## BIOLOGICAL MODELING AND SIMULATION

A Survey of Practical Models, Algorithms, and Numerical Methods

## Russell Schwartz

The MIT Press
Cambridge, Massachusetts
London, England

## © 2008 Massachusetts Institute of Technology

All rights reserved. No part of this book may be reproduced in any form by any electronic or mechanical means (including photocopying, recording, or information storage and retrieval) without permission in writing from the publisher.

MIT Press books may be purchased at special quantity discounts for business or sales promotional use. For information, please email special_sales@mitpress.mit.edu or write to Special Sales Department, The MIT Press, 55 Hayward Street, Cambridge, MA 02142.

This book was set in Times New Roman and Syntax on 3B2 by Asco Typesetters, Hong Kong. Printed and bound in the United States of America.

Library of Congress Cataloging-in-Publication Data

## Schwartz, Russell.

Biological modeling and simulation : a survey of practical models, algorithms, and numerical methods / Russell Schwartz.
p. cm. - (Computational molecular biology)

Includes bibliographical references and index.
ISBN 978-0-262-19584-3 (hardcover : alk. paper) 1. Biology—Simulation methods. 2. Biology-
Mathematical models. I. Title.
QH323.5.S364 2008
570.1'1—dc22
$\begin{array}{llllllllll}10 & 9 & 8 & 7 & 6 & 5 & 4 & 3 & 2 & 1\end{array}$

## Index

Acceleration, 211
Accuracy. See also Errors
in Adams-Bashforth methods, 223
adaptive methods, 224
centered difference, 84-85, 229-232, 235
first and second order, 157, 215, 218, 233, 238
and forward/backward Euler, 218, 222
in model validation, 358
of Neville's algorithm, 327
and Newton-Raphson, 84-85
and partial differential equations, 233
and Runge-Kutta methods, 221, 225, 237
of secant versus bisection, 79
and stability, 221, 223, 251
and stochastic differential equations, 248249
and time, 219, 233
Adams-Bashforth methods, 221-223, 225
Adams-Moulton scheme, 225
Adaptive methods, 224-225
Affine method, 104-107, 110
Aitken's $\delta^{2}$ process, 338-340
Alleles, 28-33, 280-289
All-pairs shortest path, 21
Amino acids. See also Protein folding contact energies, 5-7
and HMMs, 297-299
and Metropolis method, 145
proline cis-trains isomerization, 180-182
and proteases, 9
Animation, 333
Annealing. See Simulated annealing
Antibiotics, 45
Approximation
centered difference, 84-85, 89, 229-232, 235
and extrapolation, 337-340
forward difference, 84
and forward Euler, 214, 224
and interpolation, 327-337
and reaction-diffusion equations, 237
for step size, 224
with Taylor series, 80-81, 85, 232

Approximation algorithms. See also Traveling salesman
and branch-and-bound algorithm, 50
description, 47-59
and intractability, 47-49, 50, 55
reference, 55
traveling salesman, 36, 48, 54
and vertex cover, 47, 50-51
Approximation schemes, 48
Automated sequencing, 61-63
Backward algorithm, 298-299
Backward error, 77
Backward Euler, 217-219, 222
Bacteria
antibiotic sensitivity, 45
bacterial artificial chromosome (BAC), 64
Barrier methods, 104
Baum-Welch algorithm, 300-307
Bayesian models, 347-350, 353, 356
additional sources, 353
Bellman-Ford algorithm, 20-21
background, 33
Best-fit
in interpolation, 336
and least-squares, 356
in parameter-tuning, 275
Bias. See also Model validation
and gene network, 349
and HMMs, 360
and importance sampling, 154
and parameter choices, 362
unintended, 365
Biconjugate gradient, 319
Bilinear interpolation, 334
Billiard ball model, 206-209
Binary search, 338
Biochemical processes. See also Evolution; Reaction networks
decaying exponentials, 335
parameters, 267
whole-cell models, 253-264

BioNetGen, 261
Biophysics, 226
Bipartiteness, 23, 42
Bisection, 76-78, 338
Black-box, 75, 84, 237, 336
Block diagonals, 333
Boltzmann distribution, 7, 142-144, 146
Boltzmann's constant, 7, 142
Bootstrapping, 350, 361, 363
Boundary conditions
Dirichlet, 230-231
for multiple dimensions, 234
Neumann, 231
and PDEs, 230-233
and solute diffusion, 230-233
Box-Müller method, 120
background, 127
Branch-and-bound methods, 49-52
Branching process, 199
Brownian motion, 167, 241-249, 263
Brownian noise, 157
Brute force, 47, 50, 53
Calcium, 260
Calendar queue, 205t, 209
Canonical path, 161-166, 169
background, 171
Capillary sequencing, 61
Catalysts. See Enzymes
CellML, 264
Cells
and biochemical networks, 253-264
cycle synchronization, 323-325
Cell simulation
and CTMM, 256-259
electrophysiological components, 264
hybrid models, 259, 263
and PDEs, 253-256, 263
protein expression, 268
standards and software, 263
trends, 262
as very large reaction network, 260-262
Centered difference, 84-85, 229-232, 235
Chain rule, 220
Channel protein, 201-203
Chapman-Kolmogorov equations, 133
Chebyshev polynomials, 340
Chemical reaction. See also Reaction networks
and interpolation, 336
and law of mass action, 211
with noise, 246-248
and stability, 215-217
Chemical solutions. See Solutions
Chromatic number, 40
Chromosomes
diploid, 198
haploid, 192
haplotypes, 280-286
tagging SNP selection, 44, 47

Chromosome walking, 63
cis isomer, proline, 180-182
Cliques, 39, 342
union of, 344-345
Clone-by-clone strategy, 63
Clustering, 342-347, 351
additional sources, 353
Coalescent
background, 200
coalescent simulation, 195
definition, 193f, 194
and migration, 198
and recombinations, 198
separate populations, 197
variable population sizes, 196
Coexpression models, 342-347, 351
Collisions, 141, 206-209
Coloring
in automated sequencing, 61
in graph problems, 39, 49-50
Compartments, 253-256
Complexity, computational, 55, 260-262, 361. See also Intractability; NP-completeness
Computer graphics, 333
Concave functions, 108
Conditional probability, 295
Condition number, of matrix, 319
Conductance method, 166
background, 171
bounded random walk, 167-170
Conjugate gradient, 91, 92, 318, 319
Consensus sequence, 32
Constraint satisfaction
linear program, 96-108
nonlinear program, 108-110
parameter-tuning, 269-271
primal-dual methods, 107
Contact potentials, 5, 267
Continuous distributions
and importance/umbrella sampling, 154-156
joint distributions, 119-121, 151-152
rejection method, 121-124
transformation method, 116-121, 124f
Continuous optimization. See also NewtonRaphson method
bisection, 76-78, 338
description, 75
local versus global optima, 76
multivariate functions, 85-88
secant method, 78-80
Continuous systems
applications, 211-213
backward Euler, 217-219
definition, 211
differential equations, 212
with discrete event tracking, 206-209, 263
from discrete points, 323-326 (see also Extrapolation; Interpolation)
finite difference, 213, 226
forward Euler (see Forward Euler)
leapfrog, 221-223, 225, 236
single-step methods, 219-221, 223-225
Continuous time Markov models (CTMMs)
additional reading, 183
branching process, 199
cell simulation, 256-260
channel protein example, 201-203
and coalescence, 195
description, 173-178
versus discrete event models, 201-204
and DNA base evolution, 187
Kolmogorov equations, 178-182
Moleculizer program, 261
and population dynamics, 212
and protein folding, 180-182
rate inference, 273
and self-transition, 181
waiting time, 173-175
Convection, 237-239
Convection-diffusion, 238
Convergence, 338
order of, 248-249
Convex functions, 108-110
Cooling schedule, 148
COPASI, 260, 264
Correlation coefficients, 343, 356-358
Cross-validation, 361-362
CTMM. See Continuous time Markov models
Cubic formula polynomials, 76
Cubic formulas, 76, 329, 333
Curve, receiver operating characteristic (ROC), 360
Curve families, 334-337
Curve generation, 333
Curve linearization, 81, 86, 89, 91
Cut problems
k-cut, 38, 54, 344
maximum cut, 37,344
minimum cut, 21-23
Data. See also Noisy data
ambiguity loss, 30
and Bayesian model, 347
and continuous optimization, 75
fitting, 329-336, 340, 361
gene expression microarray, 341
gene network inference, 352
for HMMs, 299-302
input and output format, 2-3
for intraspecies phylogeny, 29-30
posting time, 205
set relationships, 357
Decision problems, 36
Density
joint, 119
probability, 116-118, 121-122, 154
detailed balance, 143-145, 164, 169
Diagnostics, 358, 360

Differential equations. See Finite difference;
Ordinary differential equations; Partial differential equations; Stochastic differential equations
Diffusion
and boundaries, 230-233
and cell simulation, 259
convection-diffusion equation, 238
of particles, in two dimensions, 325
PDE example, 227
reaction-diffusion equations, 234-237, 325
Diffusion term, 234
Dijkstra's algorithm, 20, 21
background, 33
Diploid organisms, 198
Dirichlet boundary, 230-231
Discrete distributions. See also Transformation method
and continuous models, 323-326
and Metropolis method, 146
rejection method, 124-126
and transformation method, 124
Discrete event models
artificial event, 208
background, 210
and cell simulation, 260
channel protein case, 201-203
and continuous systems, 206-209, 263, 325
versus CTMMs, 201-204
description, 203
efficiency, 204-206, 208-210
event loop, 204, 207
molecular collisions, 206-209
queuing, 205, 209-210
without queue, 208
Discretization
conversions (multigrid), 325
and gene coexpression, 344
of space, $229,233,235,255,258$
of time, 242
Disease, diagnosis of, 358, 360
Distributions. See also Continuous distributions;
Discrete distributions
Boltzmann, 142-144, 146
exponential, 118
gamma, 268
Gaussian, 348
joint, 119-121, 149-152
modified, 156
normal, 120, 123-124
Poisson, 191
prior, 153, 349
probability, 347-349
stationary, 134-138, 149, 153-155, 159, 161
uniform, 115-116
DNA. See also String and sequence problems
diploid and haploid, 198
exact set matching, 27
intraspecies phylogeny, 28-33

DNA (cont.)
motif detection, 152-154, 303-307, 347, 359-360, 362
random strings, 129-133
repetitive, 63
simulation, 191-195
tagging SNP selection, 44, 47
DNA bases
and CTMMs, 187
evolution, 185-191, 269-271
frequency analysis, 275-277, 280-286
and HMMs, 291-293, 303-307
parameter-tuning, 269-271
DNA microarrays, 64-66, 71, 341
DNA sequencing
big sequences, 61-63
computational methods, 64-72
Eulerian path, 66, 73
hybridization method, 64-66, 71, 73
Maxam-Gilbert, 57-59, 61
nanopore method, 74
overview, 73-74
Sanger dideoxy method, 59-61
shotgun methods, 67-69, 73
single molecule, 72, 74
Domain recognition, 294, 297
Double-barrel shotgun, 69
background, 73
Drosophila melanogaster, 74
Duals, 39, 46, 107
Dynafit program, 336
E-Cell system, 260, 264
Edges, graph
and Bayesian model, 349
and bipartiteness, 42
cliques, $39,342,344-345$
and CTMMs, 174
and gene network, 349-351
in hierarchical clusters, 345
in intraspecies phylogeny, 29-31, 41
in Markov model, 143
and maximum flow, 21
and mixing, 161-166, 170
negative weights, 20
in network structure, 349
in Steiner trees, 41
transition probabilities, 160
in vertex cover, $38,45,47,53$
Edit distance, 3-4
Edmonds-Karp algorithm, 22-23, 33
Eigenvalues
definition, 136
of Markov models, 136-139, 159, 186
and matrices, 318, 321, 322
Eigenvectors, 136-139, 186
Einstein, A., 364
Ellipsoid method, 104, 110

Embedded methods, 224
Energy. See also Force field
and amino acids, 5-7
and Metropolis method, 143, 147
potential, 142
and simulated annealing, 52, 148
and umbrella sampling, 157
Entropy, 343-344, 358
Enzymatic reactions, 253-256, 324f
Enzymes
concentration, 325
and ODEs, 212
protease, $8-11$
Expectation maximization, 345-347
Equilibrium
and Boltzmann distribution, 142
in chemical diffusion, 325
Hardy-Weinberg, 282
Ergodicity
and canonical path, 164
definition, 136
and Markov models, 136, 148, 159, 164, 167, 169
and Metropolis method, 143
Errors. See also Accuracy
in differential equation types, 248
and expectation maximization, 286-287
and extrapolation, 337-339
false positives/negatives, 359, 360
forward and backward, 77, 90
and intraspecies phylogeny, 30
in leapfrog method, 222
Newton-Raphson algorithm, 83-85
in noisy data, 287
and physical conservation laws, 226
and sensitivity analysis, 363
and steepest descent, 89-90
and step size, 223
Euclidian distance, 343, 345
Euclidian traveling salesman, 48-49, 54
Eukaryotic genomes
assembly, 69-70, 73
DNA sequencing, 63, 67, 73
gene prediction, 307
sequence problems, 26
Eulerian path, 66, 73. Euler-Maruyama method, 246, 249, 250
Event loop, 204, 207
Evolution. See also Continuous time Markov models; Molecular evolution
coalescent model, 193-199
and data ambiguity, 30
description, 2-4
DNA base evolution, 185-191, 269-271
DNA strand simulation, 191
genetic algorithms, 52-53
graph problems, 16-18
intraspecies phylogeny, 28-33, 41
Jukes-Cantor model, 185-188

Kimura model, 188-191
and Kolmogorov equations, 187, 190
parameter-tuning, 269-271
tree model, 2-4
Wright-Fisher neutral model, 192
Exact set matching, 27
Exon
and gene structure models, 292-293
length distribution, 129
Expectation maximization
background, 289
and clustering, 345
and goodness of model, 356
haplotype examples, 280-289
and HMMs, 300-307
noisy data, 286-289
reference sources, 289
steps, 277-278, 288-289, 300-302, 305-307
theory, 275, 277-280
weak versus strong, 280
Exponential random variables, 118, 175-178, 191
Extrapolation
Aitken's $\delta^{2}$ process, 337-340
definition, 325
infinite series, 337-340
Richardson method, 225, 337
uses, 323-326, 337
False positives/negatives, 359, 360
Feasible points, 97
Fibonacci heap, 205t, 209
Finite difference iteration, 338
Finite difference methods. See also Adams-
Bashforth methods; Runge-Kutta methods
alternatives to, 226
backward Euler, 217-219
definition, 213
forward Euler, 214-217
and independent variables, 239
multistep methods, 221-223
single-step methods, 219-221
stability, 215-217, 218-219, 221
First-order Markov model, 130
First reaction method, 257
Flow problems, 20-22
Floyd-Warshall algorithm, 21
background, 33
Fluorescence, 61-63, 268
Force field, 211
Ford-Fulkerson method, 22-23, 33
Forward algorithm, 298-299
Forward difference, 84
Forward error, 77, 90
Forward Euler. See also Euler-Maruyama method and Brownian motion, 241-246
in convection problem, 238
and coupled differential equations, 229
description, 214-217
and implicitly specified function, 272
with multistep method, 222
reaction-diffusion equations, 235
and step size, 223, 224
Fourier interpolants, 340
Fourier series, 216, 217
Fourier transforms, 226
Galileo, 365
Gamma distribution, 268
Gaussian elimination, 103, 310-316, 318
Gaussian linear model, 348-349
Gauss-Seidel method, 317
Gene expression
additional sources, 353
Bayesian models, 347-350, 353, 356
and cell cycles, 323-325
coexpression models, 342-347, 349, 351
and Gaussian distribution, 348
microarray data, 341
network inference, 341, 347-353, 358
prediction, 309
RNAi, 352
and sampling, 350, 363
General continuous optimization. See Continuous optimization
Generalized minimal residual (GMRES), 319
Gene sequences
Markov models, 129-133
motif detection, 303-307, 347, 359, 362
parameter-tuning, 276
Genetic algorithms, 52
background, 55
Genetic networks. See Gene expression
Genetics. See also Chromosomes; DNA
gene structure, 276, 292, 299-302
haplotype frequency, 280-286
haplotype inference, 287-289
molecular evolution, 185-192
population genetics, 192-199
tagging SNP selection, 44, 47
Genscan, 307
Geometric series, 337-340
GEPASI program, 253-256, 260
Gibbs sampling, 149-156, 350
background, 158
Gillespie model, 256-260, 263
Global optimum, 52
Gō models, 10
Goodness, measures of, 355-358
Gradient descent, 89
Gradient of objective, 106
Gradient $(\nabla F), 86,89$
Graphing constraints, 96
Graph problems
coloring, 39-40, 49-50
Eulerian path, 66, 73
Hamiltonian path, 37, 65

Graph problems (cont.)
independent set, 38, 42
matching, 23
maximum clique, 39
maximum cut, 37,344
maximum flow/minimum cut, 21-23
minimum spanning trees, $16-18,20,29-31$
multigraphs, 16
NP-completeness, 4, 36-42, 47, 344
phylogeny example, 28-33
and set problems, 44
shortest path, 19-21
Steiner trees, 40-41
subgraphs, 42, 54
traveling salesman, 36, 48, 54
and union-of-cliques, 344
vertex cover, $38,45,47,53,54$
Graph properties, 42
Green's function reaction dynamics (GFRD), 263
Grid box, 334
Growth factor, 223
Guilt by association method, 344
Haemophilus influenzae, 73
Hamiltonian path, 36-37, 65
Hamming distance, 41
Haploidy, 198
Haplotypes
frequency estimation, 280-286
inference from noisy data, 286-289
Hard sphere model, 206-209
Hardy-Weinberg equilibrium, 282
Hastings-Metropolis method, 160. See also Metropolis method
Heat equation, 227
background, 239
Hessian, 86-89, 109
Heuristic methods. See also Simulated annealing background, 53, 158
clustering methods, 344-347
definition, 52
and gene (co)expression, 344-347
genetic algorithms, 52
and Gibbs sampling, 152-154
and intractability, 52
kitchen sink approach, 53
and Metropolis model, 52, 147
and network inference, 349
Hexamers, 260-262
Hidden Markov models (HMMs)
and amino acids, 297-299
background and sources, 289, 307
and DNA bases, 291-293, 303-307
and expectation maximization, 300-307
gene structure, 292, 299-302
motif-finding, 303-307, 359-362
and Newton-Raphson method, 302
and output probability, 297-299
and protein domain, 294
and protein folding, 308
special features, 291
state assignment, 295-297
training, 299-302
transcription factor binding, 293
Hierarchical clustering, 345
HIV, 10
HMM. See Hidden Markov models
Huen's method, 224
Hungarian method, 24, 33
Hybridization, sequencing by, 64-66, 71
background, 73
Hydrogen bonds, 158
Hyperplanes, 97
Identity matrix, 310-312, 320
Image analysis, 325,340
Imino acid, 180
Implicitly specified functions, 271-273
Importance sampling, 154-156, 170
umbrella sampling, 155,158
Independent set problems, 38-39, 42, 46, 54
Independent variables
and finite difference, 239
multiple, 356
Infeasible points, 97
Infinite series, 337-340
Infinite sites model, 191-192
Information, mutual, 344
Information theory, 343, 358
Inheritable properties, 42
Integer linear programs, 51
Interior point methods, 104-107, 108
Interpolation
best-fit, 336
bilinear, 334
in biochemical reactions, 335
curve families, 334-337
definition, 325
examples, 323-326
Fourier interpolants, 340
Levenberg-Marquardt method, 336
linear, 272
multidimensional, 334
and Newton-Raphson method, 81, 336
and optimization, 335-337
polynomial type, 326-330
rational function, 330
and secant method, 79
splines, 331-334
and steepest descent, 90
Intractability. See also NP-completeness approximation algorithms, 47-49, 50, 55
branch-and-bound methods, 49-52
brute force approach, 47, 53
coping with, $30-32,35,46,49,53$
definition, 24-26, 35
heuristic approaches, 52
trade-offs, 30-32, 46, 49
Isomerization, 180-182
Iterative methods
finite difference, 338
Gauss-Seidel method, 317
Jacobi method, 317
Krylov subspace, 317-320
and Newton-Raphson, 82, 88
Itô integral, 244. See also Stochastic integrals;
Stochastic differential equations
Itô-Taylor series, 249
Jacobian, 86-89, 92
Jacobi method, 317
Johnson's algorithm, 21
background, 33
Joint distributions, 119-121, 149-152
Joint entropy, 344
Jukes-Cantor model, 185-189, 191
background, 200
Karmarkar's method, 104, 108, 110
k -coloring, 40
k-cut problems, 38, 54, 344
k -fold cross validation, 361
Kimura model, 188-191
background, 200
Kinetic models, 351-353
Kolmogorov criterion, 160, 164, 168
Kolmogorov equations
Chapman-Kolmogorov, 133
and CTMMs, 178-182
and discrete event simulation, 201
and evolutionary processes, 187, 190
and implicitly specified functions, 273
Kruskal's algorithm, 17, 31
background, 33
Krylov subspace, 91, 317-320, 333
kth-order Markov model, 130-131
Laplacian, 227
Latent variables, 277, 284, 288-289, 300, 345
Lattice models
background, 10
description, 5-7
and discretized states, 324f, 325
and heuristics, 52
in Markov example, 145
move sets, 10
parameters, 267
and protein folding, 5-6, 145-146
for spatial discretization of PDEs, 258-259
Law of mass action, 211
Lazy queuing, 205
Leapfrog method, 221-223, 225, 236
Least-squares, $320,336,349,356$
Leave-one-out cross validation, 361

Levenberg-Marquardt method, 90, 273, 336
background, 93
Likelihood, maximum. See Maximum likelihood
Linear congruential generators, 116
Linear interpolation, 272
Linearization, of curve, 81, 86, 89, 91
Linear programming
barrier methods, 104
cost factors, 108
definition, 96
ellipsoid method, 104, 110
primals and duals, 107
relaxation, 51
simplex method, 97-103, 108, 110
software, 107, 111
standard form, 98-99
Linear recurrence, 222
Linear regression, 310
Linear systems
definition, 309
and differential equations, 213
Gaussian elimination, 310-316, 318
and gene networks, 352
and interpolation, 330-334
iterative methods, 316-321
Krylov subspace methods, 317-319
linear regression, 310
and multivariate functions, 87
optimization in, 92
over- and under determined, 320
pivoting, 312-316
preconditioners, 319-320
pseudoinverse, 321
references, 93
and Taylor expansions, 85
Line-by-line method, 256
Local linearizing, 81, 86, 89, 91
Local optimum, 52
$L U$ decomposition, 315
Macromolecular complexes, 260-262, 264
Markov chain Monte Carlo (MCMC), 141-158, 350
Markov chains
background, 139
definition, 129
and gene network, 350
irreducibility, 136
and mixing times, $163,166-170$
in molecular evolution, 185-188
Markov models
background, 139
branching process, 199
components, 129, 291
conductance, 166-170
continuous time (see Continuous time Markov models)
and DNA bases, 185-188, 269-271, 291-293

Markov models (cont.)
and DNA motifs, 153
eigenvectors, 136-139, 186
ergodicity, 136, 148, 159, 164, 169
gene sequence types, 276
and Gibbs sampling, 149-156
hidden, 291 (see also Hidden Markov models)
and Metropolis method, 142-148 (see also
Metropolis method)
mixing time, 138, 159-160, 166, 170
and molecular evolution, 185-191
nonergodic, 137
order, 130-131
and prior distribution, 153
with random walk, 167
and spatial effects, 258
stationary distribution, 134-138, 149, 153-155, 159, 161
and waiting time (see Continuous time Markov models)
Mass action, law of, 211
Matching problems
exact set, 27
unweighted, 23
weighted, 24
Mating, 53
Matrices. See also Transition matrix
condition number, 319
inversion, 87
over/underdetermined, 310, 320, 330, 333
permutations, 314
positive (semi)definite, 92, 318, 319
Maxam-Gilbert method, 57-59, 61
Maximal matching, 47
Maximum a posteriori probability (MAP), 275
Maximum clique problems, 39
Maximum cut problems, 37, 344
Maximum edge loading, 161-166, 170
Maximum flow problems, 21
Maximum likelihood
background, 289
and clustering, 345-346
description, 268
and expectation maximization, 275, 277-280 (see also Expectation maximization)
in haplotype error correction, 286-287
in haplotype frequency estimation, 282-283
and Hardy-Weinberg equilibrium, 282
and latent variables, 284
and network inference, 347-351
and parameter-tuning, $8-10,268,275-277,283$
MCell, 258-259, 264
Metropolis criterion, 6-7, 10
Metropolis method
background, 158
caveats on use, 146
efficiency, 154-156
generalized, 146-147
and mixing time, $146,154,170$
for optimization, 147, 350
and protein folding, 142, 145, 154
and simulated annealing, 52, 148
and thermodynamics, 141-143, 146
and traveling salesman, 147
Michaelis-Menten reaction, 253-256
Microarrays, 64, 71, 341
Microreversibility, 143-145, 164, 169. See also
Detailed balance
Midpoint method, 219-222
Migration, 198
Milstein's method, 249, 251
Minimum cut, 21-23
Minimum description length (MDL), 361
Minimum set cover, 45. See also Vertex cover
Minimum spanning network, 31
Minimum spanning tree, 16-18, 20, 29-31
Minimum test set, 44
Mixing time
canonical path method, 161-166, 169, 171
conductance method, 166-170, 171
definition, 138, 159-160
and eigenvalues, 138-139
and importance sampling, 170
and Metropolis method, 146, 154
monomer-dimer systems, 171
Model space, reduction, 351
Model validation
accuracy, 358 (see also Accuracy)
cross-validation, 362
goodness measures, 355-358
overfitting avoidance, 361
receiver operating characteristic (ROC) curve, 360
scientific method, 363-366
sensitivity, 359, 360, 362
specificity, 359-361
Mode-of-action by network identification (MNI), 351
Modified distribution, 156
Molecular evolution
coalescent model, 192-198
DNA strand, 191
Jukes-Cantor model, 185-188
Kimura model, 188-191
and Kolmogorov equations, 187, 190
one-parameter, 185-188
and self-transition, 163-164
two-parameter, 185-188
Molecular modeling
and continuous optimization, 75
lattice models, 5-7, 145-146
macromolecular complexes, 260-262, 264
and numerical integration, 211
and stochastic differential equations, 245
and umbrella sampling, 156-158
Moleculizer program, 261

Monomer-dimer systems, 170-171
Monte Carlo samplers, 350
Motifs
alignment of, 152
detection of, 152, 303-307, 347, 359-362
transcription factor binding, 293
Move sets, for lattice models, 6
Multicommodity flows, 23
Multidimensional curve, 336-337
Multigraphs, 16
Multigrid methods, 324f, 325
Multiple independent variables, 356 (see also
Partial differential equations)
Multiple regression, 351
Multivariate functions, 85-88
Mutations
in genetic algorithm, 53
infinite sites model, 191-192
and Jukes-Cantor model, 187, 191
and Kimura model, 186f, 188-189
random, 163-166
simulation, 4-7, 191
transitions/transversions, 189
and Wright-Fisher neutral model, 192
Mutual information, 344
Needleman-Wunsch algorithm, 33
Network identification by multiple regression (NIR), 351
Networks
gene regulatory, 341-353
inference of, 349-353, 363
minimum spanning, 31
reaction networks, 260-264, 323-325, 340
reduced median, 33
Neumann boundary condition, 231-232
Neville's algorithm, 326-329
Newton-Raphson method
background, 93
black-box functions, 84
and HMMs, 302
and implicitly specified function, 273
and interpolation, 336
and Levenberg-Marquardt method, 90
multidimentional, 85-88
and parameter-tuning, 80-84, 269
and steepest descent, 90
Newton's second law, 211
Next reaction method, 257
Noisy data, 286-289, 323-325, 329, 347
Nonlinear programming, 108-110
Nonlinear systems, 91-92
Nontrivial graph properties, 42
Normal distributions, 120, 123-124
NP-completeness
background, 53-55
coping with, $35,46-53$
and DNA sequencing, 65
linear programming relaxation, 51
in Steiner tree, 41
and union-of-cliques graph, 344
NP-hardness. See NP-completeness
Numerical integration. See also Partial differential equations; Stochastic differential equations
additional readings, 225
backward Euler, 217-219
and black box functions, 336
definition, 213
and extrapolation, 337
finite difference method, defined, 213
forward Euler, 214-217, 222, 223, 224
implicit, 316
and interpolation, 336
and Kolmogorov equations, 273
leapfrog method, 221-223, 225, 236
line-by-line method, 256
midpoint method, 219-221
multistep methods, 221-223
and parameter-tuning, 272
single-step methods, 214-221
spectral methods, 226
speed and efficiency, 223-225
step size selection, 223-225, 233-234
and transformation method, 118
Objective function, 96, 268-271, 336
ODEs. See Ordinary differential equations
Optimization. See also Continuous optimization;
Gibbs sampling; Metropolis method; Parametertuning
background, 92
in bootstrapping, 350, 363
conjugate gradient, 91, 318
constrained (see Constraint satisfaction)
and decision problems, 36
description, 1-4
discrete, 15
and gene networks, 349
and Gibbs sampling, 152-154, 350
and interpolation, 335-337
lattice models, 5-7
Levenberg-Marquardt method, 90, 93
and Metropolis method, 147-148, 350
and model goodness, 356
(non)linear systems, 91-92, 318
and parameter-tuning, 8, 267-271
of state assignments, in HMM, 295-297
steepest descent, 89-90
without zero-finding, 89-92
Order of convergence, 248
Ordinary differential equations (ODEs)
backward Euler, 217-219
and curve fitting, 335
and errors, 248
examples, 211-213
forward Euler, 214-217, 222, 223, 224

Ordinary differential equations (cont.)
and gene networks, 351-353
leapfrog method, 221-223, 225, 236
line-by-line method, 256
living cell simulation, 253-256
midpoint method, 219-221
and reaction network, 323, 352
step size selection, 223-225
Overdetermined systems, 310, 320, 330
Overfitting, 361
Parameter selection, 267, 362
Parameter-tuning. See also Expectation maximization; Hidden Markov models; Optimization
and biochemical reactions, 267
description, 8-10, 267, 275
DNA base evolution, 269-271
and gene sequences, 276
haplotype frequency, 280-286
haplotype inference, 286-289
implicitly specified functions, 271-273
and linear systems, 309 (see also Linear systems)
maximum likelihood, 8-10, 268, 275-277, 283
motif-finding, 303-307
and Newton-Raphson method, 80-84, 269
and noisy data, 286-289
protease example, $8-10$
and protein expression, 268
protein folding example, 267
and sensitivity, 363
Parsimony, 3, 29-33
background, 10
Partial differential equations (PDEs). See also
Reaction-diffusion equations.
additional information, 239
boundary conditions, 230-233
convection, 237-239
coupled one-dimension, 228-230
diffusion example, 227
initial conditions, 230
line-by-line method, 256
cell simulation, 253-256, 263
multiple spatial dimensions, 233-234
one spatial dimension, 228-230
step size, 233
Particle collisions, 141, 206-209
Particle diffusion, 325
Particle interactions, 177
PDEs. See Partial differential equations
Pearson correlation coefficient, 343
Permutation matrix, 314
Pfam protein database, 295
Philosophy of science, 363-366
Phylogeny, intraspecies, 28-33
Pivoting, 312-316
Poisson process, 191
Poisson random variable, 191

Polymerization, 61
Polynomial reduction, 46
Polynomials
Chebyshev, 340
cubic formula, 76, 329, 333
fitting to lower order, 329-331, 340
Neville's algorithm, 326-329
quadratic formula, 76
quartic formula, 76
splines, 331-334
Polytope, 97
Popper, Karl, 364
Population dynamics, 29, 212
Population genetics, 280-286
Posting time, 205
Prediction
cut site, in proteases, $8-11$
gene expression, 307, 309
protein expression, 323
Predictor-corrector schemes, 225
Primals and duals, 107
Prim's algorithm, 18, 20
background, 33
Prior distribution. See Prior probability
Prior estimate, 303
Priority queue, $18,205,209-210$
Prior probability, 153, 298, 349
Probability. See also Sampling
of best-fit, 275
conditional, and transitioning, 295
distribution, 347-349
fundamental transformation law, 117
maximum a posteriori (MAP), 275
maximum likelihood, 8-10, 268, 275-277, 283, 356
of migration, 198
prior, 298
Proline, 180-182
Proteases
cut site prediction, $8-11$
and HIV, 10
and parameter-tuning, 8-10
Proteasomes, 11
Protein expression, 268, 323
Protein folding
and CTMMs, 180-182
and HMMs, 308
importance sampling, 154-156
lattice models, 5-7, 10 (see also Lattice models)
Markov model example, 145
Metropolis model, 142, 145, 154
parameters, 267
umbrella sampling, 155-158
Proteins
and Brownian motion, 157
channel protein, 201-203
coiled-coil, 293-295
complexes, 177, 260-262
database, 295
domain recognition, 294, 297
exact set matching, 27
growth rate example, 95
hydrogen bonds, 158
ligand binding, 75
longest common subsequence, $25,42-43$
longest common substring, 26
sampling programs, 261
string and sequence problems, 24-27
structure simulation, 4-7
translation, 268
Pseudoinverse, 321
Pseudorandom numbers, 115
P-value calculators, 343
Quadratic formula, 76
Quadratic programming, 109
Quartic polynomials, 76
Queues, 18, 205, 207-210. See also Priority queues

Random DNA strings, 129-133
Random mutations, 163-166
Random number generation
pseudorandom numbers, 115
rejection method, 121-124
transformation method, 115-121
Random variables. See Distributions
Random walk, 167-170, 324f
Rational function, 330
Rational interpolation, 330
Reaction-diffusion equations, 234-237, 325
background, 239
Reaction networks, 211, 217, 260-264, 264, 271, 323-325, 335, 340
cell simulation, 260-262
data-fitting, 340
Reaction term, 234
Receiver operating characteristic (ROC) curve, 360
Recombination, 198
Reduced median network, 33
Rejection method, 121-126
background, 127
Relaxation, 51
Reversibility, 143-145
Reweighting, 21
Richardson extrapolation, 225, 337
RNAi, 352
Runge-Kutta methods
and accuracy, 221, 225, 237
with black box, 237
and cell simulation, 260
embedded, 225
fourth order, 221
midpoint method, 219-221
and stability, 221

Run time. See also Optimization; Simulation
and accuracy, 219, 233
and boundary conditions, 231
coalescent, 195-197
and CTMMs, 173-175, 273
and discrete event models, 204-206, 208-210
and importance sampling, 155
and intraspecies phylogeny, 29
and Krylov subspace methods, 319
and Metropolis method, 146, 154
and numerical integration, 225
and stability, 215
and step size selection, 217, 233
and umbrella sampling, 156-158
Sampling. See also Gibbs sampling; Importance sampling; Markov models; Metropolis method; Umbrella sampling
continuous distributions, 116-124, 156
discrete distributions, 124-126, 146
efficiency, 154
exponential random variable, 118-119
geometric random variable, 125-126
joint distributions, 119-121, 149-152
modified distribution, 156
and network inference, 350, 363
normal distributions, 120
with optimization, 350
at point in time, 182
(pseudo)random numbers, 115
rejection method, 121-124
and simulation, 7, 115
transformation method, 116-121
uniform random variable, 116
Sanger dideoxy method, 59-61
Scaled variables, 105
Science, philosophy of, 363-366
Scientific method, 363-366
Secant method, 78-80
Selfing, 198
Self-transitions
conversion to, 168
and CTMMs, 181
and mixing time bounds, 159
and molecular evolution, 163-164
Semidefinite programming, 108-110
Sensitivity, 359, 360, 362
Sequences. See DNA sequencing; String and sequence problems
Set problems
independent set, $38,42,46,54$
minimum set cover, 45
minimum test set, 44
Shortest common supersequence, 43
Shortest common superstring, 44
Shortest path, 19-21
Shotgun methods, 67-71
background, 73

Signal processing, 340
Similarity measures, 342-344
Simplex method, 97-103, 108, 110
Simulated annealing
background, 54
and Bayesian models, 349-350
description, 52
and Metropolis method, 52, 148
Simulation
Brownian motion, 241-249
chemical, in inhomogeneous solution, 234237
continuous systems, 211-213 (see also Continuous systems)
of CTMM (pseudocode), 175f
of discrete events (see Discrete event models)
DNA, haploid, 198
DNA random string, 129-133
DNA strand, 191
DNA whole population, 192-195
implicit functions, 271-273
of macromolecular reactions, 260-262
of mutation, 4-7, 191
parameter-tuning, 267-271
of particle collisions, 141, 206-209
protein structure example, 4-7
reaction networks, 253-264
of recombination, 198
and sampling, 7, 115
Single-molecule sequencing, 72, 74
Single-pair shortest path, 19-21
Single-step methods, 219-221, 223-225
Smith-Waterman algorithm, 33
SNP selection, 44, 47
Social constructivism, 365
Solutions
convection, 237-239
diffusion, 227, 230-237, 259, 325
inhomogeneous, 234
Sparse candidate algorithm, 351, 352
Sparse graphs, 18,21
Sparse matrices, 315, 316, 322
Spatial models
discretization, 229, 233, 235, 255, 258
multidimentional, 85-89, 233, 325
one dimension, 228-230
reaction-diffusion equations, 234-236
three-dimensional, 234
and time, 233
two-dimensional, 325
Spearman correlation coefficient, 343
Species tree, 28-33
Specificity, 359-361
Spectral methods. See also Eigenvalues; Fourier transforms
interpolation, 340
numerical integration, 226, 239
Splines, 331-334

Stability
and accuracy, 221, 223, 251
of Adams-Bashforth methods, 223
additional information, 239
of backward Euler, 218
classifications, 215
disadvantages, 217
of forward Euler, 215-216
of leapfrog method, 222
and mutations, 4-7
references, 239
and Runge-Kutta methods, 221
and step size, 217
and stochastic differential equations, 249-251
unconditional, 219
von Neumann analysis, 215-217
Standards, 264
Standard Weiner process, 241
Stationary distribution, 134-138, 149, 153-155, 159, 161
Steepest descent, 89
Steiner nodes, 32, 41
Steiner trees, 31-32, 40-41
Step sizes, 233, 337
adaptive methods, 223-225
predictor-corrector schemes, 225
and stability, 217
Stochastic differential equations
accuracy, 248
additional information, 252
for Brownian motion, 241-248
and cell simulation, 256
Euler-Maruyama method, 246, 249, 250
and implicit function, 273
for protein-folding, 157
stability, 249-251
Stochastic integrals, 244
Stochastic simulation algorithm (SSA), 256-260, 263
StochSim, 256-259
Stratonovich integral, 244
String and sequence problems
applications, 24
exact set matching, 27
haplotype frequency, 280-286
haplotype inference, 286-289
HMM, 292
hybridization, 64-66, 71, 73
longest common subsequence, $25,42-43$
longest common substring, 26
Markov model example, 276
noisy data, 286-289
NP completeness, 42-44, 47
random DNA strings, 129-133
sequence alignment, 33
shortest common supersequence, 43
shortest common superstring, 44
suffix trees, 26, 27, 33

Subgraphs, 42, 54
Subsequences, 25, 42-43
Subspace. See Krylov subspace
Substrings, 26
Successive squaring, 133
Suffix trees, 26, 27, 33
Sum-of-squares. See Least-squares
Supersequences, 43
Superstrings, 44
Systems Biology Markup Language (SBML), 264
Tagging SNP selection, 44, 47
Tau leap algorithm, 259
Taylor series
approximation with, 80-82, 85, 232
and backward Euler, 218
and finite difference approximations, 229, 232
and forward Euler, 215
and midpoint method, 220
and multistep methods, 222, 225
and Newton-Raphson method, 80-82, 84-85
and Richardson extrapolation, 337
stochastic. See Itô-Taylor series
Temperature. See Simulated annealing
Terminal nodes. See Steiner trees
Terminator base, 59-61
Thermodynamics
and CTMMs, 180-182
and Metropolis method, 141-143, 146
Time. See Evolution; Mixing time; Run time
Tractability, 24-26, 35. See also Intractability
Transcription factor binding, 293
Transformation method, 116-121, 124
background, 127
trans isomer, proline, 180-182
Transition, Markov model, 130
Transition matrix
for CTMMs, 173
in Jukes-Cantor model, 186
in Kimura model, 189
of Markov models, 132, 134-137
Traveling salesman problem (TSP), 36, 48, 54, 147
Trees
minimum spanning, 16-18, 20, 29-31
and optimization, 2-4
Steiner, 31-32, 40-41
suffix, 26, 27, 33
and traveling salesman, 48
Triangle traveling salesman, 48-49, 54
True negatives, 359
True positives, 359, 360
Truth, 365
Twofold cross-validation, 361
Umbrella sampling
background, 158
and Gibbs sampler, 156-158
and Metropolis sampler, 155

Unconditional stability, 219
Underdetermined system, 310, 321, 333
Union-of-cliques, 344-347
Variation distance, 160
Vertex cover
approximation algorithms, 47, 50-51
description, 38
and genetic algorithm, 53
hardness testing, 46
and independent set, 39
and minimum set cover, 45
reference, 54
Virtual Cell, 255, 261, 264
Viterbi algorithm, 296, 299
von Neumann analysis, 215, 219, 220, 250
Waiting time, 173-175
and coalescence, 198
and CTMMs, 201-204
and Poisson process, 191
and recombination, 199
Wave equation, 238
Wavelets, 223, 226, 340
Weiner process, 241
Whole population sampling, 192-195. See also Coalescent
Wikipedia, 93, 110
Wright-Fisher neutral model, 192
Zero, avoiding, 105-107
Zero-finding
alternative approaches, 89-92
bisection method, 76-78
multivariate functions, 85-88
Newton-Raphson methods, 80-88, 90, 269
secant method, 78-80
$0-1$ integer programming, 51

