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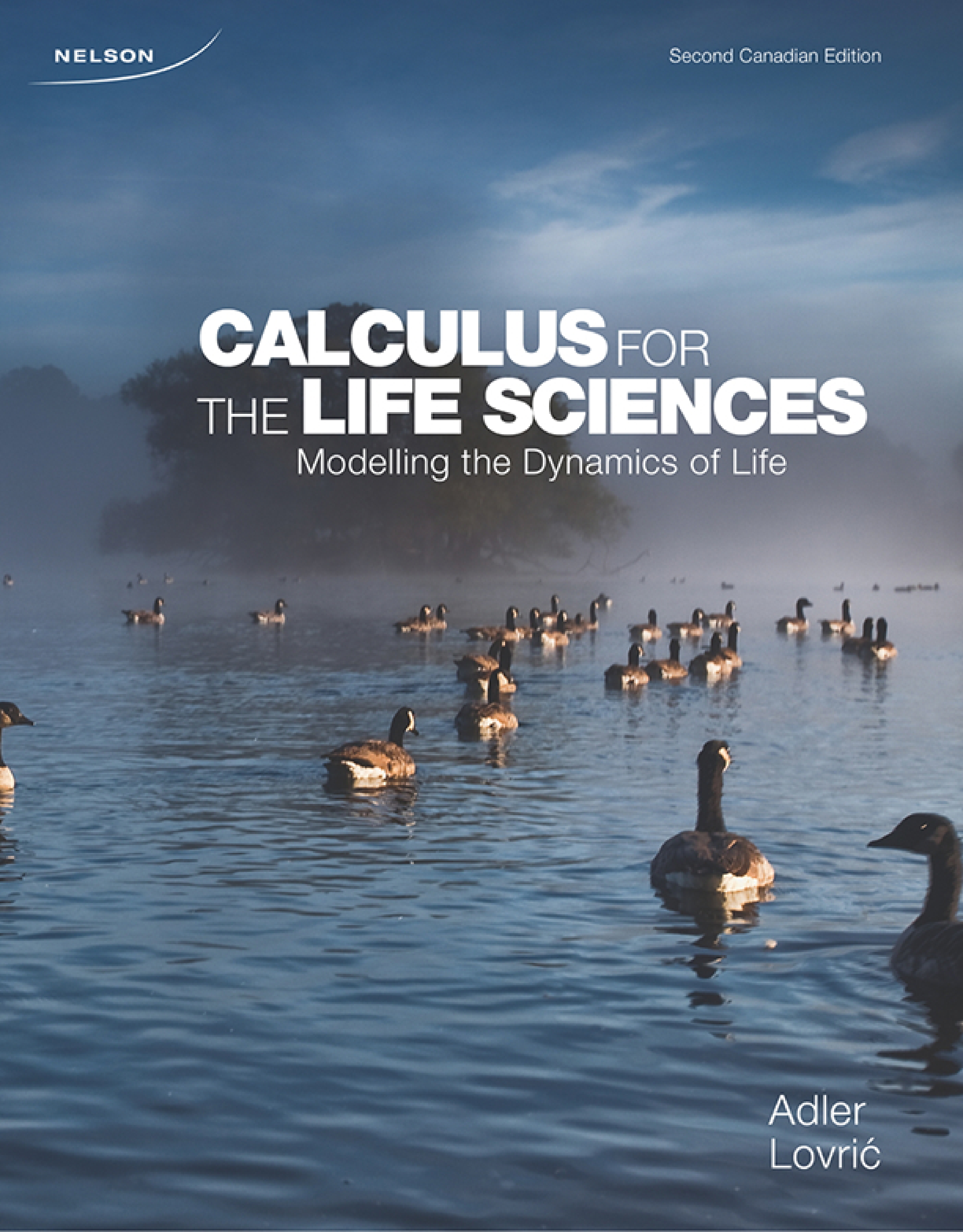
Second Canadian Edition

CALCULUS FOR THE LIFE SCIENCES

Modelling the Dynamics of Life



Adler

Lovrić

ALGEBRA

Algebraic Operations

$\frac{a+b}{c} = \frac{a}{c} + \frac{b}{c}$; note: $\frac{a}{b+c}$ is not equal to $\frac{a}{b} + \frac{a}{c}$

$\frac{a}{b} + \frac{c}{d} = \frac{ad+bc}{bd}$

$\frac{a/b}{c/d} = \frac{a}{b} \cdot \frac{d}{c} = \frac{ad}{bc}$; special cases: $\frac{a}{c/d} = \frac{ad}{c}$ and $\frac{a/b}{c} = \frac{a}{bc}$

If $a \neq 0$, then $0/a = 0$; expressions $a/0$ and $0/0$ are not defined (not real numbers)

Quadratic Formula

The solutions of $ax^2 + bx + c = 0$ are $x = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$

Completing the Square

$x^2 + ax = \left(x + \frac{a}{2}\right)^2 - \left(\frac{a}{2}\right)^2$

Powers of a Binomial

$(a+b)^2 = a^2 + 2ab + b^2$

$(a-b)^2 = a^2 - 2ab + b^2$

$(a+b)^3 = a^3 + 3a^2b + 3ab^2 + b^3$

$(a-b)^3 = a^3 - 3a^2b + 3ab^2 - b^3$

Factoring Polynomials

$a^2 - b^2 = (a-b)(a+b)$

$a^2 + b^2$ does not factor (into real factors)

$a^3 - b^3 = (a-b)(a^2 + ab + b^2)$

$a^3 + b^3 = (a+b)(a^2 - ab + b^2)$

Rules for Inequalities [the sign $<$ ($>$) can be replaced by $\leq$ ($\geq$)]

If $a < b$ and $b < c$ then $a < c$

If $a < b$ then $a + c < b + c$ and $a - c < b - c$

If $a < b$ and $c > 0$ then $ac < bc$; if $a < b$ and $c < 0$ then $ac > bc$

If $0 < a < b$ then $1/a > 1/b$

Absolute Value and Square Root [assume that $a \geq 0$]

$\sqrt{x^2} = |x|$

$|x| = a$ is equivalent to $x = -a$ or $x = a$

$|x| > a$ is equivalent to $x < -a$ or $x > a$

$|x| < a$ is equivalent to $-a < x < a$

$x^2 = a$ is equivalent to $x = -\sqrt{a}$ or $x = \sqrt{a}$

$x^2 > a$ is equivalent to $x < -\sqrt{a}$ or $x > \sqrt{a}$

$x^2 < a$ is equivalent to $-\sqrt{a} < x < \sqrt{a}$

Exponents and Radicals

$a^0 = 1$ $\qquad$ $a^1 = a$

$a^{-1} = \dfrac{1}{a}$ $\qquad$ $a^{-n} = \dfrac{1}{a^n}$

$a^m a^n = a^{m+n}$ $\qquad$ $\dfrac{a^m}{a^n} = a^{m-n}$

$(a^m)^n = a^{mn}$

$a^n b^n = (ab)^n$ $\qquad$ $\dfrac{a^n}{b^n} = \left(\dfrac{a}{b}\right)^n$

$a^{1/n} = \sqrt[n]{a}$ $\qquad$ $a^{1/2} = \sqrt{a}$

$a^{m/n} = \sqrt[n]{a^m} = \left(\sqrt[n]{a}\right)^m$

$\sqrt[n]{ab} = \sqrt[n]{a}\sqrt[n]{b}$ $\qquad$ $\sqrt[n]{\dfrac{a}{b}} = \dfrac{\sqrt[n]{a}}{\sqrt[n]{b}}$

Factorials

$0! = 1$ $\qquad$ $1! = 1$

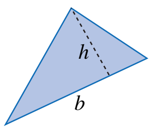
$n! = 1 \cdot 2 \cdot 3 \cdots (n-1) \cdot n$

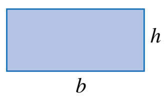
GEOMETRY

Area (A), Circumference (C), Surface Area (S), and Volume (V)

Triangle, base b and height h: $A = \dfrac{1}{2}bh$

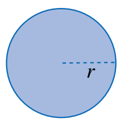
Rectangle, base b and height h: $A = bh$; $C = 2b + 2h$

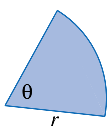




Circle, radius r: $A = \pi r^2$; $C = 2\pi r$

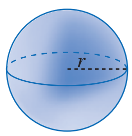
Sector of a circle, radius r and angle θ (in radians): $A = \dfrac{1}{2}r^2\theta$; $C = r\theta$

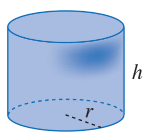




Sphere, radius r: $V = \dfrac{4}{3}\pi r^3$; $S = 4\pi r^2$

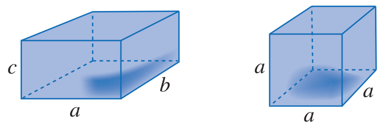
Cylinder, base radius r and height h: $V = \pi r^2 h$





Rectangular box with dimensions a, b, c: $V = abc$; $S = 2ab + 2ac + 2bc$

Cube of side a: $V = a^3$; $S = 6a^2$



Analytic Geometry

Distance between points x_1 and x_2 on a number line: $d = |x_2 - x_1|$

Distance between points (x_1, y_1) and (x_2, y_2) in a plane: $d = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2}$

Midpoint of a line segment joining (x_1, y_1) and (x_2, y_2): $M = \left(\dfrac{x_1 + x_2}{2}, \dfrac{y_1 + y_2}{2}\right)$

Slope of a line through points (x_1, y_1) and (x_2, y_2): $m = \dfrac{y_2 - y_1}{x_2 - x_1}$

Equation of a line through (x_1, y_1) of slope m (point-slope equation): $y - y_1 = m(x - x_1)$

Line of slope m and y-intercept b (slope-intercept equation): $y = mx + b$

Equation of a circle of radius r centred at the origin: $x^2 + y^2 = r^2$

TRIGONOMETRIC RATIOS AND TRIGONOMETRIC FUNCTIONS

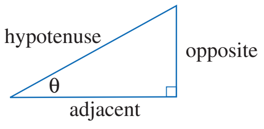
π radians = 180°; i.e., 1 radian = $\dfrac{180^{\circ}}{\pi}$ and $1^{\circ} = \dfrac{\pi}{180}$ radians

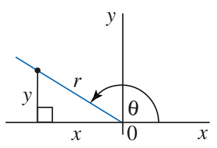
Right-angle triangle

$$\sin\theta = \frac{\text{opposite}}{\text{hypotenuse}} \qquad \csc\theta = \frac{1}{\sin\theta} = \frac{\text{hypotenuse}}{\text{opposite}}$$

$$\cos\theta = \frac{\text{adjacent}}{\text{hypotenuse}} \qquad \sec\theta = \frac{1}{\cos\theta} = \frac{\text{hypotenuse}}{\text{adjacent}}$$

$$\tan\theta = \frac{\text{opposite}}{\text{adjacent}} \qquad \cot\theta = \frac{1}{\tan\theta} = \frac{\text{adjacent}}{\text{opposite}}$$





General angles

$$r = \sqrt{x^2 + y^2}$$

$$\sin\theta = \frac{y}{r} \qquad \csc\theta = \frac{1}{\sin\theta} = \frac{r}{y}$$

$$\cos\theta = \frac{x}{r} \qquad \sec\theta = \frac{1}{\cos\theta} = \frac{r}{x}$$

$$\tan\theta = \frac{y}{x} \qquad \cot\theta = \frac{1}{\tan\theta} = \frac{x}{y}$$

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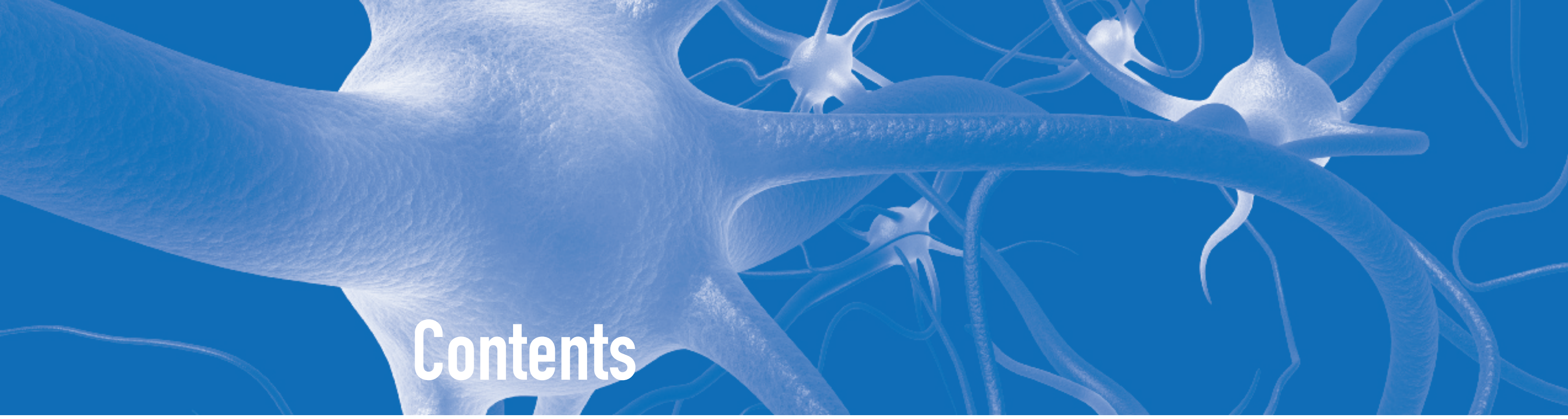

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Preface

Calculus for the Life Sciences: Modelling the Dynamics of Life is truly a *calculus* book for *life sciences* students.

This book covers limits, continuity, derivatives, integrals, and differential equations, which are standard topics in introductory calculus courses in universities. All concepts, definitions, and theorems are explained in detail and illustrated in a number of fully solved examples. A variety of approaches—algebraic, geometric, numerical, and verbal—facilitate the understanding of the material and will be of great help to any students who may read the book on their own.

As new mathematics concepts and ideas are introduced, applications illustrating their use are presented. Questions arising from life sciences situations are employed to motivate the construction of several mathematical objects (such as derivatives and integrals). A narrative introduces the context of an application and shows its relevance and importance in life sciences.

The major purpose of this book is to build *quantitative skills* and to introduce its readers to the *insights* that mathematics can provide into all branches of life sciences.

Although the importance of quantitative skills in the life sciences is a widely accepted fact, realities—in many cases—conceal their vital role. In part, this is because mathematics tends to be hidden, working in the background: once something has been figured out and becomes a standard, the mathematics that was used is no longer needed, as practitioners use software, diagrams, and charts instead. For instance, doctors and nurses do not look at half-life information to calculate a dosage every time they need to administer a medication. An ultrasound technician can "calculate" the volume of blood in a patient's heart chamber by selecting a few items from the pull-down menus in a computer program, completely unaware of the fairly sophisticated mathematics (calculation of volume by approximate integration) used to design the software.

As for the insights, a simple mathematical model explains why the heart of a mouse beats about 15 times as fast as the heart of an elephant. With mathematical formulas that describe human growth, we can understand why body mass index does not give reliable estimates of body fat in children and tall people.

Furthermore, mathematics has the power to *reveal otherwise invisible worlds* in the vast universe of numerical data that has been gathered about almost every single phenomenon related to life. Joel E. Cohen writes:[1]

> For example, computed tomography can reveal a cross-section of a human head from the density of X-ray beams without ever opening the head, by using the Radon transform to infer the densities of materials at each location within the head. Charles Darwin was right when he wrote that people with an understanding "of the great leading principles of mathematics ... seem to have an extra sense." Today's biologists increasingly recognize that appropriate mathematics can help interpret any kind of data.

[1] J. E. Cohen. Mathematics is biology's next microscope, only better; biology is mathematics' next physics, only better. PLoS Biol 2(12): e439, 2004. Published online December 14, 2004. doi: 10.1371/journal.pbio.0020439. PMCID: PMC535574.

Although a great deal of biology can be done without mathematics, the powerful new technologies that are transforming fields of biology—from genetics to physiology to ecology—are increasingly quantitative, as are many questions at the frontiers of knowledge. Along with genetics, mathematics is one of two unifying factors in the life sciences. And as biology becomes more important in society, mathematical literacy becomes as vital for an informed citizen as it is for a researcher.

Modelling and the Dynamics of Life

The goal of this book is to teach the mathematical ideas that will help us understand various phenomena in life sciences. These are the same ideas that researchers use in their work, as well as in collaborations with colleagues engaged in more empirical activities. They are not specific techniques, such as differentiation or integration by parts, but rather they revolve around building *mathematical models*.

A mathematical model is that crucial link between a life sciences phenomenon and its description in terms of mathematical objects. We will gain the skills needed to construct a model, make sure it works, and understand what it implies—we will learn how to *translate* appropriate aspects of a life sciences problem and its assumptions into formulas, equations, and diagrams; how to *solve* the equations involved; and how to *interpret* the results in terms of the original problem. For instance:

- We build several models in an attempt to predict what the population of Canada will be in the near (and not so near) future. In each case, we critically examine the assumptions that we made, as well as comment on the results of the model.
- Regular clinical breast examinations are key to early detection of breast cancer. Do these exams suffice, or should one also consider mammography? By using an exponential model to understand how cancer cells grow, we conclude that in some cases mammography gives a significant lead time over clinical examination in early detection of cancer.
- To study the interaction between populations, we take a detailed look at the predator-prey model, which could be used, for instance, to describe the interaction between foxes and rabbits in an ecosystem. In addition, a model of selection will help us understand the behaviour of two different bacterial cultures sharing the same space and resources.
- We investigate limited population growth models, such as the logistic model and the Allee effect.
- Using discrete-time dynamical systems, we build our understanding of aspects of the consumption and absorption of drugs such as alcohol and caffeine.

Content

The organization and presentation of the material in this book mirror the relationship between mathematics and the life sciences. Mathematics enables us to describe, explain, and understand biological processes. In turn, the questions life scientists would like to know the answers to stimulate the development of mathematical ideas and techniques.

A quick overview of the content of the book is contained in the following table:

An Overview of the Book

Chapter 1 Introduction	We illustrate how math is used in the life sciences (Section 1.1); introduce the idea of a mathematical model (Section 1.2); review basics about functions, such as graphs and transformations of graphs, composition, and inverse functions; and use the opportunity to discuss elementary models (Sections 1.3 and 1.4). In the final section, we talk about building blocks of math (definitions, theorems), math reasoning patterns (how to think of an implication), and interpreting math results in the context of applications in life sciences.
Chapter 2 Modelling Using Elementary Functions	We review properties of linear, power, and transcendental functions, and, at the same time, introduce important models (many of which we revisit as we learn more math). For instance, using power functions, we study heartbeat frequency in mammals and derive an important relation between the size of an animal and the size of its body cover, we predict the changes in Canadian population, we study cell growth using exponential models, and we describe various oscillations and learn how forensic technicians use blood splatters to identify the events that led to their formation.
Chapter 3 Discrete-Time Dynamical Systems	We study algebraic and geometric properties of discrete-time dynamical systems (recurrence relations) in Sections 3.1 and 3.2. We discuss a whole spectrum of models, including limited population and consumption of coffee and alcohol (Section 3.3) and a nonlinear population model of selection (Section 3.4). As we learn more math, we revisit these models and enrich our understanding. The chapter closes with a more advanced model on gas exchange in the lung (Section 3.5).
Chapter 4 Limits, Continuity, and Derivatives	This chapter contains an in-depth discussion of major calculus concepts: limits (Sections 4.2 and 4.3), continuity (Section 4.4), and derivatives (Sections 4.1 and 4.5). With applications never far from sight, we introduce several absorption functions (Section 4.3). In order to understand how practitioners reason and speak about absorption, we compare these functions in terms of how quickly they approach zero or infinity.
Chapter 5 Working with Derivatives	In this fairly technical chapter, we cover all differentiation rules (Sections 5.1 to 5.4), including implicit and logarithmic differentiation and related rates (Section 5.5). Besides traditional questions (found in all calculus texts), the reader will find exciting related rates situations from biology. We learn how to calculate higher-order derivatives and use them to study graphs (Section 5.6) and build various approximations of functions, including Taylor polynomials (Section 5.7).
Chapter 6 Applications of Derivatives	This chapter offers a wide range of applications of derivatives: computing absolute and relative extreme values (Section 6.1), identifying leading behaviour and calculating limits using L'Hôpital's rule (Section 6.4), drawing graphs of functions (Section 6.5), and approximating solutions of equations using Newton's method (Section 6.6). To illustrate how optimization works, we study the strength of bones and the feeding patterns of animals and analyze the way bees build their honeycombs (Section 6.2). Section 6.3 makes important connections between continuity and differentiability. The derivatives help us understand the stability of a dynamical system (Section 6.7) as well as gain an insight into complex dynamic behaviour such as chaos (Section 6.8). An advanced study of breathing patterns (Section 6.9) can be downloaded from the textbook's companion website.
Chapter 7 Integrals and Applications	We introduce differential equations, an important ingredient in many mathematical models in biology (Section 7.1), as motivation for a need to reverse differentiation. We proceed as usual: antiderivatives (Section 7.2) and area and the definite integral (Section 7.3) meet in the statement of the Fundamental Theorem of Calculus (Section 7.4). We work through standard integration methods (Section 7.5) and discuss improper integrals (Section 7.7). We go through a wide range of applications in Section 7.6 (area, volume, length, mass, etc.), including estimating the surface area of Lake Ontario and the volume of a heart chamber.
Chapter 8 Differential Equations	The focus of this chapter is on autonomous differential equations and their applications. We introduce and investigate several important models, such as the logistic model, the Allee effect, the law of cooling, diffusion, and the continuous model of selection (Section 8.1). We develop tools for a qualitative analysis: equilibria and display (Section 8.2), stability (Section 8.3), and then solve some equations using separation of variables (Section 8.4). The remaining sections are devoted to models based on systems of differential equations, such as predator–prey and competition (Section 8.5), and their analysis using phase-plane techniques (Sections 8.6 and 8.7). A more challenging section on the dynamics of a neuron (Section 8.8) can be downloaded from the textbook's companion website.

Presentation

Easy-to-read and easy-to-follow narratives, carefully drawn pictures and diagrams, clear explanations, large numbers of fully solved examples, and broad-spectrum applications make the material suitable for a variety of audiences with a wide range of interests and backgrounds.

In creating this book, we were guided by several important principles:

- Convey excitement about the material.
- Convey the relevance and importance of mathematics and its applications.
- Use a variety of approaches—algebraic, numeric, geometric, and verbal.
- Motivate the introduction of new mathematical objects, concepts, and algorithms.
- Review background material so it does not become an obstacle in explaining advanced material.
- Provide more examples and illustrations for more difficult material.
- Revisit important concepts as often as possible, in a variety of contexts.
- Revisit applications and enrich models as new mathematics ideas are introduced.

Conceptual Understanding and Mathematical Thinking

This text provides the reader with an opportunity to build a clear understanding of a relatively small number of ideas and concepts from the calculus of functions of one variable. It offers exhaustive discussions and carefully crafted examples; clear and crisp statements of theorems and definitions; and—acknowledging that many of us are visual learners—numerous illustrations, graphs, and diagrams. Important concepts are revisited as often as possible, placed in a variety of contexts, and applied in solving life sciences problems.

Development of Mathematical (Quantitative) Skills

It is impossible to fully master almost any topic in mathematics without adequate skills in symbolic (algebraic) manipulation. This book contains a large number of fully solved examples designed to illustrate formulas, algebraic methods, and algorithms, and to provide an ideal opportunity for students to improve on their routine in the technical intricacies of calculations.

Topics that some students may find challenging (such as Riemann sums and integration methods, working with Taylor polynomials, and graphing using leading behaviour) are accompanied by a large number of solved examples. Use of technology (graphing calculator or mathematical software such as Maple) is strongly encouraged, since it might provide insights that will enhance understanding of the material.

In-Depth Explorations of Particular Models

This book includes several extended applications. Early on, we study the phenomenon of the interaction between two types of bacteria, mutant and wild, in Section 3.4, and certain aspects of the dynamics of gas exchange in the lungs, in Section 3.5. Applications of optimization to feeding patterns of animals, calculations of the strength of bones, and a study of the ways bees build their honeycombs are found in Chapter 6.

Phase-plane methods are used in Chapter 8 to analyze two-dimensional systems representing interactions between two species. Some of these models can be assigned as individual or group study projects.

End-of-Section and End-of-Chapter Problems, Computer Exercises, and Projects

In addition to routine skills problems, each section includes a wide variety of modelling problems to emphasize consistently the importance of *interpretation.* As well, more challenging mathematics questions will be found here, including requests to construct proofs that are omitted from the text. Each chapter includes supplementary problems that introduce a variety of new applications and can be used for review or practice sessions.

The book contains more than 50 exercises designed to be explored on a graphing calculator (preferably programmable) or on a computer using software such as Maple. These exercises emphasize *visualization, experimentation,* and *simulation*—all of which are important aspects of conducting research in life sciences, as well as many other areas.

Most chapters include projects suitable for individual or group exploration. Examples include the following:

- modelling the balance between selection and mutation (Chapter 3)
- studying periodic hematopoiesis using a discrete-time dynamical system (Chapter 4)
- experimenting with different numerical schemes for solving differential equations (Chapter 7)
- carefully studying models of adaptation by cells (Chapter 8)

Teaching

Although this is a book for *life sciences,* it is a *calculus textbook* as well. It can be used to teach a variety of courses, spanning a wide range of flavours and levels of difficulty. The coverage of math theory, techniques, and algorithms, as well as applications, allows an instructor to tune the course to an appropriate balance of math rigour and applications in life sciences.

Several suggestions for courses are outlined in the chart on page xiv.

Great care has been taken to make the level of exposition—both mathematical and applications—adequate for first-year students. A course instructor can assign, with confidence, parts of the material as homework or as optional reading.

No matter which course is taught from this text, the benefits are obvious. *The modelling approach is naturally a problem-solving approach.* Students will not remember every technique they have learned. This book emphasizes understanding what a model is and recognizing what a model says. To be able to recognize a differential equation, interpret the terms, and use the solution is far more important than knowing how to find a solution algebraically. These reasoning skills, in addition to familiarity with the models in general, are what will stay with the motivated student and what will matter most in the end.

Suggestions for Courses	
One-semester, first-year calculus for life sciences	Start with Chapter 1 (introduce the subject, justify using math to model life sciences phenomena, warm-up); Chapter 2 (review linear, power, and transcendental functions, discuss numerous models); Chapter 4; Chapter 5 (might not require much time); Chapter 6 (pick among the topics and applications presented); Chapter 7 (selection of topics and applications); if time permits, discuss Section 8.1. Discrete-time dynamical systems (in this context, recurrence relations) in Chapter 3 can be skipped, or covered to a desired depth. For instance: extract basics from Sections 3.1 and 3.2 to cover models in Section 3.3 (such as limited population or alcohol consumption), or cover Sections 3.1 and 3.2 in detail, discuss many interesting models in Sections 3.3 and 3.4, and then discuss stability and further models in Sections 6.7 and 6.8.
One-semester, first-year calculus for life sciences (advanced)	Taking advantage of students' background, discuss features of models in Chapters 1, 2, and 3, perhaps including Section 3.5; Chapters 4 and 5 might not require much time; possibly include case studies in Section 6.2, or discussion of stability of equilibria and dynamics of chaos in Sections 6.7 and 6.8; cover Chapter 7 and the first four sections of Chapter 8.
Two-semester, first-year calculus for life sciences	First semester as above. Use the opportunity to finish the material in Chapters 7 and 8 to a desired depth. The remaining time could be spent discussing topics from one or more of the Modules: Several Variables, Probability and Statistics, and Linear Algebra, which are available as separate books (see page xv for a Table of Contents of each module).
One-semester calculus course of a more theoretical nature	Start with Chapters 1 and 2 (to review properties of elementary functions; some applications can be used to discuss properties of functions that involve parameters); Chapter 4 and Chapter 5, including some proofs; Chapter 6, at least Sections 6.1 and 6.3; Chapter 7 (with details regarding Riemann sums); if time permits, Sections 8.1 to 8.3.
Second-year modelling course for students who took traditional calculus	Focus on models in Chapters 1 and 2 (also a good review of functions); Chapter 3, perhaps all of it; pick themes from Chapters 4 and 5 (for instance, absorption functions in Section 4.3 or related rates with life sciences context in Section 5.5); cover Section 5.7; selection of material from Chapter 6, such as Sections 6.2, 6.7, and 6.8; focus on applications in Chapter 7 (Section 7.6); Chapter 8, including systems of autonomous differential equations. Sections 3.5, 6.9, and 8.8 contain some challenging material but are appropriate for second-year students.
One-semester introductory course on dynamics of growth, or population modelling	Start with a selection of topics in Chapter 2 (exponential model, allometry); then Chapter 3, in particular Sections 3.3 and 3.4, with application exercises and computer exercises in Section 3.4 introducing additional models, including chaotic behaviour; necessary topics in Chapters 4 and 5, using models as examples (logistic, gamma distributions, Hill functions, von Bertalanffy limited growth, etc.); Sections 6.7, 6.8 (*exercises* in these two sections and *projects* at the end of the chapter provide many opportunities for extensions [chaos, Ricker model, etc.]); Chapter 7; major focus on autonomous differential equations, systems, and phase planes in Chapter 8.
Project-driven, problem-based course (learning math through applications)	Consider questions such as the following: Why can't we use radiocarbon dating to determine the time when dinosaurs died (Section 2.2)? What happens to the amount of alcohol in our body if we consume one drink per hour (Section 3.3)? How do bones grow and what makes them strong (Sections 2.1 and 6.2)? Why do bees' honeycombs have hexagonal cross-sections (Section 6.2)? How do we approximate the area of a lake, or the volume of a heart chamber (Section 7.6)? How do we model interactions of two species (Sections 8.5, 8.6, 8.7)? This is just a sample of starting points suggested in this book—students realize that they need to learn more math if they wish to understand these life sciences problems and find good answers.

Life Sciences Modules to Accompany This Text

This book covers the calculus of functions of one variable. Quite often, longer (two-semester) life sciences courses include topics from other disciplines. To allow for flexibility in planning courses and resources, additional material has been organized in three separate modules. Intertwining math foundations and applications, the modules cover functions of several variables, basics of probability and statistics, and elementary linear algebra. These modules can be bundled with the text, or alternatively, a custom package can be compiled, including material from the textbook and the modules. Contact your sales representative for more information.

Functions of Several Variables (144 pages), ISBN: 978-0-17-657136-8

1. Introduction
2. Graph of a Function of Several Variables
3. Limits and Continuity
4. Partial Derivatives
5. Tangent Plane, Linearization, and Differentiability
6. The Chain Rule
7. Second-Order Partial Derivatives and Applications
8. Partial Differential Equations
9. Directional Derivative and Gradient
10. Extreme Values
11. Optimization with Constraints

Probability and Statistics (195 pages), ISBN: 978-0-17-657135-1

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2. Stochastic Models
3. Basics of Probability Theory
4. Conditional Probability and the Law of Total Probability
5. Independence
6. Discrete Random Variables
7. The Mean, the Median, and the Mode
8. The Spread of a Distribution
9. Joint Distributions
10. The Binomial Distribution
11. The Multinomial and the Geometric Distributions
12. The Poisson Distribution
13. Continuous Random Variables
14. The Normal Distribution
15. The Uniform and the Exponential Distributions

Linear Algebra (138 pages), ISBN: 978-0-17-657137-5

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2. Vectors
3. The Dot Product
4. Equations of Lines and Planes
5. Systems of Linear Equations
6. Gaussian Elimination
7. Linear Systems in Medical Imaging
8. Matrices
9. Matrices and Linear Systems
10. Linear Transformations
11. Eigenvalues and Eigenvectors
12. The Leslie Model: Age-Structured Population Dynamics

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NETA Test Bank: This resource was written by Andrijana Burazin and reviewed by Miroslav Lovrić, McMaster University. It includes more than 275 multiple-choice questions written according to NETA guidelines for effective construction and development of higher-order questions. The Test Bank was copy-edited by a NETA-trained editor and underwent a full technical check. Also included are almost 100 true/false questions.

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Access additional material, including online-only advanced material not included in the text, in the **Companion Website** for *Calculus for the Life Sciences*. Visit www.nelson.com/site/calculusforlifesciences.com.

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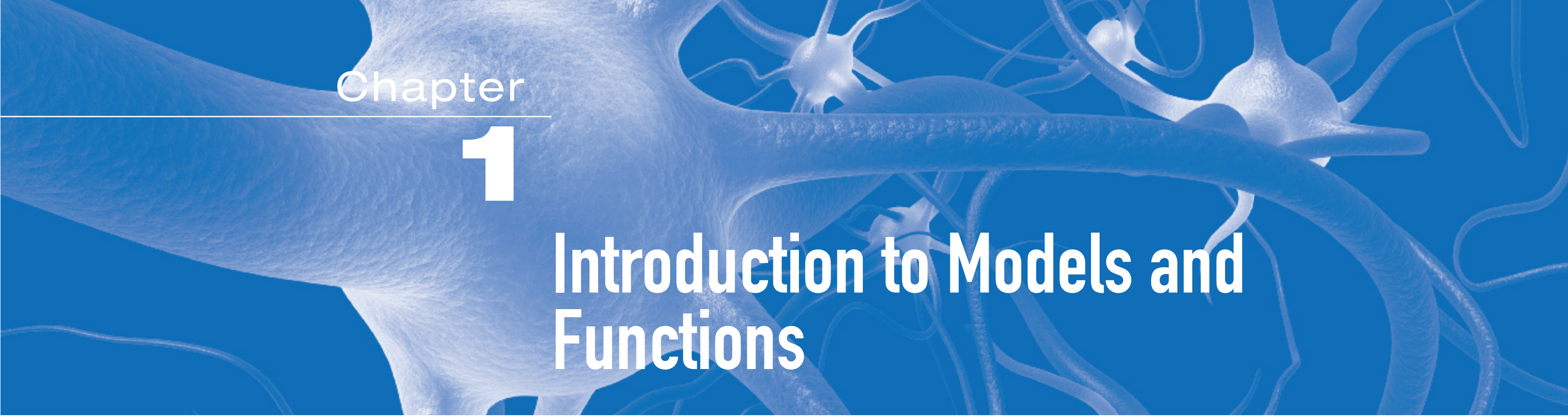
Miroslav Lovrić
Hamilton, 2014



Chapter 1

Introduction to Models and Functions

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This chapter opens by answering an obvious and easy question—why do we need mathematics in the life sciences? We list some (of many!) questions from biology, health sciences, and elsewhere that are answered—using mathematics—in this book. As well, we mention a few present-day research problems that have very little chance of being solved or fully understood without mathematics.

We introduce the main tools needed to study biology using mathematics: **models** and **functions.** A **model** is a collection of mathematical objects (such as functions and equations) that allows us to interpret biological problems in the language of mathematics. Biological phenomena are often described by measurements: a set of numeric values with units (such as kilograms or metres). Many relations between measurements are described by **functions,** which assign to each input value a unique output value.

After talking about what constitutes a mathematical model and presenting a few examples, we briefly **review functions** and their properties. In this chapter, we discuss the **domain and range** and the **graph of a function, algebraic operations with functions, composition of functions,** and **inverse functions.** We build new functions from old using shifting, scaling, and reflections. We catalogue important elementary functions and note their properties. The reader who is familiar with functions might skip this material and move to the next chapter.

We introduce the four approaches—algebraic, numeric, geometric, and verbal—that we use throughout the book to discuss functions, their properties, and their applications.

In the last section we discuss aspects of logical reasoning that we need to follow and to understand mathematical expositions. As well, we contrast the language used in mathematics and in the life sciences, in order to motivate learning an important skill—communicating scientific facts, ideas, and results across disciplines.

1.1 Why Mathematics Matters

In the summer of 2012, a team of palaeontologists from the Royal Tyrrell Museum ("Canada's dinosaur museum") in Drumheller, Alberta, unearthed the skeleton of a large triceratops, a herbivorous dinosaur that lived in what is now North America some time between 68 and 65 million years ago. An adult triceratops measured 8–9 m in length and about 3 m in height, and weighed between 6,000 and 12,000 kg (Figure 1.1.1).

FIGURE 1.1.1

Complete skeleton of a triceratops, Royal Tyrrell Museum
Photo courtesy of the Royal Tyrrell Museum, Drumheller, Alberta

No human has ever seen a living dinosaur, so how do we know all this?

Estimates of age, size, weight, and many other quantities are obtained *using mathematics*, based on the data collected from the bones and from the site where they were found. Among other techniques, potassium-argon dating (see the note following Example 2.2.13) is used to compute the time interval when triceratops lived on Earth. By counting the growth lines in the MRI scan of certain bones (unlike an X-ray, an MRI image is *calculated*), researchers can determine how old the dinosaur was when it died. Then, using the formula (adapted from G. M. Erickson, K. C. Rogers, and S. A. Yerby, Dinosaurian growth patterns and rapid avian growth rates. *Nature*, 412 (429–433), 2001)

$$M = \frac{12,000}{1 + 2.9e^{-0.87(t-7.24)}} \qquad \textbf{(1.1.1)}$$

we can find an approximation of the body mass, M (in kilograms), of the triceratops based on the age at death, t (in years).

Allometry—a branch of life sciences—is the study of numeric relationships between quantities associated with human or animal organisms. For instance, the allometric formula (adapted from M. Benton, and D. Harper, *Basic Palaeontology*, Harlow, U.K.: Addison Wesley Longman, 1997)

$$\mathrm{Sk} = 0.49\mathrm{Sp}^{0.84} \qquad \textbf{(1.1.2)}$$

relates the skull length, Sk, of a larger dinosaur to its spine length, Sp (both measured in metres). From the triceratops' vertebrae found at the Drumheller site, researchers could figure out its spine length and then use formula (1.1.2) to calculate the size of its skull. (Further examples of allometric relationships can be found in Examples 2.1.12 to 2.1.16 and Example 5.5.10.)

This example, and many more that we will encounter in this book, echo this important message:

> Mathematics is an indispensable tool for studying life sciences. It deepens our understanding of life science phenomena and helps us to figure out the answers to questions that would otherwise be hard (or impossible) to find.

To further emphasize this message, we give a sample of questions that we will discuss and answer—using mathematics—in this book. Needless to say, we view mathematics in its broadest sense, i.e., including probability, statistics, numeric techniques and simulations, and computer programming.

- My body mass index is 27 (above normal range). How much weight should I lose to lower it to 24 (healthy weight)? My body mass index is 16 (below normal range). How much weight should I gain to bring it to 18 (healthy weight)? (See Example 2.1.11.)
- According to the Statistics Canada 2011 Census, about 33.5 million people lived in Canada in May 2011 (exactly 33,476,688 people were enumerated in the census). How many people will live in Canada in 2021? (See Examples 2.1.10 and 2.2.14.)
- If a student consumes one alcoholic drink (12 oz of beer, or 5 oz of white wine, or 1.5 oz of tequila or vodka) every hour, how much alcohol will be in that student's body after five hours? How long will it take the student to sober up? (See Section 3.3, in particular Examples 3.3.6–3.3.8.)
- How do forensic pathologists identify the location of impact (say, from a bullet) by analyzing blood splatters on the floor? (Read Example 2.3.15.)
- Which part of a skeleton grows faster: the skull or the spine? (See Example 5.5.10.)
- What is the surface area of Lake Ontario? (This information is needed, for instance, when scientists study the impact of pollutants on lake fauna; see Example 7.6.6.)
- Scientists believe that the fossils found in the Burgess Shale Formation in British Columbia are about 505 million years old. The Joggins Fossil Cliffs in Nova Scotia contain fossils from the so-called coal age of Earth's history, about 310 million years ago. How were these estimates obtained? A tree trunk (Figure 1.1.2) was unearthed near the city of Kaitaia in New Zealand. How long ago did the tree die? (See the note following Example 2.2.13.)

FIGURE 1.1.2

Ancient kauri tree trunk (unearthed and placed upright for display)
Miroslav Lovric

- An MRI (magnetic resonance imaging) scan shows that a smaller blood vessel branches off the right coronary artery at an angle of 50 degrees. Is there a reason for medical concern? (Read Example 6.1.18.)
- Long bones in mammals (such as the femur) are hollow, filled with blood cell–producing marrow. Although lightweight, they are strong enough to support the entire body, enabling it to move in various ways. However, under continuous stress (often identified in athletes) or due to an acute event (such as a fall or a car crash), a femur can break. Can we somehow grow a stronger femur by making its walls thicker? (See Section 6.2.)
- How much valuable time is saved if a breast cancer is detected in a mammogram compared to a clinical breast examination detection? (See Example 2.2.15.)

Formulas (1.1.1) and (1.1.2), which describe life science quantities and phenomena using mathematical objects (in this case formulas involving exponential and power functions) are said to constitute a **mathematical model** (or just a **model,** as is common in practice). For instance, formula (1.1.1) **models** the relationship between age at death and body mass for larger dinosaurs. Formula (1.1.2) is a **model** for a relationship between skull length and spine length for large dinosaurs. We will say more about models in the next section.

In this book we study numerous ways of describing how populations (of cells, bacteria, animals, or humans) change. The simplest model, which uses elementary mathematics, assumes that the birth and the death rates are constant. If the birth rate is larger than the death rate, the model implies that the population will grow exponentially. Of course, beyond a certain point, this is neither realistic nor possible for any population.

To make this model better mimic reality, we introduce various modifications: for instance, we can make the birth and the death rates change over time, we can include the carrying capacity (carrying capacity is the largest number of individuals that can live in an ecosystem), or we might need to include a term that accounts for the minimum number of individuals needed for the population to avoid extinction. Having made some or all of these modifications to our model, we realize that *we need to know more mathematics* in order to work with it.

This is not all—we might need to add terms that account for harvesting and seasonal changes in the population size. As well, it might be necessary to include the effects of a disease, a natural disaster, or another random event that might affect the population. For all this, we need to know *even more mathematics.* Hence another important message:

> As the model—the description of a life sciences phenomenon using mathematics—moves closer to reality, it also becomes more complex, and more mathematics is needed to work with it.

In other words, as we learn more math, we are able to probe deeper into a problem, understand it better, gain new insights, and obtain more meaningful results and answers. To further stimulate interest in studying life sciences and mathematics together, we list several problems that are the topics of present research:

- What are the risks to the indigenous fish populations in the Great Lakes from the new species of fish brought in the tanks of large cargo ships?
- What are the distinct features of the trafficking of eosinophils as they migrate from bone marrow to the blood and, ultimately, to the lungs? How can this enhance our understanding of certain aspects of the development of allergic asthma? (Eosinophils are white blood cells, important components of our immune system, defending it against parasites and certain infections. Allergic

asthma is a disease of the airways that develops as a consequence of an immune-inflammatory response to allergen exposure (such as dust, pollen, or various drugs), causing inflammation in the lungs.)

- According to the Director of Biodiversity Programs at the Royal Botanical Gardens (RBG) in Hamilton, Ontario, there is a need to cut "an apparent overpopulation of deer wintering on its lands." An aerial survey of the part of the RBG lands in 2010 identified 267 deer, which is deemed (by the Ontario Ministry of Natural Resources) to be six to nine times the desired number of deer in the area. Is the ministry right? What is the carrying capacity of the RBG lands, i.e., how many deer should be removed (culled or relocated) from there?
- Due to long exposures to zero or near-zero gravity, astronauts working in the International Space Station suffer from spaceflight osteopenia (bone loss; on average, they lose about 1% of their bone mass per month spent in space). On the other hand, sea urchins are known to continue the production of calcium, unaffected by the lack of gravity. By modelling the growth and development of calcium plates in the skeletons of the urchins, researchers are trying to shed more light on the dynamics of calcium recycling, hoping to reduce the effects of osteopenia in humans.
- In order to better understand the pathophysiology of hydrocephalus (potentially brain-damaging buildup of fluid in the skull), researchers are studying the interaction between the cerebrospinal fluid and the brain tissue. Present efforts are focused on using partial differential equations (we will study differential equations in this book) to gain new insights into this interaction.

Dear Student:

This book gives you an opportunity to learn mathematics and to see how it is used in the wide spectrum of applications in the life sciences. To see applications in action (and to get more from them!) you need to understand the underlying math concepts, formulas, and algorithms. This is why you will find a large number of fully solved examples, as well as exercises, ranging from easy and routine to more complex, theoretical, and challenging. Work on as many of them as you can.

Learning mathematics is not easy. Like everything you really care for, it requires seriousness, dedication, a significant amount of time, and lots of hard work. But in the end, it will be worth it!

> No subject teaches logical thinking, develops analytic and problem-solving skills, and demonstrates how to deal with complex problems better or more effectively than math.

Have you ever wondered why math majors score at or near the top in all standardized tests, including MCAT, GMAT, and LSAT?

1.2 Models in Life Sciences

Living systems, from cells to organisms to ecosystems, are characterized by change and dynamics. Living things grow, maintain themselves, and reproduce. Even remaining the same requires dynamical responses to a changing environment. Understanding the mechanisms behind these dynamics and deducing their consequences is crucial to understanding biology, biochemistry, ecology, epidemiology, physiology, population genetics, and many other life sciences.

This dynamical approach is necessarily mathematical because describing dynamics requires quantifying measurements. What is changing? How quickly is it changing? What is it changing into?

In this book, we use the language of mathematics to describe quantitatively how living systems work and to develop the mathematical tools needed to compute how they change. From measurements describing the initial state of a system and a set of rules describing how change occurs, we will attempt to predict what will happen to the system.

For example, by knowing the initial amount of a drug taken (caffeine, Tylenol, alcohol, etc.) and how it is processed by the liver or kidneys (dynamical rules), we can predict how long the drug will stay in the body and what effects it might have. By knowing how many elephants live in a certain area and quantifying the factors that influence how they reproduce, we can predict what will happen to their population in the future.

To study a life sciences phenomenon using mathematics, we build a **model.** How does a model work?

First, we identify a **problem** we need to study, or a **question** we need to answer. Assume that a virus (say, H1N1) appears within a population. Will the virus spread? How many people will get infected? How many will die? Will our hospitals have adequate resources to treat increasing numbers of patients? These are just a handful of the questions that we would like to know the answers to. Underlying all of them is the basic question: we know (approximately) how many people are infected today. How many will be infected tomorrow? in three days? in a week? in a month?

Next, we need to **quantify the measurements** that we will use to investigate the problem. If we wish to use mathematics, we need numerical data. In our case, the basic measurement is the number of people infected with the H1N1 virus at any given time. Given the tools we have at our disposal, it is very useful to think of the number of people infected as a **function** (dependent variable). We might wish to use a symbol such as $I(t)$ to denote that function and to say that we will investigate how it changes with respect to time. As well, we have some data—we might know (or be able to estimate) how many people are infected at the moment. This is called an **initial condition;** we will denote it by $I(0)$, relabelling the time so that time = zero corresponds to the start of our investigation.

We also need to define the **rules that govern the dynamics** of the model. How does $I(t)$ change, and what affects it? What makes it grow, and what makes it decrease? Because we are studying change, we need a mathematical tool that is designed to do that—the derivative! That is why calculus is so relevant. If we wish to study change, we must use calculus.

Using functions and derivatives, we translate data, observations, measurements, and dynamic rules into **formulas, equations,** and whichever other mathematical tools we think will be useful. Two tools to which we devote a large part of this book, **discrete-time dynamical systems** and **differential equations,** are essential components of many mathematical models.

By doing all this we have just built a **model for the spread of a virus.** Other models are created in more or less the same way (Figure 1.2.3).

To obtain **solution(s),** we use a variety of mathematical techniques (differentiation, integration, numerical algorithms, solving differential equations, limits of sequences, etc.). In rare cases we obtain exact solutions; usually we can obtain an approximation from an algorithm, a calculator, or a computer.

Finally, we **interpret the mathematical results.** Do they make sense? Do they answer our question(s)? Do they help us better understand what is going on? Quite often, the answer to these questions is not an enthusiastic yes, but we can usually say yes to the following questions—can we get more out of this? can we do better? can we make it more accurate? Thus, mathematical modelling is itself a dynamical process—in light of new data that we might have obtained, or new developments or new insights, we refine or modify our model and run it again, in hopes of obtaining better answers and gaining a better understanding of the problem.

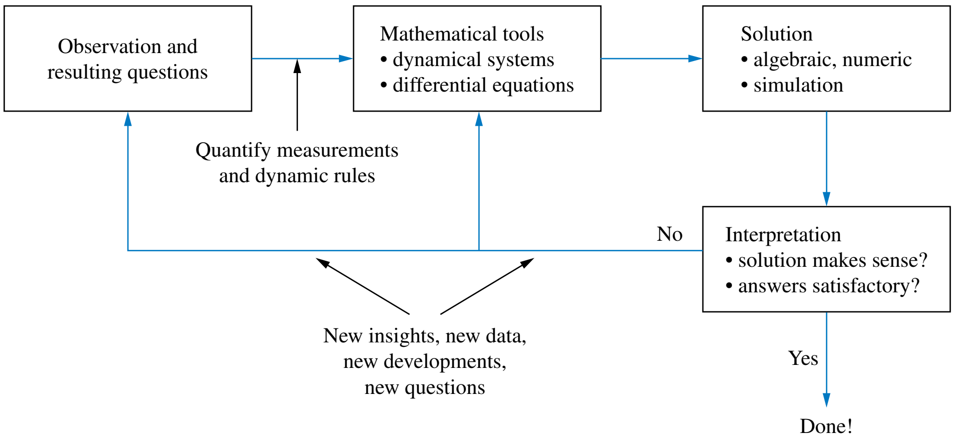


FIGURE 1.2.3
Mathematical model

Example 1.2.1 Models for the Population of Canada

In Example 2.1.10 we ask the following question about the population of Canada: based on the 2001 and 2006 Census data, what will the population be in 2011? (We picked the year 2011 so that we can compare our results with the actual 2011 Census data.)

We build a linear model (i.e., using a linear function) and solve it, obtaining the estimate of 33,219,000 for the year 2011. Not finding the answer satisfactory (following the "No" direction in the flow chart in Figure 1.2.3), we decide to try another model.

In Example 2.2.14 we use exponential growth as a model for the Canadian population, arriving at the estimate of 33,305,000. Comparing to the actual population in 2011 (33,477,000), we see that the exponential model is a bit more accurate than the linear model. However, since both models give underestimates of 170 thousand or more, we find neither truly satisfactory.

So it is back to the drawing board—but we need to learn more mathematics. To build richer, more appropriate models, we need to learn about derivatives, integrals, and differential equations.

Example 1.2.2 Models of Malaria

Early in this century, Sir Ronald Ross discovered that malaria is transmitted by certain types of mosquitoes. Because the disease was (and remains) difficult to treat, one promising strategy for control seemed to be reducing the number of mosquitoes. Many people thought that all the mosquitoes would have to be killed to eradicate the disease. Because killing every single mosquito was impossible, it was feared that malaria might be impossible to control in this way.

Ross decided to use mathematics to convince people that mosquito control could be effective. The problem can be formulated dynamically as a problem in population growth. Ross knew that an uninfected person can become infected upon being bitten by an infected mosquito and that an uninfected mosquito can be infected when it bites an infected person (Figure 1.2.4). From these assumptions, he built a **mathematical model** describing the population dynamics of malaria. With this model he proved that the disease *could* be eradicated without killing every single mosquito. We see evidence of this today in the United States, where malaria has been virtually eliminated even though the mosquitoes capable of transmitting the disease persist in many regions.

Example 1.2.3 Models of Neurons

Neurons are cells that transmit information throughout the brain and body. Even the simplest neuron faces a challenging task. It must be able to amplify an appropriate incoming stimulus, transmit it to neighbouring neurons, and then turn off and be ready

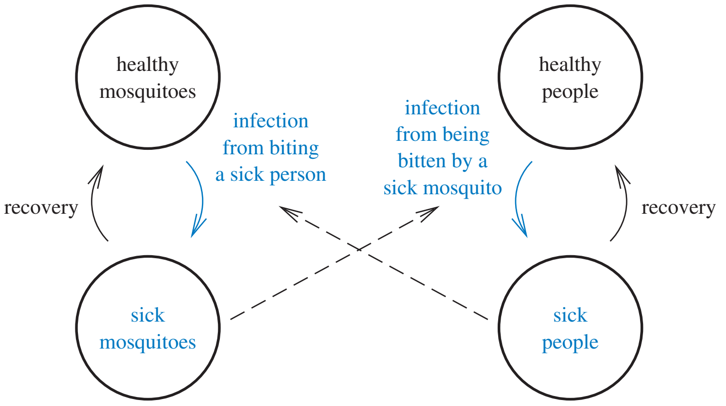


FIGURE 1.2.4

The dynamics of malaria

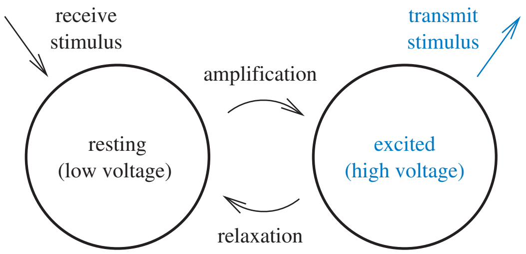


FIGURE 1.2.5

Mathematics description of the dynamics of a neuron

for the next stimulus. This task is not as simple as it might seem. If we imagine the stimulus to be an input of electrical charge, a plausible rule is "If electrical charge is raised above a certain level, increase it further." Such a rule works well for the first stimulus but provides no way for the cell to turn itself off. How does a neuron maintain functionality?

In the early 1950s, Hodgkin and Huxley used their own measurements of neurons to develop a mathematical model of dynamics to explain the behaviour of neurons. The idea is that the neuron has fast and slow mechanisms to open and close specialized ion channels in response to electrical charge (Figure 1.2.5). Hodgkin and Huxley measured the dynamical behaviour of these channels and showed mathematically that their mechanism explained many aspects of the functioning of neurons. They received the Nobel Prize in Physiology or Medicine for this work in 1963 and, perhaps even more impressive, developed a model that is still used today to study neurons and other types of cells.

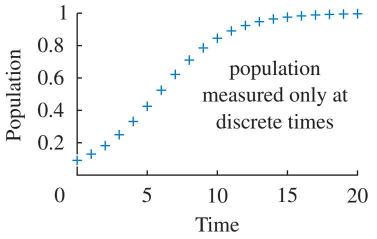


FIGURE 1.2.6

Measurements described by a discrete-time dynamical system

Types of Dynamical Systems

Biological phenomena can be studied using three types of dynamical systems: discrete-time, continuous-time, and probabilistic systems. The first two types, which are covered in this book, are **deterministic,** meaning that the dynamics include no chance factors. In this case, the values of the basic measurements can be predicted exactly at all future times. Probabilistic dynamical systems include chance factors, and values can be predicted only on average. (We do not study probabilistic dynamical systems in this book.)

Discrete-Time Dynamical Systems

Discrete-time dynamical systems describe a sequence of measurements made at equally spaced intervals (Figure 1.2.6). These dynamical systems are described mathematically by a rule that gives the value at one time as a function of the value at a previous time. For example, a discrete-time dynamical system describing population growth is a rule that gives the population in one year as a function of the population in the previous year. A discrete-time dynamical system describing the concentration of oxygen in the lung is a rule that gives the concentration of oxygen in a lung after one breath as a function of the concentration after the previous breath. Mathematical analysis of the rule can provide scientific predictions, such as the maximum population size or the average concentration of oxygen in the lung. The study of these systems requires **differential calculus** (Chapters 4, 5, and 6).

Continuous-Time Dynamical Systems

Continuous-time dynamical systems, usually known as **differential equations,** describe measurements that change continuously (Figure 1.2.7). A differential equation consists of a rule that gives the **instantaneous rate of change** of a set of measurements. The beauty of differential equations is that information about a system at one time is sufficient to predict the state of a system at all future times. For example, a continuous-time dynamical system describing the growth of a population is a rule that gives the rate of change of population size as a function of the population size itself. The study of these systems requires the mathematical methods of **integral calculus** (Chapters 7 and 8).

Quantifying Measurements

If we wish to use mathematics, we need numbers—we have to quantify all data, measurements, and relations between measurements that we plan to use.

In this book we work with the data provided and are not concerned about how they were collected, nor do we worry about their accuracy or validity.

The most important thing about numbers is that we can compare them and draw important conclusions from these comparisons. There are many possible relationships between quantities; in Table 1.2.1 we list those most commonly used.

To describe the range of (real-number) values, we use inequalities or interval notation; see Table 1.2.2 (it is assumed that $a < b$).

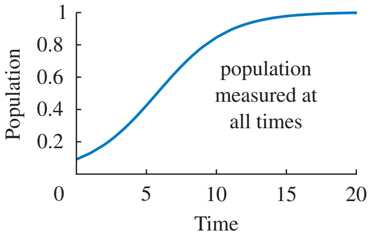


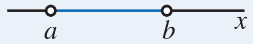
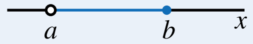
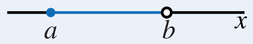
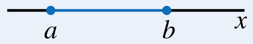
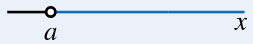
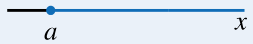
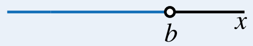
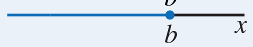
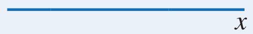
FIGURE 1.2.7

Measurements described by a continuous-time dynamical system

Table 1.2.1

Symbol	Relationship between Quantities, Meaning, and Example
$A = B$	Quantities A and B are equal, for example, $1/2 = 0.5$. In mathematics and to mathematicians, this means that the quantities are absolutely identical. In most modelling examples, however, rarely (if ever) are two phenomena equal or identical. Many times we use the equals sign when we actually mean to say "approximately equal."
$A \approx B$	A is approximately equal to B, as in $\pi \approx 3.14$. The exact meaning of "approximately equal" depends on the context (even within a context, its meaning might not be fixed). Due to a measurement error, every instrument we use returns an approximate (and not true) reading of the quantity measured.
$A \neq B$	A and B are neither equal nor approximately equal.
$A > B$	A is greater than B, or B is smaller than A.
$A \gg B$	A is much greater than B, or B is much smaller than A. The effects of B can be ignored; for instance, if $A \gg B$ then $A \pm B \approx A$ and $B/A \approx 0$.
$A \propto B$	A is proportional to B; if B triples, so does A (we will discuss examples in forthcoming sections).
$A \propto 1/B$	A is inversely proportional to B; if B doubles, then A halves (we will discuss examples in forthcoming sections).
order of magnitude (powers of 10)	One power of 10 is one order of magnitude. If A is about 10 times as large as B, then A is larger by one order of magnitude. A is three orders of magnitude larger than B if A is about a thousand times as large as B. The mass of a dog is two orders of magnitude less than the mass of an elephant.

Table 1.2.2

Interval	Inequality or Symbols	Picture	Represents All Real Numbers between *a* and *b*
(a, b)	$a < x < b$		excluding both a and b
$(a, b]$	$a < x \leq b$		excluding a and including b
$[a, b)$	$a \leq x < b$		including a and excluding b
$[a, b]$	$a \leq x \leq b$		including both a and b
			Represents All Real Numbers
(a, ∞)	$x > a$		greater than a
$[a, \infty)$	$x \geq a$		greater than or equal to a
$(-\infty, b)$	$x < b$		less than b
$(-\infty, b]$	$x \leq b$		less than or equal to b
			Represents
$(-\infty, \infty)$	$\mathbb{R}$		all real numbers

The intervals (a, b), (a, ∞), and $(-\infty, b)$ are called **open intervals,** whereas $[a, b]$, $[a, \infty)$, and $(-\infty, b]$ are **closed intervals.**

In many cases, we need to **estimate** the numbers that we need to use in our model. For instance, it is difficult (in many cases impossible) to know exactly how many bacteria are in a Petri dish, or exactly how many people are infected with a virus, or exactly how much sodium enters a cell in an hour through the process of diffusion.

Example 1.2.4 Estimating the Number of Bacteria in a Petri Dish

Bacteria might be too small to count or, for other reasons, counting is dismissed (as impractical or time-consuming or impossible). Here is one possible approach. We can estimate the area that a colony of bacteria occupies in a Petri dish. Then, knowing how thick the colony is, i.e., how many layers of bacteria there are, we can calculate the volume occupied by the colony (volume = area times thickness).

The key measurement is density, in this case defined as

$$\text{density} = \frac{\text{number of bacteria}}{\text{volume}}$$

If we know the density, then the formula

$$\text{total number of bacteria} = \text{density} \times \text{volume}$$

approximates the total number of bacteria in the colony. Note that none of the numbers involved in this calculation could possibly be exact.

Example 1.2.5 Counting Elephants

How many elephants are there in the Southern African highlands, a large ecosystem that spans several countries? It is impossible to track down every elephant and come up with an exact number.

What we can do is pick a small representative subregion of the whole region, one that—in all significant ways—mimics the whole region. Using a variety of means (air surveillance, acoustic monitoring, seismic sensors, etc.) we figure out how many elephants are in that small subregion, and based on it compute the density

$$\text{density} = \frac{\text{number of elephants}}{\text{area}}$$