

# Table of Contents

## Chapter 1 Introduction 1

- 1.1 Signal transducers are cellular components that act mainly by regulating other cellular components 3
  - 1.2 The signal transduction parts list is long 3
  - 1.3 Signal transduction in bacteria is accomplished by short, (mostly) linear, (mostly) non-interconnected pathways 4
  - 1.4 The EGFR System is Deep, Interconnected, and Complicated 6
  - 1.5 Complicated systems can be simplified by assuming modularity 11
  - 1.6 Ordinary differential equations provide a powerful framework for understanding many signaling processes 13
  - 1.7 Theory can help highlight the commonalities of diverse biological phenomena 14
  - 1.8 Six basic types of response are seen over and over again in cell signaling 15
  - 1.9 Five or six basic circuit motifs are seen over and over again in signaling systems 17
- Summary 19
- Moving forward 19
- Further reading 20

## Chapter 2 Receptors 1: Monomeric receptors and ligands 21

- 2.1 The  $\beta_2$ -adrenergic receptor can function as a monomeric receptor that binds monomeric ligands 22
- 2.2 Experiments show the receptor's equilibrium and dynamical behaviors 23
- 2.3 A simple binding-dissociation model explains the hyperbolic equilibrium response 24
- 2.4 A semilog plot expands the range but distorts the graded character of the response 27
- 2.5 The system approaches equilibrium exponentially 28
- 2.6 Increasing the association rate decreases  $t_{1/2}$ ; so does increasing the dissociation rate 30
- 2.7 Going up is faster than coming down 31
- 2.8 The dissociation rate constant  $k_{-1}$  determines the half-life and mean lifetime of a ligand-receptor complex 32
- 2.9 Partial agonists, antagonists, and inverse agonists can be explained by assuming

that binding and activation occur in distinct steps 33

Summary 37

Further Reading 37

## **Chapter 3 Receptors 2: Multimeric receptors and cooperativity 39**

Introduction 40

3.1 The hill equation is a simple expression for the equilibrium binding of ligand molecules to an oligomeric receptor 41

3.2 The hill exponent is a measure of how switch-like a sigmoidal response is 42

3.3 The hill equation accounts for hemoglobin's oxygen binding pretty well, but the assumptions underpinning the model are dubious 44

3.4 The more-plausible monod-wyman-changeux (MWC) model yields sigmoidal binding curves 44

3.5 The MWC model accounts for the binding of oxygen to hemoglobin, but not the binding of EGF to the EGFR 50

3.6 The KNF model can account for either ultrasensitive or subsensitive binding 52

3.7 Response sensitivity is customarily defined in fold-change terms 54

3.8 The relationship between binding and activation yields a variety of possible responses 56

Summary 59

Further reading 60

## **Chapter 4 Downstream signaling 1: Stoichiometric regulation 61**

Stoichiometric regulation inside the cell 63

4.1 In the high-affinity limit, does a hyperbolic response make intuitive sense? 63

4.2 The equilibrium response changes from hyperbolic to linear when depletion of the upstream regulator is not negligible 63

4.3 The dynamical response is similar even when the depletion of the upstream regulator is not negligible 65

4.4 Ligand depletion plus negative cooperativity can produce a threshold 66

4.5 Stoichiometric regulators must sometimes compete with stoichiometric inhibitors 69

Summary 72

Further reading 72

## **Chapter 5 Downstream Signaling 2: Covalent Modification 75**

- 5.1 A mass action phosphorylation-dephosphorylation cycle yields a michaelian steady-state response with exponential approach to the steady state 77
- 5.2 The steady-state response of a phosphorylation-dephosphorylation reaction with michaelis-menten kinetics can be ultrasensitive 78
- 5.3 Rate-balance plots are much like the economist's supply-and-demand plots 80
- 5.4 Rate-balance analysis explains the michaelian steady-state response 81
- 5.5 The dynamics of the system can also be understood from the rate-balance plot 83
- 5.6 Rate-balance analysis helps explain zero-order ultrasensitivity 84
- 5.7 Does zero-order ultrasensitive occur in vivo? 86
- 5.8 The temporal dynamics of a multistep activation process tells you the number of partially rate-determining steps 87
- 5.9 Assuming mass action kinetics, steady-state multisite phosphorylation is described by a KNF-type equation 89
- 5.10 Priming can impart positive cooperativity on multisite phosphorylation 92
- 5.11 Distributive multisite phosphorylation improves signaling specificity 93
- 5.12 Inessential phosphorylation sites can contribute to the ultrasensitivity 96
- 5.13 Inessential binding sites can contribute to ultrasensitive receptor activation 98
- 5.14 Variation: coherent feed-forward regulation 99
- 5.15 Variation: reciprocal regulation 101

Summary 102

Further reading 103

## **Chapter 6 Downstream signaling 3: Regulated production or destruction 105**

- 6.1 Stimulated production yields a linear steady-state response with exponential approach to the steady state 105
- 6.2 The stability of the steady state can be quantified by the exponent in the exponential approach equation 108
- 6.3 Saturating the back reaction builds a threshold into the steady-state response 109
- 6.4 Zero-order degradation makes drug dosing dicey 110

Summary 112

Further reading 112

## **Chapter 7 Cascades and Amplification 113**

Introduction 113

7.1 Cascades can deliver signals faster than single signal transducers 114

7.2 A cascade of michaelian responses leads to signal degradation 117

7.3 Fold-sensitivity decreases as a signal descends a cascade of michaelian responses 119

7.4 Ultrasensitivity can restore or increase the decisiveness of a signal 120

7.5 In xenopus oocyte extracts, responses get more ultrasensitive as the MAPK cascade is descended 125

Summary 126

Further reading 127

## **Chapter 8 Bistability 1: Systems with One Time-Dependent Variable 129**

8.1 Cell fate induction is typically all-or-none and irreversible in character 130

8.2 Xenopus oocyte maturation is an all-or-none, irreversible process 131

8.3 The response of ERK2 is all-or-none in character 132

8.4 There is positive feedback in the oocyte's MAPK Cascade 133

8.5 The response of ERK2 to progesterone is normally irreversible 133

8.6 The MOS/ERK2 system can be reduced to a model with a single time-dependent variable because of a separation of time scales 134

8.7 Rate-balance analysis shows what is required for a bistable response 135

8.8 Increasing the progesterone concentration pushes the system through a saddle-node bifurcation 137

8.9 Tweaking the model can change an irreversible response to a hysteretic one 140

8.10 The dynamics of the system can be inferred from the rate-balance plot 141

8.11 The velocity vector field can be represented as a potential landscape 142

Summary 144

Further reading 145

## **Chapter 9 Bistability 2: Systems with Two Time-Dependent Variables 147**

9.1 Two-variable positive feedback and double-negative feedback loops can function

as bistable switches 148

9.2 Linear stability analysis explains the dynamics of the system near each of the steady states 150

9.3 To apply linear stability analysis to a two-variable system, we calculate eigenvectors and eigenvalues 152

9.4 The system can change between states via a saddle-node bifurcation 155

9.5 Double-negative feedback plus ultrasensitive can yield bistability 156

9.6 Perfect symmetry can produce a pitchfork bifurcation 158

9.7 In the absence of perfect symmetry, a pitchfork bifurcation morphs into a saddle-node bifurcation 160

Summary 160

Further reading 161

## **Chapter 10 Transcritical Bifurcations in phase Separation and Infectious Disease 163**

Introduction 164

10.1 Liquid-liquid phase separation can produce discrete functional domains that lack membranes 164

10.2 Phase separation can be modeled by a single rate equation with positive feedback and a transcritical bifurcation 165

10.3 The time course of droplet formation is sigmoidal 168

10.4 The same principles underpin the formation of phospholipid vesicles 169

10.5 The sir (susceptible-infected-recovered) model explains why infectious diseases sometimes spread explosively 169

10.6 The sir model predicts exponential growth followed by exponential decay 170

10.7 The basic reproduction number  $R_0$  determines whether an infection will grow exponentially 172

10.8 The proportion of the population that will ultimately become infected depends on  $R_0$  173

10.9 Manipulating  $R_0$  can delay an epidemic, decrease the peak, and diminish the final number of infected individuals 175

Summary 176

Further reading 177

## **Chapter 11 Negative Feedback 1: Stability and Speed 179**

Introduction 179

11.1 Negative feedback can increase the stability of a steady state 179

11.2 Negative feedback can allow a system to respond more quickly 182

Further reading 183

## **Chapter 12 Negative Feedback 2: Adaptation 185**

Introduction 185

12.1 Bacteria find food sources through a biased random walk 186

12.2 Bacteria suppress tumbling in response to chemoattractants and then adapt perfectly 187

12.3 A plausible negative feedback model can account for perfect adaptation 188

12.4 The response of the ERK map kinases to mitogenic signals is typically transitory 192

12.5 Delayed negative feedback can yield near-perfect adaptation 193

12.6 Ultrasensitivity in the feedback loop improves the system's adaptation 195

12.7 Induction of immediate-early gene products is not required for ERK inactivation in many cell types 196

Summary 197

Further reading 198

## **Chapter 13 Adaptation 2: Incoherent Feedforward Regulation and State-Dependent Inactivation 199**

Introduction 200

13.1 Receptor tyrosine kinase activation is followed by transitory ras activation 200

13.2 The sequential recruitment of SOS and GAP to the EGFR can be viewed as incoherent feedforward regulation 201

13.3 Incoherent feedforward systems can yield perfect adaptation 202

13.4 Strict ordering of SOS and GAP binding to the EGFR is not required for perfect adaptation 203

13.5 The voltage-sensitive sodium channel also undergoes sequential activation and inactivation 205

13.6 EGFR internalization can be viewed as state-dependent inactivation 208

13.7 GPCR signaling is switched from G-proteins to  $\beta$ -arrestin via a mechanism akin to state-dependent inactivation 209

Summary 210

Further reading 211

## **Chapter 14 Negative Feedback 3: Oscillations 213**

Introduction 213

14.1 Biological oscillations control myriad aspects of life and operate over a ten-billion-fold range of time scales 214

14.2 The goodwin oscillator is built upon a three-tier cascade with highly ultrasensitive negative feedback 214

14.3 Linear stability analysis yields a pair of complex eigenvalues 217

14.4 Oscillations are born and extinguished at HOPF bifurcations 220

14.5 Simple harmonic oscillators are not limit cycle oscillators 221

Summary 223

Further reading 224

## **Chapter 15 Relaxation Oscillators 225**

Introduction 226

15.1 The xenopus embryonic cell cycle is driven by a reliable biochemical oscillator 226

15.2 The cell cycle oscillator includes a negative feedback loop and a bistable trigger 228

15.3 A simplified model captures the basic dynamics of the cell cycle oscillator 230

15.4 The cell cycle model has a single unstable steady state 232

15.5 Tuning the oscillator changes the period more than the amplitude 235

15.6 Phase plane analysis shows why the HOPE bifurcations occur where they do 236

15.7 Interlinked positive and double-negative feedback loops can make the mitotic trigger more all-or-none and more robust 239

15.8 The fitzhugh-nagumo model accounts for the electrical oscillations of the sinoatrial node 240

15.9 The fitzhugh-nagumo model consists of a quick bistable switch and a slower negative feedback loop 241

15.10 The cell cycle oscillator and the fitzhugh-nagumo oscillator share the same

systems-level logic 242

15.11 Depletion can take the place of negative feedback in a relaxation oscillator 243

Summary 245

Further reading 246

## **Chapter 16 Excitability 247**

Introduction 247

16.1 The receptor tyrosine kinase/map kinase system includes multiple positive and negative feedback loops 248

16.2 Excitable responses can be generated by a fast positive feedback loop coupled to a slow negative feedback loop 249

16.3 NOise Can Cause An Excitable System To Fire Sporadically 252

Summary 253

Further reading 253

## **Chapter 17 Wrap-Up 255**

17.1 The building blocks 255

17.2 Motifs 255

17.3 Signal processors 256

17.4 Nonlinear dynamics 256

Glossary 257

Index 263