



# EVOLUTIONARY DYNAMICS

EXPLORING THE EQUATIONS OF LIFE

MARTIN A. NOWAK

THE BELKNAP PRESS OF HARVARD UNIVERSITY PRESS  
CAMBRIDGE, MASSACHUSETTS, AND LONDON, ENGLAND 2006

Copyright © 2006 by the President and Fellows of Harvard College  
All rights reserved  
Printed in Canada

*Library of Congress Cataloging-in-Publication Data*

Nowak, M. A. (Martin A.)

Evolutionary dynamics : exploring the equations of life /  
Martin A. Nowak.

p. cm.

Includes bibliographical references and index.

ISBN-13: 978-0-674-02338-3 (alk. paper)

ISBN-10: 0-674-02338-2 (alk. paper)

I. Evolution (Biology)—Mathematical models. I. Title.

QH371.3.M37N69 2006

576.801'5118—dc22 2006042693

Designed by Gwen Nefsky Frankfeldt

# CONTENTS

---

Preface ix

- 1 Introduction 1
- 2 What Evolution Is 9
- 3 Fitness Landscapes and Sequence Spaces 27
- 4 Evolutionary Games 45
- 5 Prisoners of the Dilemma 71
- 6 Finite Populations 93
- 7 Games in Finite Populations 107
- 8 Evolutionary Graph Theory 123
- 9 Spatial Games 145
- 10 HIV Infection 167
- 11 Evolution of Virulence 189
- 12 Evolutionary Dynamics of Cancer 209
- 13 Language Evolution 249
- 14 Conclusion 287

Further Reading 295

References 311

Index 349



## PREFACE

*Evolutionary Dynamics* presents those mathematical principles according to which life has evolved and continues to evolve. Since the 1950s biology, and with it the study of evolution, has grown enormously, driven by the quest to understand the world we live in and the stuff we are made of. Evolution is the one theory that transcends all of biology. Any observation of a living system must ultimately be interpreted in the context of its evolution. Because of the tremendous advances over the last half century, evolution has become a discipline that is based on precise mathematical foundations. All ideas regarding evolutionary processes or mechanisms can, and should, be studied in the context of the mathematical equations of evolutionary dynamics.

The original formulation of evolutionary theory and many of the investigations of its first hundred years dealt with the genetic evolution of the origin and adaptation of species. But more recently evolutionary thinking has expanded to all areas of biology and many related disciplines of the life sciences. Wherever information reproduces, there is evolution. Mutations are caused by errors in information transfer, resulting in different types of messages. Selection among types emerges when some messages reproduce faster than others.

---

Mutation and selection make evolution. Mutation and selection can be described by exact mathematical equations. Therefore evolution has become a mathematical theory.

The life sciences in general, and biology in particular, are on the brink of an unprecedented theoretical expansion. Every university is currently aiming to establish programs in mathematical biology and to offer its students an interdisciplinary education that spans fields as diverse as mathematics and molecular biology, linguistics and computer science. At the borders of such disciplines, progress occurs. Whenever the languages of two disciplines meet, two cultures interact, and something new happens.

In this book, the languages of biology and mathematics meet to talk about evolution. *Evolutionary Dynamics* introduces the reader to the fascinating and simple laws that govern the evolution of living systems, however complicated they may seem. I will start with the basics, avoid unnecessary complications, and reach cutting-edge research problems within a few steps.

The book grew out of a course I taught at Harvard University in 2004 and 2005. The students in my first class were Blythe Adler, Natalie Arkus, Michael Baym, Paul Berman, Illya Bomash, Nathan Burke, Chris Clearfield, Rebecca Dell, Samuel Ganzfried, Michael Gensheimer, Julia Hanover, David Hewitt, Mark Kaganovich, Gregory Lang, Jonathan Leong, Danielle Li, Alex Macalalad, Shien Ong, Ankit Patel, Yannis Paulus, Jura Pintar, Esteban Real, Daniel Rosenbloom, Sabrina Spencer, and Martin Willensdorfer, and the teaching fellows Erez Lieberman, Franziska Michor, and Christine Taylor. I have learned much from you. Your questions were my motivation. I wrote this book for you.

I am indebted to many people. Most of all I would like to thank May Huang and Laura Abbott, who helped me to prepare the final manuscript and index. They turned chaos into order. I could not have finished without them. I also thank the excellent editors of Harvard University Press, Elizabeth Gilbert and Michael Fisher.

I thank Ursula, Sebastian, and Philipp for their patience and for their burning desire to understand everything that can be understood.

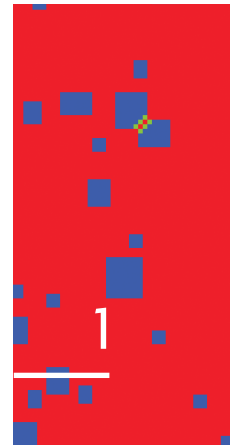
I would like to express my gratitude to my teachers, Karl Sigmund and Robert May. Both of them are shining examples of how scientists should be. They have again and again impressed me with their superior judgment, in-

---

sight, and generosity. I also appreciate the work and friendship of the many people with whom I have had the honor of collaborating and whose enthusiasm for science is woven into the ideas presented here: Roy Anderson, Rustom Antia, Ramy Arnaout, Charles Bangham, Barbara Bittner, Baruch Blumberg, Maarten Boerlijst, Sebastian Bonhoeffer, Persephone Borrow, Reinhard Bürger, Michael Doebeli, Peter Doherty, Andreas Dress, Ernst Fehr, Steve Frank, Drew Fudenberg, Beatrice Hahn, Christoph Hauert, Tim Hughes, Lorens Imhof, Yoh Iwasa, Vincent Jansen, Paul Klenerman, Aron Klug, Natalia Komarova, David Krakauer, Christoph Lengauer, Richard Lenski, Bruce Levin, Erez Lieberman, Jeffrey Lifson, Marc Lipsitch, Alun Lloyd, Joanna Masel, Erick Matsen, Lord May of Oxford (Defender of Science), John Maynard Smith, Angela McLean, Andrew McMichael, Franziska Michor, Garrett Mitchener, Richard Moxon, Partha Niyogi, Hisashi Ohtsuki, Jorge Pacheco, Karen Page, Robert Payne, Rodney Phillips, Joshua Plotkin, Roland Regoes, Ruy Ribeiro, Akira Sasaki, Charles Sawyers, Peter Schuster, Anirvan Sengupta, Neil Shah, George Shaw, Karl Sigmund, Richard Southwood, Ed Stabler, Dov Stekel, Christine Taylor, David Tilman, Peter Trappa, Arne Traulsen, Bert Vogelstein, Lindi Wahl, Martin Willensdorfer, and Dominik Wodarz.

I thank Jeffrey Epstein for many ideas and for letting me participate in his passionate pursuit of knowledge in all its forms.

## INTRODUCTION



**IN 1831**, at the age of twenty-two, Charles Darwin embarked on his journey around the world. He gazed at the breath-taking diversity of tropical flora and fauna, collected creepy-crawlies from the vast oceans that he traversed, was hopelessly seasick, saw slavery in Brazil, witnessed genocide in Argentina, and was underwhelmed by the naked humanity at Tierra del Fuego. He experienced the effects of a devastating earthquake in Chile that raised the South American continent. He led an expedition into the Andes and discovered marine fossils at high altitude. He paid little attention to which finches came from which islands in the Galápagos and ate most of the delicious turtles he had gathered on his way home across the Pacific. He saw Tahiti and the economic rise of Australia. He visited John Hershel, England's leading physicist of the time, in South Africa; Hershel told him that "the mystery of mysteries" was the as yet unknown mechanism that gave rise to new species. Darwin returned to England's shores after five years, having collected six thousand specimens that would require decades of analysis by an army of experts.

His own observations in geology and the theory of his mentor, Sir Charles Lyell, that mountains were not lifted up in one day, but rose slowly over

---

unimaginable periods of time, led Darwin to a key idea: given enough time everything can happen.

Charles Darwin did not invent the concept of evolution. When he was a student in Edinburgh in the late 1820s, evolution was already the talk of the town. But evolution was rejected by the establishment. Those who adhered to evolutionary thinking were called Lamarckists, after the French scientist Jean-Baptiste Lamarck, who was the first to propose that species are not static, but change over time and give rise to new species. Lamarck had offered this perspective in a book published in 1809. He did not, however, propose a correct mechanism for how species change into each other. This mechanism was discovered first by Charles Darwin and independently by Alfred Russel Wallace.

From reading the economist Thomas Malthus, Darwin was aware of the consequences of exponentially growing populations. Once resources become limiting only a fraction of individuals can survive. Darwin was also a keen observer of animal breeders. He analyzed their methods and studied their results. Slowly he understood that nature acted like a gigantic breeder. This was the first time that natural selection materialized as an idea, a scientific concept in a human mind. Darwin was thirty-three years old.

The one problem that Darwin did not solve concerned the mechanism that could maintain enough diversity in a population for natural selection to operate. Darwin was unaware of the Austrian monk and botanist Gregor Mendel and his experiments on plant heredity. Mendel's work had already been published but was hidden, gathering dust in the *Annals* of the Brno Academy of Sciences.

Darwin once remarked, "I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense." The engineer Fleeming Jenkin, who reviewed Darwin's *On the Origin of Species*, published in 1859, had raised a fundamental and seemingly intractable objection to Darwin's theory: if offspring inherit a blend of the parents' characteristics, then variability diminishes in successive generations. Several decades later a simple mathematical equation, independently found by the famous British mathematician G. H. Hardy and the German physician Wilhelm Weinberg, showed that Mendelian (particulate) inheritance does lead to a maintenance



---

of genetic diversity under random mating. The Hardy-Weinberg law is one of the fundamental principles of evolution under sexual reproduction.

Mendelian genetics and Darwinian evolution were unified in the new discipline of mathematical biology, which developed from the seminal investigations of Ronald Fisher, J. B. S. Haldane, and Sewall Wright in the 1920s and 1930s. Through their work, fundamental concepts of evolution, selection, and mutation were embedded in a precise mathematical framework. This line of mathematical analysis was taken up in the 1950s by Motoo Kimura, who formulated the neutral theory of evolution. Kimura realized that most genetic mutations do not affect fitness and are fixed in populations only by random drift.

Other milestones of evolutionary dynamics include William Hamilton's discovery in 1964 that selection of "selfish genes" can favor altruistic behavior among relatives and John Maynard Smith's invention of evolutionary game theory in 1973. In the mid-1970s Robert May revolutionized the mathematical approaches to ecology and epidemiology. Manfred Eigen and Peter Schuster formulated quasispecies theory, which provides a link between genetic evolution, physical chemistry, and information theory. Peter Taylor, Josef Hofbauer, and Karl Sigmund studied the replicator equation, the foundation of evolutionary game dynamics.

This very brief and incomplete account of the evolution of evolutionary dynamics brings us to the present book. It has fourteen chapters. Although there is some progression of complexity, the chapters are largely independent. Therefore, if you know something about the subject, you can read the book in whatever order you like. My aim has been to keep things as simple as possible, as linear as possible, and as deterministic as possible. I will start with the basics and in a few steps lead you to some of the most interesting and unanswered research questions in the field. Having read the book, you will know what you need to embark on your own journey and make your own discoveries.

This book represents an introduction to certain aspects of mathematical biology, but it is not comprehensive. Mathematical biology includes many topics, such as theoretical ecology, population genetics, epidemiology, theoretical immunology, protein folding, genetic regulatory networks, neural networks, genomic analysis, and pattern formation. The field is too diverse for any one book to represent it without running the risk of becoming as entertaining as a

---

telephone directory. I have chosen those topics that I know well and where my explanation can be brief and effective. I have concentrated on evolution because it is the one unifying principle of all of biology.

It might seem surprising that a book on evolutionary dynamics is not primarily about population genetics. Nevertheless the ideas and concepts of this fascinating field stand behind many of my explorations: the basic mathematical formulations of selection, mutation, random drift, fitness landscapes, and frequency-dependent selection as well as of evolution in structured populations have originated in population genetics. Several major themes of population genetics, however, such as sexual reproduction, sexual selection, recombination, and speciation, are not discussed here. In contrast, classical population genetics does not deal with evolutionary dynamics of infectious agents, the somatic evolution of cancer, evolutionary game theory, or the evolution of human language, all of which are subjects that I do explore.

The main ingredients of evolutionary dynamics are reproduction, mutation, selection, random drift, and spatial movement. Always keep in mind that the population is the fundamental basis of any evolution. Individuals, genes, or ideas can change over time, but only populations evolve.

The structure of the book is as follows. After this introduction, in Chapter 2 I will discuss populations of reproducing individuals and the basic ideas of natural selection and mutation. Simple models of population dynamics can lead to an exponential explosion, to a stable equilibrium, or to oscillations and chaos. Selection emerges whenever two or more individuals reproduce at different rates. Mutation means that one type can change into another. There are models of population growth that lead to the survival of whoever reproduces fastest (“survival of the fittest”). Other models lead to the survival of the first or the coexistence of all.

In Chapter 3, quasispecies theory is introduced. Quasispecies are populations of reproducing genomes subject to mutation and selection. They live in sequence space and move over fitness landscapes. An important relationship between mutation rates and genome length is called the “error threshold”: adaptation on most fitness landscapes is possible only if the mutation rate per base is less than one over the genome length, measured in bases.

In Chapter 4, we study evolutionary game dynamics, which arise whenever the fitness of an individual is not constant but depends on the relative

---

abundance (= frequency) of others in the population. Thus evolutionary game theory is the most comprehensive way to look at the world. People who do not engage in evolutionary game theory restrict themselves to the rigidity of constant selection, where the fitness of one individual does not depend on others. The replicator equation is a nonlinear differential equation that describes frequency-dependent selection among a fixed number of strategies. We will encounter the Nash equilibrium and evolutionarily stable strategies. Evolutionary game theory and ecology are linked in an important way: the replicator equation is equivalent to the Lotka-Volterra equation of ecological systems, which describes the interaction between predator and prey species.

Chapter 5 is dedicated to the best game in town, the Prisoner's Dilemma. The cooperation of reproducing entities is essential for evolutionary progress. Genes cooperate to form a genome. Cells cooperate to produce multicellular organisms. Individuals cooperate to form groups and societies. The emergence of human culture is a cooperative enterprise. The very problem of how to obtain cooperation by natural selection is described by the Prisoner's Dilemma. In the absence of any other assumption, natural selection favors defectors over cooperators. Cooperation has a chance, however, if there are repeated interactions between the same two individuals. We will encounter the strategy Tit-for-tat, which is defeated first by Generous Tit-for-tat and then by Win-stay, lose-shift.

In Chapter 6 we move to a stochastic description of finite populations. Neutral drift is a crucial aspect of evolutionary dynamics: if a finite population consists of two types of individuals, red and blue, and if both individuals have identical fitness, then eventually the population will be either all red or all blue. Even in the absence of selection, coexistence is not possible. If there is a fitness difference, then the fitter type has a greater chance of winning, but no certainty. We calculate the probability that the descendants of one individual will take over the whole population. This so-called fixation probability is important for estimating the rate of evolution.

Chapter 7 is about games in finite populations. Most of evolutionary game theory has been formulated in terms of deterministic dynamics describing the limit of infinitely large populations. Here we move game theory to finite populations and make surprising observations. Neither a Nash equilibrium, nor an evolutionarily stable strategy, nor a risk-dominant strategy is protected

---

by natural selection. There can be advantageous mutants against all three. In a bistable situation between two strategies, there is a simple “1/3 rule” that determines whether a strategy is favored by natural selection.

In Chapter 8, the individuals of a population are represented by the vertices of a graph. The edges of the graph specify who interacts with whom. The graph can denote spatial relationships or social networks. The first observations of “evolutionary graph theory” are reported. The classical homogeneous population is defined by the complete graph, where all vertices are connected. We will see that circulations have the same evolutionary behavior as the complete graph in terms of fixation probability under constant selection, and therefore represent a particular balance between drift and selection. Graphs that enhance drift act as suppressors of selection. Graphs that reduce drift act as amplifiers of selection. In the limit of large population size, there exist graphs that guarantee the fixation of any advantageous mutant and the extinction of any disadvantageous mutant. Games on graphs are also studied in this chapter. There is a remarkably simple rule for the evolution of cooperation.

Chapter 9 gives an account of evolutionary game dynamics on spatial grids. The primary approach will be deterministic, discrete in time, and discrete in space. This approach brings together game theory and cellular automata. We will observe evolutionary kaleidoscopes, dynamic fractals, and spatial chaos. There is all the complexity one could ever wish for—making it unnecessary for God to play dice. Moreover, cooperation can evolve on spatial grids. This is the concept of “spatial reciprocity.”

In Chapter 10, we study the evolutionary dynamics of virus infections. I will argue that the mechanism of disease progression caused by the human immunodeficiency virus (HIV) is an evolutionary one. The immune system constantly attacks the virus, but the virus continuously evolves away, appears elsewhere in sequence space, and eventually overpowers the immune system. The resulting “diversity threshold theory” can explain why people succumb to the fatal immunodeficiency disease AIDS after a long and variable infection with HIV.

Chapter 11 discusses the evolution of infectious agents, their attempts to infect new hosts, and the selection pressures that determine the level of virulence. The conventional wisdom is that well-adapted parasites are harmless to their hosts. This perspective is revised in the context of evolutionary dy-

---

namics. Competition between different mutants of a parasite maximizes its basic reproductive ratio. Superinfection takes into account that parasites compete on two levels of selection: within an infected host and in the population of hosts. Superinfection holds many surprising aspects, including the short-sighted evolution of higher and higher virulence beyond what would be optimum for the parasite.

Chapter 12 explores the evolutionary dynamics of human cancer. Cancer arises when cooperation among cells breaks down. The mutated cells revert to their primitive program of uncontrolled replication. We calculate the rate of activation of oncogenes and inactivation of tumor suppressor genes. We analyze the impact of mutations that trigger “genetic instability.” We outline the conditions necessary for “chromosomal instability” to initiate cancer progression.

Chapter 13 is devoted to the evolutionary dynamics of the one trait that is truly our own invention and that is arguably the one interesting thing that has happened in the last six hundred million years on earth. Bacteria invented all the biochemistry of life. Eukaryotes invented some advanced genetics and how to build complicated multicellular plants and animals. Humans will be remembered for language.

Chapter 14 summarizes and concludes. Further readings will be found at the back of the book.

---

All the diverse topics of this book are unified by evolutionary dynamics. The mathematical description of evolution has moved from the study of purely genetic systems to any kind of process where information is being reproduced in a noisy (= natural) environment. What you will encounter in this book is responsible for shaping life around you. Every living system, and everything that arises as a consequence of living systems, is a product of evolutionary dynamics.