

Power, Sex, Suicide

Mitochondria and the Meaning of Life

Part 5. Murder or Suicide: The Troubled Birth of the Individual

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About

Dr Nick Lane is a British biochemist and writer. He was awarded the first Provost's Venture Research Prize in the Department of Genetics, Evolution and Environment at **University College London**, where he is now a Reader in Evolutionary Biochemistry. Dr Lane's research deals with evolutionary biochemistry and bioenergetics, focusing on the origin of life and the evolution of complex cells. Dr Lane was a founding member of the UCL Consortium for Mitochondrial Research, and is leading the UCL Research Frontiers Origins of Life programme. He was awarded the 2011 BMC Research Award for Genetics, Genomics, Bioinformatics and Evolution, and the 2015 Biochemical Society Award for his sustained and diverse contribution to the molecular life sciences and the public understanding of science.



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'I think therefore I am' said Descartes, begging the rejoinder 'But what exactly am I?'

The nature of the individual has long eluded philosophers and scientists, and is only now coming into focus. We can say that an individual is an organism composed of genetically identical cells, which are specialised to perform diverse tasks for the good of the organism as a whole. From an evolutionary point of view, the question is: why did these cells subordinate their selfish interests to collaborate so altruistically in the body?

Inevitably there were conflicts between the various levels of organization in the body, between genes, organelles and cells, but paradoxically without these internecine battles the strong bonds that forge the individual might never have evolved. Such conflicts spurred the evolution of a molecular 'police force', which curbs selfish interests much as the legal system enforces acceptable behaviour in society. In the body, programmed cell death, apoptosis, is central to the policing of conflicts. Today, apoptosis is enforced by mitochondria, raising the possibility that they may have been key to the evolution of individuals. In this chapter we shall see that, back in the mists of evolutionary time, mitochondria were indeed intimately linked with the rise of multicellular individuals.

There has been more spleen vented about selfish genes, altruism, and the limits of natural selection than is seemly in polite scientific society. Underpinning many of the arguments was a simple question: what does natural selection act upon – genes, individuals, groups of individuals (such as a kin group), or the species as a whole? In 1962, Vero Wynne-Edwards' eloquent treatise on animal behaviour, *Animal Dispersion in Relation to Social Behaviour*, concentrated minds. He ascribed many aspects of social behaviour to selection not at the level of the individual, as had been assumed by Darwin, but at the level of the species. Behaviour was just the tip of the ice-berg. Many other traits seemed easier to explain by thinking of the species rather than the individual. For

example, ageing doesn't seem to benefit the individual in any way (what do we gain from getting old and dying?) but does look like a useful service to the species, for it leads to population turnover, preventing overcrowding and over-consumption of lean resources. Similarly, sex seemed pointless for individuals, so much so that we must be bribed by intense erotic pleasure; presumably, mild pleasure is not enough. Rather than simply dividing in two like a bacterium, such that one parent produces two daughter cells, sex takes two parents to produce a single offspring, making it twice as costly as clonal reproduction – the twofold cost of sex – to say nothing of the trouble of finding a mate. Worse, sex randomises the very genes that had ensured the success of the parents, making it a potential liability. Its most obvious value is the fast dissemination of variation, and beneficial adaptations, throughout a population: a benefit to the species.

The reaction to these ideas is often dismissed as ultra-darwinism, a term of disparagement meaning little. How, one must ask, does species-level selection work? There are ways in which it might. For example a fast population turnover leads to a fast rate of evolution, which might benefit one species over another if conditions change quickly (for example during rapid global warming, or after a meteorite impact). Another possibility, which Richard Dawkins refers to as the 'evolution of evolvability' relates to the genetic 'flexibility' of a species – some species have more scope for further evolution in their form and behaviour than others. In most instances, however, the blindness of evolution means that such species-level selection just can't develop. Sex is complicated and didn't evolve overnight. If the only benefits are at the species level, and are deferred until sex has actually evolved, what happens in the meantime? Any individuals in a population that take a tentative step towards sex will lose out, and eventually be eliminated by natural selection, because they suffer from the twofold cost of sex and the randomisation of any beneficial traits, before any advantages can take over. Similarly, individuals who don't age will leave their anti-ageing genes behind, which will come to dominate the population simply because the carriers have more time to have more children, who can pass on the same anti-ageing genes. Thus, on one hand there seemed few ways that selection could work at the level of the species, and on the other, some noble self-effacing traits could only be explained (at the time) by recourse to

selection at the level of the species.

From the 1960s onwards, William Hamilton, George C. Williams, John Maynard Smith, and others, sought to explain apparently altruistic traits by means of selection at the level of the individual, the kin group, or the gene. The new approach boiled down to a mathematical exploration of inclusive fitness – the idea famously expressed in a pub conversation by JBS Haldane: “Would I lay down my life to save my brother? No, but I would to save two brothers, four nephews, or eight cousins” (on the grounds that he shared 50% of his genes with his brothers, 25% with his nephews and 12.5% with his cousins, so his genes at least would break even). Much of the ensuing acrimony centred on the use of such loaded terms as ‘selfish’ – terms that have a specific definition in biology, but emotive overtones in general usage. In particular, Richard Dawkins’ *The Selfish Gene* either inspired or raised the hackles of an entire generation, at least partly because it was so well written that everyone could feel the icy blast of its conclusion – living organisms are the throwaway survival machines of their genes, temporary puppets controlled by virtually immortal puppet-master genes. The only logical way to think about evolution, said Dawkins, is to stop gazing at our own belly buttons, and take a genes’-eye view of population dynamics.

The idea that the gene is the ‘unit of selection’ has been attacked from many quarters. The most common line of attack is the claim that genes are invisible to natural selection: they are inert stretches of ticker tape that do no more than code for proteins or RNA. What’s more, there is an ambiguous relationship between a gene and the protein it encodes: the same gene may be split up in different ways, so that it codes for several different proteins; and we now realise that many proteins fulfil more than one function. Genes can also have very different effects, depending on the body they find themselves in. For example, it’s often pointed out that a variant of the haemoglobin gene protects against malaria when present in half dose (heterozygous), but causes sickle cell anaemia when present in full dose (homozygous). All this is true, but none of it undermines the power of a gene-centred approach to explain the currents of evolution: the individual may be the object of selection, but only the genes are passed on to the next generation.

The key to the selfish gene is that, in sexual reproduction, the individual does not persist from one generation to the next; no more do any of the individual cells, nor even chromosomes. Bodies dissolve and reform like wisps of cloud, each one fleeting and different. According to Dawkins, only the genes persist, resistant to being scrambled, old as the mountains. From the perspective of a population over evolutionary time, the changes in gene frequencies are the best means of quantifying evolution. To an extent this is a mathematical crutch to a complex problem, but it is also a reality, however unpalatable it may be.

From the point of view of selfish genes, the evolution of an individual is not a problem. If the conglomeration of cells that we call a body happens to be successful at passing on its genes to the next generation, then these genes will thrive to the detriment of the genes that don't collaborate in this way. A body is the product of genes collaborating together to serve their own selfish end of being copied in ever greater numbers. Dawkins is explicit on the point: "Some people use the metaphor of the colony, describing a body as a colony of cells. I prefer to think of the body as a colony of genes, and of the cell as a convenient working unit for the chemical industries of the genes."

The crux of the selfish gene is that only the gene passes from one generation to the next, so the gene is the most stable evolutionary unit: it is the 'replicator'. Dawkins makes it clear that this perspective is restricted to sexually reproducing organisms, like most (but not all) eukaryotes. It doesn't apply to bacteria with the same force, because they replicate clonally. In this case, the individual cell can be said to persist from one generation to the next, whereas accumulating mutations mean that the genes themselves do change. In fact, in physically stressful circumstances, bacteria can even speed up the mutation rate in their genes. So there is a dilemma in bacteria about whether selection is 'for' the genes or the cell as a whole. In many respects the cell is the replicator.

Mutations in a gene don't necessarily change the phenotype (the function or appearance of the organism) but by definition they must change the gene itself, perhaps even

scrambling its sequence out of recognition over aeons. Mutations accumulate because many of them have little or no effect on function, and so go unnoticed by natural selection – they are said to be ‘neutral’. Most of the genetic differences between people, on average one in every 1000 DNA letters, millions of letters in total, are likely to result from neutral mutations. When we consider very different species, two sequences can be so dissimilar that it is not possible to discern any relationship between them, unless we take into consideration the spectrum of intermediary forms in more closely related species. Then we can see that two apparently unrelated genes are indeed related. The physical structure and function of proteins encoded by utterly dissimilar genes is often strikingly well conserved, even though the amino acid components are now mostly different. Plainly, the structure and function of the protein has been selected ‘for’, whereas the sequence of the gene is relatively plastic. It’s like returning to a company that you once worked for, to discover that none of your former colleagues still works there, but that the type of business, ethos and management structures are exactly as you remembered them, a ghostly echo of the past.

Because genes can change, while the cell and its constituents remain essentially unchanged, the bacterial cell might be considered more stable an evolutionary unit than its genes. For example, cyanobacteria (the bacteria that ‘invented’ photosynthesis) have certainly changed their gene sequences over evolution, but if the fossil evidence can be believed, the phenotype has barely changed over billions of years. If, as Dawkins has argued, the worst enemy of the selfish gene is a competitive (polymorphic, or altered) form of the same gene, then neutral mutations are the selfish gene scrambler par excellence: gene sequences diverge over time as neutral mutations accumulate. There may be millions of different forms of the same gene in different species, all scrambled to varying degrees; this is the basis of any gene tree. So evolution pits the selfish interests of genes (which ‘want’ to produce exact copies of themselves) against the randomising power of mutation, which forever scrambles the sequence of genes, turning the selfish gene into its own worst enemy, the gene it used to hate.

Several other considerations militate against the gene as the ‘unit of selection’ in

bacteria. It is said that in clonal replication all the genes are passed on together, so there is no distinction between the fate of the genes and the fate of the cell. This isn't quite true. Bacteria swap genes, and are prey to viruses called bacteriophages which load up cassettes of selfish DNA. Yet whereas eukaryotes are stuffed with selfishly replicating 'parasitic' DNA (DNA sequences that replicate for their own benefit, rather than that of the organism), bacteria have small genomes and next to no parasitic DNA. As we saw in Part 3, bacteria lose excess DNA, including functional genes, because this speeds up their replication. If these genes are 'selfish', they are punished for it by being regularly thrust out into the hostile world. Perhaps it's reasonable to think of lateral gene transfer in bacteria as a selfish rearguard action on the part of the genes themselves, but in general such lateral gene transfers only last as long as the cell needs the extra genes, and then they are lost again, along with any other genes that are not needed. I don't doubt we could interpret all of this in terms of selfish genes, but I find such behaviour much easier to grasp in terms of the costs and benefits to the cells themselves, not the genes.

There is another sense in which it might be better to see the cell as the selfish unit, rather than its genes, at least in bacteria. This is that genes do not code for cells: they code for the machinery that makes up cells, the proteins and RNA that in turn build everything that is needed. This may seem a trivial distinction, but it is not. All cells have a highly elaborate structure, even bacterial cells, and the more we learn about them, the more we appreciate that cellular function depends on this structure; as we saw in Chapter 2, cells are emphatically not just a bag of enzymes. Intriguingly, there seems to be nothing in the genes that codes for the structure of cells. For example, membrane proteins are directed to their particular membranes by means of well known coding sequences, but nothing stipulates how to create such a membrane from scratch, or determines where it should be built: lipids and proteins are added to existing membranes. Similarly, new mitochondria are always formed from old mitochondria – they cannot be made from scratch. The same goes for other components of the cell like centrioles (the bodies that organise the cytoskeleton).

At the fundamental level of the cell, then, nature depends on nurture, and vice versa. In other words, the power of the genes depends absolutely on the pre-existence of the cell itself, while the cell can only be perpetuated through the action of the genes.

Accordingly, the genes are always passed on within a cell, such as an egg or a bacterium, never as a discrete packet. Viruses, which are a discrete packet, only come alive when they gain access to the machinery of an existing cell. The microbiologist Franklin Harold, whom we met in Part 2, has pondered long and deep about these matters; he put it thus some 20 years ago, and little has changed:

The genome is the sole repository of hereditary information and must ultimately determine form, subject only to limited modulation by the environment. But the inquiry into just how the genome does this leads through another set of Chinese boxes, to show the innermost one empty.... Gene products come into a pre-existing organized matrix consisting of previous gene products, and their functional expression is channelled by the places into which they come, and by the signals they receive. Form is not explicitly spelled out in any message but is implicit in its combination with a particular structural context. At the end of the day, only cells make cells.

On balance, then, there are many reasons to see the bacterial cell as the selfish unit of evolution, rather than its genes. Perhaps, as Dawkins said, the invention of sex in the eukaryotes changed all that; but if we wish to understand the deeper currents of evolution we must look to the bacteria, which alone held dominion over the world for two billion years. These differences in perspective help to explain why microbiologists, such as Lynn Margulis, are among the most prominent critics of the selfish gene. In fact, Margulis has become an outspoken critic of mathematical neo-darwinism in general, going so far as to dismiss it as being reminiscent of phrenology, that Victorian obsession with cranial shape and criminality, and likely to suffer the same ignominious fate.

While one senses that Margulis is repelled by the concept of the selfish gene, it is also true that bacteria are rather more likely to behave in a civil manner, forming communities that live together in harmony rather than 'eating' each other: the idea of bacteria as merely pathogenic is persistent but false. For Margulis, evolution is largely a bacterial affair, and can be explained in terms of mutual collaborations between consortia of bacteria, including endosymbioses, such as those which founded the eukaryotic cell. These consortia work well in bacteria because predatory behaviour doesn't pay: as we saw in Part 3, the mechanism of respiration across the cell membrane means that large, energy-rich bacterial cells capable of physically engulfing other cells (phagocytosis) are virtually precluded by natural selection. Bacteria are obliged to compete with each other by the speed of their growth, rather than the size of their mouth. Given the reality of food shortage in bacterial ecosystems, bacteria gain more by living from each others' excrement than they do by fighting over the same raw materials. If one bacterium lives by fermenting glucose to form lactic acid, then there is scope for another to live by oxidizing the waste lactic acid to carbon dioxide; and for another to convert the carbon dioxide into methane; and another to oxidize the methane; and so on. Bacteria live by endless recycling, which is best achieved via cooperative networks.

Perhaps it's worth remembering that even cooperative partnerships can only persist if the partners do better within the partnership than without. Whether we measure 'success' by the survival of cells or the survival of their genes, we still see only the survivors – the cells or genes that did copy themselves most successfully. Those cells whose altruism is so extreme that they die for another are doomed to disappear without trace, just as many young war heroes fought and died for their country, leaving behind a mourning family but no children of their own. My point is that collaboration is not necessarily altruistic. Even so, a world of mutual collaboration seems a far cry from the conventional idea, expressed by Tennyson, of 'nature, red in tooth and claw'. Collaboration might not be altruistic, but neither is it 'aggressive' – it doesn't make us think of jaws dripping in blood.

This discrepancy is partly responsible for the schism that has opened between Margulis and neo-darwinists like Dawkins. As we have seen, Dawkins' ideas about selfish genes are equivocal when applied to bacteria (which he does not try to do). For Margulis, however, the whole tapestry of evolution is woven by the collaborations of bacteria, which form not just colonies but the very fabric of individual bodies and minds, responsible even for our consciousness, via the threadlike networks of microtubules in the brain. Indeed, Margulis pictures the entire biosphere as the construct of collaborating bacteria – Gaia, the concept that she pioneered with James Lovelock. In her most recent book, *Acquiring Genomes: A Theory of the Origins of Species*, written with her son Dorion Sagan, Margulis argues that even among plants and animals, new species are formed by means of a bacterial-style merging of genomes, rather than the gradual divergence pictured by Darwin, and accepted by virtually every other biologist. Such a theory of merging genomes might be true in some instances, but in most cases it flies in the face of a century of careful evolutionary analysis. In dismissing neo-darwinism, Margulis deliberately provokes the majority of mainstream evolutionists. Few have the patience displayed by the late Ernst Mayr, who contributed a wise foreword to the book, in which he commended Margulis's vision of bacterial evolution, while cautioning the reader that her ideas don't apply to the overwhelming majority of multicellular organisms, including all 9000 species of bird, Mayr's own particular field of expertise. The reality of sexual reproduction means that genes must compete for space on the chromosomes; and the rise of predation in the eukaryotes means that nature, at this level, really is red in tooth and claw, however much we may wish it otherwise.

Given their different perspectives, it's ironic that the views of Dawkins and Margulis do not diverge as far as one might think when it comes to the individual. As we have seen, Dawkins wrote of the individual as a colony of collaborating genes, while Margulis thinks of an individual as a colony of collaborating bacteria, which might be construed as colony of collaborating bacterial genes. Both see the individual as a fundamentally collaborative entity. Here is Dawkins, for example, in his splendid book *The Ancestor's Tale*: "My first book, *The Selfish Gene*, could equally have been called *The Cooperative Gene* without a word of the book itself needing to be changed... Selfishness and

cooperation are two sides of a Darwinian coin. Each gene promotes its own selfish welfare, by cooperating with other genes in the sexually stirred gene pool which is the gene's environment, to build shared bodies.”

But the ideal of collaboration does not give proper weight to the conflict between the various selfish entities that make up an individual, and in particular to the cells and mitochondria within the cells. While conflict between various selfish entities is entirely in keeping with Dawkins's philosophy, he did not develop the idea in *The Selfish Gene* – these ideas awaited his own later book *The Extended Phenotype*, and in the 1980s and 1990s the important work of Yale biologist Leo Buss and others. Thanks to the exploration of such conflicts and their resolutions, evolutionary biologists now appreciate that colonies of cells (or genes, if you like) do not constitute true individuals, but rather form a looser association, in which individual cells may still act independently. For example, multicellular colonies like sponges often fragment into bits, each of which is able to establish a new colony. Any commonality of purpose is transitory, for the fate of individual cells is not tied to the fate of the multicellular colony.

Such cavalier behaviour is ruthlessly suppressed in true individuals, in whom all selfish interests are subordinated to a common purpose. Various means are employed to guarantee a common purpose, including the early sequestration of a dedicated germ-cell line, so that the great majority of cells in the body (so-called somatic cells) never pass on their own genes directly, and can only participate in the next generation voyeuristically, as it were. Such voyeurism could not possibly work if the individual cells within the body did not share identical genetic bonds – all derive from a single parent cell, the fertilised egg (the zygote), by asexual, or clonal, replication. Although their own genes are not passed on directly to the next generation, the germ-line cells do pass on exact copies of them, which is the next best thing, and ultimately little different. Even so, carrot measures are not enough: stick measures are also needed. The resolution of selfish conflicts between the cells themselves, even though they are genetically identical, can only be achieved by the imposition of a police state reminiscent of Stalinist Russia. Offenders are not prosecuted but eliminated.

The consequence of this draconian system is that natural selection ceases to pick and choose between the independent entities that make up an individual, and begins to operate at a new and higher level, now choosing between the competing individuals themselves. Yet even within apparently robust individuals, we can still detect echoes of dissent, a reminder that the unity of an individual was hard won, and all too easily lost. One such echo of the past is cancer, and it is to this, and the lessons we can learn from it, that we turn to in the next chapter.

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