

## THE EMERGENCE OF LIFE

Addressing the emergence of life from a systems biology perspective, this new edition has undergone extensive revision, reflecting changes in scientific understanding and evolution of thought on the question “what is life?” With an emphasis on the philosophical aspects of science, including the epistemic features of modern synthetic biology, as well as providing an updated view of the autopoiesis/cognition theory, the book gives an exhaustive treatment of the biophysical properties of vesicles, seen as the beginning of the “road map” to the minimal cell – a road map, which will develop into the question of whether and to what extent synthetic biology will be capable of making minimal life in the laboratory. Fully illustrated and accessibly written, *The Emergence of Life* challenges the reader directly with provocative questions, while also offering suggestions for research proposals taken directly from the author’s bench experience. Dialogues with contemporary authors including Humberto Maturana, Albert Eschenmoser, and Harold Morowitz make this an ideal resource for researchers and students across fields including bioengineering, evolutionary biology, molecular biology, chemistry, and chemical engineering.

PIER LUIGI LUISI is Professor Emeritus at the Swiss Federal Institute of Technology in Zurich, Switzerland (ETHZ), where he developed his professional career, notably initiating Cortona Week in 1985. He has also held the position of Professor in Biochemistry at the University of Rome 3. He has authored more than 500 peer-reviewed papers as well as a number of books, recently including *The Systems View of Life* with Fritjof Capra (2014).

THE EMERGENCE OF LIFE  
From Chemical Origins to Synthetic Biology

PIER LUIGI LUISI  
*University of Rome 3*



CAMBRIDGE  
UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom

Cambridge University Press is part of the University of Cambridge.

It furthers the University's mission by disseminating knowledge in the pursuit of education, learning and research at the highest international levels of excellence.

[www.cambridge.org](http://www.cambridge.org)

Information on this title: [www.cambridge.org/9781107092396](http://www.cambridge.org/9781107092396)

© Pier Luigi Luisi 2016

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2006

Second edition 2016

Printed in the United Kingdom by TJ International Ltd. Padstow Cornwall

*A catalog record for this publication is available from the British Library*

*Library of Congress Cataloguing in Publication data*

Luisi, P. L., author.

The emergence of life : from chemical origins to synthetic biology / Pier Luigi Luisi, University of Rome 3.

Second edition. | Cambridge : Cambridge University Press, 2016.

LCCN 2015049383 | ISBN 9781107092396

LCSH: Life – Origin.

LCC QH325 .L85 2016 | DDC 576.8/3–dc23

LC record available at <http://lcn.loc.gov/2015049383>

ISBN 978-1-107-09239-6 Hardback

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

## Contents

<i>Acknowledgments</i>	page xi
<i>Introduction</i>	xii
Part I Approaches to the origin of life	1
1 Setting the stage	3
Introduction	3
1.1 The secular view on the origin of life	4
<i>Side Box 1.1 Books on the origin of life</i>	8
1.2 A few accepted facts	10
1.3 Oparin's view, and its implications	11
1.4 Determinism and contingency in the origin of life	14
<i>Conversation with Albert Eschenmoser</i>	19
1.5 The question of creationism and intelligent design (ID)	22
1.6 SETI and the anthropic principle	24
1.7 Panspermia – and bringing in C. G. Jung	27
1.8 Only one start – or many?	28
Concluding remarks	29
2 The hardware	31
Introduction	31
2.1 What did we have 4 billion years ago?	31
<i>Conversation with Sandra Pizzarello</i>	36
2.2 Molecules from hydrothermal vents	38
2.3 The chemistry of life. From Oparin to Miller – and beyond	39
<i>Conversation with David Deamer</i>	42
<i>Conversation with Eörs Szathmáry</i>	45
2.4 Prebiotic nitrogen bases	47
2.5 Sugars	49
2.6 Redox reactions	50
2.7 The Fischer-Tropsch reaction	51

vi	<i>Contents</i>	
	2.8 The N-carboxy-anhydride condensation	53
	Concluding remarks	55
3	Ascending the ramp of complexity	57
	Introduction	57
	3.1 The creativity of contingency	58
	3.2 The primacy of structure	61
	3.3 Thermodynamic and kinetic control	63
	3.4 Self-replication – and the concentration threshold	65
	3.5 Ordered macromolecular sequences	68
	3.6 The question of homochirality	69
	Concluding remarks	70
4	Experimental approaches to the origin of life	72
	Introduction	72
	4.1 The prebiotic RNA world	72
	<i>Conversation with Ada Yonath</i>	77
	4.2 The ribocell	78
	<i>Conversation with Gerald Joyce</i>	81
	4.3 The compartmentalistic approach	82
	4.4 Primordial cells without DNA?	85
	4.5 The phenomenon of spontaneous overcrowding	86
	4.6 The “prebiotic metabolism” approach	88
	4.6.1 The universal metabolism	88
	4.6.2 Metabolism on clay and mineral surfaces	88
	4.6.3 The beauty of pyrite	89
	4.6.4 Other metabolic approaches	90
	<i>Conversation with Doron Lancet</i>	93
	Concluding remarks	95
5	Origin of life from ground zero	97
	Introduction	97
	5.1 Prebiotic amino acids and peptides	97
	5.2 Peptides with catalytic power	99
	5.3 Proteins with a reduced alphabet of amino acids	103
	5.4 How to make proteins by prebiotic means?	106
	5.5 About prebiotic vesicles	109
	5.6 Proposals of research projects from ground zero	111
	5.6.1 The catalytic properties of Ser-His: ideal project for bioorganic chemists	112
	5.6.2 Ser-His as the catalyst for the nucleotide bond	112
	5.6.3 The most stable random polypeptide sequences by the NCA method	113
	5.6.4 Protein biogenesis by fragment condensation of prebiotic peptides	113

<i>Contents</i>		vii
5.6.5 The notion of “proteases first”		114
Concluding remarks		114
Questions for the reader		115
Part II What is life? The bio-logics of cellular life		117
6 Autopoiesis – the invariant property		119
Introduction		119
6.1 The visit of the Green Man		120
6.2 Introducing autopoiesis		123
6.3 Short historical background on autopoiesis		124
6.4 Basic autopoiesis		125
6.5 Criteria of autopoiesis		128
<i>Conversation with Amy Cohen Varela</i>		130
6.6 Zooming into the core of autopoiesis		133
<i>Side Box 6.1 Autopoiesis: three research directions for future developments, by Luisa Damiano</i>		135
<i>Conversation with Evan Thompson</i>		140
6.7 What autopoiesis does not include		144
6.8 Chemical autopoiesis: the case for self-reproduction of micelles and vesicles		145
6.9 Chemical autopoiesis: a case for homeostasis		147
6.10 Second order autopoietic structures		149
6.11 Social autopoiesis		151
6.12 Autopoiesis and the chemoton: comparison with the views of Tibor Ganti		153
Concluding remarks		155
7 Cognition		157
Introduction		157
<i>Conversation with Humberto Maturana</i>		159
7.1 The notion of cognition		166
7.2 The co-emergence between the living and the environment		168
7.3 The link with classic biochemistry		172
7.4 About epistemology in autopoiesis		174
7.5 Ontogeny, evolution, information: the view from within		180
<i>Conversation with Denis Noble</i>		182
7.6 What is death?		183
Concluding remarks		186
Questions for the reader		187

viii	<i>Contents</i>	
Part III	Order and organization in biological systems	189
8	Self-organization	191
	Introduction	191
	8.1 About the term <i>self</i>	193
	8.2 Self-organization of simpler molecular systems	193
	8.3 Self-organization and autocatalysis	198
	8.4 Polymerization	199
	8.5 Self-organization and kinetic control	200
	8.6 Self-organization and breaking of symmetry	202
	8.7 Complex proteic systems	202
	8.8 Self-organization of ribosomes	205
	8.9 Self-organization in viruses	208
	8.10 Swarm intelligence	210
	8.11 Can living cells be reconstituted <i>in vitro</i> ?	211
	<i>Side Box 8.1 Phenomena of self-organization in Hydra,</i> <i>by Giorgio Venturini</i>	214
	8.12 Touching on the “divine proportion”: $\Phi$ and the golden mean	220
	8.13 Out-of-equilibrium self-organization	224
	Concluding remarks	227
9	The notion of emergence	229
	Introduction	229
	9.1 Ontic and epistemic	230
	9.2 A few simple examples of emergence	231
	9.3 Emergence and reductionism	232
	9.4 Deducibility and predictability	233
	9.5 Downward causation	235
	9.6 Emergence and dynamic systems	236
	<i>Side Box 9.1 – The sciences of complexity, by Stuart A. Kauffman</i>	238
	9.7 Life as an emergent property	240
	9.8 Self-organization and finality	242
	Concluding remarks	245
10	Self-replication and self-reproduction	247
	Introduction	247
	10.1 Self-replication and nonlinearity	248
	10.2 Self-replicating, enzyme-free chemical systems	249
	10.3 One more step towards complexity	253
	10.4 Self-reproducing micelles	255
	10.5 Self-reproducing vesicles	258
	10.6 Nanobacteria?	260
	Concluding remarks	261
	Questions for the reader	262

*Contents*

ix

Part IV	The world of vesicles	263
11	The various types of surfactant aggregates	265
	Introduction	265
	11.1 General properties of surfactant aggregates	266
	11.2 Aqueous micelles	270
	11.3 Reverse micelles	272
	11.4 Entrapment of biopolymers in reverse micelles	273
	11.5 Water-in-oil microemulsions	279
	11.6 Cubic phases	279
	11.7 Size and structural properties of vesicles	282
	11.7.1 The water pool of vesicles	286
	11.7.2 The case of oleate vesicles	289
	11.8 Local versus overall concentration	290
	11.9 Prebiotic vesicle-forming surfactants	292
	11.10 Giant vesicles	293
	Concluding remarks	296
12	Vesicle reactivity and transformations	297
	Introduction	297
	12.1 Growth and division of vesicles: some geometrical relationships	297
	12.2 Experimental studies on the growth of vesicles	300
	12.3 The matrix effect	304
	12.4 Fusion of vesicles	309
	12.5 Size competition of vesicles – and interaction with RNA	313
	Concluding remarks	317
13	Biochemistry and molecular biology in vesicles	319
	Introduction	319
	13.1 The entrapment of solutes in vesicles	319
	13.2 On the surface of liposomes	324
	13.3 The road map to the minimal cell: complex biochemical reactions in vesicles	326
	Concluding remarks	331
	Questions – and research proposals – for the reader	331
Part V	Towards the synthetic biology of minimal cells	333
14	A panoramic view of synthetic biology	335
	Introduction	335
	14.1 Main strategies and perspectives of synthetic biology	336
	<i>Conversation with Paul Freemont</i>	338
	<i>Conversation with Sarah Lau</i>	341
	14.2 The case of engineering SB	345
	14.3 A teaching phenomenon: iGEM	350



	<i>Side Box 14.1 Recent iGEM activities</i>	352
	14.4 More on epistemology	355
	14.5 Chemical SB	357
	14.6 The never born proteins	360
	14.7 The never born RNA	366
	Concluding remarks	367
15	The minimal cell	369
	Introduction	369
	<i>Conversation with Harold Morowitz</i>	371
	15.1 The notion of the minimal cell	373
	15.2 The minimal genome	377
	15.3 The road map to the minimal cell: protein expression in vesicles	378
	15.4 A confederacy of protocells	383
	15.5 About the statistics of entrapment	387
	15.6 A story of spontaneous overcrowding	389
	15.7 The origin of metabolism?	395
	15.8 And (why not?) the origin of life?	396
	Concluding remarks	397
	Questions – and research proposals – for the reader	398
	As a way of conclusion	400
	<i>Appendix The open questions about the origin of life</i>	404
	Selection of the open questions presented in the OQOL Workshop of Erice – 2006	405
	Selection of the open questions presented in the OQOL Workshop of San Sebastian – 2009	409
	Selection of the open questions presented in the OQOL Workshop of Leicester – 2012	413
	Selection of the open questions presented in the OQOL Workshop of Nara – 2014	415
	<i>References</i>	419
	<i>Names index</i>	457
	<i>Subject index</i>	461

## Acknowledgments

This book has been written immediately after the book with Fritjof Capra, *The Systems View of Life: A Unifying Vision* (2014), and the many fruitful discussions I had with Fritjof have helped to shape and enrich the new edition of the present book. I would also like to express my gratitude to Michel Bitbol, Rossella Mascolo, Michele Lucantoni, Angela Spaltro, and Pasquale Stano for their comments and continuous encouragement. The help of Pasquale Stano has been very important for the discussions in Part IV of this book. I would like to emphasize the collaboration with Angelo Merante, who was with me also in the first edition: he has been not only responsible for the many illustrations of the book, but also for the general organization of the various chapters, and for important critical comments and enrichments to the text.

## Introduction

The first edition of this book, published in 2006, was written about 10 years ago; a partial update was done in the Japanese edition, in the 2010 Spanish edition, and in the 2013 Portuguese edition. A more complete English update was deemed necessary. Not that something dramatic has taken place since the first edition: the origin of life remains an unsolved question. At the last 2004 ISSOL meeting in Nara, Japan, a discussion took place on the question “what is life?,” and this was conducted in similar terms and emphasis as the conversation 20 or 30 years back. Of course, in all these years, although not solving the core question, some particularly important research papers have appeared, and the corresponding update will be presented, to the best of my knowledge, in this second edition. However, this is not the main reason for this second edition.

Life on Earth is based on ordered sequences of proteins and nucleic acids, and on their mutual ordered interactions. And the solution to the quest for the origin of life is the answer to the question, of how this order came about. There are approaches to the origin of life that ignore this simple consideration and start from already pre-constituted ordered systems. This is the case of the (original) RNA-world, starting from a self-replicating RNA. This is a highly ordered, functional macromolecule, and to explain the origin of life from this ordered state would be akin to constructing a house roof first. The same can be said for those researchers who advocate viroids, or pristine forms of ribosomes, as the starting base to explain the origin of life. First, you should explain how this highly ordered state came about – and if you do so, perhaps, yes, you then have paved the way to explain the origin of life. To be clear on that: the research on the three areas mentioned above is often of the highest quality, and corresponds to the best pages of modern science. But in my view it will help very little to explain the origin of life on Earth.

The other approach to the origin of life starts from the opposite direction, namely from the disorder of monomers or low molecular weight compounds. The keywords here are hydrothermal sources, marine or volcanic smokes,

endogenous prebiotic molecules, or molecules coming from space. Again, beautiful research is done on these areas, but you can have all the low molecular weight compounds of this world, in any quantity you wish, and you will never be able to make life. You cannot expect that a cathedral arises by simply having all the possible bricks. With 20 different bricks, you can construct a 100-bricks-long wall in an almost infinite number of ways; the question is to discover the principle that permits the construction of only a few ordered sequences.

This book starts from the consideration that we are still a long way from having a solution to this pristine problem of the origin of ordered structures (not that this is the only one in the origin of life). It attempts to analyze why this is so, indicating that one main reason may lie in the present-day reductionist (nucleic acid-centered) philosophical thinking in the field; and it then tries to propose some way to eliminate this shortcoming, emphasizing a systemic view of life and a corresponding systems view approach to its origin.

Part I of the book examines the various aspects of the bottom-up approach to the origin of life, as generally presented in the literature. This part also contains stringent criticism of the prebiotic RNA-world as origin of life, with an invitation to look at the origin of life from “ground zero.” The discussion is enriched by a series of conversations with distinguished authors in the field, such as David Deamer, Albert Eschenmoser, Gerald Joyce, Doron Lancet, Harold J. Morowitz, Eörs Szathmáry, Sandra Pizzarello, and Nobelist Ada Yonath.

Part II is a detailed account of the theory of autopoiesis, as due to Maturana and Varela, who picture the cell as an open molecular system capable of self-maintenance, due to a regeneration of the components from within. This systems view is in sharp contrast with the reductionist, DNA- or RNA-centered visions of life according to which life is the result of the behavior of a single molecular species. Here, it is instead the system’s organization of the internal web interactions that may cause cellular self-reproduction (eventually leading to Darwinian evolution) – and Darwinian evolution, being the result of that organization, cannot be seen obviously as the *prima causa* of life.

Also considered is the interaction of the living with the environment, which leads to the important notion of cognition with its epistemic and ecological aspects. Particularly in this part of the book, but then also as a general background framework, philosophical and biological aspects are strictly interwoven with each other, with the intention of showing that philosophy and biology should not be seen as two distinct disciplines, but as an integrated unity of the systems view of life: a message that should be given to all our students. Part II also includes the conversation with Humberto Maturana and – as a tribute to Francisco Varela’s thought – the conversations with philosophically minded authors such as Amy Cohen Varela and Evan Thompson. Other enrichments of discussion on these arguments are a conversation with Denis Noble and a Side

Box concerning future developments of research on autopoiesis by Luisa Damiano.

With Part III, the book moves towards biological complexity, and here the two complementary notions of self-organization and emergence – from simpler molecular systems, as micelles and vesicles, to more complex structures (organized protein systems, ribosomes, viruses, and so on) – are presented in two distinct chapters. The following chapter concerns the most salient emergent property, namely self-replication/reproduction. Two side boxes, the first one concerning self-organization mechanisms in Hydra and the other focusing on the sciences of complexity – written by distinguished authors Giorgio Venturini and Stuart Kauffman – offer interesting points of view about the richness of the arguments handled in this section of the book.

The first chapter of Part IV concerns the world of surfactants and lipids, in particular the procedures for solute incorporation and questions about overall and local concentration. The other two chapters are focused on the world of vesicles, in particular their physical and chemical properties, with emphasis on their capability of entrapping biopolymers – whereby they are seen as the best models for the shell of biological membranes.

The information regarding the self-organization and self-reproduction of vesicles will be the basis for the last section of this book, Part V, which is devoted to synthetic biology and the attempts to construct the minimal living cell in the lab. First, general questions about synthetic biology – as today's most celebrated and ambitious laboratory approach to make new or alternative forms of life – are handled. The opening discussion about the epistemology of synthetic biology is enriched by two interesting conversations with relevant authors Paul Freemont and Sarah Lau. Then, a review of the experimental work carried out in my laboratory and others towards the synthetic biology of the minimal cells, which includes the new and unexpected finding of the spontaneous solute overcrowding in vesicles.

The general idea, the red thread that pervades this book, is to provide a unitarian view of life and its origin that departs from a reductionist, nucleic-acid-centered view, to favor instead a systems approach, in which the cellular organization, and its cognitive interaction with the environment, gives the basis for an understanding and, possibly, the reconstruction of life.