Jamie A. Davies

SYNTHETIC BIOLOGY

A Very Short Introduction

OXFORD

OXFORD
UNIVERSITY PRESS

Great Clarendon Street, Oxford, OX2 6DP, United Kingdom

Oxford University Press is a department of the University of Oxford. It furthers the University's objective of excellence in research, scholarship, and education by publishing worldwide. Oxford is a registered trade mark of Oxford University Press in the UK and in certain other countries

First edition published in 2018
Impression: 1

Published in the United States of America by Oxford University Press 198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data
Data available

Library of Congress Control Number: 2018935710

ISBN 978–0–19–880349–2
ebook ISBN 978–0–19–252528–4

Printed in Great Britain by Ashford Colour Press Ltd, Gosport, Hampshire

Contents

Acknowledgements

First, I would like to thank Latha Menon of OUP for encouraging me to write this book on the first place. I am very grateful to members of my laboratory, and the Edinburgh synthetic biology community in which it is embedded, for very helpful discussions. I am, as always, grateful to Katie for her support, patience, and advice.

List of illustrations

Note: all images other than for Figure 1 are the author's.

Chapter 1

Biology: from analysis to synthesis

Living in interesting times

Synthetic biology—the creation of new living systems by design—is a rapidly growing area of science and technology that is attracting attention well beyond the laboratory and is provoking vigorous public debate. It is seen by some economists, government ministers, and leaders of industry as having the potential to transform productivity: David Willetts, UK Minister for Universities and Science, declared 'Synthetic biology is one of the most promising areas of modern science, which is why we have identified it as one of the eight great British technologies of the future. Synthetic biology has the potential to drive economic growth.' Others view it more sceptically: Jonathan Kahn, a specialist in legal aspects of biotechnology, described synthetic biology as 'the latest in a long line of claims of grand promise ... associated with successive major biotechnological undertakings ... [that] have not, as yet, come anywhere near realizing the extravagant claims made by their initial promoters.' It is seen by some commentators as a possible solution to a range of environmental and energy problems: Renee Cho of the Columbia University's Earth Institute, hoped that 'Synbio innovations could potentially help solve the world's energy crisis ... [and] restore the environment by cleaning up the water, soil, and air.' Others are far from convinced: Jim Thomas of the ETC action group on erosion, technology and concentration, warned that 'Synthetic biology is a high-risk profit-driven field, building organisms out of parts that are still poorly understood. We know that lab-created life-forms can escape ... and that their use threatens existing natural biodiversity.' It is seen by hobbyists as an opportunity for tinkering, for fun or for potential profit, in community workshops and garden sheds. Some observers view this activity as very positive: in an editorial for *The Scientist* magazine, Todd Kiocken wrote 'Citizen scientists are dedicated to education, innovation, and problem solving, using a new model in the human spirit of curiosity and exploration.' Others see an urgent need for such tinkering to be regulated: George Church, a prominent geneticist, suggested that 'Everybody who practices synthetic biology should be licensed, including amateurs. Same as cars, right? You're an amateur car driver, you get a license.'

The arguments have been stoked by hyperbole on both sides. New technologies often elicit extreme reactions, especially when they are considered in isolation and when they are presented—falsely—as something completely novel disconnected from the rich web of traditional sciences from which they emerged. The purpose of this Very Short Introduction is to present an overview of synthetic biology in its context, with as much balance as possible. There is no intention either to promote it as a technology or to argue for its repression: rather, the aim is to describe and illustrate the scope of synthetic biology and to provide an indication of its present and potential points of interaction with society at large.

Synthetic biology has been defined in many ways for many contexts, but the most general definition works by dividing biology as a whole into analytic and synthetic branches. Analytic biology, almost the only biology for most of the history of science, is concerned with understanding how naturally evolved living things work. Synthetic biology, by contrast, is concerned with the creation of new living systems by deliberate design. This definition is independent of the techniques used. It does not, for example, require any element of genetic manipulation: indeed, the research on creating life, described later in this book, has little to do with genes. Defined this way, synthetic biology ranges from the modification of existing organisms to do entirely new things, which is now routine at least at a small scale, to the as-yet unrealized creation of a living organism from non-living components. The subject is broad partly because of the way it is defined, and partly because it has two distinct and independent historical roots, one intellectually driven and running deep into 19th-century natural philosophy, and the other more practically orientated and emerging from late 20th-century biotechnology.

The first root of synthetic biology

One of the deepest biological questions asked by philosophers and scientists is whether life can be explained entirely by the natural laws of physics and chemistry. The 19th and early 20th centuries saw vigorous debate between materialists, who viewed life as exquisitely organized chemistry and physics, and vitalists, who held that living systems required something extra—an *élan vital* or *vis vitalis*. Though often nowadays dismissed as irrational or dogmatic, vitalists of the time used hard scientific evidence every bit as much as materialists did. One of the most famous experiments of 19th-century biology was that of Pasteur, who observed that sterilized broth would remain sterile if sealed but, if contaminated with a tiny number of microorganisms, would support the production of vastly more. The multiplication of the introduced microorganisms proved that the broth contained all the raw materials for making new living cells, but the necessity for 'seeding' it with a few living organisms showed that mere presence of the raw materials was not enough for life to emerge: something else was needed, something that could be provided only by the already-living. To vitalists this missing ingredient was the *élan vital.* To materialists, it was some function of organization that allowed a cell to produce copies of itself, organization that was missing in the soup of simple chemical ingredients. Both explanations fitted the data, and to take either position was a matter more of faith than of scientific proof.

Two very different approaches have been taken towards resolving the question of vitalism—analytical and synthetic. The analytical agenda aimed to gain a full mechanistic, physico-chemical understanding of how living things work. This approach was in any case the focus of much of mainstream biology—for reasons of scientific curiosity and because analysis of living processes was important to many practical problems in medicine and agriculture. Highlights of the analytical work of the last two centuries include Mendel publishing his theory of genetics in the 1850s; Friedrich Miescher discovering DNA in the 1860s; Theodor Boveri describing the chromosome-duplicating and -sharing processes involved in cell division in the 1870s; Theodor Boveri and Walter Sutton each demonstrating, in 1902, that specific genes are associated with specific chromosomes; Oswald Avery proving in 1944 that genes could be identified with the chromosomes' DNA; and James Watson and Francis Crick proposing in 1953 that DNA has a double-helical structure that would allow it to act as a template for its own copying. In the past few decades, vast numbers of researchers have determined how genes direct the synthesis of proteins; how some proteins in their turn control the activities of genes or metabolic reactions; and how the molecular machinery of the cell that separates chromosomes and then divides a cell to produce two daughter cells actually works.

This analytic work has given materialists a far greater ability to explain the physico-chemical basis of many aspects of cellular behaviour. It has not in itself, though, given them any way of disproving vitalism except by induction. Proof by induction, which is not really 'proof' at all, is a bedrock of science. It works by assuming that a pattern that has been observed in a large number of particular cases must be universally true. Knowing that humans, dogs, cats, bats, elephants, and hundreds of other mammals have four-chambered hearts, we state confidently that having a four-chambered heart is a characteristic of being a mammal, even though we have not dissected, and have probably not even discovered, all mammalian species. Induction is ubiquitous in science, but it is dangerous. Humans, dogs, cats, bats, elephants, flies, tube worms, and many other animals use iron-containing haemoglobin to transport oxygen around their bodies, leading to the 'rule' that this is a universal mode of oxygen transport. Unfortunately for induction, horseshoe crabs turned out to use copper-containing haemocyanin instead. Examples like this remind us that the fact that many aspects of cellular life have been described in physico-chemical terms still cannot be taken as logical proof that there are no vitalistic exceptions to this rule. The analytic agenda can refute vitalism robustly only when every single aspect of life, including such aspects as consciousness, can be explained. We may be in for a long wait.

The alternative, synthetic approach to resolving the debate about vitalism aimed to meet the challenge posed by Louis Pasteur's experiments directly: if life could be made artificially from non-living components, then the need for an *élan vital* could be discounted and the materialist explanation would be proven. Synthetic chemical approaches had already made a valuable contribution in this direction. In 1828, Friedrich Wöhler had synthesized the molecule urea, hitherto known only in the context of living organisms, from inorganic precursors. Although apparently not done with the vitalism debate in mind, his synthesis united the chemistry of the living with that of the inorganic world and gave cheer to materialists. Extending the scope of creative work from synthetic chemistry to synthetic biology was the next logical step.

Obviously the production of a complete living cell would be a tall order, so attention focused at first on reproducing specific aspects of cellular behaviour using non-living systems. One of the first major works in this area, usually taken to be the foundation of synthetic biology, was Stéphane Leduc's 1912 book, *La Biologie Synthétique*. In this book, Leduc set out an uncompromisingly materialist agenda, insisting that life was a purely physical phenomenon and that its organization and development occurred by harnessing the organizing power of physico-chemical forces alone. He called this view 'physicism', and presented it in opposition to 'mysticism'. In order to demonstrate that there was nothing mysterious about the events observed in living cells and organisms, he constructed entirely physical systems that behaved analogously to cells. He stated, 'when a phenomenon has been observed in a living organism, and one believes that one understands its physical mechanism, one should be able to reproduce this phenomenon on its own, outside the living organism'. In modern language, the systems he built were not living but life-mimicking, or 'biomimetic'. Leduc was by no means the first to try to synthesize biomimetic systems from non-living components. Moritz Traube, in particular, had in the 1860s produced vesicles bounded by semi-permeable membranes by dripping glue into tannic acid, or mixing potassium ferrocyanide and copper chloride, and these were analogous enough to cell membranes that they could be used to study the laws of osmosis that applied to real cells. Leduc went a lot further, and used elaborate systems of diffusing chemicals to produce extraordinary simulacra of complex, biomimetic patterns (Figure 1). In describing the behaviours of these systems, Leduc argued that they showed, in addition to realistic physical forms, nutrition (the systems 'eating' simple components to use in building their own structures), self-organization, growth, sensitivity to the environment, reproduction, and evolution. He also argued, explicitly, that studying biomimetic systems may shed light on the ultimate origin of life far back in the history of Earth. Leduc was read closely by the great Scottish biologist D'Arcy Thompson, who cited him many times in his 1917 book *On Growth and Form,* a book that remains in print and is widely read by embryologists.

The early flowering of synthetic biology before the First World War, grounded in biomimetic systems built almost exclusively for academic research, did not transform mainstream biology; its agenda, however, has never quite been forgotten. Small numbers of researchers, drawn from both chemistry and biology, have continued to work towards improved and more capable creating life-like systems, with the aim of one day making fully living systems from non-living constituents. Some scientists with a keen interest in the origin of life have worked on the problem of how complex organic molecules capable of making living systems could have arisen in the first place. A landmark experiment in this area was that of Harold Urey and Stanley Miller who, in the 1950s, showed that complex molecules, including amino acids, appeared spontaneously from simple precursors in simulations of the environment of primitive Earth. Other scientists worked on problems of organization; in the 1950s, Boris Pavlovoch Belousov described a chemical system that spontaneously produced complex patterns in space and time and, in the 1990s, Günter Wächtershäuser and his colleagues described complex metabolic cycles being organized on the surface of the mineral pyrite. Yet others have taken the presence of large organic molecules for granted and have worked on reproduction; from the 1980s, the laboratory of Pier Luisi has produced various systems in which simple membrane-bounded spheres feed on precursor molecules, grow, and reproduce. Most of this work has been done for one of two motives, both of which would have been familiar to Leduc. The first is to gain understanding about the origin of life. The other, still, is to meet Pasteur's challenge and to repudiate vitalism not by mere induction but by actual proof.

Foundations for biotechnology

The rise of genetics and molecular biology in the 20th century

There is occasional speculation that synthetic biology might be used to adapt a natural pathogen to be active only against a specific human race. This is based on a misunderstanding of our species; humans do not have separate 'races' in the sense that a geneticist would recognize. Our species is a continuum: some versions of genes (alleles) do turn up at different frequencies in different ethnic groups, but this is a statistical property only. There are no absolute genetic differences that separate peoples on opposite sides of even a 'racial' conflict that would make one side vulnerable and the other safe.

Bioterrorism aimed at a nation's agriculture may be a more realistic worry. One of the main defences we animals and higher plants have against bacterial or viral Armageddon is sex. We reproduce not by copying ourselves but by shuffling and mixing our genes with those of another individual so that our offspring differ from us and from one another. This variation means that epidemics do not kill everyone. In a world of clones, in which all individuals were the same, there would be no herd immunity and a pathogen that evolved or was engineered to infect one individual would have a high chance of spreading through the population like wild-fire. This is essentially what happened in the Irish potato blight. If we are stupid enough to grow clones of crops in which field after field contains plants with exactly the same genomes and/or the same synthetic devices aboard, then we will be making our civilization far less resilient against fungal, bacterial, or viral attack, whether natural or deliberate. The current, very foolish, use of the same computer architecture and operating systems in everything from consumer goods to safety-critical industrial systems has allowed computer malware writers to cause much trouble in recent years. Had we still the diversity of small computers seen in earlier decades, we might have had to bear more cost in software development but our systems would

Further reading

Modification of existing life

Armstrong, R. *Living Architecture: How Synthetic Biology Can Remake Our Cities and Reshape Our Lives*. TED books/Amazon (Kindle edition only at present).

Freemont, P.S. and Kintney, R.I. *Synthetic Biology—A Primer* (Revised Edition). London: Imperial College Press, 2015.

Kuldell, N. *Biobuilder: Synthetic Biology in the Lab*. Boston, MA: MIT Press, 2015.

Regis, E. and Church, G.M. *Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves*. New York: Basic Books, 2014.

Schmidt, M. *Synthetic Biology: Industrial and Environmental Applications*. London: Wiley, 2012.

Creation of life *de novo*

Luisi, P.L.L. *The Emergence of Life*. Cambridge: Cambridge University Press, 2006.

Rasmussedn, S., Bedau, M., Chen, L., et al. *Protocells: Bridging Living and Non-Living Matter*. Cambridge, MA: MIT Press, 2009.

Culture, ethics, and art

Ginsberg, A.D., Calvert, J., Schyfter, P., Elfick, A., and Endy, D. *Synthetic Aesthetics: Investigating Synthetic Biology's Designs on Nature*. Cambridge, MA: MIT Press, 2017.

Jorgensen, E. *Biohacking—You Can Do It, Too.* TED talk. Available at: <https://www.ted.com/talks/ellen_jorgensen_biohacking_you_can_do_it_too>, nd.

Kaebnick, G.E. and Murray, T.H. *Synthetic Biology and Morality: Artificial Life and the Bounds of Nature*. Cambridge, MA: MIT Press, 2013.

Lentzos, F., Jefferson, C., and Marris, C. *Synthetic Biology and Bioweapons*. London: Imperial College Press, 2017.

Pahara, J., Dickie, C., and Jorgensen, E. *Hacking DNA with Rapid DNA Prototyping: Synthetic Biology for Everyone*. Sebastopol, CA: O'Reilly Press, 2017.

Sources of quotations

Cho, R. State of the Planet Blog, Columbia University Earth Institute. Available at: <http://blogs.ei.columbia.edu/2011/07/08/synthetic-biology-creating-new-forms-of-life/>, 2011.

Church, G. Interviewed for SynBioWatch. Available at: <http://www.synbiowatch.org/2012/10/how-synthetic-biology-will-change-us/>, 2014.

Kahn, J. 'Synthetic Hype: A Skeptical View of the Promise of Synthetic Biology', *Val. U. L. Rev.* 45/29. Available at: <http://scholar.valpo.edu/vulr/vol45/iss4/2>, 2011.

Kuiken, T. 'DIYbio: Low Risk, High Potential', *The Scientist*, 1 March. Available at: <https://www.the-scientist.com/?articles.view/articleNo/34443/title/DIYbio--Low-Risk--High-Potential/>, 2013.

Thomas, J. 'Synthia is Alive … and Breeding Panacea or Pandora's Box?', *ETC News Release* 20 May. Available at: <http://www.etcgroup.org/sites/www.etcgroup.org/files/publication/pdf_file/ETCVenterSynthiaMay202010.pdf>, 2010.

Willets, D. 'Statement Concerning the Establishment of BBSRC/EPSRC Synthetic Biology Research Centres in the UK'. Available at: <http://webarchive.nationalarchives.gov.uk/20140714082920/http://www.epsrc.ac.uk/newsevents/news/biologyresearchcentres
2014.

C

F

G

H

I

J

K

L

M