

On Intelligence in Cells: The Case for Whole Cell Biology

BRIAN J FORD

Gonville and Caius College, University of Cambridge, UK

Biology needs revolution. All my adult life, I have been lost with admiration for the achievements in molecular biology and genetics, and I have come to know many of the main proponents. Yet there is an alternative aspect: in studying the minutiae, we have lost sight of the whole cell as organism. Living cells within the body are modelled in this paper as coordinated but essentially autonomous entities. We shall see how independent cells in nature have remarkable abilities to make decisions and take constructive action, which correlate with the definitions of intelligence.

We are taught that the brain controls everything that goes on in the body, yet in this paper, we discover that most of the body's cells are invisible to the brain and are indifferent to its regulation. We encounter a novel model of the brain in which the neuron is viewed as an ingenious entity that 'thinks' within itself. The brain is not a 'super computer' but an entire community of them. We shall set the reductionism of molecular biology and the elementary mechanisms of genetics into a more realistic perspective and will recognize that the cell as organism matters above all. In future, *whole cell biology* should become the focus of the biosciences and the intelligent cell lies at its heart.

KEYWORDS Microscope, Microbiology, Cell, Intelligence, Genetics, Molecular Biology, Behaviour

Setting new science in context

When the chemical analysis of the cell was in its early years, Professor Herbert Muller asked for whom it would be a 'satisfactory description' to know which chemical elements comprised a man. It mattered only, he said, 'for those who intend to use him as fertilizer' (Muller 1943).

A decade ago, I argued that the emphasis on the vogue sciences of molecular biology and genetics had turned us away from the realities of life. I wrote: 'Molecular biology is rather like looking at the transistors in a radio and guessing how they work. But the important thing is not the radio, but

the programmes' (Ford 1999). In his introduction to that book, Professor Heinz Wolff of Brunel University wrote: 'I share the author's antipathy to the take-over that molecular biology has staged within the biological sciences, at the expense of understanding how whole creatures work'.

Recent papers have begun to move towards the standpoint advocated in my 1999 book. Some current writers point out that the term 'molecular biology' is diminishing in importance, and one can look to an age when the subject is seen to occupy a less conspicuous perspective (Morange 2008). After the triumph of decoding the human genome, we can begin to discern disillusionment with the impact of gene research (Oloparde 2004, 1683) and papers have begun to appear that reflect the unfulfilled promise of genetics (Zock and Palmer 2008, 1).

This paper advances the view that we will obtain the most fruitful insights only when we study the living cell itself as an organism. Our tendency to regard the cell as some kind of mechanistic module encourages the view that digital devices can imitate, and routinely supplant, living systems. Yet living cells are incalculably more complex than any human-made substitute. Even algae can detect cell damage, and initiate a custom-built repair that calls upon highly sophisticated and adaptive abilities. Once we consider multicellular living organisms as communities of coordinated — but inherently autonomous — entities, the nature of life is more meaningfully revealed.

The reductionist paradigm

Pick up a stone and weigh it in the hand; feel the texture with the fingers. Many people will then draw it closer to the eyes, peering at the surface; observing the colours, searching for striations, structure, subtleties of tone and sculptural characteristics. There is an instinct to seek out ultimate details, and herein lies the root of the reductionist paradigm that is the key to modern scientific investigation.

This wish to look ever closer drove the new science of microscopy, when, in 1667, the Dutch draper Antony van Leeuwenhoek travelled across the sea to England. He saw the chalk cliffs at Dartford, Kent, and wondered at their whiteness. What was the hidden nature of this bright and brilliant rock? Leeuwenhoek was soon to encounter Robert Hooke's *Micrographia* (Hooke 1665) which published the secret of how to make a high-power simple microscope (Ford 2009) and this led Leeuwenhoek to look ever closer at his chalk samples.

With his home-made microscopes, Leeuwenhoek was able to see the structure that lay within. He had many of his specimens drawn and published in the *Philosophical Transactions of the Royal Society of London* (Leeuwenhoek 1932). The microscope enthusiasts at the Royal Society had similarly speculated on the causality of familiar phenomena when looking at grains of pepper, for instance, in the hope of discerning the small sharp edges that must surely convey the hot taste of spice upon the tongue.

Since those pioneering investigators, science has been hell-bent on peering ever closer, and reductionism has dominated the biosciences. In electron

microscopy, high prices are being charged for meticulously corrected condenser systems that can further increase the resolution of the electron microscope. Much of the money is wasted. A university department has these instruments, not necessarily because of scientific necessity, but because every self-respecting department feels it needs to own them. It becomes a question of expediency and status, rather than necessity or need. An electron microscope with the right brand name, and state-of-the-art optics, is as desirable as branded designer labels on a sweatshirt, or the latest executive model car in the drive. And the imperative drives us away from realities we now need to consider. Costly instrumentation cannot create great science. No bad guitarist plays like a master just because they've been given a Fender Stratocaster; and poorly thought-out science is no better because of the latest microscope. It is our concepts that need updating, rather than the instrumentation.

In cell biology, we have seen this inexorable search for smallness lead us ever deeper into the machinations of the living cell. Molecular biology has proved to be one of the wonders of our age. At Cambridge I came to know the man who coined the term, Max Perutz (Ferry 2007) and greatly admired him. In later years, his own enthusiasms embraced topics that further extended the subject of which he was the founder-father, and he was actively advancing our understanding in fields like the study of HIV. Lunch with Perutz was inevitably accompanied by discussions that were encyclopaedic in scope.

Once kick-started, molecular biology mushroomed until it took a hold on the central consciousness of all biologists. Children in school are being taught about it, while ignoring altogether the majesty of life in all its magnificent variety. People have heard about the genetics of *Drosophila*, though hardly anyone would recognize a real fruit-fly if one landed on the table.

The reductionism that drives the research reached its peak with the unravelling of the genome. We now call the genome the cell's blueprint, but that is erroneous. A blueprint designates a single design; DNA triggers the production process. Each blueprint defines identical products, whereas no two cells are ever the same. Genes have been seen as selfish entities that underpin evolutionary progress, though I prefer to see them as the cell's inventory, rather than its captain.

In a Presidential address, Professor David Cutler of the Linnean Society reminded us: 'As Ernst Mayr has said, the gene is invisible to evolutionary pressure'. To me, the coinage of the 'selfish gene' is a social phenomenon. I see it as the spawn of the era in which it was popularized. I believe that it is a simplistic approach that stems from the era of Thatcherism in which it was coined, with its emphasis on self-interest. Scientific theories often mirror social preoccupations.

A leading physicist who questions reductionism is Robert Laughlin, a Nobel Laureate who avers that trying to find the 'simplest' (meaning 'most fundamental') causes of phenomena confuse us 'until we create self-fulfilling prophecies such as the "strings" of energy that vibrate in more dimensions than we can observe, the hypotheses holding that the extra dimensions are so

infinitesimally small that we cannot see them' (Laughlin 2005). Laughlin's view is that, although the theorists reveal nothing about the observable world, their papers may disclose something about themselves. The view was earlier expressed by Professor CEM Joad who wrote: 'When the scientist . . . speculates about the universe as a whole, the resultant conclusions are apt to tell us more about the scientist than about the universe' (Joad 1943).

I contend that concentrating on the minutiae of what goes on in the deepest recesses of the cell may be fashionable, but it can teach us little of life in the round. It is organismal biology, whole cell biology, which sets the findings of molecular biologists in context. When we look at the living cell as an organism, wonderful realities emerge — and these will alter our very perception, not only of how single cells enact their intricate lives, but of what we, ourselves, truly are.

The caddis fly and the amœba

As youngsters, we marvelled at the ingenuity of the caddis fly larva. The little homes that the larvae construct for themselves are ingenious. The larvae painstakingly select suitable components from the substrate and hold them in place, cementing them together to produce a protective shell. The larva uses its eyes and jaws, antennae and appendages, well defined musculature and a complex nervous system centred on a sophisticated brain. Naturally, it possesses cement glands that produce the glue responsible for holding the protective shell together.

It was also in our school days that we first encountered amœbae. With a shapeless body, a simple method of feeding and dividing, *Amœba* seems simple. It slowly slides across the mud at the bottom of a pond, we learn, like a diminutive blob of jelly on a plate. Yet each amœboid cell is composed primarily of water-soluble constituents, so the fact that it does not simply diffuse away and dissolve into the surrounding watery medium is something of an achievement in itself. Its ability to adjust its rate of reproduction to match the available food supply is an admirable trait that humans would do well to emulate. And many amœbae can also perform a minor miracle, by secreting secure capsules around their cells in which they can survive should their surroundings become inhospitable, and from which they can emerge unscathed when the situation improves.

The cells of *Amœba* are not as shapeless as we imagine. Although no amœboid cell is ever exactly the same shape twice, we tend to recognize and identify the species largely by their morphology. These considerations apply to the pond amœbae about which we are taught in school. How unfortunate that we are not also taught about the testate genera that mainly live among mosses, for they have a far more remarkable ability — they can construct a home.

Like the caddis fly larvae, they collect suitable raw materials and lay them down at the cell surface in exactly the right place to build a flask-like shell. In some ways, they are superior to the home that the caddis fly larva can

construct, for sometimes they have an exquisite projection at the apex of the shell. The shell homes always have a carefully constructed opening through which the pseudopodia project. Some species, such as the aptly-named *Nebela collaris*, produce a raised and rounded rim around the opening, for all the world like a comfortable collar (Ford 2008a).

The way in which the shells are built by the testate amoeba *Diffugia* was studied and reported in detail in the late nineteenth century (Verworn 1888). Verworn cultured *Diffugia* in the laboratory, and added ground coloured glass to the substrate instead of sand grains to observe the mechanisms of retrieval and construction as the cells elaborated their shells. The skill of the testate amoebae is truly remarkable. They are utilizing and adapting features of their environment to suit themselves, and that is cited as the criterion by which we recognize intelligence in more complex animals (like nest-building birds or dam-making beavers). If it is noteworthy that a weaver bird makes a spectacular flask-like home for itself, then the fact that an amoeba can also do this, in its own way, elevates these single-celled species so that they stand on a par with many multicellular taxa.

Amoeba, the ultimate lowly and humble creature, is in many respects commensurate with organisms grander by far.

Ingenuity in algae

Among the algae, the brownish-red Rhodophyta are mostly familiar as fertilizer, as the raw material for the production of fruit jellies and, to the Welsh populations who once subsisted on that glutinous concoction, as laver bread. Yet at a cellular level, rhodophyte algae indulge in extraordinarily ingenious behaviour that reveals many of the concomitants of intelligence. Think of it: intelligent algae.

The rhodophyte *Antithamnion* shows remarkably coordinated repair and regeneration mechanisms and clearly exhibits undeniable ingenuity. There are aspects of that management jargon 'systems biology' in these responses, and cell signalling also clearly plays a part. Some significant steps have been taken to elucidate the repair mechanisms of these algae. We already know that these genera utilize 'rhodomorphins' to initiate repair (Waaland 1975) – glycoproteins with a molecular weight of about 15,000, crucial for differentiation and repair. Work has also been done on a series of fluorescein isothiocyanate-labelled lectins specific for different sugar moieties which were examined as probes for the wound-healing response in *Antithamnion sparsum*. Among them are concanavalin A (ConA) and *Lens culinaris* agglutinin (LCA) which bind specifically to selected cells during the wound-healing process (Kim and Fritz 1993, 85).

Knowledge of these agents is useful, but it is not sufficient to explain the extraordinarily intricate responses that we witness under the microscope. I have examined in detail the repair of an *Antithamnion* cell that has been captured on video by my colleague Professor Jeremy Pickett-Heaps in Melbourne, Australia. He recorded on time-lapse video a cell that was torn

open with a fine dissecting needle. The empty and broken cell wall remained in two portions that were separated as clearly as cutting a drinking-straw with scissors. *Antithamnion* then embarked upon a remarkable sequence of events that restored the empty cell wall to full function. We know that adjacent cells undergo a complex series of manoeuvres to reinstate the destroyed neighbour (L'Hardy-Hamos 1971, 201; Waaland and Clevand, 1974, 407). When an intercalary cell is disrupted, cells on either side undergo divisions that result in the reoccupation of the void left by the destroyed cell body. It appears that fusion of the adjacent cells takes place, resulting in the full and functioning reinstatement of the pre-existing cell.

Yet this is a superficial and convenient overview, for it diverts attention from the intricacy of the process. Close examination of Pickett-Heaps' video, frame-by-frame, allows one to observe how it is not merely the cell contents that are restored: the broken and displaced cell wall itself is also repaired and reinstated. It is not merely patched, like a bicycle tyre, but meticulously realigned and permanently healed.

When bones heal they can leave an unsightly callus, just as a damaged tree will produce wound tissue as it recovers when a branch is broken. Rightly, we can marvel at these phenomena and recognize something of the systems of self-regulation and repair that such species can show. These, though, are highly specialized organisms and it is their sheer complexity that allows us to accept that they can recover from injury. A simple species, nothing more than an alga, seems an unlikely candidate to perform anything so specialized.

Yet when the *Antithamnion* cells come to restore a shattered and empty cell wall, they perform a greater task. In addition to reoccupying the empty cell, they perform the delicately coordinated realignment of the disrupted and misaligned cell wall that will result in a virtually invisible mend. The sequence of micrographs that I have extracted from the video shows how these mechanisms manifest themselves (Ford 2008a). The sequence reveals a list of tasks that a human repairer would find daunting. The damaged cell is recognized as such, the cell wall fragments are carefully realigned as the contents are reinstated, and the adjacent cells provide a replacement cell body. This is all sensed and diagnosed, manipulated, coordinated and completed by single cells without external mediation. Were we to repair something so efficiently, we'd expect to be regarded as skilful and intelligent; yet this is a lowly Rhodophyte rising to the occasion and problem-solving to an inconceivable extent.

Although our recognition of the factors that stimulate the response is useful and interesting, it does nothing whatever to explain the complexities that we observe. This is what molecular biologists have to grasp. The popular notion of 'quorum sensing' does little to explain how the individual cells are behaving, and that is what matters. We are obsessed with teams in modern management theory, and in my view, quorum sensing is our way of seeking out teams in the microbe world. Just as 'selfish genes' grew out of the social preoccupations of a society hell-bent on self-interest, 'quorum sensing' is science's way of finding explanations that are rich in resonances of modern

management theory. It is an unsatisfactory term, for it implies that (as in an inquorate management meeting) the individual is powerless without the support of the entire cohort. In the world of microorganisms, this is not the case. Each organism takes its own decisions, and regulates these in relationship to others in the community as and when expedient. Quorum sensing is a feeble and misleading anthropomorphism.

Miracles of healing

At the seaside some years ago, I bumped into a friend who'd just come out of hospital. 'I had a triple bypass', he told me, producing a photograph from his pocket. The postoperative scar was remarkable; it looked like a crudely constructed Cornish pasty held together with gleaming metal staples. I asked him when this had taken place. 'Just three weeks ago', he said, brightly, pulling up his tee-shirt for me to view the scar. It had almost disappeared. A thin, slightly suffused line of new skin marked the incision. Within a few more weeks, it would almost have vanished.

'Clever surgeon', he remarked.

'Clever cells', I replied, and explained more as we went for a coffee together.

Surgery is war. It is impossible to envisage the sheer complexity of what happens within a surgical wound. It is a microscopical scene of devastation. Muscle cells have been crudely crushed, nerves ripped asunder; the scalpel blade has slashed and separated close communities of tissues, rupturing long-established networks of blood vessels. After the operation, broken and cut tissues are crushed together by the surgeon's crude clamps. There is no circulation of blood or lymph across the suture.

Yet within seconds of the assault, the single cells are stirred into action. They use unimaginable senses to detect what has happened and start to respond. Stem cells specialize to become the spiky-looking cells of the *stratum spinosum*; the shattered capillaries are meticulously repaired, new cells form layers of smooth muscle in the blood-vessel walls and neat endothelium; nerve fibres extend towards the site of the suture to restore the tactile senses. Lying behind the sequence are the homeobox genes that switch on transcription factors which themselves trigger cascades of other genes to operate, and in this way they can designate what kind of cell a given stem cell can become. But this genetic determinism does not explain the intricacy of tissue repair, where microscopic plumbing and restorative architecture are involved. These phenomena require individual cells to work out what they need to do. And the ingenious restoration of the blood-vessel network reveals that there is an over-arching sense of the structure of the whole area in which this remarkable repair takes place. So too does the restoration of the skin. Cells that carry out the repair are subtly coordinated so that the skin surface, the contour of which they cannot surely detect, is restored in a form that is close to perfect. These remarkable behavioural systems owe their success to the subtle senses and refined ingenuity of the single cells themselves. This is a matter of sensory awareness and coordinated response, not mere genetics.

Autonomy and delegation

In the words of a recent popular book on the brain: '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 this is controlled by the nervous system, and so ultimately the brain' (McCrone 2002). Even the subconscious is eventually subject to what the brain imposes, according to this view. 'Everything' (note the word) is ultimately controlled by the brain. In similar words, Lewis Wolpert says 'Everything we do is determined by this impossibly complex society of nerve cells' (Wolpert 2009).

This current view dominates our teachings. It is fundamentally wrong, and evidence can be produced from many disparate disciplines in support of what I'm now saying (Ford 2006, 221). In this paper, we have already encountered the multi-talented amœbae that lurk in mossy swamps, and there are equally talented amœbae within ourselves. These are the leucocyte populations on whom we rely as a first line of defence against invading pathogens. As you are reading these words, chances are that you have inhaled a potentially harmful bacterial species, possibly a *Staphylococcus* or a *Streptococcus*, even a drug-resistant strain of something like tuberculosis. Conventional wisdom suggests that you'll develop an infection but, were that the case, you'd suffer endless concurrent infections since bacteria are inhaled every minute of the day.

What actually happens is that the patrolling leucocytes in your throat identify the organisms as invaders. Sometimes a leucocyte will chase a bacterium until it can capture and consume it. These white cells inform their fellows, and (whether by means of antibodies or by simple ingestion) the invading pathogens are quickly and efficiently eliminated. You never knew they were there because the bacteria are invisible to the brain, just as are the leucocytes.

Most of the body's cells regulate themselves independently of the brain. Those in your liver reproduce at just the right rate to replace cells lost through attrition; the follicular cells in your scalp create new hair (sometimes, notably in men, at a replacement rate that is slower than the loss) just as the cells in the bone marrow produce new circulating blood cells at the rate of millions per minute; others partake of digestion in the gut, or replace epidermal cells as your skin self-renews. Most of what happens within your body is regulated by the cells that are involved and they are not in the least concerned with the brain. They do not even know that it exists.

All this activity is invisible to the brain, and this accounts, we might estimate, for ninety per cent of everything that goes on.

Once in a while, things do not run as they should. The white cells may be overwhelmed by pathogens, so you will develop a sore throat or something worse. Sometimes they mistake a body cell for a pathogen, and habitually attack the wrong target. This 'friendly fire' manifests itself as an auto-immune condition. Many of the white cells are trained in how to conduct a war of immunity by a period of residence within the thymus gland, which is large in

the young and dwindles to insignificance in the old. It's tempting to think of the thymus as a training college for lymphocytes. In autoimmune conditions, the brain is indifferent to the disease and — just as it is unable to regulate the cell community — it has no power to influence the course of the illness. The brain matters far less than you were taught. Consciousness may reside throughout the body, and it may be that comatose persons who can return the squeezing of a concerned hand still manifest a level of whole-body awareness even if the brain, *per se*, is unresponsive. Spinal cord reflexes may not be the whole answer.

Anyway, why have a brain? Complex animals possess a brain only because they move, and the reason that plants lack one is because they remain rooted to the spot. Our brains help us rationalize, communicate, coordinate and interact, but brains are not the origin of the senses. Let me accompany you down the microscope and observe a single stomatal guard cell on the surface of a leaf. These are the cells that regulate the opening and closure of the pores through which gas exchange takes place. The pairs of guard cells look somewhat like lips, and indeed they act like them.

Reflect, for a moment, on what I have asked you to do — to move from the sheer majesty of the human brain down to single cells on the leaf of a plant. It's like moving from a walrus to a wart; from a spacecraft to a paper plane. After the unfathomable complexity of the most intricate single entity known to us, the human brain, we travel down to a microscopic speck of plant life that lies just beyond the sight of the human eye.

Or is that cell so primitive? Those stomata are sensitive to light. Each stomatal cell responds both to vibrational and chemical stimuli, for it is a sensor in its own right and it adjusts the turgor pressure within — and thus the opening of the central pore between the cells — in response to micro-environmental changes. These abilities to sense and respond to illumination levels and tactility, like the sensing of chemicals both in liquid and gaseous forms, are senses that we recognize. Sight and sound, touch and taste; our sophisticated senses have their own counterparts within this tiny cell. Even at this microscopic level, we find the same attributes that the ancients recognized as being responsible for making us what we are.

Defining intelligence

There are recent published findings that show how communities of microorganisms show decision-making abilities (Takagi *et al.* 2007). Professor Toshiyuki Nakagaki and his colleagues presented a confined culture of a migrating slime mould *Physarum* with a repellent stimulus (quinine) and observed that the crawling culture halted in its tracks. After a lengthy period, extending in some cases to hours, the colony either retreated or passed to one side of the obstacle, or even divided into two and reassembled into a single colony once the obstacle was passed. The phenomenon was reported by journalists as perhaps hinting at the origins of intelligence (Ball 2008, 385). But there is little in the report to suggest intelligence played a part; the

research was primarily concerned with memory and decision-making. In any event, this is a report on the response of a colossal community of cells, and not single cells acting alone.

In previous centuries, biologists were more concerned with observation rather than analysis. They lacked our tools, and were preoccupied with the sheer splendour of life under the microscope. This was a golden age for living cell science. Ernst Haeckel, the German biologist who coined the terms ecology and phylogeny, was consumed with admiration for the intricacies of life and classified over 4000 marine organisms (radiolarians and sponges among them). His greatest contribution to the philosophy of biology was the notion that the embryology of an organism reprises its evolutionary history, which he summarized as ‘ontogeny recapitulates phylogeny’. It was a great stride in understanding, marred somewhat by Haeckel publishing forged images of supposedly disparate embryos, that were actually made from the same original woodcut (Haeckel 1868). His observations of living cells struck him with such force that he developed a ‘theory of the cell-soul’ dating from 1866 (Haeckel 1878).

Browsing through books about living cells on the shelves of Cambridge University Library some years ago, I was intrigued to find a volume that was devoted to the capacity for intelligence in cells as a driver of evolutionary progress (Quevli 1916). My immediate reaction was that the author had already reached conclusions identical to mine, but this proved not to be the case. Although he promulgates the then-popular view that single celled organisms lived lives of great complexity, he regards the cells as the producers of organisms, rather than comprising them. Quevli takes the artefacts of a great nation – skyscrapers and ships – as analogous to trees and mammals. He writes thus: ‘The designers and builders of plants and animals were to us spiritual beings because we could not see them. In the same way the designers and builders of skyscrapers and battleships would be spiritual beings to us if we could not get near enough to the structures to see the builders’. Quevli envisages the constructions as the legacy of small, intelligent entities.

This is not what I propose; the microscopic beings *comprise* the structures, and do not simply construct them like a team of workers (Ford 2008a). It is not to buildings that we should turn if we wish to observe the constructors. We should look instead to examples like the choreographed displays at the Beijing Olympics, where we saw a group of humans acting as a single organism. The resulting spectacle was stunning – and was entirely due to the abilities inherent in every single performer. So it is within multicellular organisms, large and small.

We recognize intelligence when we encounter it, though any objective attempt to define the term is controversial. Binet was a self-taught psychologist who was so intrigued by the apparently passionate nature of sexual reproduction in protozoa that he coined the phrase ‘the psychic life of microorganisms’. He set out a definition of intelligent behaviour, emphasizing that it involved ‘the ability to learn or understand or to deal with new or trying situations’ (Binet 1905). Gardner refers to a property that enables the

individual 'to resolve genuine problems or difficulties that he or she encounters' (Gardner 1993) while Wechsler cites the ability 'to act purposefully ... and to deal effectively with his environment' (Wechsler 1939). Problem-solving skills are commonly cited. For signs of intelligence, the *Oxford English Dictionary* refers to evidence that something has been apprehended or understood and especially to 'interchange of knowledge, information, or sentiment'. *Miriam Webster's* definition centres on the 'ability to learn or understand or to deal with new or trying situations'.

In defining intelligence, adaptation of and to the environment, reaction to unforeseen circumstances and communication with others are frequently mentioned. It is the essence of such intelligence that we observe in single cells. The castaway on the island is no less intelligent than the community of people that constructed their home town. We should also note that the crude shelter that the castaway constructs won't be as durable, or as perfectly precise, as the shell homes made by testate amœbae.

Cellular memory

These models can illuminate areas that, currently, science cannot explain. One is the curious, controversial but apparently well documented phenomenon known as 'cellular memory', examples of which have been collected and discussed by a physical therapist named Leslie A. Takeuchi (2004). Takeuchi cites several examples of radical behavioural change after organ transplants from donors who had exhibited the acquired behaviour. These include a 7-month-old boy who developed a mild form of cerebral disability, like that of his donor, and a 47-year-old man who discovered a new liking for classical music, later to discover that his donor was a 17-year-old classical violinist. There was a 29-year-old fast-food eating lesbian who became a vegetarian and developed a strong preference for men and a middle-aged man who acquired an eating disorder; both these new behavioural traits being those of the organ donors. One such person wrote a book about her new craving for beer and chicken nuggets, neither of which she had liked before the transplant but to both of which her donor was devoted (Sylvia and Novak 1997). Such stories lack an explanation in orthodox science and so are usually dismissed as fanciful. Is it possible, however, that given cellular intelligence, cells in such great numbers as are transplanted could then introduce such characteristics into the cell community that has received them?

Supremacy of the neuron

We have faced cells that take decisions, act altruistically, perform judicious manipulations, adapt their surroundings to suit themselves and alter their life-styles to match changing circumstances. Yet when we discuss the brain, we are faced with the concept of the neuron as little more than a 'go' or 'no-go' gate, a kind of transistor. It is at the synapses, we are told, where intelligence emerges as large communities of neurons act in concert. Here we face a philosophical absurdity. If a 'lowly' *Amœba* is ingenious enough

to build a home for itself, how can it be that the neuron — the most highly-evolved cell we know — is essentially a mere binary switch?

Over a century ago, the notion that the roots of mental abilities resided in single cells seemed to be an inevitable outcome of the microscopical study of the complex lives of protozoa. In the era when aquatic microorganisms were popular subjects for microscopic study, Watkins postulated that ‘mentality in some sense is a property of the original cell’ (Watkins 1888). He was echoing sentiments from the 1880s, when Verworn had published the view that: ‘Elementary life phenomena are inherent in every cell’ (Verworn 1888).

The unravelling of brain structure can be traced through the eighteenth century (Ford, 2007) though it was the interrelationships between neurons, rather than the cells themselves, that came to dominate philosophy and persist to this day. The ‘nexus’ originated with Diderot in 1769 (Otis, 2001, 50) yet notions of autonomy were reiterated by Cajal (1917, 314) who reminded his contemporaries that ‘every cell always conserves its individuality’ (Otis, 2001, 64).

In my view, the brain’s capacity fundamentally resides in intraneuronal data processing rather than mere interneuronal activity. The neural network potentiates the capacity of neurons ‘thinking’ within themselves. The action potentials that we can measure can be envisioned as a language by which neurons transmit processed data from one to the next. As a first step towards understanding this, we took a recording of potentials from neurons cultured *in vitro*. Such data are well known. The neurons emit a signal of ≈ 40 Hz and because of the acute apex of each wave in the recording, these signals are categorized as neuron spikes. Successful attempts have been made to analyse these through template extraction (Cho *et al.* 2003, 2921).

Aur and Jog have shown that neurons can change as they learn — or at least that there is information related to learning in the spatial organization of electrical activity within the neuronal network. They argue that modulations of electrical flow from neurons are critical, and conclude that the observed changes relate to the dynamics of what happens in the neuronal network during behavioural learning (Aur and Jog 2007, 31).

The investigations by Cho *et al.* rely on the derivation of means from a large number of samples; those of Aur and Jog are concerned with spike timing and directionality. I am concerned with the individual signals emitted by the cells. The buzzing sound of the original recording of the neural spike, played back as an audio file, is an irritating noise; it grates on the senses as much as chalk on a board. Far more interesting to me was the possibility of information hidden within each single spike. Since we were accustomed to hearing the signals as audio, I determined to process the signal to render the sound within each discrete spike closer to the frequency of a human voice. Using Audacity software by Sourceforge (version 1.2.6), we rendered the signal within each spike so that it was approximately 300 Hz. In this way we can discern each spike as a single sound (Ford, 2004, 140).

The sounds of the resulting audio files have a hypnotic quality like seabirds calling on a cliff. There is a clear sense that each spike is modulated, not

merely in its temporal sequence, but subtly within itself. There may be perturbances introduced through the electronic or recording process, and in any event there is no evidence of what the information within the modulated recordings might signify. Examples of these recordings were first demonstrated in London in 2004, and featured on the BBC's 'Today' programme in October 2008 (Ford 2008b). The clear impression is that we are listening to the discrete signals with which one neuron in some sense addresses another (see Waite 2008).

Blinded to science

Once I was visiting Roanoke Virginia to lecture with my much-admired ecologist friend Professor John Cairns, Jr at Virginia Polytechnic University. At the wine party that followed, I was approached by a young professor who introduced herself and spoke warmly of my microscopical research. 'Why, it's just amazing what you have managed to see', she gushed. 'Those images are awesome!' I began to explain that the light microscope offered unique insights that are available to all, but she waved aside the rejoinder. 'I work on electron microscope images', she said, and then added, 'I have never looked through a light microscope in all my life'. She is not alone. Most cell biologists *never* observe the behaviour of living cells. The imperative is to seek ever smaller components, but not to study whole cells in the round.

Great scientific minds have addressed cells in a manner that is accessible to a wider public. Lewis Thomas put together a stimulating series of essays in a book entitled *The Lives of a Cell* (Thomas 1974). The style belies the publication date, for the book reads as if written a few years ago. A decade later came de Duve's two volume tour-de-force *Guided Tour of the Living Cell* (de Duve 1984) and most recent is Lewis Wolpert's *The Secret Lives of Cells* (Wolpert 2009). Yet, for all their condensed wisdom and timely insights, none of these books gives an impression of the living cell itself. Cells are similarly absent from almost every television programme, and missing from virtually all cinema films. Rare exceptions are Friedrich Wilhelm Murnau's *Nosferatu*, which shows *Hydra* disabling a water-flea; recent trailers for a documentary into anthrax, using an image of the harmless chlorophyte alga *Volvox* on the BBC programme *Panorama*; images of *E. coli* on British TV as a graphic representation of MRSA; and finally, pond protozoa momentarily featured in the title sequence of Steven Spielberg's *War of the Worlds* (2005).

The television series *Cell City* (2004) depicted the cell as a city, with its membrane as a ring-road, the nucleus as the city hall and the endoplasmic reticulum as the industrial park. In spite of the questionable analogy, there were sequences showing living cells and the viewer was left with an impression of life down the microscope. Considerably worse was *The Great Sperm Race*, released on Channel Four television in the UK in March 2009. Along with glimpses of sperm cells under phase-contrast microscopy, the viewers were regaled with teams of human extras in white suits running across mountainous vistas and climbing ladders, which the simplistic computer graphic imagery and banal explanation confused irretrievably in the mind. An

audience that could have been left with an awe-inspiring insight into the moist and majestic intricacies of reproduction had to be content with amateur actors running through undergrowth. The most recent BBC production was an error-ridden series entitled *The Cell* for BBC Four in August 2009. Many of the microscopical images were technically inadequate and decades out of date. Nobody watching would have an idea of what living cells are like in nature, for they were eventually reduced to mechanistic sacs that human scientists were close to creating for themselves.

It is time that living cells became familiar to us all. The idea of the intelligent cell can give us an overwhelming sense of insight, a calming awareness of our whole being, an intuitive grasp of how problems might usefully be addressed; and, above all, an intimate feeling of familiarity with the realities of life.

The benefits to the working scientist are many. By examining cells and watching them at work, we can gain a fuller understanding of what they do, and how they behave. The stem cell, portrayed in the media as almost magical, is (as Muller wrote in 1943) 'capable, under favourable conditions, of producing an entire individual'. Set in the terms we are addressing in this paper, stem cells are the single living entities that make us into the differentiated colonies of cells that we are destined to become — humans as microbes. We began life as microbes. The living sperm cell and ovum are representatives of the cell community that comprise the parents' bodies. In microcosm, these gametes *are* the parents.

Carefully judged genetic manipulation is not 'playing God' but is translocating a natural essence into a novel situation where it can perform a greater good. We are not creating 'Frankenstein' plants. Such things are already familiar and widely accepted; in the grafting of plants we take the 'head' of one variety and graft it onto the 'body' of another. It is a mainstay of horticulture and accepted without demur.

Only when we stop to consider the immense adaptability of the cells and vessels between the graft and rootstock at the point of union can we begin fully to appreciate the need for judicious ingenuity shown by each cell. The plumbing needs to work perfectly; the vessels carrying sap must join and remain leak-proof. Layers of cambium cells need to adapt as they grow to produce a seamless union. In time, the rootstock may become fatter by far than the grafted branches of the tree, yet the cells continue to grow, realign, and adapt perfectly to the new and artificial situation.

No child should reach the age of 10 without being familiar with the microscope and the living organisms that it reveals. The theoretical biologist Robert Rosen concludes that, 'Perhaps the first lesson to be learned from biology is that there are lessons to be learned from biology', (Rosen 2000). The greatest of these lessons, in an era of genetic determinism and digital ideology, is that the responses of cells are not amenable to predictive mathematical modelling. They are so diverse, complex, and multivariate as to defy rational analysis.

We are too easily seduced by convention and fashionable faith, in this area more than most. The study of the whole cell as organism is here advanced as the necessary focus for bioscience research while genetic engineering and molecular biology are put into their proper place. The intelligent behaviour

that we observe in the animal world (notably in *Homo sapiens*) is revealed, not simply as the result of cells acting in concert, but as the coordination of a property inherent within each single cell. It is the immortal cells that matter. We are essentially the disposable fruiting bodies that bequeath them to succeeding generations.

We need to consider the intelligence of single cells. Whole cell biology is the most enticing, attractive, enlightening and captivating aspect of biology that we now need to embrace, and do so with enthusiasm. It shows us so much, and can teach us still more.

Bibliography

- Aur, Dorian, and Mandar S. Jog. 2007. Neuronal spatial learning. *Neural Processing Letters* 25 (1): 31–47.
- Ball, Philip. 2008. Cellular memory hints at the origins of intelligence. *Nature* 451: 385.
- 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*. New York: Appleton-Century-Crofts.
- Cajal, Santiago Ramón y. 1917. *Recuerdos de mi Vida*. Madrid: Moya.
- Cho Hansang, D. Corina, G.A. Ojemann, J. Schoenfield, L. Zamora, and L. Shapiro. 2003. A new neuron spike sorting method using maximal overlap discrete wavelet transform and rotated principal component analysis. *Proceedings of the Twenty-fifth Annual International Conference of the Institute of Electrical and Electronics Engineers* 3 (17–21): 2921–4.
- de Duve, C. 1984. *A guided tour of the living cell*. New York: Scientific American Library.
- Ferry, Georgina. 2007. *Max Perutz and the secret of life*. London: Chatto & Windus.
- Ford, Brian J. 1999. *Genes, the fight for life*, 212. London: Cassells, New York: Sterling.
- . 2004. Are cells ingenious? *The Microscope* 52 (3/4): 135–44.
- . 2006. Revealing the ingenuity of the living cell. *Biologist* 53 (4): 221–4.
- . 2007. Enlightening neuroscience, microscopes and microscopy in the eighteenth century. In *Brain, mind and medicine, essays in eighteenth-century neuroscience*, ed. H. Whitaker, C.U.M. Smith, and S. Finger. New York: Springer.
- . 2008a. Microscopical substantiation of intelligence in living cells. *InFocus*, Royal Microscopical Society 12: 6–21.
- . 2008b. The sound of cells talking. *Today*, 20 October 2008. London: BBC Radio. [news.bbc.co.uk/today/hi/today/newsid_7679000/7679354.stm](http://news.bbc.co.uk/1/hi/today/newsid_7679000/7679354.stm), 21/8/09.
- . 2009. Did Physics matter to the pioneers of microscopy? In *Advances in imaging and electron physics*, ed. Peter W. Hawkes, vol. 158: 27–87, New York: Academic Press.
- Gardner, Howard. 1993. *Frames of mind: the theory of multiple intelligences*. New York: Basic Books.
- Haeckel, Ernst. 1868. *Natürliche Schöpfungsgeschichte*. Berlin: Georg Reimer.
- Haeckel, Ernst. 1878. Zell-Seelen und Seelen-Zellen, Gessamelte populäre Vorträge, I Hefte. [Cited in] Haeckel, Ernst. 1900. *The riddle of the universe at the end of the nineteenth century*. New York & London: Harper Bros.
- Hooke, Robert. 1665. *Micrographia, or some physiological descriptions of minute bodies made by magnifying glasses*. London: Martyn, J., & Allestry, J. Facsimile reprinted 1961, New York: Dover Publications.
- Joad, C.E.M. 1943. *Philosophical aspects of modern science*. London: George Allen.
- Kim, Gwang Hoon, and Lawrence Fritz. 1993. A signal glycoprotein with α -D-mannosyl residues is involved in the wound-healing response of *Antithamnion sparsum* (Ceramiales, Rhodophyta). *Journal of Phycology* 29 (1): 85–90.
- L'Hardy-Hamos, M-Th. 1971. Recherches sur les Cériamiacées (Rhodophycées, Céramiales) et leur morphogénèse. *Revue Générale de Botanique* 78: 201–6, 407–91.
- Laughlin, Robert. 2005. *A different universe: Reinventing physics from the bottom down*. New York: Basic Books.

- Leeuwenhoek, Antony van. 1932–present. *The collected letters of Antony van Leeuwenhoek*. Amsterdam: Swets & Zeitlinger.
- McCrone, John. 2002. *How the brain works — A beginner's guide to the mind and consciousness*. London: Dorling Kindersley.
- Morange, Michel. 2008. The death of molecular biology? *History and Philosophy of the Life Sciences* 30 (1): 31–42.
- Muller, Herbert J. 1943. *Science and criticism*. New Haven: Yale University Press.
- Oloparde, Olufunmilayo I. 2004. Genetics in cancer care — a promise unfulfilled among minority populations. *Cancer Epidemiology Biomarkers & Prevention* 13: 1683–6.
- Otis, L. 2001. *Networking, communicating with bodies and machines in the nineteenth century*. Michigan: University of Michigan Press.
- Quevli, Nels. 1916. *Cell intelligence, the cause of evolution*. Minneapolis: Colwell Press.
- Rosen, Robert. 2000. *Essays on life itself*. New York: Columbia University Press.
- Sylvia, Claire, and William Novak. 1997. *A change of heart*. New York: Warner Books.
- Takagi, S., Y. Nishiura, T. Nakagaki, and T. Ueda. 2007. Indecisive behaviour of *Amoeba* crossing an environmental barrier. In *Topological aspects of critical studies and networks*, 86–94. Singapore: World Scientific Publishing.
- Takeuchi, Leslie A. 2004. Cellular Memory in Organ Transplants. *San Francisco Medicine* (August). www.sfms.org, accessed 21/8/09.
- Thomas, L. 1974. *The lives of a cell*. New York: Viking Press (reprinted by New York: Penguin Group, 1978).
- Verworn, M. 1888. Biologische Protisten-Studien. *Zeitschrift für Wissenschaftliche Zoologie* 46 (4): 455–70.
- Waaland, S.D. 1975. Evidence for a species-specific cell fusion hormone in red algae. *Protoplasma* 86: 253–61.
- Waaland, S.D, and R.E. Cleland. 1974. Cell repair through cell fusion in the red alga *Griffithsia pacifica*. *Protoplasma* 79: 185–96.
- Waite, John. 2008. Repeat from Today programme. *Pick of the Week*, BBC Radio Four: 1815–1900h, 26 October.
- Watkins, G.P. 1900. Psychical life in protozoa. *The American Journal of Psychology* 11 (2): 166–80.
- Wechsler, David. 1939. *The measurement and appraisal of adult intelligence*. Baltimore: Williams & Wilkins; fourth edition 1958.
- Wolpert, Lewis. 2009. *The secret lives of cells*. London: Faber & Faber.
- Zock, Joseph, and Rebecca J. Palmer. 2008. Unfulfilled promise of predictive toxicology. *Genetic Engineering and Biotechnology News* 28 (19): 1–10.

Notes on Contributor

Brian J. Ford has published numerous scientific papers in journals from *Nature* and *New Scientist* to the *British Medical Journal*, *Scientific American*, *The Cell*, *The Microscope* and many others. He is a Fellow and Member of Court at Cardiff University, an Honorary Member of Keynes College, University of Kent and is based at Gonville & Caius College, University of Cambridge. Ford is a former Fellow of the Open University and Visiting Professor at the University of Leicester. He lectures internationally and his 30-odd books have been published in the USA, China, Japan, Germany, Spain, Poland and elsewhere. They range from *Microbiology and Food* (1970) and *Microbe Power, Tomorrow's Revolution* (1976) to *Genes, the Fight for Life* (1999) and *The Secret Language of Life* (2000). He has published several notable papers expanding the concept of cell intelligence in the UK and the US, and has frequently lectured and broadcast on this topic around the world. Correspondence to: mail@brianjford.com