Index

Page references followed by b denote boxes; those followed by f denote figures; those followed by t denote tables.

Α

Abbeel, Pieter, 80 ABI BioScope, 182 ABNER, 291t Abstraction, 7, 11 ABySS, 171, 171t Accuracy, 27, 54-55, 55f Accurate mass and time tag (AMT) approach, 193-194 Actin cytoskeleton pathway, regulation of, 235 Active contour algorithm, 97-98, 98f Additive color mixing, 85 Affymetrix, 112, 113, 180 Agglomerative clustering, 77 Agilent, 110-113, 180, 181 AILUN, 265 Akt, 242f, 243-244 Algorithm(s) active contour, 97-98, 98f CHIP-seq, 173-177 Cocke-Kasami-Younger (CKY), 290 computational image analysis, 101-103 conditioned random fields, 298, 298t constant-time, 12-13 cubic, 13 described, 11-12 Earley, 290 ease of implementation, 15 expectation-maximization (EM), 119, 212, 214 experimental time, 13 feature selection, 65-66 greedy, 72 image registration, 101-103 feature-based algorithm, 102-103 intensity-based registration, 101-102 mutual information theoretic technique, 102 k-nearest neighbors, 67-68, 298t level set, 98-99, 99f-100f linear time, 13 machine learning, 62-78

classification task, 49, 52f classifier, 49-50 clustering, 51, 52f data, 62-67 features selection, 52 probabilistic models, 72-76, 73f regression task, 50, 52f, 57 semisupervised learning, 51, 52f supervised learning, 50, 52-53, 52f, 67-72 terminology, 49-53 training phase, 50 unsupervised learning, 51, 52f, 53, 76-78, 76f maximum entropy, 298, 298t naive Bayes, 68-69, 298, 298t parallelizability, 14-15 partitioning, 71–72, 118–119 performance evaluation, 53-57, 55f quadratic, 13 random forests, 298, 298t running time analysis, 12-13 running time of, 65 SEQUEST, 191-192, 192b space complexity, 13-14 support vector machines (SVM), 298, 298t Alignment anchor, 164-165 indel, 163-164 paired-end, 164-165, 165f partners, 164-165 programs for, 166-167, 166t split-read, 168-169, 168f Alleles biallelic, 126 defined, 126 Hardy-Weinberg equilibrium, 137 major, 126 maternal, 126 minor, 126 paternal, 126

306 Index

Allelic odds ratio, in GWAS, 129-130 Alternative hypothesis, 26 Alzheimer's disease, 235 AMT (accurate mass and time tag) approach, 193-194 Anchor, alignment, 164-165 Annotation biomedical text, 292 incomplete and inaccurate annotations, 233-234, 235f ANOVA (analysis of variance), 30 Anscombe's quartet, 41, 42f, 43 Anxiety, bioinformatics, 1 Archon X Prize for Genomics, 184 Area under the curve, 56f, 57 Arginine, heavy, 198 ArrayWxpress, 261 Association genome-wide association study (GWAS), 125-150 genotype-phenotype, 128-130, 128f interpreting genetic association, 144-145 Association testing, 137-141 χ^2 test of statistical independence, 139–140 improving statistical power, 141-144 alternate tests of association, 141-142 alternate types of variation, 142 genotype imputation, 142-144, 143f meta-analysis, 144 Assortative mating, 137 Assumptions, 26 Autosomes, 126 Auxiliary space complexity, 14

В

Bagging, 72 BAM file format, 165 BANNER, 291t Base-calling error probability, 159 Bayesian networks, 73-74, 73f, 245-259 in action, 255-256 chain rule, 247 dynamic Bayesian networks (DBNs), 244-245 joint probability distribution, 245-248 learning signaling pathway structure from flow cytometry data, 256 Markov assumptions, 247 model properties, 251-255 causality, 254-255 dependencies and independencies in graph structure, 251-253 model semantics, 245-246 notation, 246-249 structure learning, 249-251 model averaging, 251 scoring, 249-250, 250b searching the space of possible graph structures, 250-251

Bayes' Rule, 20-21, 249 Bayes' theorem, 68 Benjamini-Hochberg false discovery rate, 36, 121 Biallelic, 126 Bias, described, 23 Binary images, 93 Binning 1D, 209-210 2D, 210-211, 211f Bioconductor, 113, 265, 266 Biomedical images, 87-90 computed tomography (CT), 88, 89f magnetic resonance imaging (MRI), 89, 89f microscope images, 87-88, 88f positron emission tomography (PET), 90 Biomedical text, 285-301 annotation, 292 applications, 286-287 biosurveillance, 287 consumer health informatics, 287 data integration, 287 document classification, 286-287 drug discovery, 287 health services delivery, 287 clinical document classification example, 298-300, 299t-300t goal of mining, 285-286 growth in biomedical literature, 285-301 machine learning, 297-300, 298t-300t named entity recognition, 290-291, 291t ontologies in biomedicine, 295-297, 296f preprocessing raw text, 288-290, 288f-289f chunking and parsing, 288f-289f, 289-290 part of speech tagging, 288-289, 288f stemming, 290 stop word removal, 290 tokenization, 288, 288f processing, 300-301 standard terminologies, 292-295, 294t-295t BioPortal, 297 Biosurveillance, 287 Bio Tagger-GM, 291t Bishop, Christopher M., 79 Bits in images, 86b BLAST, 158-159, 166t, 167 BLAT (BLAST-like alignment tool), 166t, 167 Blocks, 109 Bonferroni procedure, 35, 121, 145 Boolean feature, 64-65 Boolean networks, 242-244, 242f, 245 Boosting, 72 Bootstrapping, 38 Bowtie, 166, 166t Box-Cox transformation, 207 Brain images, analysis of, 96-99, 97f-98f active contour algorithm, 97-98, 98f k-means, 97, 97f level set algorithm, 98-99, 99f-100f

Index 307

BreakDancer, 183 Burroughs–Wheeler aligner (BWA), 166–167, 166t Burroughs–Wheeler aligner, Smith–Waterman alignment (BWA-SW), 166t, 167 Byte, 8

С

Candidate mapping locations, 161 Canny, John F., 104b Canny edge detection, 104b-105b CASAVA, 182 Cases, in GWAS, 128-129 Categorical data defined, 31 mixing categorical and continuous data, 33b-34b statistical tests of, 31-33 Causal interpretation, 254 Causality, 254-255 Cell images, 92-96, 92f-96f k-means clustering, 95-96, 96f Otsu's method for image segmentation, 94-95, 94f-95f Censored data, 41-42 Central dogma, 107, 187 Central limit theorem, 29 Central processing unit (CPU), 8, 8t CGH (comparative genomic hybridization), 180 Chain rule, 247 Chain-termination method, 155 Channels, 84-85, 87f Chart parsing, 290 ChIP-on-chip (chromatin immunoprecipitation on chip), 107, 172 CHIP-seq, 172-179 advantages, 178 algorithms, 173-177 filtering, 176 identification of regions of enrichment, 175-176 ranking by significance, 176-177 signal shifting, 174-175, 175f smoothed signal creation, 173-174, 173f artifacts, 176, 177f overview, 172-173 practical considerations, 177-178 confidence estimate, 177 performance, 177 usability, 178 software packages, 178, 179f χ^2 test of statistical independence, 32, 139–140 Chromatin immunoprecipitation (ChIP), 172 Chromatin immunoprecipitation on chip (ChIP-on-chip), 107, 172 Chromosomes autosomes, 126 sex, 126 Chunking, 288f-289f, 289-290 CIGAR, 166

CisGenome, 178, 179f CKY (Cocke-Kasami-Younger) algorithm, 290 Classification in a 2D feature space, 69–70, 69f Classification task, 49, 52f Classifier, 49-50 complexity of, 62 decision tree, 71-72, 71f generalization, 58 linear, 70 overfitting, 62-64, 63f performance evaluation and, 53-57, 55f testing set, 58-61, 59f training multiple, 72 training set, 58-61, 59f Closed-form expression, 142 Cloud computing services, 9 Clustering, 51, 52f agglomerative, 77 divisive, 77 example of, 76f flow cytometry, 211-215 hard clusters, 119 hierarchical, 76f, 77, 116-118, 116f-117f k-means, 77-78 brain images, 97, 97f cell images, 95-96, 96f flow cytometry, 212-215 semisupervised clustering, 117-120, 119f semisupervised clustering methods, 117-120, 119f unsupervised clustering methods, 115-117, 116f-117f unsupervised learning algorithms, 76-78 Cluster plot, 136-137, 136f CMYK image, 85, 87f CNVer, 182 CNVs (copy-number variants), 142, 180, 182 CNV-seq, 182 Cochran-Armitage trend test, 141 Cocke-Kasami-Younger (CKY) algorithm, 290 Color mixing additive, 85 subtractive, 85 Color space, 84-85 Color space encoding, 157, 157f Comparative genomic hybridization (CGH), 180 Comparative Toxicogenomics Database, 270 Compensation, 206-207, 206f Complete Genomics, 183-184 Complexity penalty, 250b Computational image analysis, 92-103 algorithms, 101-103 brain images, 96-99, 97f-98f cell images, 92-96, 92f-96f edge detection, 103, 104b-105b image registration, 99-101 Computed tomography (CT), 88, 89f

308 Index

Computers hardware components of, 8, 8t limitations of, 12 overview of, 8-9 Computer science, introduction to, 7-15 algorithms, 11-12 computers, 8-9 ease of implementation, 15 parallelizability, 14-15 programs, 9-11 running time analysis, 12-13 space complexity analysis, 13-14 Conditional independency, 246, 247, 248, 252 Conditional probability, 18, 20, 68-69 Conditional probability distribution, 74, 246-248 Conditional probability table (CPT), 248, 252 Conditioned random fields algorithm, 298, 298t Confounding factor, 67 Connectivity graph, 258 Connectivity Map, 269, 270 Constant-time algorithm, 12-13 Constant-time storage, 14 Consumer health informatics, 287 Contigs, 169 Contingency table, 31-33, 32t-33t, 129 Continuous data mixing categorical and continuous data, 33b-34b statistical tests on, 28-30 Continuous feature, 65 Contrast, 91, 91f Controls, in GWAS, 128-129 Copy-number variants (CNVs), 142, 180, 182 Correction methods Benjamini-Hochberg false discovery rate, 36, 121 Bonferroni, 35 Tukey, 36 Correlation, 39-43 covariance, 40 definitions, 128 described, 39-40 Pearson, 40-41, 42f Spearman rank, 41, 42f Correlation coefficient, 101-102 Cost function, 101 Counting rules, 19 Covariance, 40 Covariate analysis, 149 Cox proportional hazard models, 42 C programming language, 11, 15 C++ programming language, 9, 11 CPT (conditional probability table), 248, 252 CPU (central processing unit), 8, 8t Cross-validation, 58-61, 59f feature selection and, 61, 66 k-fold, 59f, 60 leave-one-out, 60 CT (computed tomography), 88, 89f cTAKES, 291t

Cubic algorithm, 13 Cubic space complexity, 14 Cufflinks, 170–171, 171t Current procedural terminology, 293 Curse of dimensionality, 206 Cyanine 3, 109–111 Cyanine 5, 109–111 Cytobank, 203, 205

D

DAGs (directed acyclic graphs), 244 Data categorical, 31-33, 33b-34b censored, 41 clean, 64 learning biomolecular pathways from, 241-259 missing, 41-43 mixing categorical and continuous data, 33b-34b output variables, 66-67 probability and, 17-21 quality, 64 statistical analysis of, 25-39 tests on categorical data, 31-33 tests on continuous data, 28-30 using machine learning algorithms, 62-67 visualization, 43-44 Anscombe's plot, 41, 42f, 43 draftsman's plot, 43, 44f Databases, 261, 270 Data integration, 287 gene expression experiments, 261-281 investigative steps, 262f paradigms integrating expression data over "unrelated" contexts, 267f, 269-275, 270f integrating expression data with other genome-wide modalities, 267f, 275-278, 276f meta-analysis of gene expression data, 266, 267f, 268-269, 268f programming exercise, 278-281 finding the data, 278 formulating a question, 278 integrating findings, 279 interpreting findings, 279 programming solution, 280 representation of differential gene expression, 278-279 question formulation, 262-263, 278 representation of differential gene expression data, 263-265, 264f, 278-279 Data representation, 263 Data snooping, 34-35 Data transforms, 24 **DAVID**, 265 DBNs (dynamic Bayesian networks), 244-245

Index 309

Decision tree, 71–72, 71f Degrees of freedom, 30 De novo assembly, 169 De novo sequencing, peptide identification and, 194-195, 195t Descriptive statistics, 21-24 Differential equation models, 257b-258b Differential gene expression, representation of data, 263-265, 264f, 278-279 Dimensionality, 91-92 Dimensionality reduction, 78 Directed acyclic graphs (DAGs), 244 Discrete feature, 64-65 Discrete ordered features, 64-65 Dispersion, statistics of, 22 Distributed systems, programs for, 9 Distribution conditional probability, 74, 246-248 F, 30 hypergeometric, 31, 32f joint probability, 74, 245-248 null, 121, 140 skewness of, 24, 24f symmetry of, 24, 24f t, 28-30, 28f, 30f Divisive clustering, 77 DNA-binding proteins, 172 DNA sequencing next-generation sequencing, 155-184 ABI SOLiD, 156t, 157, 157f alignment, 157-158 BLAST use, 158-159 CHIP-seq, 172-179 454 FLX, 156, 156t future of, 184 gene expression microarrays compared, 107 Illumina, 156, 156t RNA-seq, 167-172 sequencing services, 183-184 short-read mapping, 159-167 variation detection, 180-183 1000 Genomes Project, 142 Document classification, 286-287 Draftsman's plot, 43, 44f Drug discovery, 287 DrugNer, 291t Dye bias, 110-111 Dynamic Bayesian networks (DBNs), 244-245 Dynamic contrast ratio, of human eye, 83 Dynamic susceptibility contrast perfusion imaging (DSC-MRI), 89

E

Earley algorithm, 290 Edge detection Canny, 104b–105b described, 103 ELANDv2, 166, 166t Electronic medical records (EMRs), 287 Electron microscope, 87-88, 88f The Elements of Statistical Learning: Data Mining, Inference, and Prediction (Hastie, Tibshirani, and Friedman), 79 "Else if" statement, 10 EM (expectation-maximization) algorithm, 119, 212, 214 EMBL (European Molecular Biology Library), 265 Emission probabilities, 75 Encyclopedia of DNA Elements (ENCODE), 150 Enrichment, identification of regions of, 175-176 ENTREZ, 268, 270, 276, 277 Entropy, 102 Equivalence classes, 253b ERANGE, 170-171, 171t ERK, 246-252, 247f, 253b-254b Error family-wise error rate, 35 in multiple hypothesis testing, 35 root mean square, 57 testing, 58-59, 63-64, 63f training, 58-59, 63-64, 63f type 1, 35 type 2, 35 Estimate, biased, 23 Euclidean distance, 68, 114-115, 115f European Molecular Biology Library (EMBL), 265 Executable, 8 Exomes, 142 Expectation, 21 Expectation-maximization (EM) algorithm, 119, 212, 214 Experimental design, 57-61 Exponential-time algorithm, 13 Expression arrays, 107-122 Expression data, 107-124 Eye, human, 83 Eye color genetic association, 128-130, 128f single-nucleotide polymorphisms (SNPs), 126, 127f

F

False discovery, 34 False discovery rate (FDR), 120–122 Benjamini–Hochberg, 36, 121 ChIP-seq, 177–178 expression data, 268, 273–275 False negative, 54, 55, 55f False positive, 53, 55–56, 55f False positive rate, 35 Family-wise error rate (FWER), 35, 120–121 .fcs files, 202–204, 202f–204f, 202t F distribution, 30

310 Index

Feature(s) Boolean, 64-65 continuous, 65 discrete, 64-65 discrete ordered, 64-65 interactions between, 70 number of, 62, 65 ordinal, 64 sample, 49-50 Feature selection, 52, 61, 65-66 Feature space, 49 classification in 2D, 69-70, 69f dimensional reduction and, 78 effective dimensionality of, 62 as joint probability distribution, 74 principal component analysis and, 78 Fisher, Ronald, 29 Fisher's exact test, 31-33, 141 Fisher's method, 268, 268f Flow cytometry, 188, 200-218 analyzing, 205-206 background of, 200-201, 201f comparing across samples, 216-218 informative event problem, 217-218 quantitative difference problem, 217 sample classification problem, 216-217 data visualization of flow data, 203-205, 203f exploratory analysis, 218 .fcs files, 202-204, 202f-204f, 202t future directions, 218-219 clinical applications, 219 data variability, 218-219 structured annotation for data sharing, 219 learning signaling pathway structure from, 256 preprocessing steps, 206-208, 206f-207f compensation, 206-207, 206f transformation of data, 207, 207f probability distribution, 213b-214b states, 201 subpopulation-finding and feature extraction methods, 208-216 binning, 209-210 cluster analysis, 211-215 heatmaps, 209, 209f histograms, 209-210, 210f mixture models, 212-215 nonparametric population-finding methods, 215-216 1D methods, 208-210 2D methods, 210-211 Fluorescence microscope, 87-88, 88f Fluorophores, 109-111 fMRI (functional MRI), 89 Focus, 83, 84f, 91 Fold enrichment, 176 Fork, 252 For-loops, 10 Frequentist approach, to statistical hypothesis testing, 25 Friedman, Jerome, 79 Friedman, Nir, 80 F statistic, 27 Function, 9–10 Functional class scoring approaches, 227–228 assessing statistical significance of pathways, 232 limitations, 228 overview, 227–228 tools for, 231t Functional MRI (fMRI), 89 FWER (family-wise error rate), 35, 120–121

G

Gating, 205, 208 Gaussian smoothing, 104b Gene Association Database (GAD), 277 GeneChip, 180 Gene expression analysis of values, 114-122 metrics, 114-115, 115f semisupervised clustering methods, 117-120, 119f statistical approaches to data interpretation, 120-122, 121t unsupervised clustering methods, 115-117, 116f-117f machine learning and analysis, 49-51, 52f meta-analysis and data integration, 261-281 microarrays, 107-122 analysis of gene expression values, 114-122 one-color, 108, 112-114 overview of, 107-109 two-color, 108, 109-111, 111b, 111f Gene Expression Omnibus (GEO), 261, 262, 264, 269, 277 Gene-level statistics, 230, 231t-232t Gene Ontology (GO), 292-293, 294t incomplete and inaccurate annotations, 233-234, 235f Generalization, 58 Genes, number of human, 130 Gene set association (GSA), 271, 272-273 Gene Set Enrichment Analysis (GSEA), 269-271 Genetic association, 128-130, 128f interpreting, 144-145 testing, 137-141 χ^2 test of statistical independence, 139–140 improving statistical power, 141-144 Genetic heterogeneity, 127 Genome sequencing, 142 Genome-wide association study (GWAS), 125-150 data quality, 145-146 fundamental concepts underlying, 126-130 goal of, 126 integrating expression data with, 276-277 rationale for, 130–135 development of GWAS as research tool, 131-132 linkage disequilibrium, 132-133, 134f linkage studies different from, 133-135 what can be learned from, 130-131

Index 311

significance criterion for, 145 steps in, 135-150 association testing, 137-141, 138f causal genetic factor, 149-150 genotype calling, 135-137, 136f improving statistical power, 141-144, 143f interpreting genetic associations, 144-145 population stratification, 146-149, 148f Genome-wide significance, 140-141 Genomic inflation factor, 148-149 Genomic variants, 180-183 Genotype calling, 135-137, 136f Genotype imputation, 142-144, 143f Genotype-phenotype association, 128-130, 128f Genotypes association with phenotypes (see Genome-wide association study) described, 126, 127f genotype-phenotype, 128-130, 128f Genotypic odds ratio, in GWAS, 129-130 GEOquery, 266, 271-272 GO. See Gene Ontology Golub, Todd, 51 Gosset, William S., 29 Grayscale image, 86-87, 87f of a cell, 92-93, 92f Greedy random search, 250 GSA (gene set association), 271, 272-273 GSEA (Gene Set Enrichment Analysis), 269-271 GWAS. See Genome-wide association study

Н

Haplotype blocks, 142 Haplotype phase inference, 142 Haplotypes, 142 HapMap, 131-132 Hard drive, 8, 8t, 14 Hardy-Weinberg equilibrium, 137 Hastie, Trevor, 79 Health services delivery, 287 Heatmaps, 209, 209f Heavy water, 198 Heterozygous, 136 Heuristic search, 250 Hidden Markov model (HMM), 73f, 74-76, 298, 298t Hidden variables, 254 Hierarchical clustering, 76f, 77, 116-118, 116f-117f Histograms, flow cytometry, 209-210, 210f HITECH Act, 287 HomoloGene, 265 Homozygous, 136 Hoover Tower, photographs of, 83, 84f-85f, 87f Human Protein Reference Database, 276 Hyperbolic arcsine transform, 207, 207f Hypergeometric distribution, 31, 32f Hypergeometric experiment, 31 Hypergeometric test, 271

Hypothesis alternative, 26 null, 26, 27 testing of, 27 Hypothesis testing. *See also* Statistical hypothesis testing described, 27 multiple, 140, 145 Hysteresis thresholding, 105b

- 1

ICAT (isotope coded affinity tags), 198 ICD-10CM (international classification of diseases), 293, 294t ICP (iterative closest point), 102-103 Identical-read stacks, 176 "If" statement, 10 Illumina, 112-113, 133 CASAVA, 182 sequencing, 156, 156t Image analysis, 83-106 biomedical images, 87-90 computational, 92-103 generating images for, 90-92 imaging basics, 83-87 Image registration, 99-101 algorithms, 101-103 feature-based algorithm, 102-103 intensity-based registration, 101-102 mutual information theoretic technique, 102 multiple images, 99-100 spatial transformation, 100-101 Images biomedical, 87-90 computed tomography (CT), 88, 89f magnetic resonance imaging (MRI), 89, 89f microscope images, 87-88, 88f positron emission tomography (PET), 90 bits in, 86b dynamic, 100 imaging basics, 83-87 intermodality, 99-100 intramodality, 99-100 multiple, 99-100 serial, 100 Image segmentation defined, 93 k-means clustering, 95-96, 96f Otsu's method for, 94-95, 94f-95f Imputation, 43, 65, 272 Indel, 142 Indel alignment, 163-164 Independent events, 19 Indexed color, 90, 91f Influence, 244 Informatics anxiety, 1 Input, of the classifier, 50

312 Index

Input/output (I/O) devices, 8, 8t Intensity computation of image intensity gradient, 104b cutoff, 93-94, 93f Otsu's method for image segmentation, 94-95, 94f-95f Intensity-based registration, 101-102 Intensity plot, 136-137, 136f Intermodality images, 99-100 International classification of diseases (ICD-10CM), 293, 294t International HapMap Project, 131-132 International Society for Advancement of Cytometry (ISAC), 202 Interquartile range, 22, 24 Interventional data, 244, 253b-254b, 255 Intramodality images, 99-100 ISAC (International Society for Advancement of Cytometry), 202 Iterative closest point (ICP), 102-103 iTRAQ (isobaric tags for relative and absolute quantitation), 198

J

Jackknife technique, 38–39 Java programming language, 9, 11 Joint probability, 19–20 Joint probability distribution, 74, 245–248

К

KEGG (Kyoto Encyclopedia of Genes and Genomes), 226, 233, 235, 236 Kernel smoothing, 174 Kernel trick, 70 k-fold cross-validation, 59f, 60 Klein, Dan, 80 k-means brain images, 97, 97f cell images, 95-96, 96f clustering, 77-78 flow cytometry, 212-215 semisupervised clustering, 117-120, 119f k-nearest neighbors algorithm, 67-68, 298t Knome, 183 Koller, Daphne, 80 Kolmogorov-Smirnov test, 217 Kruskal-Wallis test, 30 Kurtosis, 22 Kyoto Encyclopedia of Genes and Genomes (KEGG), 226, 233, 235, 236

L

Language processing. *See* Natural language processing *LCT* gene, 147 Leave-one-out cross-validation, 60 Level set algorithm, 98-99, 99f-100f Libraries, 9 Life Technologies, 184 Light microscope, 87-88, 88f Likelihood ratio test, 141 Linear classification algorithms, 69-70 Linear time algorithm, 13 Linear time storage, 14 Linear transform, 207, 207f LingPipe, 291t Linkage analysis, 133-135 Linkage criteria, 77 Linkage disequilibrium, 132-133, 134f Linkage equilibrium, 133 Local maximum, 251 Location, statistics of, 22 Locus defined, 126 linkage analysis, 133-135 Logistic regression, 70 LOINC, 293, 294t Lowess normalization method, 110-111, 111f

Μ

Machine learning, 47-80 algorithm use, 62-78 data, 62-67 probabilistic models, 72-76, 73f supervised learning algorithms, 67-72 unsupervised learning algorithm, 76-78, 76f defined, 47 experimental design, 57-61, 59f performance evaluation, 53-57, 55f, 56f resources, 79-80 terminology, 49-53 MACS, 178, 179f Magnetic resonance imaging (MRI) brain images, 96-100, 97f-98f, 100f described, 89, 89f functional, 89 perfusion, 89, 96-97 structural, 89 Manhattan distance, 67-68, 114 Manhattan plots, 146, 147f Mann-Whitney U test, 30 MA plots, 111, 111b Mapping next-generation sequencing, 158-167 short-read, 159-167 alignment programs, 166-167, 166t characteristics of short reads, 159-160, 160f indel alignment, 163-164 mapping output, 165-166 mapping quality/posterior probability, 162-163, 162f paired-end alignment, 164-165, 165f practical considerations, 166-167

Index 313

quality score use in mapping, 163 repetitive reads, 161 scoring and filtering, 161-162 seeding, 160-161 Marginal likelihood, 249 Markov assumptions, 247 Mascot, 192 Mass differential equation model, 257b Mass spectrometry (MS), 188-199 overview of, 188-189, 189f peptide identification, 191-194 accurate mass and time tag (AMT) approach, 193-194 database-driven approaches, 191-193 de novo sequencing, 194-195, 195t estimating false positives, 193 target-decoy approach, 193 peptide quantitation, 196-199 labeled, 197-198, 198f label-free, 196-197 selected reaction monitoring (SRM), 198-199, 198f protein digestion for, 190 protein identification, 195-196 false positives, 195-196 one peptide mapped to many proteins, 196 protein quantitation, 199 sample preparation, 189-190 spectra example, 191, 191f tandem (MS/MS), 190-191, 191f Mass-to-charge (m/z) ratio, 190 Mating, assortative, 137 Matlab machine learning algorithms, 79 MATLAB programming language, 9, 11 Maximum, 22 Maximum entropy algorithm, 298, 298t Mean central limit theorem and, 29 comparing means between groups, 28-30, 28f population, 22, 23 sample, 21, 22 standard error of, 24 in unimodal, symmetric distribution, 24 Measures of central tendency, 22 Median sample, 21, 22 in unimodal, symmetric distribution, 24 Median Polish summation, 113 Medical dictionary for regulatory activities (MedDRA), 294t Medical subject headings (MeSH), 293, 294t MedLEE, 291t Medline, 285, 286f, 288 MEK, 242f, 243, 246-252, 247f, 253b-254b Memory defined, 8, 8t space complexity and, 13-14 Meta-analysis described, 144

gene expression experiments, 261-281 for increasing statistical power, 144 MetaMap, 291t Metathesaurus, 292-293, 294t Metrics, microarray analysis, 114-115, 115f Microarrays, 107-122 analysis of gene expression values, 114-122 metrics, 114-115, 115f semisupervised clustering methods, 117-120, 119f statistical approaches to data interpretation, 120-122, 121t unsupervised clustering methods, 115-117, 116f-117f blocks, 109 high-density DNA, 132 next-generation sequencing compared, 107 one-color overview, 112 preprocessing and normalization, 112-114 two-color compared, 108 overview of, 107-109 tiling, 107 two-color MA plots, 111, 111b one-color compared, 108 overview, 109-110 preprocessing and normalization, 110-111, 111f Microscope images, 87-88, 88f Minimum, 22 Minkowski equation, 114 Mismatch probes, 112 Missing data, 41 Mixture models, flow cytometry and, 212-215 Model averaging, 251 Modeling assumptions, 242 Models pathway Bayesian networks, 245-259 Boolean networks, 242-244, 242f, 245 challenges in, 241 differential equation models, 257b-258b dynamic Bayesian networks, 244-245 modeling assumptions, 242 network inference, 241 robust, 244 probabilistic, 72-76, 73f, 241-242 Bayesian network, 73f, 74–76 hidden Markov models (HMM), 73f, 74-76, 298, 298t proportional hazard, 42 **MoDIL**, 183 Module networks, 255-256 Monty Hall problem, 18 Moore, Andrew, 80 Moore, Gordon, 47 Moore's law, 47-48 MOSAIK, 166t, 167 MRI. See Magnetic resonance imaging

314 Index

MS. See Mass spectrometry Multiple hypotheses, correction for, 21, 35–36, 230t–232t, 232–233 Multiple hypothesis testing, 140, 145 correction methods, 35–36 Benjamini–Hochberg false discovery rate, 36 Bonferroni, 35 Tukey, 36 errors, 35 problems with, 34–35 Multiple testing, 140, 145 Mutual information theoretic technique, 102

Ν

Naive Bayes algorithm, 68-69, 298, 298t Named entity recognition (NER), 290-291, 291t National Cancer Institute (NCI) Enterprise Vocabulary Services, 292 Thesaurus and Metathesaurus, 292-293, 294t National Center for Biotechnology Information (NCBI), 265 Natural language processing, 285-301 annotation, 292 applications, 286-287 machine learning, 297-300, 298t-300t named entity recognition, 290-291, 291t ontologies in biomedicine, 295-297, 296f preprocessing raw text, 288-290, 288f-289f standard terminologies, 292-295, 294t-295t NCBI (National Center for Biotechnology Information), 265 NCI. See National Cancer Institute Negative predictive value (NPV), 54, 55f NER (named entity recognition), 290-291, 291t Network device, 8, 8t Network inference, 241 Networks Bayesian, 73-74, 73f, 245-259 in action, 255-256 chain rule, 247 joint probability distribution, 245-248 learning signaling pathway structure from flow cytometry data, 256 Markov assumptions, 247 model properties, 251-255 model semantics, 245-246 notation, 246-249 structure learning, 249-251 Boolean, 242-244, 242f, 245 dynamic Bayesian networks, 244-245 module, 255-256 Neurosphere cells, 116, 117f Next-generation sequencing, 155-184 ABI SOLiD, 156t, 157, 157f alignment, 157-158 BLAST use, 158-159 CHIP-seq, 172-179

advantages, 178 algorithms, 173-177 features of software packages, 179f overview, 172-173 practical considerations, 177-178 454 FLX, 156, 156t future of, 184 gene expression microarrays compared, 107 Illumina, 156, 156t RNA-seq, 167-172 advantages, 167-168, 171-172 applications, 167-168 approaches to identifying transcript structure, 168-170, 168f overview, 167-168 transcript quantification, 170-171, 171f sequencing services, 183-184 short-read mapping, 159-167 alignment programs, 166-167, 166t characteristics of short reads, 159-160, 160f indel alignment, 163-164 mapping output, 165-166 mapping quality/posterior probability, 162-163, 162f paired-end alignment, 164-165, 165f practical considerations, 166-167 quality score use in mapping, 163 repetitive reads, 161 scoring and filtering, 161-162 seeding, 160-161 variation detection, 180-183 copy-number variants, 180, 182 detecting large-scale variants, 182-183, 183f detecting nucleotide-level variation, 180-182, 181f genomic variants classified by scale, 180 Ng, Andrew, 80 Nimblegen, 181 Noise, 64 Nominal significance threshold, 140 Nonmaximum suppression, 105b Nonparametric population-finding methods, 215-216 Nonparametric statistics, 30, 41 Normalization one-color microarrays, 112-114 two-color microarrays, 110-111, 111f NPV (negative predictive value), 54, 55f Null distribution, 121, 140 Null hypothesis described, 26 test statistic and, 27

0

Oases, 171, 171t Object-oriented languages, 11 Octave, 79 Odds ratio, in GWAS, 129–130 Odds ratios, 37b–38b

Index 315

ODEs (ordinary differential equations), 257, 257b-258b OMSAA, 192 One-color microarrays overview, 112 preprocessing and normalization, 112-114 two-color compared, 108 One-strand peaks, 176 Online mendelian inheritance in man (OMIM), 294t Ontologies in biomedicine, 295-297, 296f ORA. See Overrepresentation analysis Ordinal features, 64 Ordinary differential equations (ODEs), 257, 257b-258b Otsu's method for image segmentation, 94-95, 94f-95f Outliers, 22, 24 Output, of the classifier, 50 Output variables, 66-67 Overfitting, 60, 62-64, 63f, 249 Overlapping reads, 169 Overrepresentation analysis (ORA), 224-227 assessing statistical significance of pathways, 232 correction for multiple hypotheses, 230t, 232 limitations of, 226-227 overview, 224-226, 225f tools for, 230t

Ρ

Pacific Biosciences, 184 Paired distance, 164-165 Paired-end alignment, 164-165, 165f Pairs of reads, 180 Palette indexing, 90, 91f PAM (prediction across microarrays), 217 Paradigm, 263 Parallelizability, of algorithms, 14-15 Parameters, 250b Parsing, 288f-289f, 289-290 Partial differential equations, 257, 257b-258b Partitioning algorithms, 71-72, 118-119 Part of speech tagging, 288-289, 288f PathBLAST, 276 Pathway, defined, 223-224 Pathway analysis comparison of existing tools, 229-233, 230t-232t assessing statistical significance of pathways, 232 correction for multiple hypotheses, 230t-232t, 232 - 233gene-level statistics, 230, 231t-232t pathway-level statistics, 230, 232 current challenges in, 233-236 inability to model and analyze dynamic response, 236 inability to model effects of external stimulus, 236 incomplete and inaccurate annotations, 233-234, 235f

low-resolution knowledge bases, 233, 234f missing condition- and cell-specific information, 234-236 weak interpathway links, 236 functional class scoring approaches, 227-228 assessing statistical significance of pathways, 232 correction for multiple hypotheses, 230t, 232 limitations, 228 overview, 227-228 tools for, 231t knowledge base-driven, 223-238 overrepresentation analysis (ORA), 224-227 assessing statistical significance of pathways, 232 correction for multiple hypotheses, 230t, 232 limitations of, 226-227 overview, 224-226, 225f tools for, 230t pathway-topology-based approaches, 228-229, 232t utility and confidence of, 236-237 Pathway-level statistics, 230, 232 Pathway models Bayesian networks, 245-259 Boolean networks, 242-244, 242f, 245 challenges in, 241 differential equation models, 257b-258b dynamic Bayesian networks, 244-245 modeling assumptions, 242 network inference, 241 robust, 244 Pathway-topology-based approaches, 228-229 Pattern Recognition and Machine Learning (Bishop), 79 PCA (principal component analysis), 78 PCR, quantitative (qPCR), 172-173 Peak finding, 174 Pearson, Karl, 29 Pearson correlation, 40-41, 42f, 114-115, 115f **PEMer**, 183 Peptide identification, by mass spectrometry (MS), 191-194 accurate mass and time tag (AMT) approach, 193 - 194database-driven approaches, 191-193 de novo sequencing, 194-195, 195t estimating false positives, 193 peptide modifications, 95 target-decoy approach, 193 Peptide modifications, mass spectrometry and, 95 Peptide quantitation, mass spectrometry and, 196-199 labeled, 197-198, 198f label-free, 196-197 selected reaction monitoring (SRM), 198-199, 198f Percentile, 22 Perfect-match probes, 112 Performance evaluation, 53-57, 55f, 56f Perfusion MRI, 89, 96-97 Perl programming language, 11 Permutation testing, 39, 141 Personalized medicine, 131

316 Index

Perturbation factor, 229 PET (positron emission tomography), 90 pFDR, 121 Pharmacogenetics, 131 Phenotypes association with genotypes (see Genome-wide association study) defined, 127-128 genotype-phenotype, 128-130, 128f Pindel, 183 Pixel bits per pixel (bpp), 85 defined, 84 pixelation, 85f volumetric, 91-92 PolyPhen, 150 Population mean, 22 Population stratification, 146-149, 148f Population variance, 23 Positive predictive value (PPV), 54, 56 Positron emission tomography (PET), 90 Posterior probability, 68, 162 Power, statistical, 127-128, 141-144 PPV (positive predictive value), 54, 56 Practical Flow Cytometry (Shapiro), 200 Precision, 27, 54, 55f Prediction across microarrays (PAM), 217 Pred probability, 159 Pred score, 159 Preprocessing raw text, 288–290, 288f–289f chunking and parsing, 288f-289f, 289-290 part of speech tagging, 288-289, 288f stemming, 290 stop word removal, 290 tokenization, 288, 288f Primer extension, 135 Principal component analysis (PCA), 78 Probabilistic Graphical Models: Principles and Techniques (Koller and Friedman), 80 Probabilistic modeling, defined, 72 Probabilistic models, 72-76, 73f, 241-242 Bayesian network, 73f, 74-76 hidden Markov models (HMM), 73f, 74-76, 298, 298t Probability Bayes' Rule, 20-21 conditional, 18, 20, 68 described, 17-21 emission, 75 expectation, 21 joint, 19-20 Monty Hall problem, 18 notation, 18 posterior, 68, 162 transition, 75 Probability distribution, 213b-214b Probes, for genotype calling, 135-136 Processors, 8, 8t, 9

Programming language choosing best suited, 15 described, 9, 11 effect on running time, 12 object-oriented, 11 Programs control flow in, 10 described, 9-11 for distributed systems, 9 ease of implementation, 15 executing, 8-9 functions and, 9 variables and, 10 Proof-of-principle, 2 Proportional hazard models, 42 Prostate cancer, meta-analysis of, 266, 268, 268f Protein identification, by mass spectrometry (MS), 195-196 false positives, 195-196 one peptide mapped to many proteins, 196 Proteins mass spectrometry (MS) of peptide identification, 191-194 peptide quantitation, 196-199 protein identification, 195-196 protein quantitation, 199 variations in, 188 Proteomics, 187-219 flow cytometry, 188-218 mass spectrometry (MS), 188-199 reasons for studying, 187 Proton, in MRI, 89 PubMed, 288 *p* value interpretation of, 27 multiple-testing correction, 35-36 significant, 25 t distribution and, 29 Pyrophosphates, 156 Pyrosequencing, 156 Python programming language, 9, 11, 15, 79

Q

QPALMA, 169, 170, 171t
qPCR (quantitative PCR), 172–173
qRT-PCR (quantitative real-time–polymerase chain reaction), 108
Quadratic algorithm, 13
Quality score, 159, 162–163, 162f
Quantile normalization, 113
Quantile-quantile (QQ) plot, 148, 148f
Quantitative PCR (qPCR), 172–173
Quantitative real-time–polymerase chain reaction (qRT-PCR), 108
QuEST, 178, 179f
Question, formulation of, 25–26
q value, 36–37

Index 317

R

Raf, 242f, 243-244, 246-252, 247f, 253b-254b Random forests algorithm, 298, 298t Random start, 251 Rank Product (RP) method, 122 Read length, 155-156, 156t Reads overlapping, 169 pairs of reads, 180 short-read mapping, 159-167 Recall, 54 Receiver operating characteristic curves (ROC), 56-57, 56f Recombination linkage disequilibrium and, 133 number per meiosis, 133 Reference panel, 143 Reference transcriptome, 168 Region finding, 174 Regression, example of, 63, 63f Regression task, 50, 57 Regression tree, 71 Regulation of actin cytoskeleton pathway, 235 Representation of differential gene expression data, 263-265, 264f, 278-279 Reproducibility, statistical hypothesis testing and, 25 Resampling methods bootstrapping, 38 jackknifing, 38-39 permutation testing, 39 Resolution, 84, 84f, 90 Reusability, in computer science, 11 RGB image, 85, 87f RMA (Robust Multiarray Analysis) model, 113-114 RNA-seq, 167-172 advantages, 167-168, 171-172 applications, 167-168 approaches to identifying transcript structure, 168-170, 168f with reference genome, 168-169, 168f without reference genome, 169-170 overview, 167-168 transcript quantification, 170-171, 171f Robust, 244 Robust Multiarray Analysis (RMA) model, 113-114 ROC (receiver operating characteristic curves), 56-57, 56f Root mean square error, 57 Root nodes, 246 **RPKM**, 170 RP (Rank Product) method, 122 R programming language, 9, 11, 113, 203, 261, 265 Bioconductor, 113, 265, 266 GEOquery, 266, 271-272 machine language algorithms, 79 programming exercise, 278-281 finding the data, 278

formulating a question, 278 integrating findings, 279 interpreting findings, 279 programming solution, 280 representation of differential gene expression, 278–279 Running time analysis of the algorithm, 12–13 RxNORM, 293, 294t

S

SAM (Significance Analysis of Microarrays), 120-122, 270, 270f, 277 SAM file format, 165-166 Sample mean, 21, 22 Samples, independent, 64 SAMtools, 166, 182 Sanger, Fred, 155 Sanger sequencing, 155 Scikit-learn, 79 Scoring, Bayesian, 249-250, 250b Search greedy random, 250 heuristic, 250 Seed, 160 Seeding, 160-161 Seed matches, 161 Segmentation. See Image segmentation Selected reaction monitoring (SRM), 198-199, 198f Self-organizing maps (SOMs), 120 Self-self hybridization, 110 Semisupervised clustering methods, 117-120, 119f Semisupervised learning, 51, 52f Sensitivity, 54-57, 55f, 56f, 244 Sequencers, DNA, 155 SEQUEST algorithm, 191-192, 192b Sex chromosomes, 126 Shifting, ChIP-seq reads, 174-175, 175f SHOGUN Machine Learning Toolbox, 79 Short Oligonucleotide Analysis Package (SOAP), 166, 166t Short-read mapping, 159-167 alignment programs, 166-167, 166t characteristics of short reads, 159-160, 160f indel alignment, 163-164 mapping output, 165-166 mapping quality/posterior probability, 162-163, 162f paired-end alignment, 164-165, 165f practical considerations, 166-167 quality score use in mapping, 163 repetitive reads, 161 scoring and filtering, 161-162 seeding, 160-161 SIFT (sorting intolerant from tolerant), 150 Signaling pathway, learning structure from flow cytometry data, 256

318 Index

Signal shifting, 174-175, 175f Significance error and, 35 experiment-wide level, 35 Significance Analysis of Microarrays (SAM), 120-122, 270, 270f, 277 Significant, 25 SILAC (stable isotope labeling by amino acids in cell culture), 198 Silhouette plot, 118-119, 119f Single-nucleotide polymorphisms (SNPs) in cluster plot, 136-137, 136f cost of SNP genotyping, 132 defined, 126 eye color and, 126, 127f genotype imputation, 142-143, 143f GWAS, 130-137, 134f, 144-146 interpreting genetic associations, 144-145 linkage disequilibrium and, 132-133, 134f number in human genome, 132 small effect sizes, 131 tag, 133 Skew, 22, 24, 24f Sliding window, 173-174 Smoothing, 173-174, 173f SNOMED-CT (systematized nomenclature of medical terminologies-clinical terms), 293, 294t SNP caller, 182 SNP genotyping, 180 SNPs. See Single-nucleotide polymorphisms SNVMix, 182 SOAP (Short Oligonucleotide Analysis Package), 166, 166t SOMs (self-organizing maps), 120 Space complexity analysis, 13-14 SPADE, 218 Spatial transformation, 100-101 Spearman rank correlation, 41, 42f, 114-115 Specificity, 54-57, 55f, 56f Spectral resolution, 206 Split-read alignment, 168-169, 168f Square errors criterion, 118 SRM (selected reaction monitoring), 198-199, 198f SSAHA2 (sequence search and alignment by hashing algorithm), 166t, 167 SSD (sum of squared differences), 101-102 Standard deviation, 23-24 State of the process, 75 Statistical analysis of data, 25-39 Statistical approaches to data interpretation, 120-122, 121t Statistical hypothesis testing, 25-28 multiple hypothesis testing, 34-36 steps in, 25-28 assumptions, 26 interpretation, 27-28

null hypothesis, 26 simple question, 25-26 summarizing data to test the statistic, 26-27 testing the hypothesis, 27 Statistically independent, 139 Statistical power of a study, 127-128 improving, 141-144 Statistical significance described, 130 of pathways, 232 Statistical tests on categorical data, 31-33 on continuous data, 28-30 Statistics bias, 23 descriptive, 21-24 of dispersion, 22 of location, 22 nonparametric, 30 odd ratios, 37b-38b q value, 36–37 resampling methods, 38-39 summary, 22 variance, 22-23 Stemming, 290 Stop word removal, 290 Storage constant-time, 14 linear time, 14 space complexity and, 13-14 Storey, J.D., 121 Structural MRI, 89 Student's t-test, 29 Study sample, 142 Subtractive color mixing, 85 Summary statistics, 22 Sum of squared differences (SSD), 101-102 Supervised learning, 50, 52-53, 52f Supervised learning algorithms, 67-72 decision tree, 71-72, 71f k-nearest neighbors, 67-68 linear classification, 69-70 naive Bayes, 68-69 partitioning, 71-72 regression tree, 71 Support vector machines (SVM) algorithm, 70, 298, 298t SVDetect, 183 Systematized nomenclature of medical terminologies-clinical terms (SNOMED-CT), 293, 294t

Т

Tag SNPs, 133 Target-decoy approach, 193 *t* distribution, 28–30, 28f, 30f Test error, 63–64, 63f

Index 319

Testing error, 58-59 Test of statistical independence, 139 Test set, 58-61, 59f Test statistic, 139-141 χ^2 , 32 described, 26-27 t, 28-30 in tests on continuous data, 28-30 Text. See Biomedical text 1000 Genomes Project, 142 Tibshirani, Robert, 79 Tokenization, 288, 288f TopHat, 169, 170-171, 171t Training error, 58-59, 63-64, 63f Training phase, of machine learning algorithm, 50 Training set, 58-61, 59f, 62-64 feature selection and, 66 multiple, 72 Trans-ABySS, 171, 171t Transcription factor, binding to promoter, 258, 258b Transformation, 100-101 affine, 101 nonrigid (elastic), 101 rigid, 100-101 Transformation of data, 207, 207f Transition probabilities, 75 tRMA method, 114 True negative, 54, 55f True positive, 53, 55f t statistic, 28-30 *t*-test, 29, 110, 120–122 Tukey method, 36 Two-color microarrays MA plots, 111, 111b one-color compared, 108 overview, 109-110 preprocessing and normalization, 110-111, 111f Type 1 error, 35, 120-121, 121t, 140

U

Type 2 error, 35

Unified medical language system (UMLS), 293, 294t-295t Unsupervised clustering methods, 115–117, 116f–117f Unsupervised learning algorithms, 76–78 dimensionality reduction, 78 hierarchical clustering, 77 *k*-means clustering, 77–78 Unsupervised learning tasks, 51, 52f, 53

V

Variability, measures of ANOVA, 30 F distribution, 30 interquartile range, 24 t statistic, 30 variance, 23 Variable described, 10 hidden, 254 sensitivity, 244 Variance bias and, 23 covariance, 40 described, 22-23 population, 23 sample, 23, 27 standard deviation, 23-24 VariationHunter, 183 Velvet, 171, 171t Visualization, 43-44, 44f Volex, 91-92 v-structure, 252-253

W

Water, heavy, 198 Web Ontology Language (OWL), 297 Weka (program), 79 Welcome Trust Case-Control Consortium (WTCCC), 131, 132 While-loops, 10 Wilcoxon rank-sum test, 30 *Wnt*/β-catenin pathway, 235 WordNet, 297

Х

X! Tandem, 192

Y

Yates, John, 191