Index

A
A-MAb case study 552, 553, 556, 564, 579
AAC see Anything And Chromatography
ABRF see Association of Biomolecular Research Facilities
accelerated stability testing 189
acetyl-CoA synthase (ACS) 515, 516
AcMNPV see Autographa californica mulinucleopolyhedrovirus
ACS see acetyl-CoA synthase
active pharmaceutical ingredients (API) 587, 601, 602, 803, 839
acyl transfer reactions 208, 209
ADA see antidrug antibodies
ADCC see antibody-dependent cellular cytotoxicity
adenine diphosphate/triphosphate (ADP/ATP) 536, 537, 621–623, 625
adenylyltransferase 536, 537
adherent HEK-293 cells 821, 822, 831
ADP/ATP see adenine diphosphate/triphosphate
adventitious agent tests 597
AF4 see asymmetric flow field-flow fractionation
affinity chromatography 225–282
– alternative ligands 229, 250, 251
– avidin and streptavidin 248, 249
– bacterial proteins 227, 228, 242–246
– benzhydroxamic acid 256, 257
– biological ligands 226–228, 239–251
– biomimetic ligands 251, 258–269
– biopharmaceutical applications 269–271
– boronate 228, 256
– chromatographic theory 230–232
– continuous countercurrent chromatography 776, 777, 781
– de novo affinity ligands 260–269
– dye-based ligands 228, 257, 258
– future perspectives 271, 272
– glutathione 248
– heparin 247, 248
– histidine 254, 255
– history and context 225, 226
– hydrophobic ligands 228, 253
– immobilized metals 228, 252, 253
– immunoaffinity adsorbents 239–242
– lectins 227, 246, 247
– matrix selection and ligand immobilization 232–237
– mixed-mode 229, 255, 256
– monoclonal antibodies 127–129
– nucleic acids 227, 228, 249, 250
– process design and management 667, 682
– protein purification 108
– purification pyramid 238
– role in the separation sciences 229, 230
– single-use technologies 798
– synthetic and designed ligands 228, 229, 240, 251–269
– theory and methods overview 230–239
– thiophilic ligands 228, 253, 254
– virus-like particles 152
– vitamins and hormones 227, 249
– see also hydroxyapatite chromatography affinity precipitation 229, 272
agarose-based matrices 233, 234, 236
aggregation
– continuous countercurrent chromatography 787
– efficiency of bioprocesses 632–638
– hydroxyapatite chromatography 284, 285, 317, 319, 320
– membrane chromatography 404–406
– monoliths 342

Index

– therapeutic proteins 165, 166, 173, 174, 180, 182, 183, 186, 192, 193
– virus-like particles 149, 150, 153, 154
– air–liquid interfaces 170, 171
– albumin 341
– Alzheimer’s disease 499, 508
– amine conjugation 204–206
– amino acids
  – affi nity chromatography 235–237
  – effi ciency of bioprocesses 643, 644
  – fed-batch processes 518–520, 535, 536
  – plasmid DNA 9, 19
  – proteomics 485, 493–495, 500, 501
  – therapeutic proteins 177
– ammonia production 626, 629–631
– amplifi cation systems 8, 9, 18, 19
– analytical ultracentrifugation (AUC) 155, 193
– animal-derived products 587, 589, 592–596
– antibiotics
  – biosensors 463, 465–467
  – hydroxyapatite chromatography 297–300, 313–321
  – membrane chromatography 390, 391, 403–406
  – monoliths 340–342
  – single-use technologies 820, 821
  – see also monoclonal antibodies
– antibody-dependent cellular cytotoxicity (ADCC) 546, 575, 576
– antidrug antibodies (ADA) 165, 173
– antigens
  – affi nity chromatography 249
  – plasmid DNA 6, 7
– antisense RNAs 8, 9, 11
– antitrypsin ligands 264
– Anything And Chromatography (AAC) concept 679–685
– AOX genes 55
– API see active pharmaceutical ingredients
– apparent cell growth 626
– aqueous two-phase systems (ATPS) 22, 23
– Arthrobacter spp. 98
– aseptic connections 801, 806, 824–833
– aseptic transfer systems 797, 798
– asparagine deamidation 171, 172
– aspartate isomerization 171, 172
– Aspergillus japonicus 361, 362
– A. niger 360
– Association of Biomolecular Research Facilities (ABRF) 479, 480
– asymmetric fl ow fi eld–fl ow fractionation (AF4) 193
– ATPS see aqueous two-phase systems
– AUC see analytical ultracentrifugation
– autoclaving 798, 800, 801, 824, 831
– Autographa californica
  – multinucleopolyhedrovirus (AcMNPV) 55, 56, 144
– autolysis 19, 20
– automation systems 806–809
– auto-oxidation reactions 172, 173
– auxotrophic markers 10–12
– avidin 248, 249

b

– β-methylnorleucine (β-MNL) 518
– B19 virus 608
– baby hamster kidney (BHK-21) 52
– Bacillus cereus 83, 84
– B. subtilis
  – cell disruption processes 88, 89
  – fed-batch processes 514–517, 522
  – hydroxyapatite chromatography 323
  – protein production technologies 49, 50
  – bacteria
  – affi nity chromatography 227, 228, 242–246, 268
  – cell disruption processes 82–84, 88, 89, 91, 95, 98, 99, 102, 103
  – fed-batch processes 514–518, 520, 522, 531–537
  – hydroxyapatite chromatography 322, 323
  – membrane chromatography 377–379
  – PEGylated proteins 205
  – plasmid DNA 3, 4
  – process design and management 666
  – protein production technologies 43, 44, 47–50, 63, 65, 66
  – single-use technologies 812–814
  – virus-like particles 139–141, 143, 146, 147
  – bacteriophages 352, 353, 358
  – baculovirus 346, 353
  – baculovirus–insect cell expression 43, 55–57, 144, 145
  – bags 755–757, 794–798, 809, 823, 824, 829
  – barrier properties 756, 757
  – baseline risk 590–599
  – batch processes
  – cell disruption processes 96
  – continuous chromatography 113, 114, 121–124, 126, 127, 130, 135
– continuous countercurrent chromatography 783, 789
– efficiency of bioprocesses 625, 626
– process design and management 672–679, 726, 727
– protein production technologies 63, 64
– see also fed-batch processes
batch-to-batch variability 235, 236
BDNF see brain-derived neurotrophic factor
bead milling 81, 95–98, 103
Beadle and Tatum’s one gene/one enzyme concept 490, 496, 497
benzhydroxamic acid 256, 257
1,6-benzyl elimination reactions 209, 210
BHK-21 see baby hamster kidney
Biacore biosensors 453, 457, 460–465
big 1-string facilities 669, 670
bind-and-elute mode 377, 379, 381, 390, 391
bioconversion of target molecules 360–362
bioinformatics 506
bio-layer interferometry (BLI) 453, 456–465, 467–470
biological ligands
– affinity chromatography 226–228, 239–251
– avidin and streptavidin 248, 249
– bacterial proteins 227, 228, 242–246
– glutathione 248
– heparin 247, 248
– immunoaffinity adsorbents 239–242
– lectins 227, 246, 247
– nucleic acids 227, 228, 249, 250
– vitamins and hormones 227, 249
biological state variables 641, 642
biomarkers 479, 503–505, 507
biomimetic ligands 251, 258–269
biomineralization 295, 296
bioreactors
– plastics 748, 757–763
– single-use technologies 821, 824–835, 848–850, 854–856
biosafety levels 848
biosensors 447–471
– bio-layer interferometry 453, 456–465, 467–470
– biopharmaceutical production and processing 464–469
– characterization of biopharmaceuticals 466–468
– commercial applications 448–464
– comparison of biosensor chips 458–464
– context 447, 448
– current technologies 451–453
– kinetic analysis 466–468
– labeled versus label-free 449–455, 464–467
– monoliths 360
– principles 448, 449
– purification on chromatography columns 465, 466
– quantification of therapeutics and minor impurities 464, 465
– resonant waveguide grating 452–455, 458–464
– sample handling 455–458
– surface plasmon resonance 452–458, 460–465, 467–470
– throughput comparison 462–464
– vaccine design and efficacy 468, 469
bioseparations 112, 113
BioSMB™ technology 780, 781, 786–789
biotin–streptavidin 248, 249, 383
BL21 strain (E. coli) 48
BLI see bio-layer interferometry
Bodenstein numbers 527–529
boronate affinity chromatography 228, 256
bovine serum albumin (BSA)
– affinity chromatography 226
– membrane chromatography 387
– PEGylated proteins 199, 204, 215
bovine viruses 593–596
brain-derived neurotrophic factor (BDNF) 507
breakthrough curves 384–386, 415, 421, 422
Brevundimonas diminuta 812
brute-force optimization 726, 727
BSA see bovine serum albumin
bubble plots 725, 735, 736

\textbf{C}
Cache valley virus (CVV) 599
camid antibodies 241, 242
cAMP see cyclic adenosine monophosphate
Campylobacter jejuni 47
capacity planning 719, 731–735
capillary zone electrophoresis (CZE) 191, 192
capsomeres 141, 142, 152–154
capsule filter devices 800, 801, 824–833
capture agents 459
capture, intermediate purification, and polishing (CIPP)
– affinity chromatography 230
– continuous countercurrent chromatography 772, 778, 781, 785, 786
– hydroxyapatite chromatography 302, 303
– process design and management 665
capture and polish from supernatant 127–129, 131
carbohydrate oxidation 208
carbon catabolite proteins (Ccp) 517
carbon microspheres 333
carrousel chromatography systems 773, 774, 786, 787
casein 59
CAT see chloramphenicol acetyl transferase
cation-exchange chromatography see ion-exchange chromatography
CBA see Critical Business Attributes
Ccp see carbon catabolite proteins
CD see circular dichroism
CDC activity 562, 563, 566–568, 575, 576
CDMO see contract development and manufacturing organizations
CDS see centrifugal disk sedimentation
CECF see continuous exchange cell-free reactor
cell banks 6, 586, 587, 835, 837
cell-based bioassays 190, 191
cell–cell adhesion 632–638
cell compression 86–89
cell culture
– microenvironments 617, 618, 650
– plastics 747, 748
– single-use technologies 821, 824–827
– see also bioreactors
cell disruption processes 81–105
– bead milling 81, 95–98, 103
– cell mechanical strength 85–89
– cell structure and disruption strategies 83–85
– cellular debris 100–103
– chemical/enzymatic techniques 82–84, 98–100, 103
– context 81–83
– high-pressure homogenization 81, 89–95, 102, 103
– mechanical techniques 81–98, 102, 103
– mechanisms 90, 91
– modeling 88, 91–98, 102, 103
cell-free assembly 140–142, 147, 157, 158
– plasmid DNA 6, 19, 20
– protein production technologies 64
– cellular debris 100–103
– cellulose 748, 751
– protein production technologies 64
– protein production technologies 64
cell-free protein production 44, 62–65
cell lysis
– efficiency of bioprocesses 634
cellulose-based matrices
– affinity chromatography 233, 234, 236
– membrane chromatography 380–382
centrifugal disk sedimentation (CDS) 101, 102
centromeric plasmid (YCP) vectors 54, 55
ceramic hydroxyapatite spheres 286–289, 314–319
cerebrospinal fluid 499
cetuximab 126
CFCF see continuous mode cell-free reactor
CFD see computational fluid dynamics
chaotropes 168, 169
charge variant separation 125–127
chelating agents
– affinity chromatography 252, 253
– hydroxyapatite chromatography 285, 287, 288, 296, 297, 311, 312, 319
– therapeutic proteins 178
cell-free assembly 140–142, 147, 157, 158
– plasmid DNA 6, 19, 20
– protein production technologies 64
– cellular debris 100–103
– cellulose 748, 751
– affinity chromatography 233, 234, 236
– membrane chromatography 380–382
centrifugal disk sedimentation (CDS) 101, 102
centromeric plasmid (YCP) vectors 54, 55
ceramic hydroxyapatite spheres 286–289, 314–319
cerebrospinal fluid 499
cetuximab 126
CFCF see continuous mode cell-free reactor
CFD see computational fluid dynamics
chaotropes 168, 169
charge variant separation 125–127
chelating agents
– affinity chromatography 252, 253
– hydroxyapatite chromatography 285, 287, 288, 296, 297, 311, 312, 319
– therapeutic proteins 178
– continuous countercurrent chromatography 776
– glycosylation 549
– monoliths 341, 358
– plastics 759, 761–763
– process design and management 659, 660
– risk management 601, 603, 604
– virus-like particles 145, 146
– Chinese hamster ovary (CHO) cell lines
– continuous countercurrent chromatography 776
– glycosylation 549
– monoliths 341, 358
– plastics 759, 761–763
– process design and management 659, 660
– risk management 601, 603, 604
– virus-like particles 145, 146
– plasmid DNA 23–26
– plastics 760, 761, 764, 765
– process design and management 664, 665, 667, 677–689, 692–694, 725–728, 735, 736
– protein production technologies 59
– purification pyramid 238
– single-use technologies 798, 799, 804, 834, 839–844
– therapeutic proteins 191–193
– virus-like particles 150–152
– see also individual techniques and materials
– chromosomal DNA 17–21, 302, 322, 323

Chinese hamster ovary (CHO) cell lines
– continuous countercurrent chromatography 776
– glycosylation 549
– monoliths 341, 358
– plastics 759, 761–763
– process design and management 659, 660
– risk management 601, 603, 604
– virus-like particles 145, 146
– plasmid DNA 23–26
– plastics 760, 761, 764, 765
– process design and management 664, 665, 667, 677–689, 692–694, 725–728, 735, 736
– protein production technologies 59
– purification pyramid 238
– single-use technologies 798, 799, 804, 834, 839–844
– therapeutic proteins 191–193
– virus-like particles 150–152
– see also individual techniques and materials
– chromosomal DNA 17–21, 302, 322, 323
CI see confidence intervals
CIM see convective interaction media
CIP see cleaning-in-place
CIPP see capture, intermediate purification, and polishing
circular dichroism (CD) 187, 194
CLC see conjoint liquid chromatography
click chemistry 209
clinical trials 605, 606, 728–730
closed loop bioprocess control 614, 615, 648, 649, 651, 652
CMO see contract manufacturing organizations
CMV see cytomegalovirus codon use 7
COG see cost of goods
Committee for Proprietary Medicinal Products (CPMP) 602–606
comparability 545–583
component transfer 797, 798
ccomputational fluid dynamics (CFD) – cell disruption processes 93–95 – fed-batch processes 514, 515, 521
cconcanavalin A 246, 247
cconfidence intervals (CI) 427–430, 432, 433
conjoint liquid chromatography (CLC) 340, 341
connectors 801, 806, 822–829
cconsensus immunogens 7
ccontainers and closures 179
ccontamination events 585, 586, 589
– four-column MCSGP with separate CIP position 116–118
– four-column MCSGP with separate continuous feed position 118, 119
– generic purification problem 114
– limitations of SMB 112
– monoclonal antibodies 107, 111, 125–129
– multicolumn countercurrent solvent gradient purification 107, 109, 112–135
– polypeptide purification 120–125
– principles of MCSGP 113–120
– protein purification 107–137
– purification overview 108
– separations with more than three fractions 119, 120
– simulated moving bed process 109–113
– six-column MCSGP principle 114
– size-exclusion chromatography 129–133
– three-column MCSGP principle 114, 115
continuous countercurrent chromatography 769–791
– affinity chromatography 776, 777, 781
– aggregation 787
– biopharmaceutical industries 776–781
– BioSMB™ technology 780, 781, 786–789
– capture chromatography 772, 778, 781, 785, 786
– case studies 786–789
– evolution of process technology 769–773
– fractionation chromatography 774, 775, 783, 784
– hydrophobic interaction chromatography 781, 787
– industrial applications 774–776
– industry drivers 776–778
– ion-exchange chromatography 769–773, 775, 776, 781
– key challenges 779, 780
– mass transfer kinetics 782, 783
– multicolumn systems 772–774, 779–781, 786, 787, 789
– performance prediction 783
– polishing processes 778
– prepacked columns 780, 781
– process design and management 779–786
– protein A chromatography 786, 787
– simulated moving bed process 770–775, 778–781, 784, 786–789
– single-use technologies 777, 778, 780, 786, 789
– size-exclusion chromatography 782, 784, 788, 789
Critical Quality Attributes (CQA)
- efficiency of bioprocesses 615, 616, 626, 646
- glycosylation 551–553, 556, 557, 563–571
- integrated process design 707–709
cross-competition analysis 463
cross-contamination
- biosensors 456, 469
- membrane chromatography 389, 392
- plastics 745, 746
- process design and management 679
cross-flow ultrafiltration 798, 800, 804
cross-interactions 433, 434, 437
cross-linking 234, 235–237, 380, 381
cryogels 334
cryogenics 755
crystallization processes 684, 685
CS see Control Space
CSA see cumulative sedimentation analysis
CSTR see continuous stirred tank reactors
cultivation devices 757–763
cultivation media 6, 16–19
cumulative sedimentation analysis (CSA) 102
CVV see Cache valley virus
cyclic adenosine monophosphate (cAMP) 516
cysteine conjugation 206, 207
cytochrome c 390, 391
cytomegalovirus (CMV) promoters 10
cytoplasmic inclusion bodies 99, 100
CZE see capillary zone electrophoresis

d
Damköhler numbers 527–530
DAPI see 4′,6-diamidino-2-phenylindole
Darwin’s theory of evolution 490
data acquisition 808
data visualization 721, 722
DCS see distributed control systems
de novo affinity ligands 260–269
decision-support tools 719–723, 739
Define–Measure–Analyze–Design–Verify (DMADV) 428, 429
Define–Measure–Analyze–Improve–Control (DMAIC) method 428
density gradient methods
- membrane chromatography 395–397
- ultracentrifugation 351
deoR genes 14
deoxyribonucleic acid see DNA
Design of Experiments (DoE) 411, 428, 440
- glycosylation 551–553, 579
- process design and management 690, 691
Design Space (DS)
   – glycosylation 547, 551–580
   – integrated process design 707–715
   – risk management 585
deterministic analysis 721, 722
development costs 392
DH5α strain (E. coli) 14–16
DHFR see dihydrofolate reductase
diafiltration 798, 800, 804
4′,6-diamidino-2-phenylindole (DAPI) staining 632, 633, 636
differential gel electrophoresis (DiGE) 482
differential scanning calorimetry (DSC)
   – biosensors 450
   – therapeutic proteins 166, 167, 177, 185–187
differential scanning fluorimetry 187
differentiation of multicellular organisms 501, 502
DiGE see differential gel electrophoresis
dihydrofolate reductase (DHFR) 50
Dip and Read format 455, 457, 459–461, 470
diseasome concept 503, 504
displacement chromatography 309–313
disposables see single-use technologies
dissolved oxygen (DO)
   – efficiency of bioprocesses 627
   – scale-up 514, 522–525, 529–532
distributed control systems (DCS) 806
disulfide bridges
   – affinity chromatography 236, 237
   – PEGylated proteins 206, 207
DLS see dynamic light scattering
DMADV see Define–Measure–Analyze–Design–Verify
DMAIC see Define–Measure–Analyze–Improve–Control
DNA aptamers 227, 228, 249, 250
DNA delivery 817
DNA removal
   – membrane chromatography 398, 404
   – monoliths 357, 358, 361
   – process design and management 659
   – single-use technologies 798
DNA sequencing 491–493, 632, 633, 641
DNA structure 490, 491
DNA vaccines 3–41
DO see dissolved oxygen
DoE see Design of Experiment
domain ontology model (DOM) 557, 577, 578
drug development 507
drug discovery 506, 507
drying 170
DS see Design Space
DSC see differential scanning calorimetry
dye-based affinity ligands 228, 257, 258
dynamic binding capacity
   – biosensors 466
   – membrane chromatography 384–386
   – monoliths 335, 351, 352, 354–358
   – Quality by Design 415, 422
dynamic light scattering (DLS) 101, 154, 155
dynamic object-oriented quality concept 614, 615
eEBC see expanded-bed chromatography
economic factors
   – continuous chromatography 106, 134, 135
   – continuous countercurrent chromatography 787
   – optimization and comparability 545–547, 576
   – plastics 746
   – proteomics 477, 478
   – Quality by Design 428, 429
   – single-use technologies 800, 801, 821, 838, 842, 843, 848–854, 856, 857
economical modeling 391–393
ECP see elution at characteristic point
Edman degradation 497, 498
EDTA see ethylenediamine tetraacetic acid
efficiency of bioprocesses 613–656
   – biological demands 617–626
   – byproducts of metabolism 624, 626, 629–631
   – cell culture microenvironments 617, 618
   – cell–cell adhesion and aggregation 632–638
   – context 613, 614
   – data analysis 644–645
   – engineering meets biology 616, 617
   – extended growth model 635–638
   – glycosylation 626–632
   – knowledge-based process understanding 646
   – nutrient metabolism 618–626
– PAT and QbD compliant bioprocesses 613–616, 626, 638–653
– primary data acquisition 640–644
– process understanding and control 639–649
– proof-of-concept 647, 648
– speed and quality in bioprocess development 649–652
– technical and engineering solutions 638–652
electrical sensing zone 101
electron microscopy 101, 598
electrospray differential mobility analysis (ES-DMA) 156, 157
electrospray ionization (EPI) 500
ELISA see enzyme-linked immunosorbent assays
elution at characteristic point (ECP) method 415, 416
elution chromatography 305–309
end of production (EOP) cells 602–604
end-product filling 802
endA mutations 12, 15–17
denatured retroviruses 597–599
endotoxins see lipopolysaccharide
enhanced QbD 554–580
enterprise resource planning (ERP) 806
enveloped viruses 600, 601, 605
environmental factors 753–755
enzymatic cell disruption processes 82–84, 98–100
enzyme inhibition 363, 364
enzyme-intrinsic properties 362–364
enzyme-linked immunosorbent assays (ELISA)
– biosensors 449, 464, 466, 467, 469
– monoliths 339
– enzyme reactors 358–364
– enzymes 227
EOP see end of production
EPI see electrospray ionization
Epic biosensors 458–464
epidemiology 592–596
epigeneons 489
episomal plasmid (YEP) vectors 54, 55
EPO see erythropoietin
epoxy membranes 383
equipment qualification 809–811
ERP see enterprise resource planning
erythropoietin (EPO)
– glycosylation 567
– therapeutic proteins 165, 167, 168, 173, 188, 190, 191
ES-DMA see electrospray differential mobility analysis
Escherichia coli
– affinity chromatography 252, 253, 268
– cell disruption processes 82–84, 91, 95, 99, 102, 103
– fed-batch processes 515–518, 520, 522, 531–537
– hydroxyapatite chromatography 322
– monoliths 340, 352
– PEGylated proteins 205
– plasmid DNA 3–41
– process design and management 666, 695, 696
– protein production technologies 43, 44, 47–50, 63, 65, 66
– virus-like particles 139, 140, 143, 146, 147, 152
ethylene vinyl acetate (EVA) 748, 749, 751, 756
ethylene vinyl alcohol (EVOH) 756
ethylenediamine tetraacetic acid (EDTA) 178, 296, 312, 319
EVA see ethylene vinyl acetate
EVOH see ethylene vinyl alcohol
evolution by natural selection 490
excipients see formulation processes
expanded-bed chromatography (EBC) 679–681
experimental model parameter determination 414–425
– fluid dynamics 416–418
– isocratic pulses 415, 416, 419, 420
– isotherm parameters 414, 416, 419, 426, 427
– mass transfer kinetics 417–425
– robustness analysis 426–431, 437–439
extended growth model 634–638
extractables 753–755
extraction processes 6, 19, 20
f
facility design
– robustness and uncertainty 719, 725–737
– single-use technologies 842–849
facility-fit issues 737
Factory Acceptance Test (FAT) 809, 834
failure mode and effects analysis (FMEA) 552, 553, 563, 564
FAT see Factory Acceptance Test
fat globule dispersion 90
fed-batch processes
– amino acid synthesis 518–520
– E. coli cultivations in two-compartment reactors 531–537
– future perspectives 537, 538
– hydrodynamic conditions 526–529
– main carbon metabolism 515–518
– oxygen transfer processes 529–531
– performance characteristics 532–535
– plasmid DNA 17–19
– process design and management 723, 725
– protein production technologies 52, 53
– quality control 513–538
– scale-down reactors 520–523
– scale-up consistency 513–538
– single-use technologies 836–840
– substrate concentration 513–515
– two-compartment reactors 521–538
FEM see finite-element models
FFF see field-flow fractionation
FIA see flow injection analysis
fibril formation 173, 174
field-flow fractionation (FFF) 155, 156
filling applications 802, 810
film diffusion 417, 423–425
filtration techniques
– plasmid DNA 22
– single-use technologies 800, 801, 812–815, 824–833
– see also ultrafiltration membranes
finite-element models (FEM) 88
fixed costs 667–678
flasks 757
FlexFactory™ 837–839
flow injection analysis (FIA) 360
flow-through chromatography see negative chromatography
flow-unaffected resolution 335, 336
fluid dynamics 416–418
fluidized-bed adsorption 681
fluorescence-based biosensors 450
fluorescent product enhanced reverse transcriptase (FPERT) 598, 599
FMEA see failure mode and effects analysis
formulation processes
– amino acids and organic buffers 177
– chelating agents 178
– containers and closures 179
– freeze-drying 180–185
– freezing 179, 180
– liquid formulations 175, 176, 181, 182
– PEGylated proteins 204
– pH effects 176
– plasmid DNA 7, 26–28
– redox potential 179
– salts 177, 178
– specific binding sites 178
– sugars and polyols 177, 180–185
– surfactants 178
– therapeutic proteins 165, 166, 175–185
four-column MCSGP principle 116–119
four-zone SMB systems 784
Fourier transform infrared (FTIR) spectroscopy 170, 194, 754
FPERT see fluorescent product enhanced reverse transcriptase
fractionation chromatography 774, 775, 783, 784
freeze-drying 180–185
freezing 166, 169, 170, 179, 180
fructose-1,6-phosphate 622, 623
FTIR see Fourier transform infrared fungi
– cell disruption processes 95
– fed-batch processes 522
– monoliths 339, 340, 360
– see also yeasts
future-proofing 715
gamma-irradiation 601, 602, 798, 800, 801, 810, 824
G-CSF see granulocyte colony-stimulating factor
GAL see galactose-regulated genes
galactose 632
galactose-regulated genes (GAL) 54, 55
GAM see glycoform activity modeling
Gardasil 148, 149
gas chromatography–mass spectrometry (GC-MS) 754
GDH see glutamic acid dehydrogenase
gel electrophoresis 475
gel filtration/size-exclusion chromatography 24
gene silencing 61
gene therapy vectors 588
genetic algorithms 723
genomic DNA
– hydroxyapatite chromatography 307, 322
– monoliths 355–357, 361, 362
genomics 489, 491–493, 505–507
glass transition temperatures 182, 183
glucosamine 632
glucose oxidase (GOX) 360
Index

glucose-6-phosphate 623

glutamic acid dehydrogenase (GDH) 535, 536

glutamic acid synthase (GOGAT) 535, 536

glutamine 535, 536, 618–626

glutamine synthase (GS) 50, 535, 536

glutathione 248

glutathione peroxidase 248

glutathione S-transferase (GST) 248, 401, 465

glycerol cultivation media 17, 18

glycogen (GAM) 573–580

glycolysis 618–626

glycoprofiling systems 571–573

glycoprotein-binding ligands 264

glycoproteins 208, 227, 228

glycosylation

- A-MAb case study 552, 553, 556, 563, 579

- affinity chromatography 266
- biosensors 447, 448
- cost analysis 545–547
- domain ontology model 557, 577, 578
- efficiency of bioprocesses 626–632
- enhanced QbD 554–580
- glycoform activity modeling 573–580
- homogenous human-like glycoproteins 45–47
- Impact Maps 568–571, 575, 578
- informatics tools 554, 555, 557–561
- monoclonal antibodies 546, 552, 553
- Myozyme scale-up 548, 549
- Ontology Map 557–561, 564–568, 573–575
- optimization and comparability 545–583
- plant molecular farming 60
- population model 555, 556, 561
- proteomics 476, 505
- QbD DS approach to comparability 546, 547, 551–580
- quality control 545–583
- scale-up processes 548–551
- SE Board 562–580
- traditional approach to comparability 547–551
- tuned glycoprofiling systems 571–573
- yeast protein production 54, 55

GMP see Good Manufacturing Practice

GOX see glucose oxidase

gradient experiments 416, 422, 423, 426

granulocyte colony-stimulating factor (G-CSF) 629, 631

graph theory and ontology (GTO) tools

GS see glutamine synthase

GST see glutathione S-transferase

GTO see graph theory and ontology

guanosine tetraphosphate (ppGpp) 516

GyrA mutations 15

H

HAC see hydroxyapatite chromatography

HAR see human accelerated regions

HCIC see hydrophobic charge induction chromatography

HCP see host cell proteins

HDPE see high-density polyethylene

heat lysis 19, 20

HEK-293 see human embryonic kidney

hemacytometry 632, 633, 636

hemagglutination inhibition (HI) test 469

Henderson–Hasselbalch equation 630, 631

Henry coefficients 414, 415, 419–422, 430, 431

heparin 247, 248, 383

hepatitis B vaccines 139–141, 145–147

hepatitis viruses 818, 820

HEPES buffer 297, 298

HI see hemagglutination inhibition

HIC see hydrophobic interaction chromatography

high-density polyethylene (HDPE) 747, 755, 756

high internal phase emulsions (HIPE) 333, 334, 337

high-performance affinity chromatography (HPAC) 226, 234

high-performance liquid chromatography (HPLC)

- biosensors 464, 466

- efficiency of bioprocesses 641

- monoliths 339–346

- process design and management 692–694

- plastics 745, 746, 754, 764

- risk management 585, 601

- single-use technologies 803, 808, 810, 839, 849, 850

- virus-like particles 145, 151

Gorrod’s view of inborn errors of metabolism 496, 505

GMP see Good Manufacturing Practice

- integrated process design 714

- membrane chromatography 401

- monoliths 338, 354, 355

- single-use technologies 803, 808, 810, 839, 849, 850

- virus-like particles 145, 151
index

– Quality by Design 412, 413, 416, 417
– therapeutic proteins 191, 192
- high-pressure homogenization 81, 89–95, 102, 103
- high-throughput (HTP) bioprocesses 482, 650–652
- high-throughput screening (HTS) 384
- HIPE see high internal phase emulsions histidine 254, 255
- histidine-tagged proteins 383
- hok genes 11
- hollow fiber bioreactors 748
- homogenization 81, 89–95, 102, 103
- homogenous diffusion model 782
- homogenous human-like glycoproteins 45–47
- hormones 227, 249
- horseradish peroxidase (HRP) 256, 257
- host cell proteins (HCP)
  - continuous chromatography 128, 129
  - membrane chromatography 379, 398, 402, 403, 407
  - process design and management 659
  - single-use technologies 798, 803
- host strains 6, 11–16
- HPAC see high-performance affinity chromatography
- HPLC see high-performance liquid chromatography
- HPV see human papillomavirus
- HRP see horseradish peroxidase
- HSA see human serum albumin
- HTP see high-throughput
- HTS see high-throughput screening
- human accelerated regions (HAR) 492, 493
- human cell-based therapies 588, 600
- human embryonic kidney (HEK-293) 52, 822–824, 833
- human genome 492, 493
- human insulin 695–697
- human papillomavirus (HPV) 140, 147–152
- Human Proteome Organization (HUPO) 479, 480
- human serum albumin (HSA) 174, 178
- HUPO see Human Proteome Organization
- hybrid technologies 805
- hybridization chromatography 250
- hydrodynamic conditions 526–529
- hydrogen bonding 174
- hydrophobic affinity chromatography 228, 253
- hydrophobic interaction chromatography (HIC)
  - affinity chromatography 253, 254
  - continuous chromatography 108
  - continuous countercurrent chromatography 781, 787
  - membrane chromatography 405, 406
  - PEGylated proteins 212, 213, 217
  - plasmid DNA 24
  - process design and management 682, 685–689
- Quality by Design 414, 437
- hydroxyapatite chromatography (HAC) 255, 256, 283–331
- advantages and disadvantages 303
- aggregation 284, 285, 317, 319, 320
- applications 313–323
- context 283–285
- displacement mode 309–313
- elution mode 305–309
- materials and interaction mechanisms 285–301
- NaCl/phosphate gradient protocol 306, 307
- plasmid DNA protocol 307–309
- plasmid DNA protocol 305, 306
- retention mechanisms 294–301
- set-up 301–312
- stationary phase properties 288
- structure–function relationships 289–294
- virus-like particles 150, 151

ICH see International Conference on Harmonization

IDA see iminodiacetic acid

IGF see insulin-like growth factor

IMAC see immobilized metal affinity chromatography

iminodiacetic acid (IDA) 297, 383

immobilization chemistry 234, 235

immobilized metal affinity chromatography (IMAC) 228, 252, 253

membrane chromatography 383

plasmid DNA 24

immunoaffinity adsorbents 239–242

immunogenicity

plasmid DNA 7

therapeutic proteins 165, 166

immunoglobulins see antibodies

immunoprecipitation, proteomics 483

IMP see investigational medicinal products

Impact Maps 568–571, 575, 578
in silico process design 661, 662
in vitro adventitious agent tests 597
in vitro assembly/disassembly 141, 142, 152–154, 157, 158
in vitro binding assays 190, 191
in vivo adventitious agent tests 597
in vivo assembly 140–142, 147, 157, 158
inborn errors of metabolism 496, 505
inclusion bodies 99, 100
infectivity tests 597, 598
influenza viruses
– membrane chromatography 396, 397
– monoliths 347, 348, 353
– single-use technologies 845–848
– virus-like particles 145, 152
inheritance 490
inner particle diffusion 417, 423–425
inorganic monoliths 333
inorganic nanoparticles 28
insect cell lines 144, 145
insect glycoproteins 46, 55–57
insoluble protein inclusion bodies 99, 100
Installation Qualification (IQ) 809, 810, 814, 815, 834
insulin
– continuous chromatography 107
– process design and management 695–697
insulin-binding ligands 264
insulin-like growth factor (IGF)-1 99, 100
integrated process design 707–715
– Critical Quality Attributes 708–711
– knowledge spaces 710, 711, 713–715
– Process Control Strategies 710, 711, 713, 714
– Quality Target Product Profile 712, 713
– Target Product Profile 708, 709, 711
integrating plasmid (YIP) vectors 54, 55
interactomics 489, 501–503
interferons 205
International Conference on Harmonization (ICH)
– integrated process design 707–715
– risk management 585, 602–605
– therapeutic proteins 188, 195
– see also Quality by Design
intrinsic factors 9–11
intrinsic fluorescence spectroscopy 187
investigational medicinal products (IMP) 602–606
ion-exchange chromatography
– continuous countercurrent chromatography 769–773, 775, 776, 781
– hydroxyapatite chromatography 284, 285, 294, 295, 301, 311
– membrane chromatography 379, 400
– monoclonal antibodies 126, 131
– monoliths 342–346, 351, 355, 358
– PEGylated proteins 203, 204, 211, 212, 215–217
– plasmid DNA 23, 24
– polypeptide purification 121
– process design and management 681, 682, 685–689
– protein purification 108
– Quality by Design 414
– single-use technologies 834
– therapeutic proteins 191, 192
– virus-like particles 152
ion-trap mechanism 630, 631
IQ see Installation Qualification
isobaric labeling 485, 486
isocratic pulses 415, 416, 419, 420
isoelectric point 475
isoenzyme composition 339, 340
isotherm parameters 414, 416, 419, 426, 427
isothermal titration calorimetry (ITC)
– biosensors 450, 468
– therapeutic proteins 166
j
jet machines 90
k
K-12 strains (E. coli) 4–6, 11, 48
Kaizen exercises 850, 851
kallikrein ligand 264
KC see Kozeny–Carman
key performance indicators (KPI) 854
kinetic analysis 466–468
knowledge spaces 710, 711, 713–715
knowledge-based process understanding 646
Kozeny–Carman (KC) equation 336
KPI see key performance indicators
l
label-free biosensors 449–455, 464, 467
labeled biosensors 449, 450
lactate dehydrogenase (LDH) 634–638
lactate production 624, 626, 629
large decision spaces 720, 721, 731–736
LDH see lactate dehydrogenase
LDPE see low-density polyethylene
leachables 174, 175, 753–755
least-square errors 416
lectins 227, 246, 247
legacy purification facilities 725–728
Leishmania tarentolae 64
lentiviruses 353
Lepidoptera spp. 144
ligand density 234
ligand immobilization 232–237
lignin peroxidase isoforms 339, 340, 363, 364
linear driving force model 782
lipopolysaccharide (LPS)
– affinity chromatography 270
– cell disruption processes 83, 98
– hydroxyapatite chromatography 302, 307
– membrane chromatography 399–401
– monoliths 358
– protein production technologies 49
– single-use technologies 798
liquid formulations 175, 176, 181, 182
liquid hold bags 794, 795
liquid–liquid extraction 682–684
live virus vaccines 588
low-density polyethylene (LDPE) 756
low-molecular weight contaminants 210–212
LPS see lipopolysaccharide
Ludger tools 554, 555, 578
lyophilization
– PEGylated proteins 204
– therapeutic proteins 166, 170, 175, 181, 182, 184
lysozyme clarification 7, 21–23
lysozyme 296, 301, 380, 381
mAb see monoclonal antibodies
MALDI-TOF see matrix-assisted laser
desorption ionization time-of-flight
mammalian cell lines 145, 146
mammalian glycoproteins 45, 50–53
manifolds 801, 823–833
mannitol 180–185
mannose glycosylation 46, 47
manufacturing costs 392
manufacturing executions systems (MES) 806, 809
market demands 745–747
marketing authorization 605, 606
mass loss index (MLI) 695, 696
mass spectrometry (MS)
– proteomics 482–486, 499–501
– therapeutic proteins 192
mass transfer kinetics 413, 417–425, 782, 783
master cell banks (MCB) 588
matrix selection 232–237
matrix-assisted laser desorption ionization
time-of-flight (MALDI-TOF) 483, 484, 500, 501
MCB see master cell banks
MCSGP see multicolumn countercurrent solvent gradient purification
Measurement Maps 571–573
mechanical cell disruption processes 81–98, 102, 103
medium dispensing 827–829
membrane chromatography 24, 25, 377–408
– aggregation 404–406
– applications 392–406
– bind-and-elute mode 377, 379, 381, 390, 391
– construction of absorbers 380–382
– DNA removal 398, 404
– economical modeling 391–393
– host cell proteins 379, 398, 402, 403, 407
– ligand types 382, 383
– lipopolysaccharide removal 399–401
– negative chromatography 379, 381, 389, 390
– plastics 761
– process design and management 681, 682
– resin-based chromatography comparisons 387–396, 398–407
– scaling-up with membrane adsorbers 384–387
– single-use technologies 798, 799, 804, 841, 842
– technical specifications of absorbers 377–387
– validation of membranes into purification process 392–395
– virus purification and vaccine manufacture 395, 396
– virus removal 396–398
membrane technologies
– biosensors 758, 759
– PEGylated proteins 203, 210–212, 214, 216
– single-use technologies 822–832
– virus-like particles 150
Mendel’s principles of inheritance 490
MES see manufacturing executions systems
metabolism 618–626
metabolomics 489, 505, 506
metal chelate adsorbers 383
metathesis polymerization 333
methacrylate monoliths 333, 334, 338–351, 355, 356, 361, 362
methionine sulfoximine (MSX) 50, 51
methotrexate (MTX) 50, 51
methylation 489
Michaelis–Menten equation 362, 363
microfluidics-based biosensors 455, 457, 462, 464
micromanipulation 93–95
microRNA 492
MIP see molecularly imprinted polymers
mixed-integer nonlinear programming 723
mixed-mode affinity chromatography 229, 255, 256
mixing operations 795–797, 814, 825–829
MLI see mass loss index
MMV see mouse minute virus
model error 425, 426
model parameter determination see experimental model parameter determination
modular manufacturing environments 842–849
molecularly imprinted polymers (MIP) 229, 239–242, 250, 251
monitoring systems 808
monoclonal antibodies (mAb)
– affinity chromatography 227, 230, 269–271
– biosensors 447
– capture and polish from supernatant 127–129, 131
– charge variant separation 125–127
– continuous chromatography 107, 111, 125–129
– continuous countercurrent chromatography 776, 786, 787
– glycosylation 546, 552, 553, 556, 578
– hydroxyapatite chromatography 303, 304, 313–321
– membrane chromatography 377–379, 388, 389, 396–399
– monoliths 341, 342, 350
– plastics 763, 764
– single-use technologies 819, 820, 836–840, 845–850
monolayer film structures 756
monoliths 333–375
– affinity chromatography 229, 251
– antibodies 340–342
– bioconversion of target molecules 360–362
– biosensors 360
– context 333
– downstream applications 340–348
– enzyme reactors 358–364
– enzyme-intrinsic properties 362–364
– hydroxyapatite chromatography 323
– negative chromatography 357, 358
– PEGylated proteins 342–344
– plasmid DNA 354–357
– preparative chromatography 348–358
– process analytical technology applications 338–348
– properties and characteristics 333–338
– protein purification 349–350
– proteome analysis 358–360
– upstream applications 339, 340
– viruses and VLPs 344–348, 351–353, 357, 358
mono-product facilities 669, 671
monosulfone activation 206, 207
Monte-Carlo simulations
– Quality by Design 409, 426–428, 432, 433, 440
– robustness and uncertainty 722, 732, 737
mouse minute virus (MMV) 586, 600, 601, 604, 605, 608
mouse myeloma cell lines 52
MS see mass spectrometry
MSX see methionine sulfoximine
MTX see methotrexate
multicolumn continuous countercurrent chromatography 772–774, 779–781, 786, 787, 789
multicolumn countercurrent solvent gradient purification (MCSGP) 107, 109, 112–135
– applications 120–133
– batch chromatography 113, 114, 121–124, 126, 127, 130, 135
– bioseparations 112, 113
– decision tree 135, 136
– enabling features and economic impact 134, 135
– four-column MCSGP with separate CIP position 116–118
– four-column MCSGP with separate continuous feed position 118, 119
– generic purification problem 114
– monoclonal antibodies 125–129
– polypeptide purification 120–125
– principles 113–120
– separations with more than three fractions 119, 120
– six-column MCSGP principle 114
– size-exclusion chromatography 129–133
– three-column MCSGP principle 114, 115
multicomponent reactions 267, 268
multicriteria decision making 722, 723, 728
multifraction separations 119, 120
multiple conflicting outputs 720, 721, 728–730
multiple immobilization spots 457, 458
multiplex isobaric labeling 485, 486
multiproduct facilities 669–671
multivariate analysis 643–646, 720–723, 736–738
Mus dunni cell lines 598
Myozyme 548, 549

n
N-linked glycosylation
– efficiency of bioprocesses 627
– protein production technologies 45–47, 54
– virus-like particles 146
N-terminal conjugation 208
natural selection 490
negative chromatography
– membrane chromatography 379, 381, 389, 390
– monoliths 357, 358
NEPAF see North East Proteome Analysis Facility
net present value (NPV) 719, 725, 732–735
New Zealand 593–596
NMR see nuclear magnetic resonance
nonenveloped viruses 600, 601, 605
nonpeptide mimetics 260
norleucine 518
North East Proteome Analysis Facility (NEPAF) 474, 478
norvaline 518
NPV see net present value
NTU see number of transfer units
nuclear magnetic resonance (NMR) 166, 167, 501
nucleic acids
– affinity chromatography 227, 228, 249, 250
– efficiency of bioprocesses 632
– monoliths 337, 338
nucleoside pathways 14, 15
nucleotide synthesis 5
number of transfer units (NTU) 783, 785, 786
nutraceuticals 663
nutrient concentration 629
nutrient metabolism 618–626
nylon 747

o
O-linked glycosylation 45, 46, 627
Octet biosensors 453, 455–457, 459–465, 467–469
oligogalacturonides 361–363
oligonucleotides 338
oligosaccharides 626, 627
one gene/one enzyme concept 490, 496, 497
Ontology Map 557–561, 564–568, 573–575
open loop process control 648, 649
operating costs
– process design and management 667–678
– single-use technologies 819, 841, 842, 851, 856
Operational Qualification (OQ) 809, 810, 814, 815, 834
operator skills
– process design and management 691
– proteomics 478
– single-use technologies 815
optical biosensors 450–452
optimization 545–583
OQ see Operational Qualification
orbitally shaken bioreactors 759
organic buffers 177
oxygen transfer processes 529–531

p
p10 gene promoters 56
package unit engineering 691–694
pallet tank systems 794, 795
PAM see protein A mimetic
pandemic diseases 4
PAR see proven acceptable ranges
paramagnetic matrices 234
Parex frontiers 726, 727, 732–735
Parex process 774
particle size distribution
– affinity chromatography 234
– cell disruption processes 100–103
– Quality by Design 414
PAT see process analytical technology
PCA see principal component analysis
PCR see polymerase chain reaction
Index

PCS see photon correlation spectroscopy;
Process Control Strategies
PDVS see process development value streams
PE see polyethylene
PEGylated proteins 199–222
– amine conjugation 204–206
– chemistry of PEGylation 204–210
– click chemistry 209
– context 199, 200
– efficiency of PEG conjugation 200, 201
– free PEG removal 212, 213
– low-molecular weight contaminant removal 210–212
– monoliths 342–344
– number of PEG adducts 202
– oxidized carbohydrate and N-terminal conjugation 208
– positional isomerism 201, 202
– purification processes 203, 204, 210–217
– reversible PEGylation 209, 210
– separation from native protein forms 213–215
– separation of PEGylation species 215–217
– thiol conjugation 206, 207
– transglutaminase-mediated enzymatic conjugation 208, 209

Penicillium chrysogenum 522, 696–699
Peptostreptococcus magnus 243–245
PER.C6 cell line 52, 819, 831–839

Peptide mimetics 258, 259
peptides
– process design and management 685
– proteomics 484, 495
Peptostreptococcus magnus 243–245
PER.C6 cell line 52, 819, 831–839

Peptostreptococcus magnus 243–245
PER.C6 cell line 52, 819, 831–839
performance prediction 783
Performance Qualification (PQ) 809, 814, 815

perfusion cultures 52, 53, 723
periplasmic inclusion bodies 99, 100
personalized medicine 506, 507
PFR see plug flow tube reactors
pH effects
– efficiency of bioprocesses 627
– therapeutic proteins 168, 169, 171, 172, 176
pH sensors 523–525

Phanerochaete chrysosporium 339, 340
phenyl isothiocyanate 497, 498
phosphoenolpyruvic acid-to-pyruvic acid ratio 515, 516
phosphofructokinase-1 624
phosphorylation 300, 503–505
photon correlation spectroscopy (PCS) 101

Pichia pastoris
– protein production technologies 43, 44, 53–55, 66
– virus-like particles 146
pillars of safety 590–602, 607, 608
PIMS level data management 644, 647, 651, 652
plant-based pharmaceuticals 663
plant cell lines 146
plant molecular farming (PMF) 46, 47, 59–62
plant-wide automation structures 808, 809
plasma-derived products
– continuous chromatography 107
– risk management 588, 600
plasmid DNA 3–41
– amplification systems 8, 9, 18, 19
– antigen selection 6, 7
– cell lysis 6, 19, 20
– chromatographic techniques 23–26
– context 3, 4
– cultivation media and process conditions 16–19
– endA and recA mutations 12, 15–17
– extraction processes 6, 19, 20
– formulation processes 7, 26–28
– gyrA mutations 15
– host strains 6, 11–16
– hydroxypatite chromatography 297, 307–309, 322, 323
– inorganic nanoparticles 28
– intrinsic factors 9–11
– lipoplexes 27
– lysate clarification 7, 21–23
– monoliths 354–357
– nucleoside pathways 14, 15
– polyplexes 27, 28
– production requirements 4–6
– protein production technologies 49, 50, 54, 55
– purification processes 7, 20–26, 354–357
– relA mutations 12–14, 16
– strains for production processes 15, 16
– structure of production process 6, 7
– vector constructs 6, 8–11

Plasmodium falciparum 146

plastic modulus 85, 86
plastics 745–767
– case study 761–763
– cultivation devices 757–763
– driving forces 745–747
– environmental factors 753–755
– future prospects 763–765
– leachables and extractables 753–755
– material to function 747–753
– purification devices 760, 761
– single-use technologies 821, 824
– storage devices 755–757
plastid transformation 60
plate theory 232
platform processes 605, 606, 662, 776, 777,
805, 806
plug flow tube reactors (PFR) 521–538
PMF see plant molecular farming
Poisson ratio 86
polh gene promoters 56
polh promoters 144
polyacrylamide-coated ceramics 333
polyacrylamide gel monoliths 333
polyamides 752, 753
polycarbonate 752
polyclonal antibodies 390, 391
polyethylene glycol) see PEGylated proteins
polyethylene (PE) 747–749, 755, 756
polyethylene terephthalate 756
polyHIPE monoliths 333, 334, 337
polyhistidine-tagged proteins 383
polymerase chain reaction (PCR)
– proteomics 491
– risk management 592, 593, 598, 599
polymerizable monoliths 333
polynucleotides 302–312, 318, 319, 322,
323
polyols 177
polioviruses 152, 153
polypeptides
– continuous chromatography 120–125
– hydroxyapatite chromatography 296, 300
polyplexes DNA 27, 28
polypropylene (PP) 748, 749, 755, 756
polysaccharides 227, 228
polystyrene (PS) 747, 748, 750
polysulfones 748, 750
polytetrafluoroethylene (PTFE) 749
polyvinyl chloride (PVC) 751, 752, 756
polyvinylidene 749
population balance theory 103
population model 555, 556, 561
porcine circovirus (PCV) 585, 586, 592
pore diffusion 417, 423–425, 431
pore size
– affinity chromatography 233, 234
– hydroxyapatite chromatography 287
– monoliths 337, 354
– single-use technologies 798, 799
porosity
– membrane chromatography 380, 381, 387, 388
– monoliths 336
– Quality by Design 430, 431
porous-media chromatography 151
porous monolithic supports 25, 26
portfolio management 720, 731–736
positional isomerism control 201, 202
post-transcriptional modifications 503–505
PP see polypropylene
ppGpp see guanosine tetraphosphate
PQ see Process Qualification
precipitation processes
– monoliths 342
– plasmid DNA 21, 22
– process design and management 684, 685
– protein production technologies 59
– therapeutic proteins 173, 174
predictability 647, 648
prepacked columns 780, 781
preservatives 813, 814
primary protein structure 493–495
principal component analysis (PCA) 723,
737
probes 758, 759
Process Analytical Technology (PAT)
– continuous countercurrent
chromatography 778
– efficiency of bioprocesses 613–616, 626,
638–653
– monoliths 338–348
– process design and management 690
– risk management 585
– single-use technologies 808, 849–851
process condition variability 431–439
Process Control Strategies (PCS) 711, 713,
714
process design and management 659–705
– antibiotics 696–699
– Anything And Chromatography concept
679–685
– batch to continuous manufacturing 672–679
– context 659–662
– continuous countercurrent
chromatography 779–786
– data visualization 721–723
– decision-support tools 719–723, 739
– downstream of downstream processing
694, 695
– downstream processing 659–661,
663–665, 667–689, 692
– facility design 719, 725–737
– human insulin 695–697
– integrated process design 707–715
Index

- large decision spaces 720, 721, 731–736
- management strategies 717–741
- monoclonal antibodies 667–672, 683–687, 695
- multiple conflicting outputs 720, 721, 728–730
- multivariate analysis and stochastic simulations 720–723, 736–738
- package unit engineering and standardization 691–694
- process concepts in biomanufacturing 663–665
- process integration 685–689, 699
- production technologies 662–679
- Quality by Design 661, 689–691, 699
- robustness 719–721, 723–728
- single-use technologies 793, 804–806, 840
- synergies 662, 663
- total process analysis 664, 666–672
- uncertainty 717–730
- upstream processing 659–661, 663, 664, 671, 672, 679
process development value streams (PDVS) 849–854
- process integration 685–689, 699
- process modeling 411–414
- process understanding and control 639–649
- process validation 811–815
- product bacteria challenge tests 812–814
- product complexity 587–590
- product life cycle 708, 709, 714
- product transfer 797, 798
- proof-of-concept 647, 648, 852
- proof-of-principle 686, 781
- protease inhibitors 62
- protein A chromatography
  - affinity chromatography 242–245, 269–271
- continuous countercurrent chromatography 786, 787
- hydroxyapatite chromatography 283–285, 319, 320
- membrane chromatography 378
- single-use technologies 798, 834, 840, 841
- protein A mimetic (PAM) 259, 262–264
- Protein Data Bank 501
- protein G chromatography 242–245
- protein G monoliths 340, 341
- protein L chromatography 243–246
- protein L mimetic 264, 268
protein production technologies 43–77
- bacteria as protein factories 43, 44, 47–50, 63, 65, 66
- baculovirus–insect cell technology 43, 55–57
- cell-free protein production 44, 62–65
- context 43, 44
- future prospects 65, 66
- glycoengineering for homogenous human-like glycoproteins 45–47
- mammalian cell technology 45, 50–53
- plant molecular farming 46, 47, 59–62
- transcription/translation efficiency 61, 62
- transgenic animal technologies 43, 44, 57–59
- yeast protein production 43–46, 53–55, 66
protein stability 165–175
- air–liquid and solid–liquid interfaces 170, 171
- chaotropes, solvents and pH 168, 169
- chemical stability 171–173
- drying 170
- freezing 169, 170
- leachables 174, 175
- physical stability 165, 167–171, 185, 186
- precipitation, aggregation and fibril formation 173, 174, 180, 182, 183, 186, 192, 193
- shear 169
- stability testing 166, 188–194
- structural stability 167, 168
- thermal stability 168, 186, 187
protein–carbonate interactions 266
protein–protein interactions 502, 503
proteins
- affinity chromatography 227, 228, 230, 235–237, 242–246
- biosensors 464, 465
- continuous chromatography 107–137
- hydroxyapatite chromatography 293–300, 302–315
- monoliths 339, 349, 350
- risk management 587
- structure 493–495
- see also proteomics; therapeutic proteins
proteomics 473–487
- applications 475–477, 506–508
- availability problem 474
- biological advances 489, 490, 495–498
- biomarkers of human diseases 503–505, 507
- brain diseases 499, 508
- case studies 481–486
– complex diseases and personalized medicine 506, 507
– context 473
– definition and characteristics 474, 475
– differentiation of multicellular organisms 501, 502
– diseasome concept 503, 504
– drug development 507
– drug discovery 506, 507
– expertise and training 478
– genomics 489, 491–493, 505–507
– historical development 489–492, 495–501
– industrialization 480, 481
– interactomics 489, 501–503
– isobaric labeling 485, 486
– mass spectrometry 482–486, 499–501
– matrix-assisted laser desorption ionization 483, 484, 500, 501
– Mendel’s principles of inheritance 490
– metabolomics 489, 505, 506
– monoliths 358–360
– myths and misconceptions 477–480
– one gene/one enzyme concept 490, 496, 497
– protein identification and characterization 475, 476
– protein interactions 476
– protein modifications 476
– protein separation, sequencing and throughput technologies 492
– protein structure 493–495
– quality control 480, 481
– quantitative approaches 477, 484–486
– reproducibility 479, 480
– robustness and reliability 481
– sciences of omics 489, 490
– set-up costs 477, 478
– stable isotope labeling 484, 485
– technological advances 491, 492, 497–501
– throughput and time-consumption 478, 482
– two-dimensional PAGE 477, 479, 481, 482, 498, 499
– Watson–Crick structure of DNA 490, 491
– X-ray crystallography and NMR 501
– ProteOn biosensors 457, 461, 464
– proven acceptable ranges (PAR) 646
– pseudoviruses (PSV) 139
– purity–yield plots 438, 439, 686
– PVC see polyvinyl chloride
– pyruvate 621, 623–625
– pyruvate kinase 623, 624
– pyruvic acid 515, 516, 520, 533–535

q

QA see quaternary amine
QbD see Quality by Design
QMS see Quality Management System
QRM see quality risk management
QSPR see quantitative structure–property relationships
QTPP see Quality Target Product Profile

qualification processes 809–811, 834
– A-Mab case study 552, 553, 556, 564, 579
– context 409
– continuous countercurrent chromatography 778
– domain ontology model 557, 577, 578
– efficiency of bioprocesses 613–616, 638–653
– enhancement 554–580
– experimental model parameter determination 414–431, 437–439
– fluid dynamics 416–418
– fundamental principles 410, 411
– glycoform activity modeling 573–580
– glycosylation 546, 547, 551–580
– Impact Maps 568–571, 575, 578
– informatics tools 554, 555, 557–561
– integrated process design 707–715
– isocratic pulses 415, 416, 419, 420
– isotherm parameters 414, 416, 419, 426, 427
– mass transfer kinetics 417–425
– method overview 410
– model error 425, 426
– modeling principles 413, 414
– Ontology Map 557–561, 564–568, 573–575
– population model 555, 556, 561
– process challenges 412
– process design and management 661, 689–691, 699
– process modeling 411–414
– robustness analysis 409, 424–439
– SE Board 562–580
– single-use technologies 849–851
– tuned glycoprofiling systems 571–573
– variation of process conditions 431–439
Index

quality control
- efficiency of bioprocesses 613–656
- fed-batch processes 513–538
- glycosylation throughout the drug life cycle 545–583
- optimization and comparability 545–583
- proteomics 480, 481
- risk management 585–612
- scale-up consistency 513–543
- virus safety 585–612
Quality Management System (QMS) 551
quality risk management (QRM) 585–590
Quality Target Product Profile (QTPP) 547, 551–553, 556, 558–561, 573–578, 711, 712
quantitative proteomics 477, 484–486
quantitative structure–property relationships (QSPR) 299, 312
quarantine 595, 596
quaternary amine (QA) monoliths 340, 341, 343–345, 352, 353
quaternary ammonium (Q) membranes 389–394, 396–398, 402–404
quaternary protein structure 493–495
quiescent normal cells 622, 623
rabies virus 819, 820
Raman spectroscopy 194
rate theory 232
recA mutations 12, 15, 17
recombinant proteins
  - affinity chromatography 246, 248, 249, 265
  - glycosylation 550
  - hydroxyapatite chromatography 293, 294, 297, 298
  - process design and management 666
  - protein production technologies 43, 44, 51, 52, 58–62
  - proteomics 485
  - risk management 587
  - virus-like particles 139–141, 145
recycling and recovery processes 694, 695
red biotechnology 659, 663
red cell aplasia 165
redox potential 179
refractive index 451, 453, 455
regulatory issues
  - efficiency of bioprocesses 613–617
  - process design and management 659, 660, 717
  - quality control 546–549
  - risk management 585, 595, 596, 602–606
  - therapeutic proteins 188
regulated targets 621–624
relA mutations 12–14, 16
release of biopharmaceuticals see cell disruption processes
reliability 481
reproducibility 479–480, 647, 648
residence time distributions (RTD) 97
residual risk 600, 601
resonant waveguide grating (RWG) 452–455, 458–464
retention mechanisms 294–301
retroviruses 597–599
reverse transcriptase assays 598, 599
reversed-phase chromatography
  - efficiency of bioprocesses 641
  - PEGylated proteins 215, 216
  - polypeptide purification 121
  - protein purification 108, 109
  - therapeutic proteins 191, 192
  - reversible PEGylation 209, 210
Rhizopus oryzae 361
ribonucleic acid see RNA
ribosomal RNA 492
risk management 585–612
  - biopharmaceutical product classes 587, 588
  - clearance and residual risk control 600, 601
  - contamination events 585, 586, 589
  - CPMP guidance 602–606
  - epidemiology 592–596
  - generic data 603
  - integrated process design 709, 711, 713, 714
  - media and API supplier control 601, 602
  - pillars of safety 590–602, 607, 608
  - plastics 754
  - platform purification processes 605, 606
  - product complexity 587–590
  - quality risk management 585–590
  - risk minimization strategy development 607, 608
  - sourcing and baseline risk 590–596, 599, 600
  - testing and baseline risk reduction 596–600
  - uncertainty 722
  - validation requirements 604–606
  - virus safety 585–612
  - well-characterized cell lines 603, 604
RNA aptamers 227, 228, 249, 250
RNA I/RNA II complex 8, 9
RNA removal 361
RNA sequencing 492
robustness analysis
– model error 425, 426
– model parameter determination error 426–431, 437–439
– proteomics 481
– Quality by Design 409, 424–439
– uncertainty 719–721, 723–728
– variation of process conditions 431–439
rom genes 8, 9
rotavirus vaccines 586
RTD see residence time distributions
RWG see resonant waveguide grating

Saccharomyces cerevisiae
– affinity chromatography 242, 265
– cell disruption processes 83–85, 92–94, 102, 103
– fed-batch processes 521, 522
– monoliths 360
– process design and management 666
– protein production technologies 43, 44, 53–55
– virus-like particles 146, 148
safety–efficacy space (SE Board) 562–580
safety issues 793, 800, 848
– see also risk management
safety tripod 590–602, 607, 608
salts 177, 178
sample handling 455–458
Sankey diagrams 695, 697, 698
SAR see structure–activity relationship
SAT see Site Acceptance Test
SCADA see supervisory control and data acquisition
scale-down reactors 520–523
scale-up processes
– efficiency of bioprocesses 638, 639
– glycosylation 548–551
– optimization and comparability 548–551
– quality control 513–543
– single-use technologies 824–829
scatter plots 433–435
screening kits 482, 483
SDS–PAGE see sodium dodecyl sulfate–polyacrylamide gel electrophoresis
SDVB see styrene–divinylbenzene
SE Board 562–580
SEC see size-exclusion chromatography
secondary protein structure 493–495
secretory proteins 627, 628
selective displacement chromatography 313
SELEX see systematic evolution of ligands by exponential enrichment
semi-continuous processes 63, 64
sensitivity analysis
– model parameters 430
– process conditions 436, 437
– robustness and uncertainty 723, 730
Serratia marcescens 520
set-up costs 477, 478
shear 169
sialylation 629–632
silica-based affinity chromatography 234
silica monoliths 333, 334
silica xerogel monoliths 333
simulated moving bed (SMB) process 109–113, 770–775, 778–781, 784, 786–789
single nucleotide polymorphisms (SNP) 492, 493
single-use technologies 793–816
– assessment 854–856
– automation systems 806–809
– continuous countercurrent chromatography 777, 778, 780, 786, 789
– Crucell NV case study 817–858
– current applications 793
– data acquisition 808
– downstream opportunities 804, 837, 842
– equipment qualification 809–811
– facility design 843–849
– filling applications 802, 810
– filtration applications 800, 801, 812–815, 821–833
– future applications 802–806
– future prospects 856, 857
– industrialization and simplification 829–835
– liquid hold bags 794, 795
– mixing operations 795–797, 814
– modular manufacturing environments 842–849
– monitoring and control 808
– operator training 815
– plant-wide automation structures 806, 809
– plastics 745–747
– process development value stream 849–854
– process engineering 804–806
– process validation 811–815
– product and component transfer 797, 798
– purification applications 798–800
– robustness and uncertainty 728–730
– scale-up, capsules and coupling 824–829
– small-scale plastic cell culture units 821, 822
– sterile connections 801, 806, 822–832
– three phase evolution 821–836
– upstream opportunities 803, 837, 840
SIP see sterilization-in-place
Site Acceptance Test (SAT) 809, 834
site-specific PEGylation 202, 209
six-column MCSGP principle 114
size-exclusion chromatography (SEC)
– continuous chromatography 782, 784, 788, 789
– hydroxyapatite chromatography 284, 285
– PEGylated proteins 203, 210–217
– therapeutic proteins 192, 193
SMMA see steric mass action
small- and medium-sized enterprises (SME) 662, 692, 731, 732
small RNA 492
small-scale stirred disposable bioreactors 759
SMB see simulated moving bed
SME see small- and medium-sized enterprises
SNARE interactions 468
SNP see single nucleotide polymorphisms
SOD see superoxide dismutases
sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) 193, 194, 347, 348
soft-gel-based matrices 233, 234
sox genes 11
solid–liquid interfaces 170, 171
solvent effects 168, 169
SOP see Standard Operating Procedures
Sorbex process 773
sourcing animal-derived materials 590–596, 599, 600
spacer arms 234–236
spider plots 730
spiking studies 394, 397
spin–filter perfusion culture 723, 725
Spodoptera spp. 56, 144, 145
sporulation cascade 517
SPR see surface plasmon resonance
stability testing
– accelerated 189
– analytical techniques 189–194
– cell-based bioassays and in vitro binding assays 190, 191
– regulatory issues 188
– therapeutic proteins 166, 188–194
stable isotope labeling 484, 485
stainless steel 728–730, 794, 801
Standard Operating Procedures (SOP)
– proteomics 479
– single-use technologies 805, 810, 815, 852–854
standardization 691–694
Staphylococcus aureus
– affinity chromatography 242–245
– membrane chromatography 377–379
– monoliths 352, 353
– protein production technologies 49
static batch shaking experiments 415, 420
steam sterilization see autoclaving
tem cells 588
steric effects 207, 235
steric mass action (SMA) model 414
sterile connections 801, 806, 822–832
sterile transfer systems 797, 798
sterilization 798, 800, 801, 810, 821, 831, 834, 838
sterilization-in-place (SIP)
– affinity chromatography 251, 259, 263
– single-use technologies 820, 821, 839
sterilizing-grade filters 800, 801, 812–815
stirred tank reactors (STR) 513, 520–538
stochastic simulations 720–722, 736–738
Stokes equation 100
storage
– plastics 755–757
– therapeutic proteins 166, 169, 170, 180
STSTR see stirred tank reactors
streptavidin 248, 249, 383
Streptococcus spp. 140, 141, 242–245
stress–strain tests 85, 86
structural stability 167, 168
structure–activity relationship (SAR) model 547, 560, 561, 564, 565
structure–function relationships 289–294
Student’s deviation 428
styrene–divinylbenzene (SDVB) monoliths 347, 348
subcellular targeting 62
sublimation processes 183
succinic acid 535
succinimidyl carbonate activation 205
succinimidyl propionate activation 214
succinimidyl succinate activation 205
sugars 177, 180–185
superhelicity 5, 16, 17, 355, 356
superoxide dismutases (SOD) 209
supervisory control and data acquisition (SCADA) 806, 809
surface plasmon resonance (SPR)
– biosensors 452–458, 460–465, 467–470
– therapeutic proteins 166
Index

surfactants 178
synthetic and designed ligands
  – affinity chromatography 228, 229, 240, 251–269
  – benzhydroxamic acid 256, 257
  – biomimetic ligands 251, 258–269
  – boronate affinity chromatography 228, 256
  – de novo affinity ligands 260–269
  – dye-based ligands 228, 257, 258
  – histidine 254, 255
  – hydrophobic ligands 228, 253
  – immobilized metals 228, 252, 253
  – mixed-mode affinity chromatography 229, 255, 256
  – thiophilic ligands 228, 253, 254
  – systematic evolution of ligands by exponential enrichment (SELEX) 227, 228, 250
  – protein stability 165–175, 185, 186
  – redox potential 179
  – salts 177, 178
  – screening methods 185–187
  – shear 169
  – specific binding sites 178
  – structural stability 167, 168
  – sugars and polyols 177, 180–185
  – surfactants 178
  – thermal stability 168, 186, 187
  – thermal stability 168, 186, 187
  – thermo-responsive displacers 311, 312
  – Thermus thermophilus 361
  – thiol conjugation 206, 207
  – thiophilic affinity chromatography (TAC) 228, 253, 254
  – three-column MCSGP principle 114, 115
  – tissue engineering 588
  – tissue plasminogen activator (tPA) 50
  – tomato mosaic virus (ToMV) 351, 352
  – total process analysis 664, 666–672
  – tPA see tissue plasminogen activator
  – TPP see Target Product Profiles
  – track-and-trace systems 809
  – training
    – process design and management 691
    – proteomics 478
    – single-use technologies 815
    – transcription efficiency 61
    – transfection efficiency 5
    – transfection-grade DNA 5, 6
    – transfer RNA (tRNA)
      – fed-batch processes 518
      – plasmid DNA 9, 10
      – proteomics 492
    – transfer systems 797, 798, 822, 823
    – transferrin 341
  – transgenic products
    – protein production technologies 43, 44, 57–59
    – risk management 588
    – transglutaminase-mediated enzymatic conjugation 208, 209
  – translation efficiency 61, 62
  – transmission electron microscopy (TEM) 154
  – triangle theory 784
  – triazine-based affinity ligands 228, 262–266
  – tricarboxylic acid (TCA) cycle
    – efficiency of bioprocesses 619–621, 625
    – scale-up 515–518, 535, 536
  – Trichoplusia ni 56, 144, 145
  – tRNA see transfer RNA
  – trypsin 359, 360
  – trypsinogen 390, 391

T7 RNA polymerase 48, 49
TAC see thiophilic affinity chromatography
tangential flow applications 842
Target Product Profiles (TPP) 134, 135, 708, 709, 711
TCA see tricarboxylic acid technology transfer 737, 765
TEM see transmission electron microscopy
temperature-sensitive mutations 9
tertiary protein structure 493–495
testing animal-derived materials 596–600
TGase see transglutaminase
therapeutic proteins 165–198
  – accelerated and long-term stability testing 188–194
  – air–liquid and solid–liquid interfaces 170, 171
  – amino acids and organic buffers 177
  – analysis and characterization 166
  – chaotropes, solvents and pH 168, 169, 171, 172, 176
  – chelating agents 178
  – chemical stability 171–173
  – containers and closures 179
  – context 165–167
  – drying 170
  – formulation processes 165, 166, 175–185
  – freeze-drying 180–185
  – freezing 166, 169, 170, 179, 180
  – leachables 174, 175
  – liquid formulations 175, 176, 179, 180
  – physical stability 165, 167–171, 185, 186
  – precipitation, aggregation and fibril formation 173, 174, 180, 183, 184, 186, 192, 193
tubes 757
tumor cells 622–624
tuned glycoprofiling systems 571–573
two-compartment reactors 521–538
two-dimensional polyacrylamide gel electrophoresis (PAGE) 477, 479, 481, 482, 498, 499
two-film model 782

UDP-GlcNAc pools 629–632
Ugi ligands 228, 267–269
ultra-low-density polyethylene (ULDPE) 756
ultrafiltration membranes
  – PEGylated proteins 203, 210–212, 216
  – single-use technologies 798, 800, 804
ultraviolet (UV) fluorescence spectrometry 194
ultraviolet (UV) inactivation 799, 800
uncertainty 717–730
  – multiple conflicting outputs 720, 721, 728–730
  – risk management 722
  – robustness 719–721, 723–728
untranslated regions (UTR) 61
uptake curves 416, 421
urine-derived products 588
UTR see untranslated regions
UV see ultraviolet

vaccines
  – biosensors 468, 469
  – continuous countercurrent chromatography 788, 789
  – design and efficacy 468, 469
  – membrane chromatography 395, 396
  – plasmid DNA 3–41
  – risk management 586, 588
  – single-use technologies 819, 821, 845–849
  – virus-like particles (VLP) 139–141, 145–148
validation
  – integrated process design 707
  – membrane chromatography 393–395
  – risk management 604–606
  – single-use technologies 793, 811–815
volumetric yields 5, 6
von Mises stress/strain 86, 103

water for injection (WFI)
  – process design and management 695, 696
  – single-use technologies 794, 800, 824–829, 845
Watson–Crick structure of DNA 490, 491
wave-mixed bioreactors 759, 760, 795
Western blotting 193, 194
wetting agents 814
WFI see water for injection
wheat germ agglutinin (WGA) 246, 247
white biotechnology 663

x
X-ray crystallography 167, 501
Xcellerex bioreactors 833, 834, 837–841, 848–850, 854–856
xenogeneic cell-based therapies 588
xenotransplantation products 588

y
YCP see centromeric plasmid
yeasts
– affinity chromatography 242, 265
– cell disruption processes 83–85, 87–95, 102, 103
– fed-batch processes 517, 518, 520, 521
– monoliths 360
– process design and management 666
– protein production technologies 43–46, 53–55, 66
– virus-like particles 139, 140, 146, 148
YEP see episomal plasmid
yield/productivity performance 133
yield/purity trade-offs 126, 127
yield stress 85, 86
YIP see integrating plasmid
Young’s modulus 85, 86, 88

z
zinc-modified hydroxyapatites 293, 294
zoonotic viruses 591, 593–596