

Contents

Preface	xi
1 Microbial Design	1
How to Read; Theoretical Background; The Design of Metabolism	
PART 1: THEORETICAL BACKGROUND	
2 Forces of Design	11
What Is Fitness?; The Difficulty of Measuring Fitness	
3 Comparison and Causality	17
Comparative Predictions; Evolutionary Response versus Organismal Response; Fundamental Forces and Partial Causes; Causal Inference; Structure and Notation of Comparative Predictions; Recap and Goal	
4 Brief Examples	29
Metabolism and Growth Rate; Support by Empirical Test; Patch Lifespan and Microbial Cancer; Heterogeneity in Public Goods; Stage-Dependent Growth; Summary	
5 Theory: Forces	43
Tragedy of the Commons; Similarity Selection and Kin Selection; Tradeoffs and Marginal Values; Repression of Competition; Heterogeneity in Vigor and Public Goods; Demography and Reproductive Value; Stage-Dependent Traits in Life Cycle; The Three Measures of Value; Scaling of Time and Space; Variable Environments	
6 Theory: Traits	83
Nature of Traits; Modification of Traits; Origin of Traits	

7	Theory: Control	95
	Error-Correcting Feedback and Robustness; Principles of Control; Error Correction and Signal Amplification; Robustness to Process Uncertainty; Responsiveness versus Homeostasis; Sensors; Control Tradeoffs	
8	Studying Biological Design	115
PART 2: THE DESIGN OF METABOLISM		
9	Microbial Metabolism	121
10	Growth Rate	123
	Comparative Hypotheses in the Study of Design; Testing Comparative Predictions; Comparative Predictions about Growth Rate; Comparative Predictions about Tradeoffs	
11	Thermodynamics: Biochemical Flux	141
	Entropy Production; Force and Resistance Determine Flux; Mechanisms of Metabolic Flux Control	
12	Flux Modulation: Driving Force	155
	Near-Equilibrium Glycolysis; Overflow Metabolism: Mechanisms; Overflow Metabolism: Design Puzzles; Evolutionary Timescale; Alternative Glycolytic Pathways	
13	Flux Modulation: Resistance	189
	Resistance Impedes Flux; Mechanisms to Alter Resistance and Flux; Genetic Drift; Challenges in Control Design; Problems of Flux Modulation; Limitations and Prospects	
14	Variant Pathways	205
	Glycolytic Yield; Final Electron Acceptors; Weak Redox Gradients; Electron Flow between Cells; Alternative Carbon Sources; Hierarchical Usage of Complex Carbohydrates; Puzzles of Design	

Contents	ix
15 Tradeoffs	227
Biophysical Constraints and Cellular Allocation; Exploration versus Exploitation versus Regulation; Thermodynamics and Biochemical Flux; Fitness Components and Life History; Warfare versus Productive Traits; Cooperative Traits; Timescale Tradeoffs; Bet-Hedging Tradeoffs; Control Tradeoffs; Summary	
16 Predictions: Overflow Metabolism	253
Comparative Predictions and Partial Causes; Background; Proteome Limitation; Membrane Space Limitation; Response to Environmental Challenge; Summary	
17 Predictions: Diauxie, Electrons, Storage	291
Switching between Food Sources; Distributed Electron Flux; Storage When Resources Fluctuate; Challenges in the Study of Design	
18 Design Revisited	331
References	333
Index	369

1 Microbial Design

In the past, changes in gene expression and metabolic strategies across growth conditions have often been attributed to the optimization of ... growth rates. However, mounting evidence suggests that cells are capable of significantly faster growth rates in many conditions. ... Based on these observations, it is clear that [design] objectives other than optimization of ... growth rates must be considered to explain these phenotypes.

—Markus Basan²⁷

Why don't microbial cells grow as fast as possible? Perhaps cells trade growth rate for other attributes of success.

One widely discussed tradeoff concerns rate versus yield. Growing faster uses resources inefficiently. Resources wasted to increase metabolic rate lower the resources available to build new biomass. Fast growth rate reduces the reproductive yield.^{317,444}

Suppose we observe microbes that grow more slowly than the maximum rate that they could achieve. We see mutations that enhance growth. How can we know if the tradeoff between growth rate and yield dominates in metabolic design?

Typically, we cannot know. An observed rise in rate and decline in yield supports the tradeoff. But rejecting the rate-yield tradeoff hypothesis is difficult. For example, the microbes may produce toxins to kill competitors. If competitors are absent in our study, we may see increases in both rate and yield as the unobserved toxin production declines.

Other tradeoffs may be hidden. Perhaps growth trades off with dispersal. Maybe the microbes typically grow under iron-limited conditions and must trade growth rate for scavenging iron.

We could measure more tradeoffs. Although helpful, that approach ultimately fails. We can never estimate the many tradeoffs across the full range of natural conditions that shaped design.

Given those difficulties, how can we understand why growth rate is sometimes maximized and other times not? In general, how can we understand the forces that shape the design of microbial traits, such as dispersal, resource acquisition, defense, and survival?

I advocate comparative hypotheses. As a focal parameter changes, we predict the direction of change in a trait. For example, as the genetic heterogeneity among competitors rises, we predict an increase in growth rate.^{130,317} If the predicted direction of change tends to occur, then the focal parameter associates with a causal force that shapes the trait, revealing the fundamental forces of biological design.

This book divides into two parts. The first part presents the conceptual tools for making comparative predictions. The second part develops comparative predictions for metabolic traits.

We can use this approach to make comparative predictions for the full range of microbial traits, providing a general method for the study of biological design.

1.1 How to Read

Part 1 sets the theoretical background. How does one form and test predictions about the forces that shape biological design?

Part 2 turns to unsolved puzzles in microbial metabolism. How can we use Part 1's principles for the study of design to advance the understanding of microbial evolution?

Readers primarily interested in microbes may wish to start with the second part. As particular concepts arise in that second part, one may follow the pointers to the first part to fill in the background.

Readers primarily interested in evolutionary concepts may wish to start with the first part. The second part illustrates how to turn those concepts into a fully realized program of empirical study.

Although each part stands alone, the real value comes from the synergy between parts. Full progress demands combining Part 1's evolutionary concepts and general principles for studying causality with Part 2's application to metabolism, the engine of life.

That pairing between theory and application provides the best way to study the forces that have shaped biological design.

To help readers find their preferred starting point and path through the book, the following sections briefly summarize each chapter.

1.2 Theoretical Background

Organismal traits often seem designed to solve environmental challenges. Presumably, natural processes have shaped design. However, the underlying processes can be difficult to observe.

How can we study those causal forces of design? Somehow, we must link the hidden forces to the observed traits. Part 1 develops the theoretical background to meet that challenge.

Chapter 2 defines design in relation to biological fitness, the ultimate measure of success. Three fundamental forces of design often dominate. Marginal values measure trading one design for another. Reproductive values weight different components of fitness, such as reproduction, survival, and dispersal. Generalized kin selection links the similarity of interacting individuals with the transmission of traits through time.

Chapter 3 turns to the causal analysis of design. We can rarely match organismal traits to the forces of design that shaped those traits. Many particular forces played a role. We cannot measure or infer all of them.

Instead, we must focus on change. Can we predict how change in a specific factor alters a particular trait? For example, how does increasing genetic variability between competitors alter reproductive rate?

Comparing states of a particular factor isolates partial causality, the change caused holding all else constant. Comparative prediction becomes the building block of causal understanding. How does a changed factor alter a trait, mediated by a fundamental force of design?

Chapter 4 illustrates comparative predictions. The examples link changes in environmental factors to predicted changes in the metabolic traits of microbes. Each hypothesis associates the predicted change in a metabolic trait to a causal force of biological design.

The following chapters of Part 1 fill in the theoretical background needed to develop comparative predictions. Part 2 uses that theory to make comparative predictions about organismal design, with emphasis on microbial metabolism.

Chapter 5 reviews various forces that shape biological design. Marginal values, reproductive values, and generalized kin selection play key roles, as noted above. Natural history modulates forces of design. Examples include demography and complex life cycles, the scaling of spatial and temporal environmental variability, and the different timescales over which competing design forces act.

Chapter 6 notes that biological design concerns organismal traits. However, the nature of traits often remains vague. Different problems arise when studying the evolutionary origin of traits versus the modification of traits. Some traits change within an organism in response to the environment. Other traits may be genetically fixed, varying only between individuals rather than within them.

Chapter 7 extends discussion of traits that vary within an individual. Much of evolutionary design concerns the control of such traits in response to environmental signals. This chapter reviews principles of engineering control theory as they may be applied to biological design. Error-correcting feedback is perhaps the single greatest principle of design in both human-engineered and biological systems.

Chapter 8 contrasts this book's comparative predictions with historical antecedents. Darwin developed comparison in the study of adaptation. Classic phylogenetic comparative methods extended Darwin's vision.

This book differs primarily in the scale of change. Prior analyses typically studied change between species or higher taxa. By contrast, design forces often act at smaller scales of change. Those smaller scales set the focal point for this part's theory and the following part's application to microbial metabolism.

1.3 The Design of Metabolism

In microbes, large populations and short generation times provide opportunity to observe small-scale changes in action. Progress in technology and measurement opens new windows onto those small-scale changes. Part 2 takes advantage of this new era in the study of biological design to advance the testing of comparative hypotheses.

Chapter 9 explains the focus on metabolism. Extracting and using the free energy driving force from food is a universal challenge of life. Microbial metabolism provides a good starting problem to sharpen our tools in the study of biological design.

Chapter 10 illustrates comparative hypotheses and tests by analyzing microbial growth rate, typically measured as the increase in biomass. Growth rate seemingly provides the simplest trait by which to measure fitness, the long-term contribution to the future population.

However, tradeoffs arise. Faster short-term growth may use resources inefficiently. Lower efficiency reduces reproductive yield per unit food

uptake, slowing long-term growth as food gets used up. Comparatively, decreasing the available food raises the marginal gains for yield efficiency. Enhanced gains for yield predict lower short-term growth rate, driven by the fundamental force of marginal valuations between alternatives.

This chapter lists many comparative hypotheses. Those hypotheses link changes in natural history to predicted changes in growth rate. The analysis then turns to testing comparative hypotheses. Examples illustrate the kinds of data that have recently been collected in natural and laboratory populations.

Chapter 11 develops the universal challenge of extracting free energy from food to drive the processes of life. The thermodynamic driving force of free energy comes from moving low entropy electrons in food to high entropy electrons in final electron acceptors, such as oxygen.

Metabolic design exploits the increasing entropy between food and final electron acceptors to drive coupled reactions that decrease entropy. The decreased entropy of the driven reactions creates the ordered molecules of life or the entropy disequilibria, such as ATP versus ADP, that act as storage batteries to drive subsequent order-creating processes.

Textbook descriptions of biochemical thermodynamics often fail to emphasize how the entropy disequilibria in food drive the entropy disequilibria of life.^{18,47,294} Studying metabolic design requires focus on the flux of those coupled disequilibria through metabolic cascades.

Metabolic flux also depends on the resistance to reactions from chemical activation barriers. Cells modulate resistance by using enzyme catalysts or by changing the biochemical conditions. Net flux depends on the thermodynamic driving force divided by the resistance to reaction, an analogy with Ohm's law of electric current flow.

Chapter 12 describes how cells modulate flux by altering the thermodynamic driving force. The greater the displacement of a reaction from equilibrium, the greater the driving force and the rate of reaction. High driving force also causes the loss of potentially usable entropy change, typically dissipated as heat.

This chapter analyzes the design of glycolysis in terms of the thermodynamic tradeoff between reaction rate and usable entropy yield. Recent technical advances allow direct *in vivo* measurement of the driving force for individual reactions within the glycolytic cascade.

Those direct measurements open up new possibilities to study comparative hypotheses. For example, environmental changes in cellular

competition and genetic variability may alter the fine-scale design of metabolic flux control. Large-scale biochemical changes between alternative glycolytic pathways also pose interesting puzzles of design.

Overflow metabolism presents a key challenge. Many microbes excrete post-glycolytic products that contain most of the usable entropy in the original food source. Why overflow usable food? Disequilibria, thermodynamic driving force, and the tradeoff between rate and yield play important roles. Changed conditions alter overflow, providing a model to test comparative hypotheses about metabolic design.

Chapter 13 discusses the modulation of flux by altering the resistance of reactions. Mechanisms include varying enzyme concentration, modifying enzyme structure, and spatially separating reactants.

Changes in metabolic design may alter thermodynamic driving force or the resistance to reactions. Small changes typically occur by modulating current biochemical pathways. Larger changes may lead to different biochemical pathways. Other design goals shape pathways, such as the need for precursors to build particular molecules.

Constraining forces interact with design forces. For example, cell size constrains space for protein catalysts. Limited proteins impose tradeoffs between the potential to modulate different reactions.

Flux control has been widely discussed. However, clearly specified comparative hypotheses remain scarce with regard to the forces of design and constraint that have shaped metabolic diversity. This book sets the foundation on which to build comparative hypotheses and provides many examples of such hypotheses.

Chapter 14 turns to the observed diversity in metabolic pathways. The biochemical detail in this chapter raises many puzzles, setting a challenge for comparative predictions and tests of metabolic design.

In one example, different glycolytic pathways have different yields of ATP, NADH, and NADPH, each of which create distinct disequilibria that drive different cellular processes. In another example, the diverse final electron acceptors of catabolism create different entropy gradients, which greatly influence metabolic design. Weak gradients pose special design challenges.

Metabolic electron flow sometimes happens between cells of the same or different species. Distributed electron gradients raise novel puzzles in metabolic design. Those puzzles often depend on how particular biochemical disequilibria enhance or limit electron flow.

This chapter also analyzes the regulation of alternative sugar catabolism within cells and cellular shifts between different complex carbohydrate food sources. The chapter's conclusions synthesize puzzles of design for variant pathways.

Chapter 15 emphasizes tradeoffs, which set the basis for design. For example, faster growth reduces food use efficiency. Less permeable membranes protect against attack but slow resource uptake.

However, particular tradeoffs often fail to reveal design. Suppose growth rate, yield efficiency, and defense trade off. Less attack reduces investment in defense, potentially increasing both growth rate and yield. Without measurement of defense, one might see only the simultaneous rise in rate and yield, apparently contradicting the rate-yield tradeoff.

Comparative hypotheses about the tradeoffs themselves may help. For example, more abundant food weakens the tradeoff between growth rate and yield efficiency.

The more completely one understands the range of potential tradeoffs, the more effectively one can make comparative predictions. This chapter provides a preliminary catalog of the tradeoffs that shape the metabolic design of microbes.

Chapter 16 highlights the forces that shape overflow metabolism, the cellular excretion of usable food. Several challenges for inferring design emerge. Forces act over different timescales. Each empirical method reveals particular forces and timescales while hiding others.

Progress requires explicit consideration of the challenges and limitations in the study of biological design. The importance of clear comparative predictions and partial causation rises once again.

Chapter 17 continues the analysis of model problems in metabolic design. Part 1's forces of design play an important role as we broaden the range of metabolic traits and natural history.

When exposed to multiple foods, how do cells express alternative catabolic pathways? Sometimes, preferred foods repress pathways for other foods. Other times, cells simultaneously express different pathways. In some clonal populations, cells differ in expression patterns. Various design forces shape expression. Testable comparative predictions follow.

How do cells overcome limited access to final catabolic electron acceptors such as oxygen? Cable bacteria form filaments with electric wires. The wires pass electrons from anoxic zones to oxic zones, creating strong catabolic flux. Linked cells form various multicellular lengths, altering

life cycles, spatial competition, and the forces of design.

Other species use extracellular shuttle molecules to move electrons from cell surfaces to distant electron sinks. Shuttles, once released from producing cells, can be used by any neighboring cells. Such publicly shareable resources create special challenges. Demography and genetic mixing alter design forces in predictable ways.

When life cycles pass through habitats that prevent catabolism, how do cells store and use resources? Microbial wastewater treatment provides an interesting model system. The treatment passes bacteria through alternate anaerobic and aerobic habitats. Food is available only during the anaerobic phase. However, lack of oxygen prevents catabolism.

In that anaerobic habitat, cells transform food into internal storage. During the aerobic phase, cells catabolize the internal stores. Varying the alternative habitats changes the demographic forces of design.

Wastewater treatment and other industrial applications provide excellent model systems to test comparative predictions about the forces that shape metabolic design.

Chapter 18 revisits problems in the study of biological design.

Index

- ACTase (aspartate transcarbamoylase), 195–196
- activation energy, 150, 190–191, 193
- aerobic respiration, 161, 208
- age-specific fitness, 240
- age-specific forces, 292
- age-specific tradeoffs, 241
- agent-based computer simulation, 328, 330
- aging rate, and stress resistance, 242
- allosteric control, 195–196
- alternating habitats, 320–328
 - See also* wastewater treatment
- altruistic traits
 - Hamilton's rule for, 47, 244
 - in cable bacteria, 225, 303–304
 - See also* cooperation; public goods
- anabolic metabolism, and proteome allocation, 260, 264, 282–283
- anaerobic conditions, electron sinks in, 312–313
- anaerobic fermentation, 208, 312
- anaerobic respiration, electron acceptors in, 208
- anthrax, 19–20
- antibiotic resistance
 - genes for, 130–132
 - in quiescent state, 249
 - membrane permeability and, 171, 243
- antibiotics, oxidative damage caused by, 184
- antioxidant processes, 183, 284–285
 - See also* oxidative stress
- ATP
 - at equilibrium with ADP, 147
 - binding to ACTase, 196
 - generated by cable bacteria, 305–308
 - in wastewater treatment, 319
 - major catabolic pathways and, 160
 - membrane area limitation and, 168, 274
 - per unit protein, 168, 274
 - phosphorylation of enzymes by, 194–195
 - species differences in glycolytic driving force and, 161
 - yield with typical glycolytic pathways, 181
 - yield with variant pathways, 206–207
- ATP synthase, 274, 276
- ATP-ADP disequilibrium
 - alternative glycolytic pathways and, 179–182, 186–188, 206–207
 - driving coupled reactions, 147–148
 - driving force and, 152, 165
 - in aerobic metabolism, 162, 208
 - in balance between efficiency and growth, 199
 - in cellulose digesting species, 207, 223
 - overflow metabolism and, 164
 - powering cellular work, 180
 - storing negative entropy, 145–146, 180
- attack
 - by bacteriophage and bacteriocins, 316
 - growth rate and, 138, 140, 270
 - membrane pores and, 281
 - See also* warfare
- bacteriocins, 316

- bacteriophage, 218, 241, 243, 316
- Bacteroides*, polysaccharide
 - utilization by, 220
- bath surrounding the system, 143, 146
- bet-hedging, 79, 82, 216, 220, 249–250, 298
- biofilms
 - electrically conductive, 213
 - gene expression and, 131
- Bode plots, 110
- cable bacteria, 213, 225, 302–311
 - altruistic traits, 225, 303–304
 - ATP generation by, 305–308
 - budding and breaking, 310
 - competition and dispersal in, 310
 - cooperation in, 225, 310
 - electron acceptors for, 213, 302–303, 305, 308, 312
 - electron sink of, 213, 312
 - growth rate–yield tradeoff in, 309
 - habitat heterogeneity, 305
 - habitat niche construction, 309
 - hookups between cables, 311
 - interspecies links, 311
 - lengths of cables, 304–305
 - movement of cables, 304, 310
 - nickel-protein wires, 213, 303
 - population density, 304
 - sulfur cycling by, 307–308
- cancer-like overgrowth mutants
 - rate–yield tradeoff and, 35–38, 247
 - timescales of forces and, 72
- carbon dioxide, and methanogens, 208, 210, 213
- carbon limitation, and aerobic respiration, 169
- carbon sources
 - preference hierarchies, 214, 218, 220–222
 - See also* complex carbohydrates; diauxic shift
- catabolism
 - branching pathways, 209, 224
 - design of variant pathways, 121, 221–226
 - major pathways, 160
 - proteome efficiency of, 168
 - tradeoffs with anabolism, 282–283
- catalysts, 150
 - See also* enzymes
- causal inference
 - comparative predictions and, 2, 18–19, 116, 227, 331
 - direction of causation and, 25
 - partial causes and, 24–26, 39
- cell size
 - proteome constraint and, 174, 197, 200–201, 229, 281
 - spatial partitioning and, 229
 - See also* surface to volume (S/V) ratio
- cellulose digesting bacteria, 207, 223
- cheater control, 56–58
- chemical warfare
 - antibiotic resistance and, 130, 132
 - excluded in lab study, 251
 - oxidative stress caused by, 259
- chemostats, 134–135
- clades, selection between, 248
- Clostridium cellulolyticum*, 207, 223
- Clostridium thermocellum*, 207
- colony life cycle, stage-dependent traits in, 65–68
- comparative predictions
 - advantage of, 18
 - aggregated over different conditions, 18, 34, 125, 127, 135
 - alternative descriptions of, 39, 126
 - by Darwin, 21–22, 116
 - causal inference and, 2, 18–19, 116, 227, 331
 - direction of change and, 2, 19, 21, 26, 34, 116, 255
 - environmental changes and, 174, 178

- experimental evolution and, 134-136
- for complex dynamics, 328
- for growth rate, 32-34, 84-85, 137-139
- for membrane space limitation, 274-277
- for tradeoffs, 19-22, 34-35, 126, 139-140, 252
- for traits, 26-27, 32-34, 252, 254, 331
- general tendency and, 124-125
- genetic drift and, 198
- Lactobacilli as foundation for testing, 127-128
- mechanisms and, 85
- natural isolates in lab studies and, 131-133
- natural populations for testing of, 128-131
- not emphasized in the literature, 117
- partial causes and, 116, 254-255, 328
- PYK isoforms and, 286-287
- structure and notation of, 26-27
- testing of, 35, 127-137
- tradeoffs as building blocks of, 227-228
- competition
 - antibiotic resistance genes and, 130-132
 - by nonproducers, 18, 49, 313, 315-316
 - in cable bacteria, 310, 311
 - in two-habitat life cycle, 326-328
 - kin or similarity selection and, 12, 13, 30-31, 46-47, 49-51
 - local vs. global, 69-70, 72-73
 - of *E. coli* strains in experimental evolution, 136
 - of mixed species in experimental evolution, 135-136
 - opposing partial causes and, 24
 - pyruvate kinase variants and, 286-287
 - relative fitness and, 77
 - repression of, 56-58
 - sequential resource consumption and, 295
 - spatial scale of, 69, 72-73, 77, 79-80, 300-302
 - stage in colony life cycle and, 67-68
 - timescale of, 69-70, 72, 77
- complex carbohydrates, 27, 29, 40, 220-222, 245
 - cellulose digesting bacteria and, 207, 223
- complex life cycles, 320-328
- confounding factors
 - causal inference and, 24-26
 - comparative predictions and, 116, 125-126, 255
 - tradeoffs and, 19, 21
- consistent explanations, 117, 220, 221
- constraints
 - as nonadaptive forces, 198
 - cellular allocation and, 228-235
 - design forces and, 23, 163, 170-171, 174, 175, 178-179, 264-265, 273
 - evolutionary timescale and, 174-175, 178
 - genetic drift as, 198-199
 - mechanisms and, 163, 170, 179
 - modified by cells, 196-197
 - on evolutionary change, 265-269
 - sugar usage patterns and, 219
 - See also* membrane space limitation; proteome limitation
- control
 - frequencies of input and, 110, 112
 - of temperature, 198
 - performance metrics for, 102-104, 106, 109-110
 - principles of, 97-104
 - production of food receptor and, 95

- response to challenge signal and, 287
- signal amplification in, 105, 112
- small-scale biochemical modules and, 202
- tradeoffs in, 106, 108–113, 236–238, 250–251
- See also* error-correcting feedback; feedforward control
- cooperation
 - between species, 52–54
 - in cable bacteria, 225, 310
 - kin or similarity selection and, 12, 13, 18, 23–24, 49, 225
 - spatial scale of, 72–73
 - stage in colony life cycle and, 67–68
 - tradeoffs involving, 244–246
 - variant catabolic pathways and, 225–226
 - See also* altruistic traits; public goods; tragedy of the commons
- counterfactual analysis, 26
- coupled disequilibria, 145–148
- covariate, 24–26
 - See also* confounding factors
- Crabtree effect, 163
- cross feeding, 246
- cytidine triphosphate (CTP), 195
- cytochromes
 - ATP production in *E. coli* and, 276–277, 279
 - elemental limitation affecting, 257
 - extracellular electron transfer by, 312
 - in archaeal methanogens, 210, 224
 - interspecies electron transfer by, 212, 213
 - membrane space for, 274
 - trading off speed vs. efficiency, 178, 269
- Darwin, Charles, 21–22, 116
- decay rate
 - of secreted exoenzymes, 41
 - of transporters, 37, 38
- demographic cycle
 - challenge of empirical study, 15
 - long-term fitness and, 35–36, 138–139
 - with two food sources, 292–295, 297–302
- demography, 12–13
 - fitness value of traits and, 151, 161, 170, 197, 221
 - in alternating habitats, 320–328
 - patch lifespan and, 32, 39, 41
 - reproductive value and, 12–13, 23, 44–45, 60–65, 243, 322–323
 - wastewater treatment and, 318
- design forces
 - changes in, 115
 - comparative predictions and, 26–27, 35, 39, 254, 331
 - constraint forces and, 23, 163, 170–171, 174, 175, 178–179, 264–265, 273
 - control systems and, 99
 - environmental changes and, 174, 178, 221, 264, 314, 329
 - fitness components and, 170, 171
 - focus on clear understanding of, 328–330
 - fundamental forces, 12–14, 23, 26, 27, 29, 39, 41, 68
 - genetic drift and, 198–199
 - genetic variation and, 172, 174
 - in a complex life cycle, 320–328
 - in simple models, 329–330
 - mutational overgrowth and, 38
 - partial causes and, 23–26
 - physiological variation and, 174
 - pyruvate kinase isoforms and, 287
 - rate-yield balance and, 258
 - siderophore traits and, 313–317
 - sugar usage patterns and, 219
 - within-group vs. between-group, 69
 - See also* design, biological

- design, biological
 - advantages of microbes for studying, 117, 175, 331
 - biochemical mechanisms and, 151, 161
 - causes of, 115–116, 227
 - central role of tradeoffs and, 227
 - challenges in understanding of, 161
 - choice of glycolytic pathways and, 184–188
 - environmental factors and, 151, 156
 - fitness value of traits and, 151
 - insufficient focus on comparison and, 117
 - of cellular control, 98–99, 202
- diauxic shift, 214–218
 - bet-hedging and, 220, 250
 - classic studies, 214–215
 - gene expression patterns, 218–220
 - glucose as typically preferred sugar, 215
 - glycogen stores and, 231
 - growth rate–regulatory tradeoff and, 236
 - patch lifespan and, 292–295
 - proteome limitation and, 215, 296–297
 - variability among genotypes, 216–217
 - variability within clones, 215–216, 218
 - with unpredictable resource influx, 297–302
- differential equation analysis, 328, 329
- diffusion
 - across membranes, 197, 281
 - limited cellular volume and, 229
 - of electron shuttles, 311–313
 - of siderophores, 316
 - similarity and, 245
 - temperature and, 197
- diffusion-limited reactions, 197, 229
- disequilibria
 - coupled, 145–148
 - free energy change and, 148
 - membranes and, 197
 - See also* ATP–ADP disequilibrium; NADH–NAD⁺ disequilibrium; NADPH–NADP⁺ disequilibrium; storage disequilibria
- dispersal
 - as fitness component, 13
 - bet-hedging and, 249
 - in class-structured model, 60–65
 - in demographic cycle, 35–36
 - of cable bacteria, 310
 - patch lifespan and, 39, 41, 125, 126, 139
 - population growth rate and, 63, 65
 - reproductive value and, 68, 243
 - tradeoff with growth rate, 125, 126, 136, 138
 - tradeoff with reproduction, 13
 - tradeoff with survival, 60, 62–64
 - tradeoffs involving, 242–243, 247
- dormancy, 131, 242–243, 249
- driving force
 - flux control and, 150, 152–153
 - flux rate and, 150, 182, 184, 258
 - flux ratio and, 148
 - free energy of food inputs, 155
 - in glycolysis, 157, 161
 - mechanisms to modify, 190
 - of electrons flowing toward attractors, 182–183
 - proteome cost and, 185–186
 - tradeoffs involving, 237–240
 - weak redox gradients and, 205, 208–210
 - yield efficiency and, 181–182, 184
- dual function of a molecule, 237
- dynamical models, 329–330
- E. coli*
 - bacteriophages that attack, 241
 - cross feeding with *Salmonella enterica*, 246

- cytochromes in, 276–277, 279
 - diauxic shift in, 214–215, 231
 - growth rate–maintenance tradeoff, 241
 - growth rate–motility tradeoff, 136
 - membrane space limitation, 274–276, 278–279
 - overflow metabolism, 163, 176–178, 256, 259–261, 265–268, 274, 278–279
 - phosphate or carbon limitation, 230
 - proteome limitation, 278–279
 - pyruvate kinase isoforms, 286
 - redox imbalance in, 239
 - stress response, 241, 242, 282
 - sugar usage hierarchy, 218, 222
 - surface to volume ratio, 276, 278, 279
- ED (Entner-Doudoroff) pathway, 180–188
- efficiency of reactions
 - as useful fraction of entropy, 146–147, 149
 - flux trading off against, 148–153
 - See also* yield efficiency
- electrodes, multispecies biofilms on, 213
- electron acceptors
 - alternative, 208, 302
 - carbon dioxide for methanogens, 208, 210, 213
 - elemental sulfur, 208, 306–309
 - entropy increase in catabolism and, 165, 302
 - ferric iron, 212, 312
 - for cable bacteria, 213, 302–303, 305, 308, 312
 - nitrate for cable bacteria, 302, 305, 308
 - overflow metabolism due to scarcity of, 257, 263
 - strength of, 207–208
 - sulfate, 208
 - variant pathways leading to, 209, 224
 - See also* electron sinks; oxygen as electron acceptor
- electron donors, 211
 - cable bacteria in anoxic sediment, 213
 - See also* food sources
- electron flow between species, 211–213
- electron shuttles, extracellular, 212, 225, 291, 311–313, 317
- electron sinks
 - abiotic, 225
 - challenge of anoxic conditions and, 211, 312
 - extracellular, 312
 - of internal catabolic cascade, 312
 - See also* electron acceptors
- electron transport
 - by extracellular shuttles, 225
 - in anaerobic respiration, 208
 - in archaeal methanogens, 210, 224
 - inner bacterial membrane and, 279, 281
 - membrane space limitation and, 167, 171, 256–257, 274, 275, 281
 - NADH–NAD⁺ disequilibrium and, 165, 168, 178, 256–257, 268–269, 274
 - oxidative damage associated with, 184, 187
 - oxygen availability and, 159
 - proteome allocation and, 262
 - speed vs. efficiency of, 178, 269
 - tradeoff with food uptake, 167–168, 228
 - See also* cytochromes
- elemental limitation, 235, 257, 263
- EMP (Embden–Meyerhof–Parnas) pathway, 180–181, 183–188
- variants of, 206–207, 223
- energy, 142–145
 - See also* free energy
- Entner-Doudoroff (ED) pathway, 180–188

- entropy change, 142-145, 147-149, 182
- environmental change
 - design forces and, 174, 178, 221, 264, 314, 329
 - frequencies of control input and, 110, 112
 - generative processes enhanced by, 85
 - switch in isoform expression and, 288
 - timescales and, 315
- environmental conditions
 - altering fitness costs and benefits, 161, 170
 - design forces and, 174, 178-179
 - in experimental evolution, 175, 177, 178
 - in two habitats, 320-323
 - modifying proteome size and, 196-197
- environmental fluctuations
 - fitness and, 287-289
 - in resource flows, 297-302
- environmental heterogeneity
 - favoring evolvability, 139, 140
 - growth lag in diauxic shift and, 217
- enzymes
 - elemental constraints and, 263
 - metabolic flux control and, 152-153, 193-196, 237
 - nitrogen upshift and, 158
 - oxygen upshift and, 159
 - phosphorus upshift and, 159
 - phosphorylation of, 194-195
 - proteome limitation on, 196
 - shifts in concentrations of, 193-194, 196, 237
 - transcription and translation rates, 193-194
 - transcription factors for, 196
 - See also* exoenzymes
- equilibrium, 147-148
- equilibrium constant, 147-148
- error-correcting feedback, 96-97
- costs of, 250
- design architecture and, 98-100
- optimal control and, 103-104
- performance metrics for, 102-103, 106, 109-110
- robust design and, 97, 106-108, 111, 250
- signal amplification in, 105, 112
- steering a car and, 105-107
- eukaryotes
 - almost all lacking ED pathway, 187
 - enzyme modification in, 195
 - localization of reactions in, 197
 - mitochondrial membrane, 168, 277
 - overflow metabolism in, 163
 - pyruvate kinase isoforms, 286
 - See also* yeast
- evolutionary constraints, 265-269
- evolutionary rate, and generative processes, 85
- evolutionary response
 - in complex life cycles, 320
 - physiological constraints and, 265-266, 271
 - vs. organismal response, 22-23
 - See also* natural selection
- evolutionary stochasticity, 198-199
- evolutionary theory, and
 - comparative predictions, 117
- evolutionary timescale, 174-179, 264, 315
 - See also* experimental evolution
- evolvability
 - growth rate and, 139, 140
 - tradeoffs involving, 248
- exoenzymes, 23, 41, 47
 - for digesting complex carbohydrates, 27, 29, 40, 221-222, 245
- experimental evolution, 175-179
 - favoring yield over rate, 271-273
 - limited by taxonomic level, 137
 - of overflow metabolism in *E. coli*, 176-178, 265-268

- rate-yield tradeoff in, 134–136, 245
 - See also* evolutionary timescale
- FADH₂, 160
- fecundity
 - colony life cycle and, 65–68
 - See also* reproduction
- feedback. *See* error-correcting feedback
- feedforward control, 95, 99, 100, 106
 - See also* open loop control
- fermentation
 - anaerobic, 208
 - in *S. cerevisiae* diauxic shift, 215
 - mixed-acid, 209
- ferric iron, 212, 312, 313, 317
 - See also* siderophores
- ferrous iron, 313, 317
- Fisher information, 111
- fitness, 11–12
 - absolute vs. relative, 75–77
 - colony life cycle and, 65–66
 - defined, 11
 - difficulty of fully measuring, 16, 27
 - environmental fluctuations and, 287–289
 - fundamental forces and, 12–14, 68
 - genetic drift and, 198
 - in class-structured model, 61–64
 - in two alternating habitats, 322–328
 - lowered by variation in reproduction, 73–75
 - organismal design and, 151
 - similarity and, 46–51
 - spatial scale of competition vs. cooperation and, 72–73
 - See also* reproductive success; success
- fitness components
 - cellular control traits and, 202
 - colony life cycle and, 65–66
 - design forces and, 170, 171, 174, 178
 - marginal gains and losses of, 68
 - reproductive values of, 13, 44, 60–62, 68
 - spatial scales and, 73
 - tradeoffs involving, 240–243
- fitness landscape
 - multipeak, 90
 - phenotypic plasticity and, 90–93
 - stochasticity and, 87–90, 93
- fitness matrix, 61–63
- flavin shuttles, 317
- flux
 - as force divided by resistance, 150
 - tradeoff with captured free energy yield, 182, 184, 258
 - tradeoff with redox imbalance, 239
 - tradeoffs between efficiency and, 150–153
 - See also* reaction rate
- flux modulation, 155
 - enzymes and, 152–153, 193–196
 - genetic drift and, 198
 - mechanisms for, 150–153, 193–198
 - metabolite concentrations and, 152–153, 156
 - of near-equilibrium flux, 156, 200
 - overflow metabolism and, 155
 - problems of, 200–201
 - See also* driving force; resistance against flux
- flux ratio, 148, 149, 157
- food sources
 - negative entropy in, 143, 145–146, 150, 164
 - of archaeal methanogens, 210
 - pathways for absent sources, 282
 - tradeoffs in acquisition of, 229
 - tradeoffs involving limitations of, 234–235
 - See also* carbon sources
- force, metabolic. *See* driving force

- forces of design. *See* design forces
- free energy change
 - entropy change and, 142, 144-145
 - equilibrium and, 147-148
 - final electron acceptors and, 207-208, 223-224
 - fraction captured by storage disequilibria, 181
 - reaction rate and, 148-149
- free energy, of intermediate complex, 190-191, 193
- free radicals, and oxidative stress, 173, 183, 187
- frequencies of competing genotypes, 76-80
- frequencies of control input, 110, 112
- futile cycling, 167, 223, 240
- gene expression
 - explanations of sugar usage and, 218-220
 - patterns in lab studies, 131-134
 - transcription factors and, 196
 - variability in diauxic shift and, 215-217
- generative processes, 85
- genes, horizontally vs. vertically transmitted, 14
- genes-first pathway to new traits, 86, 92
- genetic drift, 198-199
- genetic mixing, and growth rate, 33, 84, 137
- genetic variation, and design forces, 174
- genome size, 200, 230, 235-236, 244
- genomic competition within cells, 247
- genomic rearrangements, 85
- genotypes-first pathway to novelty, 86, 92
- Geobacter*, conducting pili of, 212, 312
- geochemical cycles
 - cable bacteria in, 303
 - weak driving force gradients and, 205
- geometric mean, 74-75
 - of individual's reproductive success, 81
 - spatial scale of competition and, 79-80
- Gibbs free energy. *See* free energy
- glucose uptake
 - membrane limitation and, 276-277
 - proteome demand for building biomass and, 169
 - tradeoff with electron transport, 167-168, 274
 - uptake of oxidizing agents and, 184
 - See also* nutrient uptake; transporters, cell surface
- glucose uptake rate, and yield, 265-268
- glucose, ATP yield of, 160
- glycogen, storage of, 231-234, 319-320
- glycolysis, 156-161
 - alternative pathways of, 179-188
 - catabolic pathways connected to, 160
 - in eukaryotes, 277
 - nitrogen or phosphorus upshift and, 157-159
 - oxygen upshift and, 159
 - proteome efficiency of, 168-169, 274
 - species differences in anaerobic driving force, 161
 - thermodynamic inhibition of driving force, 164-169
 - weak redox gradients in, 210
 - with excess enzyme, 237
 - See also* overflow metabolism
- group selection, 51
- growth
 - as reproduction in microbes, 240

- evolutionary timescale and, 136-137
- of multicellular organisms, 240
- storage molecules and, 231-234, 319
- growth rate
 - anaerobic glycolytic driving force and, 161
 - as primary fitness component in labs, 217
 - comparative predictions for, 32-34, 84-85, 137-139
 - definitions of, 170, 176
 - fast PYK isoform and, 286
 - literature emphasizing maximization of, 221
 - long-term, 123-124, 139
 - mechanistic basis of, 84-85
 - oceanic bacterial genomes and, 130
 - overflow metabolism and, 163, 169, 260-261
 - oxidative damage and, 240
 - patch lifespan and, 33-34
 - phosphorus requirement and, 230
 - proteome demand and, 168-169
 - proteome limitation and, 196-197, 257
 - stress response and, 242, 282
 - timescales of competition and, 246-247
 - See also* population growth rate
- growth rate tradeoffs
 - with aging rate, 242
 - with dispersal, 138, 140
 - with long-term success, 139
 - with maintenance, 241
 - with motility, 136
 - with nickel tolerance, 130-131
 - with regulatory control, 236
 - with stress resistance, 241-242
 - with survival, 241
 - with yield and maintenance, 125, 127, 129
- growth rate-yield tradeoff, 1, 30-32, 123-124, 241
- biochemical reaction rates and, 238
- cell surface transporters and, 30, 36, 37, 84-85
- comparative predictions for, 34-35, 269-270
- competition among mixed species and, 135-136
- confounding factor and, 21, 251
- cooperation with other lineages and, 244
- demographic factors and, 170
- design forces acting on, 269-270
- environmental factors and, 170
- in cable bacteria, 309
- in chemostat, 134-135
- in experimental evolution, 266-268
- in sequential sugar usage, 293
- in two-habitat life cycle, 326-328
- increased resources and, 85, 128-129, 134, 138, 139
- long-term success and, 139
- mitochondria in yeast and, 230
- overflow metabolism and, 164, 257-259, 261
- patch lifespan and, 31-32, 35-38, 124, 126, 140, 270, 309
- proteome limitation and, 264
- pyruvate kinase variants and, 173, 283
- resource reallocations and, 258
- ribosomal number and, 128-130, 230
- sugar availability and, 34
- time limitation and, 268, 270
- timescales and, 246-247
- with cancer-like overgrowth mutants, 35-38, 247
- Hamilton's rule, 47, 244
- heat, 143-146, 148, 152
- HMP (hexose monophosphate) pathway, 180-182, 184-185
- homeostasis
 - internal sensors for, 110

- performance metric and, 102–103
- vs. responsiveness, 108–110, 112, 251
- human gut microbes, 222
- hydrogen
 - as methanogen food source, 210–212, 224
 - cable bacteria generating ATP with, 306
 - in bacteria-methanogen syntrophy, 211
- hydrogen sulfide, hydrolyzed by cable bacteria, 213, 225, 302–309
- inclusive fitness, 51, 244
- industrial microbiology. *See* wastewater treatment
- intermediate reaction complex, 150, 190–191, 193
- interspecies electron transfer, 211–213
- intervening variable, 25
- iron. *See* ferric iron; ferrous iron; siderophores
- kin or similarity selection
 - as fundamental design force, 12, 68, 329
 - as interchangeable phrases, 52
 - as mediating force, 115
 - between different species, 72
 - cooperative tradeoffs and, 245
 - genetic relatedness in a patch and, 31
 - growth rate–yield tradeoff and, 269
 - in cable bacteria, 225
 - in multicellular organisms vs. microbes, 71–72
 - in simple models, 329
 - publicly shared factors and, 18
 - reproductive value and, 61
 - timescales and, 71–72
 - See also* similarity
- kinases, 195
- kinetic control, 191–193
- kinship group, 51
- Lactobacilli, for testing comparative hypotheses, 127–128
- Lactococcus lactis*, 215–216, 271–272
- life cycles. *See* colony life cycle; complex life cycles
- life history analysis, 61, 240–243
- Listeria monocytogenes*, electron shuttles, 317
- maintenance
 - rate–yield association and, 125, 127, 129–130
 - transcription factors and, 241
- mammalian cells, overflow metabolism in, 163
- marginal value, 13–14, 68, 329
- tragedy model and, 55–56
- mechanisms
 - altering driving force and resistance, 190
 - comparative predictions and, 84–85, 178
 - constraints and, 163, 170, 178
 - of metabolic components, 199
 - tradeoffs and, 19–20
 - understanding design and, 161
- mediating force, 24, 27, 115–116, 126
- membrane permeability
 - design forces and, 171
 - oxidative stress and, 184, 242
 - susceptibility to attack and, 238, 241, 243
- membrane space limitation
 - cell surface transporters and, 167, 170, 217, 228, 257, 274–277, 281
 - combined with proteome limitation, 277–280
 - comparative predictions and, 274–277
 - electron transport and, 256–257, 274, 275, 281

- overflow metabolism and, 167-168, 273-281
- tradeoffs imposed by, 228, 281
- membranes
 - disequilibrium and, 197
 - of gram negative bacteria, 280-281
 - tradeoffs involving, 238
- metabolic rate. *See* flux
- metabolite concentrations, 152-153, 156
- metagenomic analysis, 130, 131
- metal ions, as final electron acceptors, 208
- Methanococcus maripaludis*, 129
- methanogens, archaeal
 - allocation to maintenance, 129
 - bacterial syntrophy with, 211-212, 225
 - carbon dioxide as electron acceptor, 208, 210, 213
 - cytochromes in, 210, 224
- Methanosarcinales clade, 210, 224
- mitochondria in yeast, and growth rate-yield tradeoff, 230
- mitochondrial membrane
 - free radical confinement by, 187
 - glycolytic overflow and, 168
 - surface and volume tradeoffs, 277
- mixed-acid fermentation, 209
- motility, 136, 229, 236, 249
- mRNA, tradeoffs of, 236
- mutants, fast-growing, 35-38, 247
- mutations
 - as traits, 85
 - similarity and, 51
 - tradeoffs involving, 248
- mutualism, 54
- NADH-NAD⁺ disequilibrium
 - alternative glycolytic pathways and, 180-182
 - driving ATP-ADP disequilibrium, 180
 - in major catabolic pathways, 160
 - overflow metabolism and, 166, 168, 178, 256-257, 263, 268-269, 274
- NADH-NAD⁺ redox imbalance, 164-167, 178, 239, 256
- NADPH-NADP⁺ disequilibrium
 - alternative glycolytic pathways and, 180-187
 - oxidative stress and, 180, 182-184, 187, 284, 286, 287, 289
 - primary functions of, 180
- natural history, 194, 203, 251
- natural selection
 - at multiple levels, 247-248
 - climbing a fitness gradient, 91, 92
 - constraints setting boundaries on, 290
 - cooperative traits and, 244
 - evolutionary forces working against, 220
 - forces of, 23
 - growth rate in experimental evolution and, 265, 267
 - making small adjustments in traits, 85
 - phenotypic plasticity and, 90-92
 - reducing variation in performance, 75
 - within-group vs. between-group, 70
- near-equilibrium flux, 156, 200, 209
- near-equilibrium glycolysis, 156-161, 237
- negative entropy
 - captured in disequilibria, 179-181
 - in food, 143, 145-146, 150, 164
- nickel tolerance to toxicity, 130-131
- nickel-protein wires, 213, 303
- nitrate, as electron acceptor for cable bacteria, 302, 305, 308
- nitrogen upshift, and glycolysis, 157-159
- nitrogen, oxidized, as final electron acceptor, 208
- nonadaptive forces, 198

- nucleotide synthesis, regulation of, 195-196
- nutrient uptake
 - alternative systems for, 229
 - membrane space limitation and, 274, 275, 281
 - oxidative stress and, 184
 - See also* glucose uptake; transporters, cell surface
- observable effect, 115-116
- observable partial cause, 115
- oceanic prokaryotes
 - extracellular enzymes of, 246
 - genome size, 236
 - rare vs. dominant bacteria, 130
- Ohm's law, 150
- open loop control, 99, 100, 107, 111
 - See also* feedforward control
- opposing partial causes, 24, 39-40
- optimal control, 103-104
- organismal response, vs.
 - evolutionary response, 22-23
- overflow metabolism, 255-256
 - design puzzles, 155-156, 170-171, 255-256, 259
 - experimental evolution in *E. coli*, 176-178, 265-268
 - growth of neighboring cells and, 185
 - mechanisms, 161-169
 - membrane space limitation and, 274-280
 - natural variation in, 172-174
 - possible explanations for, 256-259
 - proteome limitation and, 174, 257, 259-262, 269, 271, 273, 274
 - pyruvate kinase variants and, 172-173, 283, 285-287
 - small free energy gradients and, 208-210
 - thermodynamic product
 - inhibition and, 155-156, 208-210, 239, 256, 262
 - with a second organism
 - completing oxidation, 211
- oxidative phosphorylation, 160, 208, 223, 228, 256-257, 268
- oxidative stress
 - aerobic respiration and, 173, 187, 259
 - cable bacteria and, 303
 - HMP pathway and, 181
 - in chemical warfare between species, 259
 - in mitochondria of eukaryotes, 187
 - in plants with ED pathway, 187
 - increased death due to, 259
 - membrane permeability and, 184, 242
 - NADPH-NADP⁺ disequilibrium and, 180, 182-184, 187, 284, 286, 287, 289
 - overflow metabolism and, 259
 - pentose phosphate pathway and, 284-287, 289
 - pyruvate kinase variants and, 173, 286, 287
 - strong electron acceptors and, 240
 - tradeoffs involving resistance to, 283
 - See also* stress response
- oxygen as electron acceptor
 - as strong final acceptor, 208, 211, 240, 302
 - for cable bacteria, 213, 302-303, 305, 308
 - overflow metabolism due to limitation of, 257, 263
 - pathway architecture and, 224
- oxygen upshift, and glycolysis, 159
- parameters, 2, 24-27, 254-255
 - sensors as estimators of, 111
- parasite virulence, 15-16
- Pareto frontier, 21
- partial causes, 23-26, 39

- comparative predictions and, 116, 254-255
- observable, 115
- of siderophore traits, 316
- opposing, 24, 39-40
- separating from alternatives, 126
- simple models and, 329-330
- patch lifespan
 - as time constraint, 270
 - demography and, 32, 41
 - dispersal and, 41, 125, 126, 139
 - functional gene classes and, 131-132
 - growth rate and, 33-34, 39
 - growth rate-yield tradeoff and, 31-32, 35-38, 124, 126, 140, 270, 309
 - mutational overgrowth and, 35-38
 - sequential sugar usage and, 292-295
 - tradeoffs involving, 139-140
- pentose phosphate pathway (PPP), 180, 184, 284-287, 289
- performance metrics for control systems, 102-104, 106, 109-110
- performance versus stability, 106, 112, 251
- PHA (polyhydroxyalkanoate), 232-234, 319
- phenazines, 212, 225
- phenotype-first pathway to novelty, 86-93
- phenotypic plasticity, 22-23, 90-93
 - of switching between PYK isoforms, 287
- phenotypic similarity, 12, 49-51
- phosphatase enzymes, 195
- phosphorus
 - removal from waste, 233-234, 318-320
 - restricted, 235
- phosphorus upshift, and glycolysis, 159
- phosphorylation of enzymes, 194-195
- phylogenetic methods, 116, 186, 331
- physiological variation, and timescale, 174
- pili, electric, 213, 312
- policing, 56-58
- polyhydroxyalkanoate (PHA), 232-234, 319
- polyphosphate, 232-234, 319-320
- polysaccharide utilization loci (PULs), 220
- population growth rate
 - dispersal and, 63, 65
 - variation in, 73-75
 - See also* growth rate
- porins, 280-281
- PPP (pentose phosphate pathway), 180, 184, 284-287, 289
- product inhibition, and overflow metabolism, 155-156, 208-210, 239, 256, 263
- proteome allocation
 - for anabolic metabolism, 260, 264, 282-283
 - for sequential sugar usage, 293-297
 - tradeoffs in, 230, 234-235, 282-283
- proteome cost
 - for enzymes, 182, 185-186
 - of EMP vs. ED, 185-186
- proteome efficiency, 168-169, 260-261, 274
 - plants with ED pathway and, 187
- proteome limitation
 - cell size and, 174, 197, 200-201, 229, 281
 - combined with membrane limitation, 277-280
 - diauxic shift and, 215, 296-297
 - experimental increase in, 282
 - flux modulation and, 196-197, 200-201
 - food unpredictability and, 282-283

- overflow metabolism and, 174, 257, 259–262, 269, 271, 273, 274
- phosphorus restriction and, 235
- stress resistance and, 282, 283, 289
- warfare and, 244
- public goods
 - cable bacteria and, 309, 310
 - cellular heterogeneity and, 40, 58–60
 - colony life cycle and, 66–68
 - cooperation and, 12, 18, 23, 49
 - defined, 49
 - dispersal model with, 64
 - external digestion and, 221–222
 - extracellular electron shuttles as, 311
 - flavin shuttles as, 317
 - repression of competition as, 58
 - secreted proteins in natural populations, 128
 - siderophores as, 12, 18, 313–314
 - similarity and, 12, 19, 22, 47–49
 - spatial scales and, 72–73
 - stage-dependent benefit of, 41
 - vigor and, 40, 58–60
- pyruvate, 160
- pyruvate kinase (PYK), 172–173, 283, 285–289
- quinones, 212, 225
- quorum sensing, 29, 40, 131
- random mutagenesis method, 133
- randomization, controlled, 25, 116–117
- rare vs. dominant oceanic bacteria, 130
- rare-type advantage, 76–80, 301
- rate efficiency, 182
- rate-yield tradeoff. *See* growth rate-yield tradeoff
- reaction intermediate, 150, 190–191, 193
- reaction quotient, 147–148
- reaction rate, 148–149, 152, 238–240
 - See also* flux
- reactive oxygen species (ROS), 240, 286, 287
- receptors
 - for siderophores, 313, 315–316
 - See also* transporters, cell surface
- redox gradients, 205, 208–211
- redox imbalance. *See* NADH-NAD⁺ redox imbalance
- redox potential, 164
- regulation. *See* control
- relative fitness, 75–77
- reproduction
 - defined as growth for microbes, 240
 - survival and dispersal relative to, 11–13
 - variation in, 73–74
 - See also* fecundity
- reproductive success
 - hierarchical structure of
 - variability in, 78–79
 - multiple traits determining
 - variability in, 80–82
 - relative fitness and, 76–77
 - See also* fitness
- reproductive value, 12–13, 68
 - colony life cycle and, 66, 68
 - demography and, 12–13, 23, 44–45, 60–65, 243, 322–323
 - dispersal and, 68, 243
 - in simple models, 329
 - similarity selection and, 61
- resistance against flux
 - altering in short term, 192
 - intermediate reaction complex and, 190–191
 - mechanisms to alter, 150–153, 190, 193–198
 - tradeoffs involving, 237–239
- resource patches. *See* patch lifespan
- resource-poor environments
 - allocation to maintenance and, 129–130

- functional gene classes in, 131, 132
- reproduction vs. dispersal in, 13
- slow growth of rare microbes in, 130
- tradeoffs in, 229, 234–236
- resource-rich environments
 - fast growth in, 128–130, 134
 - functional gene classes in, 131
 - limiting benefits of dispersal, 140
 - limiting benefits of warfare, 140
 - marginal attack benefit and, 138
 - rate-yield tradeoff and, 138, 139
 - reproduction vs. dispersal in, 13
 - tradeoffs in, 229, 230
- response functions, 22–23, 135
- responsiveness
 - performance metric and, 102–103
 - vs. homeostasis, 108–110, 112, 251
- ribosomal number, 128–130, 196, 230
- robust design, 97, 106–108, 112, 250
 - See also* error-correcting feedback
- RpoS, 241, 282
- Saccharomyces cerevisiae*
 - diauxic shift, 215–217, 292
 - overflow metabolism, 163, 166, 256
 - rate-yield tradeoff in chemostat, 134–135
 - stress resistance vs. growth rate, 242
- Salmonella enterica*, cross feeding with *E. coli*, 246
- Schizosaccharomyces pombe*, 172–174, 242
- sensors, 99, 110, 113
 - tradeoffs of, 235–237
- Serratia marcescens*, 135–136
- siderophores, 313–317
 - analogies with electron shuttles, 313, 317
 - as public goods, 12, 18, 313–314
 - diffusion of, 316
 - diversifying forces of competition, 315–316
 - genetic structure, 314–315
 - heterogeneity in vigor, 40, 315
 - partial causes of traits, 316
 - receptors for, 313, 315–316
 - relatedness and secretion of, 314, 316, 317
 - response to changed conditions, 22
 - simple tragedy model and, 47
 - spatial scale of competition, 316
- similarity
 - basic model of, 46–48
 - causes of, 12, 51, 71–72
 - cooperative traits and, 244–246
 - dispersal and, 64
 - growth rate and, 137
 - of cable bacteria cells, 303–304
 - patch lifespan and, 139
 - phenotypic, 12, 49–51
 - public goods and, 12, 19, 22, 47–49
 - rate-yield tradeoff and, 30–31
 - reproductive success and, 68
 - restrictive assumptions about, 51
 - timescales and, 70–72
 - tragedy of the commons and, 46, 48, 64, 71
 - See also* kin or similarity selection
- social network of cells, 197
- social selection, 52
- spatial scales, 69, 70, 72–73, 77, 79–80, 300–302
 - siderophores and, 316
- spatial separation, intracellular, 197, 229
- sporulation, 131
 - See also* dormancy
- stability
 - of metabolic products, 150
 - vs. performance, 106, 112, 251
- stage-dependent traits, 41, 65–68
- steering a car, 105–107
- stochasticity
 - fitness landscape and, 87–90, 93

- of biological functioning, 96–97
- of system components, 112
- storage disequilibria
 - as negative entropy in usable form, 145–146
 - final electron acceptors and, 207–208
 - glycolytic pathways and, 179–182, 184, 206–207
- storage molecules, 230–231
 - in wastewater treatment, 231–234, 318–320
 - intracellular in two habitats, 320–328
- stress response
 - aging-growth tradeoff and, 242
 - proteome limitation and, 282, 283, 289
 - pyruvate kinase variants and, 283
 - vs. growth rate, 242, 282
 - See also* oxidative stress
- success, 123
 - long-term, 138–139
 - See also* fitness; reproductive success
- sugar usage hierarchy, 218, 222
 - See also* diauxic shift
- sulfate, as final electron acceptor, 208
- sulfide, and cable bacteria, 213, 225, 303–309
- sulfidogens, 208
- sulfur cycling, 307–309
- sulfur, elemental, as final electron acceptor, 208, 306–309
- surface to volume (S/V) ratio, 275, 278, 279, 281
 - See also* cell size; membrane space limitation
- survival
 - colony life cycle and, 65–68
 - in a complex life cycle, 321, 325–328
 - pyruvate kinase variants and, 173
 - reproductive value and, 68
 - tradeoff with dispersal, 20, 23, 60, 62–64
 - tradeoff with reproduction, 13
 - vs. growth rate, 241
- synergistic traits, 12, 54, 92, 229, 245, 311
- syntrophic bacteria, 211–212, 225
- system dynamics, of second-order systems, 100–104, 106
- system, thermodynamic, 143
- taxonomic variation, 175
- TCA cycle
 - glycolytic pathways and, 185
 - major catabolic pathways and, 160
 - NADH-NAD⁺ disequilibrium and, 166–168, 178, 256–257, 274
 - NADH-NAD⁺ redox imbalance and, 256
 - overflow metabolism and, 260–261, 263, 274
 - oxygen availability and, 159
 - temperature, and flux modulation, 198
- Thermincola*, electron shuttle of, 312
- thermodynamic control, 191–193
- thermodynamic driving force. *See* driving force
- thermodynamic rate versus yield, 258
- time limitation, 268, 270
- timescales, 14, 69–72
 - demographic life cycle as, 138–139
 - evolutionary, 174–179, 264, 315
 - fast-growing mutants and, 36
 - of metabolic flux control, 152–153
 - relative fitness and, 77
 - tradeoffs involving, 246–248
- tradeoffs
 - as building blocks of comparisons, 227–228
 - as observable effects, 115

- comparative predictions for, 19–22, 34–35, 127, 139–140, 252
- conflicting, 126
- cooperative traits and, 244–246
- dual function and, 237
- fitness components and, 240–243
- impossibility of estimating all, 1, 227–228
- in control of systems, 106, 108–113, 236–238, 250–251
- in modulation of driving force and resistance, 237–240
- marginal values and, 55–56
- multidimensional embedding of, 21
- of cellular allocation under constraints, 228–235
- of exploitation vs. regulation, 235–237
- of exploration vs. exploitation, 235–236, 248–250
- reproductive value of classes and, 68
- role in relation to design, 227
- shifting dominance of
 - alternatives, 129–130, 139–140, 251, 278, 282
- timescales and, 246–248
- tragedy of the commons, 45–46, 48, 50
 - colony life cycle and, 65–68
 - dispersal and, 64
 - in two-habitat life cycle, 327
 - marginal values and, 55–56
 - repression of competition and, 56–58
 - within-group vs. between-group forces and, 71
- traits
 - abstract and mechanistic perspectives on, 84–85
 - as observable effects, 115
 - bet-hedging of alternative states for, 249–250
 - comparative predictions for, 26–27, 32–34, 254, 331
 - generative processes as, 85
 - modification of, 85
 - organismal design and, 151
 - origin of, 85–93
 - partial causation of, 24–26
 - relative success of, 75–77
 - stage-dependent, 41, 65–68
 - three measures of value and, 68
 - tradeoffs in regulatory control of, 111–113
 - variable performance of multiple traits, 80–82
- transcription factors, 196, 241
- transcription rate, 193–194, 237
- translation rate, 193–194
- transporters, cell surface
 - bacteriophage attack at, 218, 243
 - for alternative sugars, 217
 - in gram negative bacteria, 281
 - membrane space limitation and, 167, 170, 217, 228, 257, 274–277, 281
 - nutrient uptake rate vs. cost of, 229
 - overflow metabolism and, 257
 - rate-yield tradeoff and, 30, 36, 37, 84–85
 - tragedy of the commons and, 46
 - variant catabolic pathways and, 223
 - with dual function, 237
 - See also* glucose uptake; nutrient uptake
- variability
 - as observable effect, 115
 - discounting long-term value, 74–77
 - resulting from robust control, 108, 112
- vigor, 40, 58–60, 315
- virulence-transmission tradeoff, 15–16, 19–20

- Warburg effect, 163
- warfare
 - tradeoffs involving, 140, 243, 251
 - tuning of catabolic pathways and, 222
 - See also* attack; chemical warfare
- wastewater treatment, 231–234, 318–320, 328
- weak redox gradients, 205, 208–211
- yeast
 - aerobic, lacking ED pathway, 187
 - cooperative tradeoffs in, 245
 - mitochondria of, 230
 - overflow metabolism in, 163, 256
 - oxidative stress resistance, 283
 - pyruvate kinase variants, 283, 286–289
 - redox imbalance in, 239
 - sensors in, 236
- yield
 - definitions of, 30, 170, 176
 - literature emphasizing maximization of, 221
 - See also* growth rate–yield tradeoff
- yield efficiency
 - of glycolytic pathways, 181–182, 184
 - predicted experimental evolution of, 179
 - timescales of competition and, 247