. ISBN 978 0824 708245. CRC Press, Boca Raton.
Margulis, Lynne, Fester, R. (Eds.), 1991. Symbiosis as a Source of Evolutionary Innovation, Speciation and Morphogenesis. MIT Press, Cambridge.
Martin, William, Kowallik, Klaus, 1999. Annotated English translation of Mereschkowsky's 1905 paper Über Natur und Ursprung der Chromatophoren im Pflanzenreiche. Eur. J. Phycol. 34 (3), 287–295.
McCrone, John, 2002. How the Brain Works. Dorling Kindersley, London.
Mereschkowsky, Konstantin, 1910. Theorie der zwei Plasmaarten als Grundlage der Symbiogenesis, einer neuen Lehre von der Ent-stehung der Organismen. Biol. Cent. 30, 353–367.
Merriam-Webster Dictionary, 2008, Springfield, MA: Merriam-Webster Inc.
Mine, Ichiro, Yuasa, Ken, Uesugi, Maki, Sekida, Satoko, Okuda, Kazuo, 2011. Band growth and localization of vesicle exocytosis in the red alga *Antithamnion nipponicum* (Ceramiales). Eur. J. Phycol. 46 (3), 263–270.
Niu, Ben, Wang, Hong, 2012. Bacterial Colony Optimization, Discrete Dynamics in Nature and Society. Article ID 698057, 28 pages. http://dx.doi.org/10.1155/2012/698057.
Noble, Denis, 2006. The Music of Life. University Press, Oxford.
Noble, Denis, 2010. Biophysics and systems biology. Philosophical Trans. R. Soc. 368, 1125–1139.
Noble, Denis, 2016. Dancing to the Tune of Life. University Press, Cambridge.
Nurse, Paul, Hayles, J., 2011. The cell in an era of systems biology. Cell 144 (6), 850–854.
Peake, J., Della Gatta, P., Suzuki, K., Nieman, D., 2015. Cytokine expression and secretion by skeletal muscle cells : regulatory mechanisms and exercise effects. Exerc. Immunol. Rev. 21, 8–25.
Pickett-Heaps, Jeremy, Pickett-Heaps, Julianne, 2000. Reproduction in the Red Algae. CD published on. www.cryptographics.com.
Pickett-Heaps, Jeremy, West, John, Wilson, Sarah, McBride, Douglas, 2001. Time-lapse videomicroscopy of cell (spore) movement in red algae. Eur. J. Phycol. 36 (1), 9–22. http://dx.doi.org/10.1080/09670260110001735148.
Puppe, D., Kaczorek, D., Wanner, M., Sommer, M., 2014. Dynamics and drivers of the protozoic Si pool along a 10-year chronosequence of initial ecosystem states. Ecol. Eng. 70, 477–482.
Quevli, Nels, 1916. Cell Intelligence, the Cause of Evolution. Colwell Press, Minneapolis, p. 52.
Robison, A.J., Nestler, E.J., 2011. Transcriptional and epigenetic mechanisms of addiction. Nat. Rev. Neurosci. 12, 623–637. http://dx.doi.org/10.1038/nrn3111.
Saigusa, Tetsu, Tero, Atsushi, Nakagaki, Toshiyuki, Kuramoto, Yoshiki, 2008. Amoebae anticipate periodic events. Phys. Rev. Lett. 100, 018101. Published 3 January 2008.
Schröter, Manuel, Paulsen, Ole, Bullmore, Edward T., 2017. Micro-connectomics: probing the organization of neuronal networks at the cellular scale. Nat. Rev. Neurosci. 18, 131–146. http://dx.doi.org/10.1038/nrn.2016.182.
ISBN 1-412-81537-1. In: Sheehan, Thomas (Ed.), 1981. Heidegger: the Man and the Thinker. Transaction Publishers, Piscataway, New Jersey, pp. 45–67.
Shepherd, Lois, 2009. If that Ever Happens to Me: Making Life and Death Decisions after Terri Schiavo. University of North Carolina Press.
Smith, H.G., Bobrov, A., Lara, E., 2008. Diversity and biogeography of testate amoebae. Biodivers. Conservation 17, 329. http://dx.doi.org/10.1007/s10531-007-9260-9.
Soen, Y., Knafo, M., Elgart, M., 2015. A principle of organisation which facilitates broad Lamarck-like adaptations by improvisation. Biol. Direct 10, 68.
Sullivan, K.G., Emmons-Bell, M., Levin, M., 2016. Physiological inputs regulate species-specific anatomy during embryogenesis and regeneration. Commun. Integr. Biol. 9 (4), e1192733. http://dx.doi.org/10.1080/19420889.2016.1192733. Jul 2016 15.
teachers.sduhsd.net/sschirripa/Defining%20Intelligence.doc, 2017.
Trembley, Abraham, 1774. Mémoires pour servir à l'histoire d'un genre de polypes d'eau douce. Gebr. Verbeek, Leiden.
Vaughan, Kevin, 2006. Conversion of the searching hyphae of dodder into xylic and phloic hyphae – a cytochemical and immunocytochemical investigation. Int. J.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012

Plant Sci. 167 (6), 1099–1113.
Verworn, M., 1888. Biologische protisten-studien. Z. für Wiss. Zool. 46 (4), 455–470.
Waaland, Susan, 1975. Evidence for a species-specific cell fusion hormone in red algae. Protoplasma 86, 253–261.
Wallace, Robert A., 1990. [cites Nagyrápolt, Albert Szent-Györgyi von] Biology, the World of Life. ISBN 067 338 0440. Harper Collins, New York & London.
Washburn, M.F., 1908. The Animal Mind: a Text-book of Comparative Psychology. The MacMillan Company, New York, NY.
Wechsler, David, 1958. The Measurement and Appraisal of Adult Intelligence. Williams & Wilkins, Baltimore.
Wright, W.C., 1930. Hieronymii Fracastorii De Contagione, Libri III, Translation and Notes. G. P. Putnam's sons, New York & London.
Young, J.Z., 1938. The functioning of the giant nerve fibres of the squid. J. Exp. Biol. 1938 (15), 170–185.
Zhimin, Lia, Shang, Charles, 2017. Where have the organizers gone? – the growth control system as a foundation of physiology. Prog. Biophys. Mol. Biol. 123, 42–47.

Please cite this article in press as: Ford, B.J., Cellular intelligence: Microphenomenology and the realities of being, Progress in Biophysics and Molecular Biology (2017), http://dx.doi.org/10.1016/j.pbiomolbio.2017.08.012