BOOKS & ARTS

Building life from the bottom up

Engineering biological systems and organisms is a costly team effort and may be incompatible with an open-source regulatory environment, finds **Michael A. Goldman**.

Biology is Technology: The Promise, Peril, and New Business of Engineering Life
by Robert H. Carlson
Harvard University Press: 2010. 288 pp.
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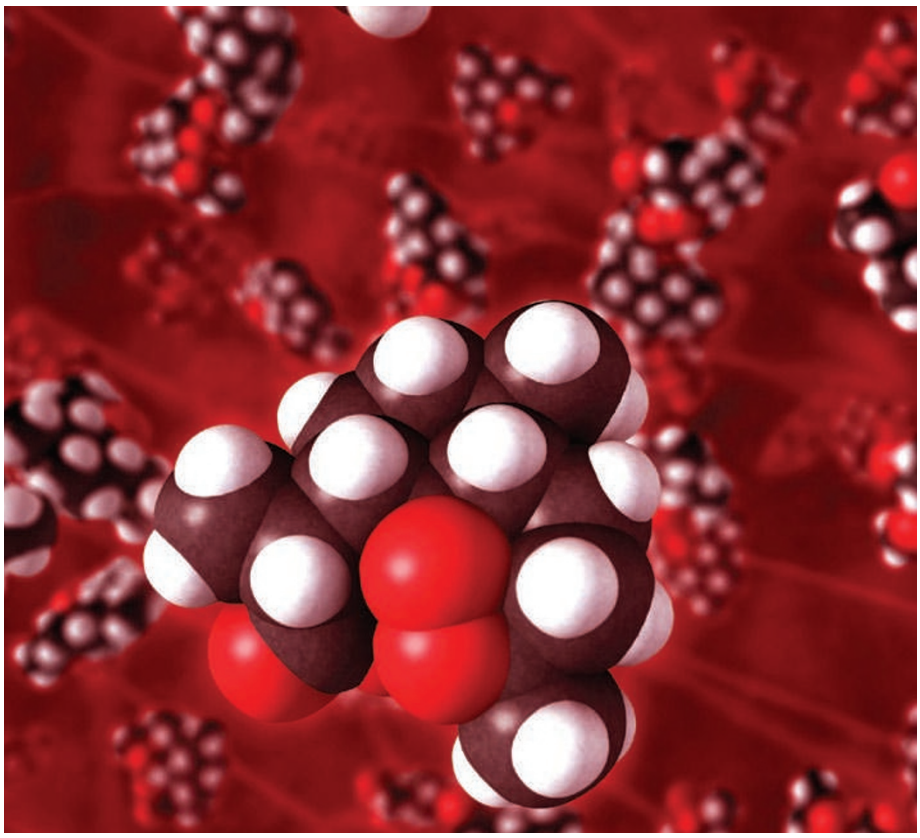

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The malaria drug artemisinin is artificially made in bacteria using components from other organisms.

By focusing his book only on those biological components that can be combined as if they were Lego bricks, Robert Carlson ignores much of biology. Nevertheless, in *Biology is Technology*, he presents an informative view of the future prospects for biotechnology and its regulation.

Carlson, who is the head of Biodesic, a bioengineering consulting firm in Seattle, Washington, explains how biotechnology can be applied to solve problems across agriculture, pharmacology, vaccines and biofuels. He takes a mechanistic approach, reflecting his background in physics and electrical engineering. Using developments in aviation as a model for the evolution of biological technologies, he argues that: "Just as we learned to fly aircraft, so must we learn to 'fly' biology."

To demonstrate the scale of the challenge, he compares a Boeing 747 jet — made up of 50,000 different parts and built using 50-year-old technology — to a 'simple' yeast cell. Its 4,800 or so genes make more than ten million proteins and metabolites, based on a 3-billion-year-old 'technology' that we do not yet comprehend. By analogy with aviation, he argues, biotechnology is now in a Wright Brothers era, just getting off the ground. But one day, he says, we will have enough knowledge of biology to design and build a cell from component parts, in the way we now build a jet straight from digital plans with minimal testing in between.

> "It could be a long time before we see real open-source biotechnology."

Systems biologists are using computers to model metabolic processes for drug testing and development, for example, but progress has been limited. Carlson appreciates the complexity of biological components — for example, humans comprise more than 10^{13} cells and 20 times this number of microorganisms. He notes the primitive state of our understanding of this complexity, as illustrated by the unintended consequences of our attempts at gene therapy, such as the occurrence of leukaemia in some individuals treated for immune deficiency. Yet he urges us to learn how each part works individually and together, so that we will "truly be able to produce engineered biological systems".

Carlson's building-block approach is exemplified by the artificial synthesis of the drug artemisinin. This compound is part of an effective cocktail used to treat malaria, but it is expensive when obtained from its natural source, the plant *Artemisia annua*. By combining the relevant genes from different organisms in the bacterium *Escherichia coli*, chemical engineer Jay Keasling and his colleagues reconstructed the multi-step metabolic pathway that synthesizes the artemisinin precursor amorphadiene, thus creating a small-scale bacterial factory for the manufacture of this molecule.

Carlson does not take synthetic biology much farther than stringing together components to produce useful products. By contrast, genomics pioneer Craig Venter imagines designing and building from scratch a minimal genome that will direct the simplest of 'living' organisms. But higher forms of life are not self-assembling: they often require a sophisticated array of cellular components to aid gene expression and assemble the products of the genome during development. Venter's efforts to synthesize a cell using the DNA of *Mycoplasma genitalium* — which has the smallest known genome of any free-living organism — could improve our understanding of what makes simple organisms tick, and of how organisms might be designed to carry out specific operations, such as the production of biofuels. But in the wrong hands, that same technology could be used to commit acts of bioterrorism; for example, by exploiting sequence data to unleash historical infectious agents such as Spanish influenza.

Although he overemphasizes the perils of regulating new science, Carlson's conclusions are sound. In the Internet era, it is impossible to keep information away from potential bioterrorists. Doing so would fuel a black market and the parallel development of technologies beyond the view of the public and regulators. Carlson cites the example of the drug methamphetamine, which commands a larger illegal market now than it did when enforcement began. By making information widely available, scientists can keep cutting-edge developments in the public eye and ensure that the best tools for combating terrorism are left in the hands of authorities. "Restricting research," he says, "will merely leave us less prepared for the inevitable emergency of natural and artificial biological threats."

Carlson is also concerned about the web of patent protections and licensing fees that threaten to stifle innovation. His solution is 'open-source biology', analogous to open-source software — a commons-based rights framework that allows rapid and inexpensive licensing and minimizes litigation. Open source, he says, "works precisely because it gives value to the process of innovation and allows innovators to set the terms under which their exclusive right is utilized by others". He sees a part of this implementation in the work of the BioBricks Foundation (see http://bbf.openwetware.org), a non-profit organization that encourages the development and use of a standard set of biological parts, made available in the Registry of Standard Biological Parts at the Massachusetts Institute of Technology in Cambridge (see http://partsregistry.org).

The parallels between information technology and synthetic biology break down when we recognize that we are looking at more than the movement of biological information and electrons. Carlson quotes one of the founders of the open-source software movement, Bruce Perens, who asserted that the open-source model works best for products whose value lies mostly in their design: "It only takes a cent's worth of resources to make a copy of a piece of software, but it takes a pound of flour to make a loaf of bread." For the foreseeable future, the engineering of biological systems will remain a costly team effort, requiring investment in reagents, personnel and equipment. It could be a long time before we see real open-source biotechnology: after all, we still pay for bread. ■

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A. NICHOLSON/STONE/GETTY

Why twins age differently

Epigenetics of Aging
Edited by Trygve O. Tollefsbol
Springer: 2009. 448 pp. $199, £135

Signs of ageing in animals originate from accumulated damage to the genome, proteins or corrupted cell components that reflect a decline in bodily maintenance. Others arise not from this primary damage, but through damage-limitation mechanisms that are provoked by cellular malfunctions. These frequently involve epigenetic processes — mechanisms that modify the information content of the genome without changing its DNA sequence.

Epigenetics of Aging, a collection of articles assembled by molecular biologist Trygve Tollefsbol, gives us a contemporary view of the epigenetic processes involved in ageing. The most significant of these, and the subject of several chapters, is the development of cellular senescence: a major reorientation of cell behaviour that becomes a formidable barrier to cancer.

Cellular senescence is a response to genomic damage and other insults, which activate the tumour suppressor proteins $p16^{INK4a}$ and p53 that promote DNA repair and stop cell division. The genome is then reorganized so that large regions form tight clumps in which genes that are normally active in cell proliferation are silenced. Senescent cells contribute to many characteristics of the ageing body, such as wrinkles.

The book explores a number of epigenetic mechanisms. However, by confining their scope to biochemistry, the authors divulge little of the recent progress in understanding the nature of senescent cells, from the ways in which they induce their neighbours to become senescent using secreted signals, to their capacity to remodel the cell interior and exterior — including loss of skin elasticity.

The book describes how, in the transition to senescence, the epigenetic role of Polycomb proteins — which sustain cell proliferation and repress differentiation genes — is abandoned. The sirtuins are another family of proteins with many epigenetic roles; by modifying the structure of histones and other proteins that are bound to DNA, they control how tightly clumped the genome becomes and facilitate DNA repair.

The advance of senescence is marked epigenetically by a steady loss of methyl groups from some genes and by sporadic gains of these groups in others. These random events can activate or suppress other genes. An important and intriguing contribution to the book shows that in humans, epigenetic markings change in response to life experience: by middle age, a cohort of identical twins developed diversity in their patterns of DNA methylation. This may be related to the variation in lifespan noted between identical twins.

Other articles link the loss of DNA methylation to the development of pathology, including the breakdown of cartilage in osteoarthritis and the production of the amyloid protein associated with Alzheimer's disease. The loss