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EDITORIAL

Systems and Synthetic Biology: Physiology and Biochemistry Strike Back

Biology has advanced on a very broad front over the past half a century. By the mid-1970s the recombinant DNA revolution was on and the term genetic engineering became commonplace. The Boyer–Cohen experiment of 1973 produced the first 'cloned DNA', a key step in the thrust to produce protein pharmaceuticals. Genentech, the first modern biotechnology company, was born in 1976. Four years later when the company went public, its initial stock offering raised over $38 million and its share price more than doubled in a few minutes of trading. At that moment, the company had no marketed product and its dramatic initial success in the world of business rested on the promise of the new biotechnology (*Genentech*: *The Beginnings of Biotech*, Sally Smith Hughes, University of Chicago Press, 2011). For the past three decades biotechnology has been propelled forward by several major scientific advances that have emerged from research laboratories, the polymerase chain reaction, DNA sequencing and synthesis, methodologies for protein expression and purification and, of course, the dramatic progress of biological research cutting across the disciplines of cell biology, microbiology, plant and animal science. Physics and chemistry have repeatedly intruded, as structural biology has, time and again, demonstrated the virtues of reductionism. By the 1990s biology's leading front was genomics, fuelled by the rapid pace of advance in DNA sequencing technologies. Whole genome sequencing promised to reveal 'genetic blueprints' for organisms as diverse as bacteria and man. A decade has passed since the successful completion of the campaign to sequence the human genome. The champions of genomics proudly proclaim that individuals can now have their genomes sequenced; a first step in entering the brave new world of pharmacogenomics and personalized medicine. Even as the power of sequencing has grown and costs have fallen there appears to be an air of disquiet. Has genomics delivered on the many promises of its most ardent champions? Has the cause of human health been advanced by our intimate knowledge of the genome? Has Nature concealed more than it has revealed in the genome? In a thoughtful commentary, a prominent geneticist voices the concerns of an insider: 'Translating current knowledge into medical practice is an important goal for the public who support medical research, and for the scientists and clinicians who articulate the critical research needs of our time. However, despite innumerable successful gene discoveries through genomics, a major impediment is our lack of knowledge of how these genes affect the fundamental biological mechanisms that are dysregulated in disease. If genomic medicine is to prosper, we need to turn our attention to this gaping hole' (Chakravarti, A., *Science*, 2011, **334**, 15). Translating the successes of basic research in biology into practical medical application can be an extremely difficult task. In making the connection between variations in DNA sequence and disease, the complexities of the mechanisms that underlie clinical problems intrude, rather rudely.

Mendelian diseases, caused by variations in single genes, sickle cell anaemia being the classic example, are easily identified by genetic analysis. The greatest challenges of our times, cancer, diabetes and neurodegenerative disease amongst them, are more complex, leading Chakravarti to note that, 'we need to answer not only which DNA variants in which genes lead to disease, but how they do so'. He is succinct and emphatic: 'The lessons from genome biology are quite clear. Genes and their products almost never act alone, but in networks with other genes and proteins…. Genome biology now needs to move to cell biology and physiology (systems biology) to understand how genetic perturbations lead to downstream dysregulation of proteins, their networks, and cells in disease.'

Genomic research was marketed in the aftermath of the sequencing successes as the driver of a revolution in clinical medicine. The euphoria of the early days is now muted and some pessimists have begun to wonder if genomics and high throughput genetics will indeed have a significant impact on medical practice. What then does the future hold for biology in the post-genomic era? Bruce Alberts argues that biology's 'grand challenge' would be to 'aim at a complete understanding of the simplest free-living cells'. He quotes Richard Feynman – 'What I cannot create, I do not understand' – in arguing that the growing field of 'synthetic biology', with its aim of 'creating networks' has the 'promise to become a powerful new tool' in fuelling biology's next major advance (*Science*, 2011, **333**, 1200). Are the terms systems and synthetic biology descriptors of a new approach to biology? Has the reductionist approach of studying individual components of complex biochemical systems finally reached the end of the road? Has the deluge of data,

genomic, proteomic and metabolomic finally drowned reductionist biochemistry? In confronting these uncomfortable questions we might draw solace from Sydney Brenner's view: 'The problem of biology is not to stand aghast at the complexity but to conquer it'. Brenner is acerbic in his characterization of biology's current fashion: 'You see, everybody's running around talking about systems biology and integrative biology. It's nothing new. It's called physiology' (*Discover*, April 2004).

Molecular biology in its tumultuous advance in the second half of the 20th century completely overwhelmed two classical disciplines, physiology and biochemistry. Ironically, it is these very disciplines which now appear critical in advancing biology's new frontiers. In tracing the roots of 'systems biology' Denis Noble, an eminent physiologist, draws attention to the fact that one of the field's most famous successes was when Hodgkin and Huxley 'integrated their equations for the nerve impulse in 1952'. Noble notes that Claude Bernard could legitimately be called 'the first systems biologist' and also the first proponent of mathematical biology. Bernard 'formulated the systems principle of control of the internal environment' in 1865, a cornerstone of modern physiology. He also believed that the 'application of mathematics to natural phenomena is the aim of all science, because the expression of the laws of phenomena should always be mathematical' (Noble, D., *Philos. Trans. R. Soc. A*, 2010, **368**, 1125). The growing emphasis on systems biology is a consequence of the recognition that the connection between single genes (and their products) and physiological function is often tenuous. The new technologies of 'gene knockouts' have led to the conclusion that organismal functions often remain unimpaired even when a gene is rendered dysfunctional, leading to the conclusion that underlying protein networks are robust, clearly buffered against individual failure at some connections (Noble, D., *J. Physiol*., 2011, **589**, 1007). Noble suggests that individual gene-centric approaches must give way to discussions of 'cooperative genes', conceptually and metaphorically distinct from Richard Dawkins' 'selfish gene'. Noble emphasises the need for physiology to 'reconnect with developmental and evolutionary biology', with computational systems biology developing as a key tool.

If systems biology hopes to provide a broad understanding of the complexities of cellular processes, synthetic biology will provide a test of the emerging conceptual framework. Understanding must precede design. Much can be learnt when design strategies do not yield the desired result. 'The allure of synthetic biology' rests to a large extent on the possibility that gene manipulation can be extended to 'DNA-encoded circuits' (protein networks and metabolic processes with complex interconnections). Synthetic biologists talk of 'rewiring cellular circuitry to control biological processes' (Vinson, V. and Pennisi, E., *Science*, 2011, **333**, 1235); a language that bears a resemblance to the control of networks, so well understood in the world of electrical engineering and communications technology. Synthetic biology appears to promise a control over cellular chemistry that could hardly have been taken seriously in the era before the genomics revolution. A recent special section in *Science* (2 September 2011) highlights the potential of synthetic biology, drawing attention to many projects that might have been considered inconceivable even in the last decades of the 20th century. Rewiring cells may appear a difficult process, but there is a hope that this area will also succumb to the power of the new technologies. Ongoing work attempts to develop a methodology called multiplex automated genome engineering (MAGE), where millions of normal bacteria, *E. coli*, enter a 'contraption' and a 'menagerie of microbes with new genomes comes out the other end' (Bohannon, J., *Science*, 2011, **333**, 1236). The special section in *Science* emphasises the promise of synthetic biology in transforming the drive to produce algal biofuels, a process that would not compete for agricultural land. The promise in biomedicine and in the clinic appears immense; cynics may recall that this was true also of genomics in the midst of the sequencing revolution. Bioengineering, a field that is yet to emerge as a coherent discipline from its intensely interdisciplinary origins, will undoubtedly be an area where synthetic biology will make its major contributions. It is here that a hard question will be asked: 'How synthetic can synthetic biology be?' (Schwille, P., *Science*, 2011, **333**, 1252).

The passing of the golden age of molecular biology, where reductionism triumphed repeatedly in advancing our understanding of cellular processes, has been acknowledged, even by the pioneers of the field. Sydney Brenner notes that 'no use will be served by regretting the passing of the golden years of molecular genetics'. He argues that 'we should welcome with open arms everything that modern technology has to offer us but we must learn to use it in new ways. Biology urgently needs a new theoretical basis to unify it and it is only theory that will allow us to convert data into knowledge'. In contrast to many of the proponents of systems biology, Brenner argues for a new thrust to the reductionist view. In his view it is not DNA or the genome that is the focus as the fundamental element of biology; rather, 'the correct level of abstraction is the cell' (*Philos. Trans. R. Soc. A*, 2010, **365**, 207). Where does all of this leave biochemistry? Brenner once remarked 'that two things disappeared in 1990: one was communism, the other was biochemistry and that only one of these should be allowed to come back'. He went on to add: 'We do not have to resurrect biochemistry, and it will flourish because it provides the only experimental basis for causal understanding of biological mechanisms' (*Trends Biochem. Sci*., 2000, **25**, 584). Biology's future may rest on returning to its roots, as physiology and biochemistry strike back in the age of systems and synthetic biology.

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