DANCE TO THE TUNE OF LIFE
BIOLOGICAL RELATIVITY

In this thought-provoking book, Denis Noble formulates the theory of biological relativity, emphasising that living organisms operate at multiple levels of complexity and must therefore be analysed from a multi-scale, relativistic perspective. Noble explains that all biological processes operate by means of molecular, cellular and organismal networks. The interactive nature of these fundamental processes is at the core of biological relativity and, as such, challenges simplified molecular reductionism. Noble shows that such an integrative view emerges as the necessary consequence of the rigorous application of mathematics to biology. Drawing on his pioneering work in the mathematical physics of biology, he shows that what emerges is a deeply humane picture of the role of the organism in constraining its chemistry, including its genes, to serve the organism as a whole, especially in the interaction with its social environment. This humanistic, holistic approach challenges the common gene-centred view held by many in modern biology and culture.

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Preface

The central message of this book is that living organisms are open systems. That refers to all parts of organisms. All the molecules, organs and systems dance to the tune of the organism and its social context. Those molecules include the sequences of DNA we now call genes.

- How do all these components of life dance together in harmony?
- When did their billion-year dance begin?
- What makes them dance?
- Why is their dance relativistic?
- What do we mean by a 'gene'?
- What do we mean by 'life'?
- How can 'life' depend on 'dead' molecules?
- And what is Biological Relativity?

The answers to these questions form the subject of this book. We will also address the question of meaning. Could all this really happen as a consequence of 'blind chance'? And what could that commonly used phrase possibly mean? What, indeed, do we mean by 'meaning'? Could meaning itself be subject to a relativity principle: a relativity of epistemology?

If these questions fascinate you, then read on.

You will not need to know a lot of science to understand the book: what you will need is a new set of eyes. I will encourage the reader to adopt the eyes and mind of an inquisitive explorer. The scientific knowledge you need to know will mostly be in the book. If you already know a lot of science, you may need to relearn what you thought you knew. Because the central message is that twentieth-century biology went up the wrong street in the interpretation and presentation of its many impressive discoveries.

The reason is that some very influential twentieth-century biologists presented a simplistic gene-centred view of biology using memorable metaphors and brilliant writing to encourage you to adopt their view. And in this they were very successful. Hardly any biological discovery

today is presented in the popular media without reference to the discovery of this or that gene 'for' something or other.

This book will show you that there are no genes 'for' anything. Living organisms have functions which use genes to make the molecules they need. Genes are used. They are not active causes.

This book will show you that there is no complete programme in our DNA. Programmes, if useful at all as a concept in biology, are distributed across scales in the organism.

This book will show you that there is no privileged level of causation, which is a central statement of the theory of Biological Relativity.

It will also show you that we are now far from certain what a gene is, and that many of the confusions and misrepresentations of biology arise from mixing up different definitions of genes and genetics.

We don't know when DNA first evolved. But it is virtually certain that it already existed two billion years ago. It seems likely that it must have existed for at least a billion years before that. There are fossils of the simplest cells that go back to over three billion years ago.[1] So, if genes dance, then they have been doing so for billions of years, in fact for most of the period of the Earth's existence, which is about 4.5 billion years.

For the Fainthearted

In spite of the sub-title of this book, don't be afraid if you are not mathematically trained. I promise you that, with the sole exception of Einstein's iconic equation $e = mc^2$, there are absolutely no equations in the main body of the book. Science could not function properly without mathematics. But, even in the most mathematical areas of science, and biology is rapidly becoming one of those, it is usually possible to explain the concepts in common language, once they have been distilled down from the abstract world of equations.

To help you through some uncharted territory, like the Bellman in Lewis Carroll's nonsense poem *The Hunting of the Snark*, remember that 'what I tell you three times is true'. I have deliberately included a certain amount of repetition in the different chapters, usually by expressing the same concept from a different angle or in a different context. Don't be alarmed if you think you have read something before. I turn some basic ideas in biology upside down. That takes a certain amount of getting used

to. As you read on you may come to welcome those nice reminders of a point that is already half-appreciated. We are all used to this phenomenon in other ways. When we first see an unfamiliar object we easily mistake it for something else, and have to look again. That is even more true for unfamiliar concepts.

As an example, the fact that organisms are what we call open systems is employed in several chapters, from different perspectives. It is by appreciating the full extent of the development of this concept that a reader can come to understand its profound significance.

Although this book is critical of the simplistic way in which twentieth-century biology was often presented, my purpose is certainly not to minimise the phenomenal experimental achievements. It is rather an appeal for scientific humility. We are all prisoners of the cultures in which we find ourselves. Particularly in its theoretical aspects, science cannot be immune from culture even though it often challenges common and received ideas. Perhaps the ultimate principle of relativity is the relativity of knowledge, of epistemology. That is the title of the last chapter. As you journey from chapter to chapter, fasten your intellectual seatbelts. The ride through the book may jolt many of your present assumptions about the nature of living organisms.

The Sub-Title of the Book: A Challenge for the Future

The first complete draft of this book was finished in 2015, the centenary year of Einstein's General Theory of Relativity. That was not the initial reason for the sub-title, but it is a nice and appropriate coincidence. But, before the reader should judge me for being so presumptuous, let me hasten to add that what is developed in this book is more like a sketch when compared to the beautiful mathematical expressions of Special and General Relativity. Furthermore, I very much doubt whether the principle of Biological Relativity could be so expressed. We may not have the appropriate mathematics for an evolutionary process that has been as much a history as a phenomenon that could be predicted mathematically, except over relatively short time scales. Many biologists follow the lead of Stephen J. Gould in thinking that if the evolutionary clock could be set back to any point in history, the process would not follow the path that it has.

The extension of the principle of relativity to biology, as outlined here, is therefore more a set of signposts to a path. It opens up vistas that others better equipped than I might follow wherever they may lead. This is a challenge to younger scientists. I wrote the book while having the privilege of being the President of the International Union of Physiological Sciences. I believe it could be the union of those sciences with the relevant branches of physics, engineering and mathematics that could lead the way forward in the future.

Chapter Guide

Chapter 1 introduces the general principle of relativity as it developed in the study of the universe. Understanding the steps by which the idea of relativity was reached will prepare you for application of the general principle to biology, which is the core of the book.

Chapters 2–4 contain the background knowledge of biology required to understand the later chapters. Chapter 2 is a complement to Chapter 1 since instead of reaching out to the larger scales of the universe as a whole it reaches down to the microscopic and molecular components of our bodies. It will guide you through the various levels of organisation from molecules to the whole organism. Chapter 3 then introduces the processes that characterise life in the form of networks of interactions. I will give some examples of networks that involve multiple levels. Multilevel interactions form a central aspect of Biological Relativity since causation is then not restricted to one level and is necessarily bi-directional. Chapter 4 shows how these components and processes work in the smallest living things – single cells. The great majority of organisms on Earth are unicellular, and even multicellular organisms go through a single-cell stage when they reproduce.

Chapter 5 outlines the current widely held theory of evolution (Neo-Darwinism) and analyses its main conceptual problems. You will learn that it is a gene-centric, molecular-oriented view of biology. By focusing on genes and molecules it cannot answer the question 'what is life?' Moreover, it was not Darwin's theory of evolution.

Chapter 6 explains the central principle of Biological Relativity. You will learn that organisms are alive precisely because their processes operate at and between many different scales and levels. The molecular and

other components are constrained by all levels, including the environment.

Chapters 7 and 8 describe the experimental findings that enable an integrative relativistic theory of evolution to be developed to replace Neo-Darwinism. Chapter 7 focuses on the ways in which the genetic material, DNA, has been rearranged during evolution. Chapter 8 focuses on the epigenetic and related mechanisms by which the genome is controlled.

Chapter 9 returns to the questions asked in Chapter 1 and develops a form of relativity of our knowledge of the universe: a relativity of epistemology. It is through this idea that we arrive at answers that science can give to the big questions about the universe and ourselves and to an understanding of the limits of those answers.

Chapter 10 is written as a brief postscript that summarises the central argument of the book.

Each chapter begins with an easy way in, often using stories from my personal experience. As you read on, you will see the relevance of the story to the main message of the chapter.

You might initially wonder how such a diverse range of topics hangs together since the book begins with the fundamentals of physics and cosmology, yet ends with the fundamentals of biology and the limits to our knowledge. You will discover, perhaps surprisingly, that there are many links between these various threads. The insights of Chapter 1 inform important conclusions in many of the subsequent chapters, and the general principle of relativity informs the whole book.

It will be clear from this introduction to the various chapters, and how they link together, that this book is not a textbook of the systems approach to biology. My aim is rather different. It is to contribute to the new trends in biology that have become evident during the first decade or so of the twenty-first century by creating a coherent conceptual framework within which those trends and their experimental basis can be understood. In any case, there is no need for me to write a textbook since an excellent one has been published already: Capra and Luisi's (2014) *The Systems View of Life: A Unifying Vision* (Cambridge University Press, 2014). At various points in my book I will cross-reference this text to guide readers to the relevant parts of their book. Their vision of the systems approach is very similar to mine.

Notes and glossary. The glossary is an important part of the book. Some key words have significantly different interpretations and

definitions used by different writers. These include reductionism, Neo-Darwinism, Darwinism, Lamarckism and epigenetics. When you first encounter these words, you may benefit from consulting the glossary entries on them.

Note

1 Fossils of microbes metabolising sulphur have been identified in rocks dating from 3.4 billion years ago: Wacey, D., M.R. Kilburn, M. Saunders, J. Cliff and M.D. Brasier (2011) Microfossils of sulphur-metabolizing cells in 3.4 billion-year-old rocks of Western Australia. *Nature Geoscience* 4:698–702.

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Working towards writing this book has been a very long journey. Many colleagues, friends and critics have been companions on that journey.

First, both in time and in what I owe him, is my PhD supervisor, Otto Hutter, who first set me out on the journey at University College London way back in 1958. Even nearly 60 years later he is still my best critic, and kindly read many of the draft chapters.

Second is my brother, Ray, who has inspired many of the ideas of this book ever since his undergraduate days in zoology at Manchester University and more recently as a medical ethicist at University College London. He spotted the problems with gene-centric accounts of biology well before I did.

Third are the innumerable students who have studied with me and, in the process, often taught me their own wisdom over a period of 50 years. Nothing can prepare you for the 'wow' moment when a student brings a razor sharp new mind to an old problem and cuts through the standard textbook guff.

Fourth are fellow academics from all over the world who have criticised and helped to smooth the wilder aspects of my journey. They have particularly included scientists and philosophers at Balliol College over many years. I am deeply privileged to have worked in such a richly interdisciplinary Oxford college.[1] Some of the lectures and videos referred to in this book were recorded by *Voices from Oxford*, based at Balliol College, and I am very grateful to the Director, Professor SungHee Kim, for all the advice and help she and the *Voices from Oxford* team have given.

Finally, I especially thank those who have trenchantly disagreed with me. Some of them may well say that I didn't take much notice of them. Not really true. But it is true that often enough they influenced me in ways that they might not recognise.

An intellectual journey in which you end up in a place very different from your starting point can often be lonely, a kind of pilgrim's progress with many doubts on the way. To all who have helped, hindered or just lent a kindly ear, I thank you.

The full technical details for parts of this book were first published as invited articles in *Science*, *Molecular Systems Biology*, *Philosophical*

Transactions of the Royal Society, *Interface Focus*, *Journal of Experimental Biology*, *Journal of Physiology*, *Experimental Physiology*, *Physiology News* and other journals and books published between 2008 and 2015. I am grateful to the editors of these journals and books and to the referees for many valuable comments and criticisms. The ideas in this book have been through extensive peer review.[2]

Finally, I thank those who kindly read and criticised early drafts of particular chapters or of the whole book. I am particularly grateful to Geoffrey Bamford, Sir Patrick Bateson, Nicholas Beale, Steven Bergman, Dario DiFrancesco, Yung Earm, Martin Fink, Otto Hutter, Eva Jablonka, Mike Joyner, Sir Anthony Kenny, Ard Louis, Colin Meyer, Derek Moulton, Raymond Noble, Susan Noble, Kazuyo Tasaki, Toshiaki Tasaki, David Vines and Michael Yudkin, many of whom gave me valuable feedback and detailed corrections. I also thank the Press reviewers for very helpful feedback.

Notes

1 The philosophers include particularly Stuart Hampshire, Charles Taylor, Alan Montefiore, Anthony Kenny and Peter Hacker.

2 The full list of these publications for those who want to study the technical detail is as follows, with the key publications starred:

Systems biology:

* Noble, D. (2008) Claude Bernard, the first Systems Biologist, and the future of Physiology. *Experimental Physiology* 93:16–26.

Auffray, C. and D. Noble (2009) Conceptual and experimental origins of integrative systems biology in William Harvey's masterpiece on the movement of the heart and the blood in animals. *International Journal of Molecular Sciences* 10:1658–1669.

Kohl, P. and D. Noble (2009) Systems biology and the virtual physiological human. *Molecular Systems Biology* 5:291–296.

* Kohl, P., E. Crampin, T.A. Quinn and D. Noble (2010) Systems biology: an approach. *Clinical Pharmacology and Therapeutics* 88:25–33.

Noble, D. (2010) Mind over molecule: systems biology for neuroscience and psychiatry. In *Systems Biology in Psychiatric Research*. F. Tretter, G. Winterer, J. Gebicke-Haerter and E.R. Mendoza, editors (Wiley-VCH, Weinheim; pp. 97–109).
Noble, D. (2010) Biophysics and systems biology. *Philosophical Transactions of the Royal Society A* 368:1125–1139.
Noble, D., R. Noble and J. Schwaber (2014) What is it to be conscious? In *The Claustrum*. J. Smythies, V.S. Ramachandran and L. Edelstein, editors (Academic Press, San Diego, CA; pp. 353–364).

Genes and causation:

* Noble, D. (2008) Genes and causation. *Philosophical Transactions of the Royal Society A* 366:3001–3015.
Noble, D. (2008) For a redefinition of god. *Science* 320:1590–1591.
* Noble, D. (2011) Editorial. *Interface Focus* 1:1–2.
Noble, D. (2011) Differential and integral views of genetics in computational systems biology. *Interface Focus* 1:7–15.
Ellis, G.F.R., D. Noble and T. O'Connor (2012) Top-down causation: an integrating theme within and across the sciences. *Interface Focus* 2:1–3.
* Noble, D. (2012) A theory of biological relativity: no privileged level of causation. *Interface Focus* 2:55–64.
Noble, D. (2013) A biological relativity view of the relationships between genomes and phenotypes. *Progress in Biophysics and Molecular Biology* 111:59–65.

Evolution:

Noble, D. (2010) Letter from Lamarck. *Physiology News* 78:31.
Noble, D. (2011) Book review: Evolution. A view from the 21st century. *Physiology News* 85:40–41.
* Noble, D. (2011) Neo-Darwinism, the modern synthesis, and selfish genes: are they of use in physiology? *Journal of Physiology* 589:1007–1015.
Noble, D. (2013) Life changes itself via genetic engineering. Comment on 'How Life Changes Itself: The Read-Write (RW) Genome' by James Shapiro. *Physics of Life Reviews* 10:344–346.

* Noble, D. (2013) Physiology is rocking the foundations of evolutionary biology. *Experimental Physiology* 98:1235–1243.

Noble, D. (2014) Secrets of life from beyond the grave. *Physiology News* 97:34–35.

* Noble, D., E. Jablonka, M.M. Joyner, G.B. Müller and S.W. Omholt (2014) Evolution evolves: physiology returns to centre stage. *Journal of Physiology* 592:2237–2244.

* Noble, D. (2015) Evolution beyond neo-Darwinism. *Journal of Experimental Biology* 218:7–13.

Noble, D. (2015) Conrad Waddington and the origin of epigenetics. *Journal of Experimental Biology*, 218:816–818.

Noble, D. (2015) Central tenets of neo-Darwinism broken: response to 'Neo-Darwinism is just fine'. *Journal of Experimental Biology* 218:2659.