Physical Models of Living Systems

Philip Nelson
University of Pennsylvania

with the assistance of Sarina Bromberg, Ann Hermundstad, and Jason Prentice
Brief Contents

Prolog: A breakthrough on HIV 1

PART I  First Steps

Chapter 1  Virus Dynamics 9
Chapter 2  Physics and Biology 27

PART II  Randomness in Biology

Chapter 3  Discrete Randomness 35
Chapter 4  Some Useful Discrete Distributions 69
Chapter 5  Continuous Distributions 97
Chapter 6  Model Selection and Parameter Estimation 123
Chapter 7  Poisson Processes 153
PART III  Control in Cells

Chapter 8  Randomness in Cellular Processes  179
Chapter 9  Negative Feedback Control  203
Chapter 10 Genetic Switches in Cells  241
Chapter 11 Cellular Oscillators  277

Epilog  299

Appendix A  Global List of Symbols  303
Appendix B  Units and Dimensional Analysis  309
Appendix C  Numerical Values  315

Acknowledgments  317
Credits  321
Bibliography  323
Index  333
Detailed Contents

Web Resources xvii
To the Student xix
To the Instructor xxiii

Prolog: A breakthrough on HIV 1

PART I  First Steps

Chapter 1  Virus Dynamics 9
1.1  First Signpost 9
1.2  Modeling the Course of HIV Infection 10
  1.2.1  Biological background 10
  1.2.2  An appropriate graphical representation can bring out key features of data 12
  1.2.3  Physical modeling begins by identifying the key actors and their main interactions 12
  1.2.4  Mathematical analysis yields a family of predicted behaviors 14
  1.2.5  Most models must be fitted to data 15
  1.2.6  Overconstraint versus overfitting 17
1.3  Just a Few Words About Modeling 17
Key Formulas 19
Track 2 21
  1.2.4  Exit from the latency period 21
  1.2.6 a  Informal criterion for a falsifiable prediction 21
Detailed Contents

1.2.6'b  More realistic viral dynamics models  21
1.2.6'c  Eradication of HIV  22
Problems  23

Chapter 2  Physics and Biology  27
2.1  Signpost  27
2.2  The Intersection  28
2.3  Dimensional Analysis  29
Key Formulas  30
Problems  31

PART II  Randomness in Biology

Chapter 3  Discrete Randomness  35
3.1  Signpost  35
3.2  Avatars of Randomness  36
   3.2.1  Five iconic examples illustrate the concept of randomness  36
   3.2.2  Computer simulation of a random system  40
   3.2.3  Biological and biochemical examples  40
   3.2.4  False patterns: Clusters in epidemiology  41
3.3  Probability Distribution of a Discrete Random System  41
   3.3.1  A probability distribution describes to what extent a random system is, and is not, predictable  41
   3.3.2  A random variable has a sample space with numerical meaning  43
   3.3.3  The addition rule  44
   3.3.4  The negation rule  44
3.4  Conditional Probability  45
   3.4.1  Independent events and the product rule  45
      3.4.1.1  Crib death and the prosecutor’s fallacy  47
      3.4.1.2  The Geometric distribution describes the waiting times for success in a series of independent trials  47
   3.4.2  Joint distributions  48
   3.4.3  The proper interpretation of medical tests requires an understanding of conditional probability  50
   3.4.4  The Bayes formula streamlines calculations involving conditional probability  52
3.5  Expectations and Moments  53
   3.5.1  The expectation expresses the average of a random variable over many trials  53
   3.5.2  The variance of a random variable is one measure of its fluctuation  54
   3.5.3  The standard error of the mean improves with increasing sample size  57
Key Formulas  58
Track 2  60
Detailed Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.4.1’a</td>
<td>Extended negation rule</td>
<td>60</td>
</tr>
<tr>
<td>3.4.1’b</td>
<td>Extended product rule</td>
<td>60</td>
</tr>
<tr>
<td>3.4.1’c</td>
<td>Extended independence property</td>
<td>60</td>
</tr>
<tr>
<td>3.4.4’</td>
<td>Generalized Bayes formula</td>
<td>60</td>
</tr>
<tr>
<td>3.5.2’a</td>
<td>Skewness and kurtosis</td>
<td>60</td>
</tr>
<tr>
<td>3.5.2’b</td>
<td>Correlation and covariance</td>
<td>61</td>
</tr>
<tr>
<td>3.5.2’c</td>
<td>Limitations of the correlation coefficient</td>
<td>62</td>
</tr>
</tbody>
</table>

Problems 63

Chapter 4 Some Useful Discrete Distributions

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>Signpost</td>
<td>69</td>
</tr>
<tr>
<td>4.2</td>
<td>Binomial Distribution</td>
<td>70</td>
</tr>
<tr>
<td>4.2.1</td>
<td>Drawing a sample from solution can be modeled in terms of Bernoulli trials</td>
<td>70</td>
</tr>
<tr>
<td>4.2.2</td>
<td>The sum of several Bernoulli trials follows a Binomial distribution</td>
<td>71</td>
</tr>
<tr>
<td>4.2.3</td>
<td>Expectation and variance</td>
<td>72</td>
</tr>
<tr>
<td>4.2.4</td>
<td>How to count the number of fluorescent molecules in a cell</td>
<td>72</td>
</tr>
<tr>
<td>4.2.5</td>
<td>Computer simulation</td>
<td>73</td>
</tr>
<tr>
<td>4.3</td>
<td>Poisson Distribution</td>
<td>74</td>
</tr>
<tr>
<td>4.3.1</td>
<td>The Binomial distribution becomes simpler in the limit of sampling from an infinite reservoir</td>
<td>74</td>
</tr>
<tr>
<td>4.3.2</td>
<td>The sum of many Bernoulli trials, each with low probability, follows a Poisson distribution</td>
<td>75</td>
</tr>
<tr>
<td>4.3.3</td>
<td>Computer simulation</td>
<td>78</td>
</tr>
<tr>
<td>4.3.4</td>
<td>Determination of single ion-channel conductance</td>
<td>78</td>
</tr>
<tr>
<td>4.3.5</td>
<td>The Poisson distribution behaves simply under convolution</td>
<td>79</td>
</tr>
<tr>
<td>4.4</td>
<td>The Jackpot Distribution and Bacterial Genetics</td>
<td>81</td>
</tr>
<tr>
<td>4.4.1</td>
<td>It matters</td>
<td>81</td>
</tr>
<tr>
<td>4.4.2</td>
<td>Unreproducible experimental data may nevertheless contain an important message</td>
<td>81</td>
</tr>
<tr>
<td>4.4.3</td>
<td>Two models for the emergence of resistance</td>
<td>83</td>
</tr>
<tr>
<td>4.4.4</td>
<td>The Luria-Delbrück hypothesis makes testable predictions for the distribution of survivor counts</td>
<td>84</td>
</tr>
<tr>
<td>4.4.5</td>
<td>Perspective</td>
<td>86</td>
</tr>
</tbody>
</table>

Key Formulas 87

Track 2 89

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4.2’</td>
<td>On resistance</td>
<td>89</td>
</tr>
<tr>
<td>4.4.3’</td>
<td>More about the Luria-Delbrück experiment</td>
<td>89</td>
</tr>
<tr>
<td>4.4.5’a</td>
<td>Analytical approaches to the Luria-Delbrück calculation</td>
<td>89</td>
</tr>
<tr>
<td>4.4.5’b</td>
<td>Other genetic mechanisms</td>
<td>89</td>
</tr>
<tr>
<td>4.4.5’c</td>
<td>Non-genetic mechanisms</td>
<td>90</td>
</tr>
<tr>
<td>4.4.5’d</td>
<td>Direct confirmation of the Luria-Delbrück hypothesis</td>
<td>90</td>
</tr>
</tbody>
</table>

Problems 91
Chapter 5  Continuous Distributions  97
  5.1  Signpost  97
  5.2  Probability Density Function  98
      5.2.1  The definition of a probability distribution must be modified
             for the case of a continuous random variable  98
      5.2.2  Three key examples: Uniform, Gaussian, and Cauchy
             distributions  99
      5.2.3  Joint distributions of continuous random variables  101
      5.2.4  Expectation and variance of the example distributions  102
      5.2.5  Transformation of a probability density function  104
      5.2.6  Computer simulation  106
  5.3  More About the Gaussian Distribution  106
      5.3.1  The Gaussian distribution arises as a limit of Binomial  106
      5.3.2  The central limit theorem explains the ubiquity of Gaussian
             distributions  108
      5.3.3  When to use/not use a Gaussian  109
  5.4  More on Long-tail Distributions  110

Key Formulas  112
Track 2  114
  5.2.1’  Notation used in mathematical literature  114
  5.2.4’  Interquartile range  114
  5.4’a  Terminology  115
  5.4’b  The movements of stock prices  115

Problems  118

Chapter 6  Model Selection and Parameter Estimation  123
  6.1  Signpost  123
  6.2  Maximum Likelihood  124
      6.2.1  How good is your model?  124
      6.2.2  Decisions in an uncertain world  125
      6.2.3  The Bayes formula gives a consistent approach to updating our
             degree of belief in the light of new data  126
      6.2.4  A pragmatic approach to likelihood  127
  6.3  Parameter Estimation  128
      6.3.1  Intuition  129
      6.3.2  The maximally likely value for a model parameter can be
             computed on the basis of a finite dataset  129
      6.3.3  The credible interval expresses a range of parameter values
             consistent with the available data  130
      6.3.4  Summary  132
  6.4  Biological Applications  133
      6.4.1  Likelihood analysis of the Luria-Delbrück experiment  133
      6.4.2  Superresolution microscopy  133
          6.4.2.1  On seeing  133
          6.4.2.2  Fluorescence imaging at one nanometer
                  accuracy  133
### Detailed Contents

6.4.2.3 Localization microscopy: PALM/FPALM/STORM 136

6.5 An Extension of Maximum Likelihood Lets Us Infer Functional Relationships from Data 137

**Key Formulas** 141

**Track 2** 142

- 6.2.1’ Cross-validation 142
- 6.2.4’a Binning data reduces its information content 142
- 6.2.4’b Odds 143
- 6.3.2’a The role of idealized distribution functions 143
- 6.3.2’b Improved estimator 144
- 6.3.3’a Credible interval for the expectation of Gaussian-distributed data 144
- 6.3.3’b Confidence intervals in classical statistics 145
- 6.3.3’c Asymmetric and multivariate credible intervals 146
- 6.4.2.2’ More about FIONA 146
- 6.4.2.3’ More about superresolution 147
- 6.5’ What to do when data points are correlated 147

**Problems** 149

---

### Chapter 7 Poisson Processes 153

7.1 Signpost 153

7.2 The Kinetics of a Single-Molecule Machine 153

7.3 Random Processes 155

- 7.3.1 Geometric distribution revisited 156
- 7.3.2 A Poisson process can be defined as a continuous-time limit of repeated Bernoulli trials 157
  - 7.3.2.1 Continuous waiting times are Exponentially distributed 158
  - 7.3.2.2 Distribution of counts 160
- 7.3.3 Useful Properties of Poisson processes 161
  - 7.3.3.1 Thinning property 161
  - 7.3.3.2 Merging property 161
  - 7.3.3.3 Significance of thinning and merging properties 163

7.4 More Examples 164

- 7.4.1 Enzyme turnover at low concentration 164
- 7.4.2 Neurotransmitter release 164

7.5 Convolution and Multistage Processes 165

- 7.5.1 Myosin-V is a processive molecular motor whose stepping times display a dual character 165
- 7.5.2 The randomness parameter can be used to reveal substeps in a kinetic scheme 168

7.6 Computer Simulation 168

- 7.6.1 Simple Poisson process 168
- 7.6.2 Poisson processes with multiple event types 168
PART III  Control in Cells

Chapter 8  Randomness in Cellular Processes  179

8.1  Signpost  179
8.2  Random Walks and Beyond  180
  8.2.1  Situations studied so far  180
    8.2.1.1  Periodic stepping in random directions  180
    8.2.1.2  Irregularly timed, unidirectional steps  180
  8.2.2  A more realistic model of Brownian motion includes both random step times and random step directions  180
8.3  Molecular Population Dynamics as a Markov Process  181
  8.3.1  The birth-death process describes population fluctuations of a chemical species in a cell  182
  8.3.2  In the continuous, deterministic approximation, a birth-death process approaches a steady population level  184
  8.3.3  The Gillespie algorithm  185
  8.3.4  The birth-death process undergoes fluctuations in its steady state  186
8.4  Gene Expression  187
  8.4.1  Exact mRNA populations can be monitored in living cells  187
  8.4.2  mRNA is produced in bursts of transcription  189
  8.4.3  Perspective  193
  8.4.4  Vista: Randomness in protein production  193

Key Formulas  194
Track 2  195
  8.3.4'  The master equation  195
  8.4'  More about gene expression  197
  8.4.2'a  The role of cell division  197
  8.4.2'b  Stochastic simulation of a transcriptional bursting experiment  198
  8.4.2'c  Analytical results on the bursting process  199

Problems  200

Chapter 9  Negative Feedback Control  203

9.1  Signpost  203
9.2  Mechanical Feedback and Phase Portraits  204
  9.2.1  The problem of cellular homeostasis  204
9.2.2 Negative feedback can bring a system to a stable setpoint and hold it there 204

9.3 Wetware Available in Cells 206
9.3.1 Many cellular state variables can be regarded as inventories 206
9.3.2 The birth-death process includes a simple form of feedback 207
9.3.3 Cells can control enzyme activities via allosteric modulation 207
9.3.4 Transcription factors can control a gene’s activity 208
9.3.5 Artificial control modules can be installed in more complex organisms 211

9.4 Dynamics of Molecular Inventories 212
9.4.1 Transcription factors stick to DNA by the collective effect of many weak interactions 212
9.4.2 The probability of binding is controlled by two rate constants 213
9.4.3 The repressor binding curve can be summarized by its equilibrium constant and cooperativity parameter 214
9.4.4 The gene regulation function quantifies the response of a gene to a transcription factor 217
9.4.5 Dilution and clearance oppose gene transcription 218

9.5 Synthetic Biology 219
9.5.1 Network diagrams 219
9.5.2 Negative feedback can stabilize a molecule inventory, mitigating cellular randomness 220
9.5.3 A quantitative comparison of regulated- and unregulated-gene homeostasis 221

9.6 A Natural Example: The trp Operon 224

9.7 Some Systems Overshoot on Their Way to Their Stable Fixed Point 224
9.7.1 Two-dimensional phase portraits 226
9.7.2 The chemostat 227
9.7.3 Perspective 231

Key Formulas 232

Track 2 234
9.3.1’a Contrast to electronic circuits 234
9.3.1’b Permeability 234
9.3.3’ Other control mechanisms 234
9.3.4’a More about transcription in bacteria 235
9.3.4’b More about activators 235
9.3.5’ Gene regulation in eukaryotes 235
9.4.4’a More general gene regulation functions 236
9.4.4’b Cell cycle effects 236
9.5.1’a Simplifying approximations 236
9.5.1’b The Systems Biology Graphical Notation 236
9.5.3’ Exact solution 236
9.7.1’ Taxonomy of fixed points 237

Problems 238
Chapter 10 Genetic Switches in Cells

10.1 Signpost 241
10.2 Bacteria Have Behavior 242
   10.2.1 Cells can sense their internal state and generate switch-like responses 242
   10.2.2 Cells can sense their external environment and integrate it with internal state information 243
   10.2.3 Novick and Weiner characterized induction at the single-cell level 243
      10.2.3.1 The all-or-none hypothesis 243
      10.2.3.2 Quantitative prediction for Novick-Weiner experiment 246
      10.2.3.3 Direct evidence for the all-or-none hypothesis 248
      10.2.3.4 Summary 249
10.3 Positive Feedback Can Lead to Bistability 250
   10.3.1 Mechanical toggle 250
   10.3.2 Electrical toggles 252
      10.3.2.1 Positive feedback leads to neural excitability 252
      10.3.2.2 The latch circuit 252
   10.3.3 A 2D phase portrait can be partitioned by a separatrix 252
10.4 A Synthetic Toggle Switch Network in E. coli 253
   10.4.1 Two mutually repressing genes can create a toggle 253
   10.4.2 The toggle can be reset by pushing it through a bifurcation 256
   10.4.3 Perspective 257
10.5 Natural Examples of Switches 259
   10.5.1 The lac switch 259
   10.5.2 The lambda switch 263

Key Formulas 264
Track 2 266
   10.2.3.1 More details about the Novick-Weiner experiments 266
   10.2.3.3a Epigenetic effects 266
   10.2.3.3b Mosaicism 266
   10.4.1a A compound operator can implement more complex logic 266
   10.4.1b A single-gene toggle 268
   10.4.2 Adiabatic approximation 272
   10.5.1 DNA looping 273
   10.5.2 Randomness in cellular networks 273

Problems 275

Chapter 11 Cellular Oscillators

11.1 Signpost 277
11.2 Some Single Cells Have Diurnal or Mitotic Clocks 277
11.3 Synthetic Oscillators in Cells 278
   11.3.1 Negative feedback with delay can give oscillatory behavior 278
Web Resources

The book's Web site (http://www.macmillanhighered.com/physicalmodels1e) contains links to the following resources:

- The Student's Guide contains an introduction to some computer math systems, and some guided computer laboratory exercises.
- Datasets contains datasets that are used in the problems. In the text, these are cited like this: Dataset 1, with numbers keyed to the list on the Web site.
- Media gives links to external media (graphics, audio, and video). In the text, these are cited like this: Media 2, with numbers keyed to the list on the Web site.
- Finally, Errata is self-explanatory.