

HINTS TO EXERCISES

A First Course in Systems Biology, Third Edition

This website contains hints that may help you get started with some of the exercises in *A First Course in Systems Biology* Third Edition. You will see that many of the exercises are structured to be open-ended and stimulate self-motivated learning and exploration. As a consequence, they often do not have unique solutions. If you are used to calculus or physics questions, you might initially find this ambiguity uncomfortable, and maybe you would rather be sure that there is one single correct solution and then find it. However, biology is messy, and most realistic questions and their answers depend on assumptions and on experimental or environmental conditions. As a consequence, true biological inquiries are open-ended, and the exercises reflect this fact. The upside is that you have a lot of flexibility in structuring your solutions. Maybe you like conceptual approaches or are intrigued by rigorous proofs. Or maybe you prefer computer simulations and explore what a system can possibly do. In some cases you will have the choice of either figuring out the solution on your own or of searching for hints or even complete solutions on the Internet or in the literature. In some cases, you will be asked to “explore a system.” A valid question is, How many simulations do you have to do to? There is actually no easy answer, but a good guideline is the following: before you execute a simulation, make a prediction each time of what you expect to happen. If your predictions are consistently correct, at least qualitatively, you may stop. However, if your predictions are sometimes correct and sometimes false, there are aspects of the system you don’t really understand yet. You need to keep on simulating, analyzing, and interpreting. At the end, you need to make decisions about numerical or graphical results that are most representative and should be included in your answer. From the beginning, make sure you document what you do, because it is very easy to make a lot of changes in a model and not to remember exactly what these changes did to the system responses. It is a good idea to have a text file open when you do simulations and to keep track of all changes by recording your actions and copying pertinent figures into this document.

Most of the simulation exercises may be executed with a variety of software. Some exercises can even be done in Excel. If you are not particularly trained in writing computer code, you may want to consider the free software PLAS, which lets you analyze systems of differential equations in a very easy manner. The software itself can be downloaded from <https://arquivo.pt/wayback/20230321162314/http://enzymology.fc.ul.pt/software/plas/> and a tutorial can be found on the website accompanying this book. Unfortunately, PLAS only runs directly on PCs, but software like Winebottler (<http://winebottler.kronenberg.org/>) or Wine (www.davidbaumgold.com/tutorials/wine-mac/) lets you run PC software on a Mac. A PLAS template (AAATemplate.plc) can be downloaded from the website accompanying this book and copied right into a blank PLAS file. Tables with data can also be found on this website.

Throughout the book, various exercises ask you to write a report. The rationale for these types of exercises is for you to read and digest more material than was discussed in the book. It is probably a good idea to discuss what is expected with your instructor. Does your instructor want you to write a full report? If so, how long? Or is a listing with a brief explanation of key points sufficient? Should you report on the given topic in general terms or within the context of a particular example? Does your instructor allow you to work in teams? No matter what your instructions are, please keep in mind that Wikipedia is often a good starting point but that it is considered plagiarism if you copy sections from the internet or from published articles or other sources. Instead, you must collect enough information from different sources to answer the questions, understand, analyze, and interpret the material you found, and then formulate a report in your own words. This report must contain full citations of all sources you used. Finally, while generative artificial intelligence may seem like a good source for report-style exercises, as of the publication date of this textbook chatbots are quite unreliable for accuracy in content and citations. Moreover, using these tools prevents the synthesis of information that these exercises are designed to help you learn, the topics pertinent to the discipline of systems biology.

Hints to Exercises in Chapter 1

- 1.1. If you search a lot, including websites, research papers, books, and dictionaries, you will find an incredible number of definitions. Try to find essential features of systems that appear in most of the definitions and descriptions. A precise definition will be difficult.
- 1.3. A good starting point is a textbook on human physiology. But don't stop there. Think about specific tasks the body has to perform, and you will come up with an uncounted array of much smaller systems.
- 1.4. Try to describe the responses of both systems with intuitive arguments ("if this goes up then that goes down") and add magnitudes to these arguments (a lot, a little bit, etc.). This start will give you some clues about the significant differences between the two systems.
- 1.6. Start at the top with ABA and follow various paths toward the bottom (closure of stomata). Remember that two negative signals correspond to a positive effect. Consider that different paths may run at different speeds (why?). What is the consequence?
- 1.8. Use common sense. Imagine a black box with fixed inputs going in and fixed responses coming out. Are there several ways of connecting these inputs and responses? Remember that the box may contain different numbers of components and processes.
- 1.11. Argue like a mathematician: what happens if we do **not** have strong, unambiguous terminology? If this line of arguing leads you to problems, you can use them as arguments for indeed needing a good terminology.

Hints to Exercises in Chapter 2

- 2.2. Several options are possible. If you already know about parameter estimation or nonlinear regression, you can use such techniques to solve the problem. If not, you might want to formulate $L(S)$ in Excel along with a Hill function. Alter the parameters in the Hill function one by one or in combination, until the values of the Hill function are sufficiently close to those of $L(S)$. Plot both in the same graph. Does it matter which values of S you use?
- 2.4. Use a similar strategy as for 2.2; that is, create a file (e.g., in Excel) that displays an MMRL and a power-law function (PLF) side by side. Alter the parameters in the PLF one by one or in combination. You will see that, even under the best of circumstances, the PLF matches the MMRL only for certain ranges of S . Fit the same MMRL with different PLFs for different ranges of S .
- 2.7. Nobody truly knows the best functions for describing this cascade. The standard default is a mass action formulation, where each process is modeled as a rate constant multiplied by the dependent variable that is directly involved in the process. For instance, the equation for \dot{P}_0 would be

$$\dot{P}_0 = \alpha_1 P_1 - \sigma_0 P_0.$$
 Formulate equations for P_1 and P_2 , set all parameters as 0.5 and all P as 1. Implement all this in PLAS, *Matlab*, or some other program that can solve ODEs and alter the settings for the parameters to get a feel for the system. Study the overall changes in the system.
- 2.8. Revisit the definitions of these two quantities. Use common sense to predict what values of 0 would entail. Only after you have thought about the consequences and have come to confident predictions, start the actual simulations, for instance in PLAS.
- 2.9. Again, as in 2.8, use common sense. Imagine no input to S and follow the arrows in the diagram to predict what will happen. Similarly, imagine that nobody dies or otherwise disappears, but people continue to be born. Distinguish cases in which the pool I disappears or does not disappear.
- 2.11. As before, use common sense to guide you. Create a diagram that contains the original and new processes. Formulate extension of the equations in the same manner as it was done in the text (using mass-action format). The question of death rates can be argued in many ways; there is no unique correct answer.
- 2.14. As in many of these cases, there are several possible solution strategies, depending on how vaccination is administered. For instance, are all S offered vaccination? Are only newborns vaccinated? Is a certain percentage of S vaccinated on a more or less continuous basis? Is a fixed number of S vaccinated every day for a certain time period? Think about how the various scenarios should be formulated, first in a diagram and then in equations. Implement at least some of them for simulation studies.
- 2.16. Again, this scenario may be modeled in different ways. In particular, one has to decide whether the infection of a susceptible individual by an infected individual can lead to an asymptomatic case and whether infection by an asymptomatic can lead to an infected individual (see different case scenarios in the text). In the simplest case (Case 1 in the text), S becomes A if infected by A , and S becomes I if infected by I . In addition, some A secondarily become I ; what does that mean in reality? Formulate this process first in the diagram of the disease and then in the equations. Run comparative simulations with no, a small, or a larger flux from A to I , while all other settings are the same.
- 2.18. Use common sense to answer this question. The more detail you include, the more data you would need and the more complicated the equations will become. Sketch out various scenarios.
- 2.20. Before you set up equations, sketch a diagram with all processes mentioned. Then use as a default a

mass-action formulation to write equations. Implement the equations in PLAS, select rates (typically rather small numbers) and do some representative simulations.

- 2.21. Implement the equations in PLAS or some other software and confirm that your system reproduces the figures in the sidebar. It might be that even numerical inaccuracies of the solver lead to different time courses. Once you have implemented the model, make small (!) changes to A , $x(0)$ and/or $y(0)$. Once you have tested these small changes, check larger variations. For instance, try $A = 0$.
- 2.24. Since the outcomes of 0, 1, 2, or 3 heads are independent of each other and can never happen simultaneously, you are allowed to add them to each other. It is important not to forget $P(0; 10)$. Thus, compute $P(0; 10) + P(1; 10) + P(2; 10) + P(3; 10)$.

Hints to Exercises in Chapter 3

- 3.1. Think first about the following question: Does it make a substantial difference whether a node has an odd or an even number of edges? If you figure this out, the problem will be much easier to solve.
- 3.2. The hint to 3.1 applies here as well, to both questions.
- 3.3.7. This is best solved by putting the adjacency matrix into Excel or *Matlab* so that you can raise this to the 3rd power, which will indicate all 3-step paths.
- 3.5. This question can be answered with concepts from probability theory. If you start with N_i , how many choices do you have for a possible neighboring node? Continue to the next node in a similar fashion. Write down the adjacency matrices of two examples and develop an idea regarding the general pattern.
- 3.7. Recall what a clique is. Come up with a network of maybe eight nodes of which the first four form a clique. Write down the adjacency matrix and develop an idea regarding the general pattern.
- 3.9. The solutions are collectively given by the third power of \mathbf{A} . Check how to compute integer powers of a square matrix. Interpret each element in the resulting matrix.
- 3.11. Keep in mind that the graphs are undirected. Look in the text for the correct definition and plug in numbers for e and k .
- 3.15. Consider that the clustering coefficient C_N can be interpreted as the ratio of the number of edges among all neighbors and the maximally possible number of such edges.
- 3.17. To get started, you may want to look for articles by the group of Albert-László Barabási, who has contributed greatly to this field.
- 3.18. A good starting point may be the following article: Agarwal S, C.M. Deane, M.A. Porter, and N.S. Jones. Revisiting date and party hubs: novel approaches to role assignment in protein interaction networks. *PLoS Comput. Biol.*, 2010. **6**: p. e1000817.
- 3.20. Analyze the structure of the left-most network in Figure 1 of Box 3.2. Plot k vs. frequency.
- 3.21. Recall that a graph's tolerance to random or targeted attacks depends on its degree distribution.
- 3.22. Begin by interpreting $P(C \text{ spont})$ as the probability of $(C \mid \text{no } R \text{ and no } S)$ and determine what the probabilities of "no R" and "no S" are.
- 3.26. There are very many examples of stoichiometric and flux balance analyses. For instance, check out the following article: Varela, C., E. Agosin, M. Baez, et al. Metabolic flux redistribution in *Corynebacterium glutamicum* in response to osmotic stress. *Appl. Microbiol. Biotechnol.*, 2003. **60**: p. 547.
- 3.27.1. Make sure you maintain conservation in mass (carbon units) between the left-hand side and the right-hand side of the reactions
- 3.27.3. This can be set up by simple algebraic substitution to solve for the unknown flux values or set up in matrix format.
- 3.28. In order not to be distracted by detail, redraw the graph just with nodes (X_i) and edges (V_{ij}) . Revisit the meaning of \mathbf{S} , \mathbf{N} , and \mathbf{R} , when the system equation is $\mathbf{S}' = \mathbf{N} \times \mathbf{R}$.
- 3.30. For the mathematical aspect, forget the biological interpretation of the linear equations. For the biological aspect, forget about math and use common sense. Instead of doubling, think first about a 100-fold change.
- 3.32. Distinguish nodes along the borders and in the corners of the array. Note that appropriate rules are not unique. Many formulations are possible.
- 3.34. Again, many rule sets are possible. You can actually turn the term "eventually" into a single step. Try several options.
- 3.36. Start with the center node and see how you can make it "move." Then worry about wrapping from the left and bottom to the right and top of the array. As before, many rule sets are possible. Construct one that is as simple and elegant as possible.
- 3.38. Recall how black-and-white blinking patterns can be generated. Then introduce a third color. You can actually figure this out with an array consisting of a single node.
- 3.40. Introducing memory requires some cleverness, because Boolean networks are designed to depend on only the previous state. One possible trick is to double the number of nodes and to use one set for states at t and one for states at $t - 1$. Formulate rules for such a setup.
- 3.42.1. This problem is most easily solved by first setting up an adjacency matrix. Also, all nodes with a single edge can be disregarded because their clustering coefficient = 0.

Hints to Exercises in Chapter 4

- 4.1. Clearly distinguish between the structure of a process (its recursive equation) and its initial value. Compute a few examples to develop general ideas. Then test them with further examples.
- 4.3. Try out a few examples where three or four bacteria start dividing (with the same τ) at slightly different times, such as 1, 1.1, and 1.2. Secondly, start the bacteria at exactly the same time, but with slightly different τ . Draw conclusions for more complicated scenarios.
- 4.5. Distinguish mathematical and biological arguments. For the former, ignore the latter, and vice versa.
- 4.7. Think before you simulate! Consider what a linear process does when started with different initial values. Look out for trivial and non-trivial examples. Use the same types of arguments for a nonlinear process. Study differences.
- 4.9. Recall that the recursion $R_{n+1} = (1-f)R_n + M_n$ is independent of the index n . Express R_{n+2} as a function of R_{n+1} and M_{n+1} and then of R_n and M_n .
- 4.10. Explore r value between -1 and -2 ; then explore values smaller than -2 .
- 4.11. This problem is probably solved the easiest in Excel. Create a column for t and one for P_t ; they should have lengths of anywhere between 20 and 100 elements. Define the first element in the P_t column as P_0 and all others in reference to the element above. Insert charts that plot P_t against t .
- 4.12. Typical starting values are $(1,1)$. Execute several hundred times in order to plot y versus x .
- 4.13. Code this problem in Excel. Create a column for n , one for x_n , and one for y_n ; they should have lengths of at least 100 elements. Define the first element in the x_n and y_n columns as x_0 and y_0 , all others in reference to the element above. Insert charts that plot x_n and/or y_n against n . To see the features of the attractor, create a phase-plane plot of y_n against x_n . Redo the latter plot only for the last 20 values, ignoring the first 80.
- 4.14. Remember that at any steady state, $x = x_{n-1} = x_n$ and $y = y_{n-1} = y_n$.
- 4.17. Once the system has reached a steady state, all further states should be the same. For the a 's, the result is not difficult to see. For the b 's, substitute the ratios and do simple algebraic rearrangements.
- 4.18. Generate a series of random numbers by using `RAND()` in Excel or other software. Set up a conditional formula for stopping criteria.
- 4.21. Recall the interpretation of the elements of a Markov matrix. Infer what other elements in the matrix are. Then use common sense to predict the behavior of the system.
- 4.23. Recall that the elements of a Markov matrix are probabilities. What does each probability represent? Which probabilities must sum to one and which do not necessarily do so?

- 4.27. Make sure that you understand why the given equation represents the limiting distribution. Write the equation in "long-hand" (that is, as three linear algebraic equations) to see how to deal with the left-hand side.
- 4.30. Inspect the Markov matrix for where the probabilities would need to be changed.
- 4.31. Compute the Jacobian \mathbf{J} of the system per partial differentiation. \mathbf{J} is the matrix that defines the linearization of the system, which is actually already given in (4.41). This linear system operates around $(0, 0, 0)$. For comparisons with the original system, its entire dynamics need to be shifted to the steady state of the original system.

Hints to Exercises in Chapter 5

- 5.5. The exercise only requires one differentiation (of $N(t)$) and some clever rearranging of the result to show that you can express dN/dt as a function of $N(t)$. The rearranging is not unique, and it may take you several attempts before you obtain the solution.
- 5.7. Separate mathematical and biological considerations. Start with the former, think about the situation and your best answer, and/or run a few simulations, for instance, in PLAS. For the latter, first interpret the start situation: Is it somehow possible? Is it realistic? If you find the situation unrealistic, explain why. If not, interpret the simulation results from the first part in terms of biological events.
- 5.10. Return to the original Michaelis-Menten mechanism and determine what exactly K_M and V_{\max} represent. Are they two independent quantities or can one somehow be inferred from the other?
- 5.12. There are different ways of proving the correctness of the shortcut. In the most straightforward approach, remember that the power-law approximation is a linearization in logarithmic space. Thus, replace x with $\ln(y)$ and F with $\ln(\phi)$, express $F(x)$ in terms of $\phi(y)$ and compute the linearization.
- 5.14. Begin with the kinetic orders (one per X -variable). Compute derivatives symbolically. Use the symbolic terms to compute the rate constant. At the end, substitute different operating points.
- 5.16. Think before you crunch numbers! What will the format of the power-law approximation look like?
- 5.19. Intermediate steps (with dotted lines) can be ignored.
- 5.20. Compute the kinetic order g and the rate constant α of the Hill function symbolically, that is, without plugging in specific numerical values. See what happens to g if the substrate concentration is close to 0 or close to infinity. Convince yourself that g changes monotonically in between (why is that?). Compute the corresponding values of the rate constant.

- 5.24. If you are more of a math-thinker, compute the steady state symbolically and draw your conclusions. If you are more of a numerical trial-and-error person, put the system into PLAS with different kinetic orders and compute the steady state in each case. Draw your conclusions and possibly prove them mathematically.
- 5.26. Are there conditions for Exercise 5.18 where the GMA and S-system are equivalent for all X_1 ?
- 5.27. This problem looks deceptively simple. The non-trivial steady state is straightforward, but you need to consider trivial steady states as well, where one or more variables are 0.
- 5.28. Not every term in this system needs to be power-law approximated! Look at the mathematical form of each positive and negative term for B' and E' .
- 5.29. Code the system in PLAS or some other software. See what the system does under different conditions. Formulate the power-law equations symbolically in PLAS and define the kinetic order(s) and rate constant(s) as shown in Boxes 5.3 and 5.4.
- 5.31. Look at the symbolic formats of these representations. In their general forms, they are all different. Set numbers of equations and or terms to zero and see whether special cases satisfy two or three of the formats.
- 5.34. Stable spirals require $\det > 0$, $tr < 0$ and $disc < 0$. Use this information to help you construct a matrix A that satisfies these constraints.
- 5.37. Set up steady-state equations. Remember to convert to logarithms and solve for the nontrivial solution(s). How many solutions are there? Are there trivial solutions? Implement the system in PLAS. See whether the responses confirm your computation.
- 5.39. Before you simulate, ponder how you could interpret this operation. What does interchanging alpha- and beta-terms mean? What will this operation do to the steady state and to the dynamics? Once you have tentative answers, implement the original system in PLAS and multiply each equation with +1 (original) or -1 (altered). Compare dynamics, steady states, and eigenvalues. Compare simulation results with your predictions.
- 5.41. Try to make intuitive predictions of responses to transient changes in X_1 or X_2 or to persistent changes in X_3 . Do you have doubts about your predictions or are you confident? If the former, what makes you doubt your predictions? Implement the system in PLAS and run simulations. Check your predictions. Inspect not only the dynamics but also the steady state and the eigenvalues of the system.
- 5.46. Look at the definition of a parameter sensitivity. What exactly would it mean if such a sensitivity had a value of 1,000? Formulate the result in words and interpret it; it will lead you to the answer.
- 5.51. This problem addresses a well-known method for creating chaos (see Box 2.2 and Chapter 12). But the frequency of the sine-function has to be just right. So, change a in small steps.
- 5.52. Implement the system with the given settings in PLAS. Simulate for a sufficient time period (that is, start at $t_0 = 0$ and try different t_f). Try out the time course option, as well as the 2D and (pseudo-)3D representations. See whether any patterns emerge within the chaos. Study different initial values. Also try slightly (or very) different values for a , b , and/or c . Since there are many combinations, establish an efficient record-keeping system with numerical settings and plots.
- 5.53. Recall Exercise 5.52, which showed wildly chaotic oscillations. Is it possible that a steady state exists? Set up steady-state equations. Under what conditions can they be solved in a trivial or non-trivial fashion?
- 5.55. Set up steady-state equations and solve them. Predict what the stability of such a steady state is. Check in PLAS. Predict what happens if you initiate the system close by. Confirm (hopefully) your prediction.
- 5.58. For some values of a , the pattern of the oscillation becomes evident relatively quickly. For others, you have to solve for a long time period.

Hints to Exercises in Chapter 6

- 6.1. You may do this analysis in Excel. Enter the original data, transform *Size* logarithmically, and transform both *Size* and *Time* logarithmically. Compute linear regressions for the different situations and plot the data. Interpret results.
- 6.3. Before you convert the variables, think about why it is of interest to know whether you can convert the system to linearity. Now do the conversion by straightforward algebra. Discuss the effect of the inhibitor concentration.
- 6.5. For the nonlinear regression, you could use **nlinfit** in *Matlab*. Determine V_{\max} and K_M . For the degradation process, $M = -c \times M$, $M(0) = 8$, use again **nlinfit** or remember that the ODE corresponds to an exponential function, which can be converted to linearity. Thus, you may do the conversion and use linear regression.
- 6.7. Confirm the various conversions to linearity. Execute the conversions, for instance, in Excel, and execute linear regressions. Also execute the nonlinear regression, for instance with **nlinfit** in *Matlab*. Compare the accuracy of the deduced V_{\max} and K_M values. Distinguish the accuracies of various approximations for high and low substrate concentrations.
- 6.9. A priori it is entirely unclear what appropriate values for V_{\max} , K_M , and K_I may be. So, set the grid size generously; for instance, as $V_{\max} \leq 100$, $K_M \leq 100$, and $K_I \leq 100$. Compute all combinations with a step size of 1 or 2. Check for the smallest errors and refine the grid locally.

- 6.11. It might be a good idea to pursue a combined strategy by first starting a coarse search with a genetic algorithm, and then refining the solution with a gradient-based method that allows you to specify constraints, such as the **lsqcurvefit** function in *Matlab*.
- 6.12. Use an algorithm similar to the one available on the website of the book. Start with wide upper bounds, such as $V_{\max} \leq 100$, $K_M \leq 100$, and $K_I \leq 100$. Remember that genetic algorithms are stochastic. As a consequence, a new run is likely to produce a new solution. Also try as initial bounds $V_{\max} \leq 25$, $K_M \leq 25$, and $K_I \leq 25$ or $V_{\max} \leq 10$, $K_M \leq 10$, and $K_I \leq 10$. Compare results and run times.
- 6.14. Running a nonlinear regression algorithm 100 times with different initial guesses may return distinctly different solutions. Retain solutions with minimal errors. Compute solutions with averaged parameter values. Execute linear regression on the transformed data. How many solutions do you obtain? Do the algorithms issue warnings? What do they mean? Parts (3) and (4) should be straightforward.
- 6.16. Implement the smoothing algorithm, compute the functions and slopes and compare for different time points with values in Table 5.7, which can be downloaded from the website of the book. Once you have estimated parameter values, compare these with the true values. What does it mean if an estimated parameter is negative, while the true parameter is positive?
- 6.18. Use a genetic algorithm, a *Matlab* implementation of which can be downloaded from the website of the book. Remember that this is a stochastic algorithm, which could lead to different solutions every time it is run. Is it possible that the algorithm does not converge to a satisfactory solution? Compare results for estimations with and without slope estimation. Compare results for data with and without noise.
- 6.20. While you could use again a genetic algorithm, a *Matlab* implementation that can be downloaded from the Website of the book, it might be faster to use a gradient-based method, such as **lsqcurvefit** in *Matlab*. Constrain the parameters within bounds such as $0 \leq \alpha_i$, $\beta_i \leq 20$; $-2 \leq g_{ij}$, $h_{ij} \leq 2$.
- 6.22. The group of R.N. Gutenkunst has written several papers on this topic. But they are not the only ones.
- 6.24. Over-fitting refers to a situation in which too many parameters are being estimated, given the type, quantity, and quality of the available data. Before you read what others have to say about this issue and get lost in details, do a thought experiment where you construct a simple model with too many parameters and imagine what different consequences of over-fitting might be.
- 6.28. As a representative strategy, discuss four types of regulation:
1. X_1 , X_2 exert no feedback.

2. X_1 exerts negative feedback.
3. X_2 exerts negative feedback.
4. X_1 , X_2 both exert negative feedback.

Analyze and compare nine strategies that involve a similar “effort” of change:

- S1: Increase v_{12} four-fold
- S2: Decrease v_{10} by a factor of four
- S3: Double v_{12} and halve v_{10}
- S4: Increase v_{24} four-fold
- S5: Decrease v_{23} by a factor of four
- S6: Double v_{24} and halve v_{23}
- S7: Double v_{12} and v_{24}
- S8: Double v_{24} and halve v_{10}
- S9: Increase v_{12} and v_{24} and decrease v_{10} and v_{23} by the same factor, with a total effort of four units

Hints to Exercises in Chapter 7

- 7.2. Remember that eggs and sperm contain other molecules outside DNA.
- 7.4. The strength of holding a base pair together is related to the enthalpy (~ energy; see a biophysics book for subtle differences) of a hydrogen bond.
- 7.5. Before you google, consider that, according to the central thesis of evolution, each new species derives from an earlier species, with the result that the two have quite some similarities. Imagine how this sequential branching off of new species could be visualized. Once you have come up with some ideas, check the internet and literature.
- 7.8. Go to the GO website and check out the definition and constraints of a GO term.
- 7.10. Consider how many base pairs we have and what percentage is believed to be located in coding genes. A rough estimate will do.
- 7.12. Collectively, these processes are called “proofreading” or “editing” mechanisms. Search for them to get started.
- 7.13. Investigate which parts of an miRNA actually have to bind to a target mRNA in order to regulate it. Also find out whether one or more specific miRNAs can bind to a target mRNA. Once you know, do some simple math.
- 7.15. There is more than one correct way to represent this system. For example, the mRNA products of transcription can be considered as a single variable or be described for each gene. Think about which system components are changing with time and which ones are not.
- 7.18. Think about (or look up) what is special about mitochondrial DNA. Where does it come from? Where does every Y chromosome come from? What are the implications over many generations?

- 7.19. The statistical method for this type of analysis is usually Bayesian inference. Use this term for an initial search for material to be included in your report.
- 7.21. Does a gene itself “regulate” something? Characterize direct (if there are any) and indirect interactions between genes in this context.
- 7.22. Discuss methods from Chapters 3 and 4 for alternative approaches addressing this issue. Read the paper of Kimura and collaborators. Is it more in line with methods from Chapter 3 or Chapter 4?
- 7.24. Look in Chapter 5 for a rationalization of the model structure presented here. Implement the system in PLAS or *Matlab*. For each value of α , start the system at its steady state, perturb X_1 or X_2 , and record the response. Disciplined bookkeeping will be helpful in the long run.
- 7.26. Remember (or look in Chapter 5) how power-law models are constructed. Distinguish between the flow of material and signals when setting up the equations. Implement in PLAS or *Matlab* and analyze.
- 7.27. It helps to mentally walk through the permutations of 1 and 0 assignments for inputs in order to make sure that a mathematical expression reflects the logic gate of interest.
- 7.29. There are infinite combinations to explore. Focus on the assignment of β s to rapidly explore system behavior.
- 7.32. As frequently in real life, there are some typos in the supplements of this paper that you should correct first. To this end, compare the diagram in the paper (Figure 1a) with the model equations (Table S1) and the representations of reactions (Table S2) of the Supplements. Also, set $RE = 0$. The initial value for S depends on the magnitude of the stimulus. Begin with a value between 0 and 2. Keep in mind that the target figures (Figure 1b, c) are lines of steady states, rather than time courses.
- 7.34. Look at one of the original articles by the group of Ingo Potrykus and also browse through the website dedicated to this project.
- 7.36. Deconstruct this circuit into simpler components. Refer to the discussion of the NOT and NAND gates and their mathematical implementation as examples.
- 7.37. It is useful to study the details of the repressilator in the original paper. Implement this system. For a first simulation, assign parameters such as $\alpha_0 = 0$, $\alpha = 100000$, $b = 100$, $n = 2.1$ and use random initial states for the six variables close to 1. Subsequently, reduce α or make other changes.
- 8.4. Distinguish between mathematically possible sequences and biologically realistic sequences that account for different relative frequencies of amino acids.
- 8.5. Go to www.rcsb.org/pdb/ and, for instance, type “hemoglobin” into the search line. Scroll down to the different structures in the database and click on one of them. On the right of the new screen, the structure is shown in default view. Click on “View in Jmol” and try out several options for visualization. Right-clicking permits operations such as zooming and saving (under File).
- 8.7. Of course, plants and animals are very different in many respects. As a good starting point, think about processes that only plants can do and look for proteins in charge of these plant-specific processes.
- 8.10. A good starting point may be: Fisch, C., et al., Ultrastructure of cilia and flagella—back to the future! *Biol. Cell.*, 2001. **103**: p. 249–270.
- 8.12. Read about “V(D)J recombination.”
- 8.13. As the names indicate, these two types work antagonistically. Read up on interleukins, interferons, and tumor necrosis factors. Is it always clear whether a cytokine is “pro” or “anti”?
- 8.16. Think about what exactly the task of protein structure prediction is. What is known, and what is to be found out? Then trace the challenges back to features of amino acids.
- 8.18. Follow the different signaling paths within the system and remember that two negative signals tend to have a positive signaling effect.
- 8.20. Before starting, it is advisable to define what exactly the different symbols mean. As the amount of DNA in a cell varies little, except during cell division, X_1 should be defined as the base expression level of a gene, and arrows in and out of X_1 describe the processes maintaining this level. If so, X_4 might be a promoter or transcription factor level that is normally present. The other variables are more straightforward, with X_5 representing the ribonucleoside triphosphates, and X_6 amino acids. X_7 could be some metabolic activator or transcription factor that enhances the expression of the gene. If you don’t remember, look at Chapter 5 how you might set up a power-law model of the cascade. To get started, use kinetic orders of 0.5 or 1.
- 8.22. If you have not already done so, set up a system for Exercise 8.20. Formulate the additional layer in the same manner and include Z with a negative kinetic order in the positive term of the equation for X_1 . Explore the consequences of different values of this negative kinetic order (-0.1 , -0.5 , -1 , -2 , \dots). Study stability and dynamic features. Always start your simulations at the steady state.
- 8.24. Assume that the phosphorylation steps at positions A and B of a protein called X_3 are independent and do not require a specific order. Set up a mass-action model quantifying the following diagram:

Hints to Exercises in Chapter 8

- 8.2. Start small: If there are 20 amino acids, how many different pairs could you construct? Scale up to 3, 4, 100, and 1,000. Discuss how codon bias enters into the equation.

Analyze the model for different, representative settings.

- 8.25. Set up a mass action model, representing every step as a rate constant times the involved variable(s). Include signal S as a factor in the appropriate term. Define the “Response” with an indicator variable, defined through an equation such as $R' = a P2P - b R$. For unstimulated conditions, define parameter values such that $R = 1$.
- 8.27. Look in Chapter 3 for features of these types of static networks.
- 8.34. Use steady-state assumption to solve algebraically for L as a function of the parameters and S .

Hints to Exercises in Chapter 9

- 9.1. Really large molecules are often polymers. Thus, search the internet and literature for polymers in biology. Also look for other types of molecules that are large but not quite as large as proteins and nucleic acids.
- 9.3. One way of approaching this exercise is to confirm that the total mass (sum of all pools) remains constant, even though the material in the different pools becomes redistributed through the Michaelis–Menten mechanism.
- 9.5. Realize that P' is equivalent with v_p . Also, formulate the quasi-steady-state assumption as an equation. Then express v_p as a function of the total enzyme concentration and of S . The rest is algebraic maneuvering.
- 9.6. A crucial point to notice is that the solutions of (9.7)–(9.9) are functions of time, whereas vp in (9.10) is a function of S , which however is a function of time. Thus, the challenge is to compare the right quantities.
- 9.8. Follow the generic rules for setting up equations in mass-action format. In contrast to a simple Michaelis–Menten reaction, assume that two substrate molecules form a complex with the enzyme. Check how this “two” enters the equations.
- 9.10. This exercise may be done in Excel or in PLAS. For the latter, define S as the differential equation $S' = 1$, with initial value $S = 0.001$, and define t_0 also as 0.001. Pick one inhibitor concentration at a time and formulate v . Solve up to a reasonable tf value (maybe 20). For each inhibitor concentration, plot the result (as a phase-plane plot), either as v against S or $1/v$ against $1/S$. Superimpose the plots.
- 9.13. Using KEGG, for example, obtain the appropriate pathway maps for *E. coli*, *S. cerevisiae*, and *H. sapiens*. Note that various strains of *E. coli* could be studied. Determine which enzymes are known to exist in each species. Highlight differences between species.
- 9.15. You can approach this problem either by tinkering (good for small systems) or by using linear algebra (advisable for large systems). In the former case, you can immediately infer, for instance, that F_5 must be 8 units for D to be in balance. In the latter case, construct linear equations that balance fluxes at all nodes and solve these equations.
- 9.17. As an example, the first equation could be formulated as

$$dA/dt = a C^{gAC} D^{gAD} - b A^{hA}$$
 Start with $a = b = 1$, $gAC = gAD = -0.5$, and $hA = +0.5$. Other baseline equations are designed in the same manner (see Chapter 5). Alter parameter values as instructed. Every time after selecting new parameter values, run the system first toward its steady state and use its values as the start values for your analysis. Predict the system responses before every simulation.
- 9.19. If you have a large computer screen, two screens, or very good eyes, the most convenient strategy is probably to open KEGG (or BioCyC) twice and display the maps of ascorbate metabolism for *E. coli* and for *Mycoplasma pneumoniae*. Look for similarities and differences. Interpret your findings.
- 9.21. Many groups in academia and industry have studied this pathway. As an example, look at papers by the group of Néstor V. Torres of the University of La Laguna in Spain.
- 9.23. Formulate equations by including in each term the variable(s) involved with a reaction, a rate constant and, where needed, a stoichiometric constant. As an example, the first equation could be written as

$$\dot{X}_1 = k_{71}X_7 + k_{61}X_6 - k_{12}X_1 - k_{45}X_1X_4$$
 Recall what it means that the system is in steady state. Ponder whether you should expect a unique solution.
- 9.25. Compute the steady state of the system that you developed in Exercise 8.22. Use these values as start values for the various dependent variables. Then investigate bolus perturbations.
- 9.27. Consider renaming each arrow as a reaction number to help organize the naming convention for your stoichiometric matrix. Then it is easier to consider what species participates in the reaction. You can also rewrite the flux vector in terms of the mathematical form (L, PL, HRL).
- 9.31. Recall that elementary modes describe distinct pathways through the system. Thus enter the system through some input flux, determine internal paths, and leave the system through some output flux.
- 9.33. B, C, respectively, and the columns to the reactions. For reversible reactions, assign a “preferred” direction.
- 9.35. Construct some artificial GMA system and formulate its steady state. Now consider equal scaling throughout the pathway system.

Hints to Exercises in Chapter 10

- 10.1. Biologically, it makes sense for the baseline state of the system to exist in the “resting” form, with most—if not all—of the protein being unphosphorylated. Start your analysis with $P_0(0) \gg P_1(0)$.
- 10.2. There are some excellent literature references that describe the dynamic advantages of type 1 incoherent feedback loops (I1-FFL) for biological signaling systems. (e.g. Kaplan et al., *Molecular Systems Biology*, 2008. 4: p. 203). You can explore these features through this exercise.
- 10.3. This exercise uses continuous models to generate almost step-function signals.
- 10.5. Use the OR and AND outcomes from Exercise 10.3 for constructing the continuous version of this circuit.
- 10.6. The best-studied example is bacteriophage lambda, and the classic book in the field is Ptashne, M, *A Genetic Switch*, Cell Press, Palo Alto, CA & Blackwell Publishing, 1986. There are many newer papers that discuss the “decisions” made by the phage either to “choose” lysis or lysogeny.
- 10.8. The dynamics of X is determined by input term and output terms; it has two steady states, which are around 4.5 and 145 for low and high S , respectively. Approach the task with simulations that add noise to the signal with a magnitude of maybe $\pm 10\%$ of typical S values.
- 10.10. Figure 10.8 demonstrates that the system has three steady states. Start the system with each of them and perturb it slightly. Check the dynamics of the system. Record your findings.
- 10.11. An easy approach is to study these equations in PLAS. Either keep the signal as an independent variable and try different values or formulate it as a slowly changing differential equations, such as $dS/dt = 0.1$, $S(0) = 0.1$, which allows you to “watch” when the system responds. Use one or both of these types of approaches to study hysteresis.
- 10.13. The dynamics of X is determined by input term and output terms; it has two steady states, which are around 4.5 and 145 for low and high S , respectively. Approach the task with simulations that add noise to the signal with a magnitude of maybe $\pm 10\%$ of typical S values.
- 10.14. Use the same methods as for Exercises 10.10 and 10.11. Study whether the system switches from low to high, or from high to low, for the same signal strength or for different strengths. Interpret the results.
- 10.16. Once implemented, initiate the cascade with values similar to those in Table 10.4 for the different X , Y , and Z variables. Expose the cascade to weak and strong, short and long-lasting signals. Analyze the latter for systems (with different parameter settings) that reside primarily in the phosphorylated or dephosphorylated state.
- 10.18. Use the system from Exercise 10.17 and test how the system responds to increases in k_3 and k_6 . For dynamic simulations, always start at a/the steady state.
- 10.20. Predict, and then verify, what happens in a simple pathway with two sequential reactions that are each modeled as regular Michaelis–Menten rate laws. Then consider the same system but with back reactions. Study situations with different enzymes or with the same enzyme catalyzing both reactions. The situation becomes interesting when the enzyme becomes limiting. To investigate this situation, formulate Michaelis–Menten ODEs (for all substrates, complexes, and products) and define the free enzyme concentration as a dependent variable, such as $E = E_{tot} - XE - XPE$. Demonstrate under what conditions E changes significantly over time and what the effects are on the system.
- 10.22. Use the implementation of the cascade as presented in the text and reset the relevant parameters (k_7 and k_8) as $1/10$ of their original values. Simulate different situations and compare responses with those of the original cascade. For instance, model several repeated signals and report responses in XP , YPP , and ZPP .
- 10.24. Formulate a PLAS file with the extended equations for XP and YPP . For instance,

$$\begin{aligned} XP' = & k_3XE - k_7XP - k_1YXP + k_2YE + k_3YE \\ & - k_4YPXP + k_5 \end{aligned}$$
 Also formulate a PLAS file with the original equations. Plot results for both and use the MERGE option to compare them.
- 10.25. The effect of noise can be easily inspected by repeating the analysis performed in Exercise 10.16 with the new model.
- 10.26. For the steady state, all three equations are set equal to zero. Because the initial steady state is $(1, 1, 1)$, we know that $\alpha_i = \beta_i$ for $i = 1, 2, 3$. Move the beta-terms to the left-hand side, divide each equation by α_i , and take logs. Solve the resulting steady-state equations. Do all this symbolically, that is, without plugging in numerical values. The result for $S = 1.2$ (typical perturbation in Ma’s paper) and $C = 1.02$ (acceptable difference from original steady state) will give you conditions for adaptation.
- 10.28. Unlimited scenarios may be simulated. For instance, reset KaiA = 0 (for instance, at $t = 40$), and study KaiC. Or reset the system to a relatively small positive value, such as KaiA = 0.7, or to a much larger value, such as KaiA = 2.0. Study at what points the responses change qualitatively. Also initiate the system with dominance by other forms of Kai and study its responses.

Hints to Chapter 11

- 11.1. In PLAS, the computation of eigenvalues and sensitivities (at a non-zero steady state) is easy. Check how many sensitivity values are between -1 and $+1$ (what does that imply?). Where are the largest sensitivities located in the system? What happens if the corresponding parameter is changed by, say, 2%? Is it always biologically feasible to change just one parameter in one equation or does the change in one parameter necessitate other changes?
- 11.3. A priori you don't know what the steady state values are. Thus, do an initial (long-term) simulation to determine them. Then normalize the existing dependent variables by defining additional variables.
- 11.5. The task is actually easier to implement with (11.2) which shows the corresponding enzymes TPS1p and TPS2p explicitly as X_{17} and X_{18} , but you can also use (11.1) and alter the corresponding rate constants. Study knock-downs and knock-outs. In the latter case, take the variable out of the equations to avoid raising 0 to a non-integer power.
- 11.6. Think about this question before you simulate. Would you expect changes to be additive? Multiplicative? Neither? Do they depend on specific settings? Argue with slight changes and with extreme changes to get a feel for the situation. Investigate the meaning of the terms "epistasis," "synergism," and "antagonism" in this context.
- 11.8. Check the pathway for direct and indirect effects of TPS1 on the dynamics of glucose. Form some hypotheses. Then search the literature. The group of J.M. Thevelein has worked in this field since the 1990s.
- 11.11. Think in terms of model simulations (math) and in terms of biology. In the latter context, will increasing the external concentration always lead to higher uptake? Test with simulations where the bulk of additional glucose ends up.
- 11.16. Return to the SIR analysis (e.g., Figure 5.4) performed in Chapter 5 if you need a refresher on the process for linearization.
- 11.17. Start from the known steady-state of the system, $(V, E) = (0, 1,000,000)$. Test small bolus additions of V as a way to "titrate" the virus level.
- 11.19. Think of this exercise like a dial that either creates a lag between the VE module and the rest of the system or speeds it up. Will the system approach a regular SIR model at a high scaling value?
- 11.23. NetLogo allows for if-else conditional statements. Use the condition of sickness to control whether the "move" function can occur.
- 11.24. Return to the continuous multiscale model and inspect what parameter would be altered for an anti-viral effect.
- 11.26. From an ecological perspective, there is an advantage to having the population not all behave exactly the same. This might be reflected in the sensitivity of the population in this scenario.

Hints to Exercises in Chapter 12

- 12.2. Implement the van der Pol equation, in the format of two first-order equations, in PLAS or some other software. The parameter k has an inverse effect on the frequency of the oscillation: The simulations should show that larger k values lead to lower frequencies.
- 12.3. Before you simulate, think! The system exhibits a stable limit cycle. What does this fact suggest for an answer to part 1? Part 2 is a matter of straightforward simulation, but check out the following article for additional features and explanations. Yin, W., and E.O. Voit. Construction and customization of stable oscillation models in biology. *J. Biol. Systems*, 2008. 16: p. 463–478.
- 12.5. Implement the LV equations (without the factor 50) in PLAS, along with the sine function. By setting the sine input to 0, confirm that the PLAS file produces the same output as Figure
- 10.13. Multiply the equations by 50. Predict what will happen and then confirm. Now activate the sine input and try out many combinations of p and q . There is no shortcut to doing this.
- 12.6. Recall what the main difference between dependent and independent variables is. How do the concentrations of $[Ca^{2+}]_{ext}$, $[Ca^{2+}]_{cyt}$, and $[Ca^{2+}]_{SR}$ have to compare in magnitude so that the assumption is valid?
- 12.8. By far the easiest approach is a simulation. What does stability of a limit cycle mean? Ponder what kind of simulation would confirm stability. Are eigenvalues useful? Implement your ideas and test them. What is a necessary condition for a system to be closed?
- 12.10. Use the formulae in the text to compute the approximate equilibrium potentials. The relative contributions to the membrane potential are complicated, because they depend on the permeability of the membrane, which may differ between cell types. Look in the literature for further caveats when using the Goldman-Hodgkin-Katz equation.
- 12.12. Use the values $v_{Na} = 120\text{mV}$, $v_K = -12\text{mV}$, $v_L = 10.6\text{mV}$, $C = 1$ and $I_{app} = 1$, and study with simulations the effects of changing $v(0)$, $n(0)$, $m(0)$ and/or $h(0)$ on depolarization.
- 12.14. Using simulations, show that resetting both n and h is necessary to let the original action potential fire again. Interpret this finding in terms of different ion fluxes.
- 12.16. Implement the combined system in PLAS or *Matlab*. What does it mean (a) that the system

has a limit cycle and (b) that this limit cycle is stable? Test with appropriate simulations.

- 12.19. Implement both systems in the same file and replace p in the first equation with s , which links the two models together. At first set $ts = 0$, which renders s constant at its default value of 1 (why?). Why is it beneficial to start with $ts = 0$? Now, explore different values for ts .
- 12.21. Read the following article and then look for newer information along the same lines.
Borlak, J., and T. Thum. Hallmarks of ion channel gene expression in end-stage heart failure. *FASEB J.*, 2008. **17**: p. 1592–1608.
- 12.23. To get started, look at the following article and then identify and read some other papers.
Cherry, E.M., and F.H. Fenton. Visualization of spiral and scroll waves in simulated and experimental cardiac tissue. *New J. Phys.*, 2008. **10**: p. 125016.

Hints to Exercises in Chapter 13

- 13.2. Think before you simulate! Just look at the equation for X_4 and pretend the influx is constant. What does a change in β_4 do to X_4 ? What do you expect to happen if $\beta_4 = 0$? Once you are confident about your answer, implement the system and simulate.
- 13.3. This exercise is similar to 13.2, but there is a major difference: Check and compare the roles of X_4 and X_6 and predict what the consequences of a decreased efflux from X_6 might be.
- 13.5. This seemingly simple definition task turns out to be very difficult. Argue what exactly it means if you think you are healthy or if a doctor tells you so. Is either situation necessarily true? Read the following article and relate it to the question asked here.
Black, W.C., and H.G. Welch. Advances in diagnostic imaging and overestimations of disease prevalence and the benefits of therapy. *N. Engl. J. Med.*, 1993. **328**: p. 1237–1243.
- 13.6. Turn the question around: Recall what the roles of parameters and dependent or independent variables are in a dynamic model. Can you conceptually construe cases of disease where any of them could be biomarkers? Search for examples.
- 13.8. Identify what is special about the pink and green points. What do they have that points in the center of the health domain lack? Use the distinguishing features to answer the question.
- 13.10. Many biomarkers are proteins, but lipids and other metabolites can qualify as well. Search for examples.
- 13.12. More or less arbitrarily define a specific disease state, such as X_4 being more than roughly ten times the normal level. Select maybe three parameters (such as β_{31} , β_4 , and K_{M5}) and allow them to range between zero to twenty times their original values. Study many combinations, for instance, with a Monte Carlo simulation to test the question asked. If necessary, change other parameters.
- 13.14. A starting point might be the work of J.A. DiMasi, L. Feldman, A. Seckler, and A. Wilson. Trends in risks associated with new drug development: duccess rates for investigational drugs. *Clin. Pharmacol. Ther.*, 2010, **87**: p. 1532–1535. Note that most compounds never proceed far enough in the drug pipeline to be tested on humans.
- 13.16. An easy way to implement this situation in PLAS is the `@` command. Add a term (+ Bolus) to the equation of M , set Bolus = 0 at the beginning and add pairs of statements like
- ```
@ 240 Bolus = 100
@ 241 Bolus = 0
```
- Test several scenarios. What happens if the second statement is set at time 242 instead of 241?
- 13.17. Assume exponential decay processes. Now you can use math or simulations. For the former, find out how the half-life is computed. For the latter, compare half-lives of processes  $X' = -b_i X$  ( $i = 1, \dots, 4$ ) with that of  $X' = \Sigma(-b_i X)$ .
- 13.19. Use a strategy as in Exercise 13.16. Study different timing schedules.
- 13.21. First, think about whether you might be able to achieve a constant concentration in blood, when the drug is administered three or four times per day. Predict what the concentration time profile will look like in response to such a treatment. Confirm your predictions with simulations. After testing several scenarios, answer the question and confirm again with simulations.
- 13.24. In contrast to a flux of the toxicant from the liver back to the bloodstream, the degradation destroys some of the toxicant. Don't worry about break-down products. Obviously, the equation for  $L$  is affected. How? What about the equation of  $B$ ?
- 13.26. In the text, the MTX administration was modeled as an increased initial value for  $P$ , while the input variable  $IN$  in the equation of  $P$  was set to 0. Instead, set the initial value of  $P$  to 0 (or 0.001) and formulate the input with the `@` command in PLAS, such as
- ```
IN = 66
@ 1 IN = 0
```

Hints to Exercises in Chapter 14

- 14.1. Use any of the methods in Chapter 6. For instance, adjust the algorithm that can be downloaded from the website of the book, for the specifics of the task here. Consider the feasibility of substituting differentials with slopes.

- 14.3. The easiest approach is probably to compare in a single plot the original Richards function and the solution of the approximating ODE for different values of ν . You may need to use different time scales for different ν . An alternative is a strict mathematical analysis where you compute the limit for ν approaching 0.

- 14.4. The term “super-exponential” is not precisely defined mathematically and could simply mean “faster than exponential.” One option for a specific characterization is the assumption that the growth rate is exponential in time. With this definition, the super-exponential model may be formulated as the differential equation

$$\frac{dy}{dt} = (r_0 \cdot e^{r_1 t}) \cdot y$$

You could use this formulation in your analysis and/or look for other reasonable definitions. You could also try to fit the population data with a typical growth model, such as the Gompertz, Richards, or logistic growth law. If you use one of these growth functions, check which carrying capacity it predicts. Repeat the fitting upon leaving out (or slightly altering) the last data point(s) in order to see how reliable the estimates are.

- 14.6. Before you rush into a formal analysis or simulation study, use common sense to address this question. What could possibly happen to some generic population and what would the effects be if the population is either very small or large? Afterward, use mathematical arguments and/or simulations to test representative scenarios with artificial populations that you construct in a reasonable fashion.
- 14.10. Formulate the total population size in terms of expressions used in the Leslie process. Constancy means that this size is the same τ time units later. Develop specific conditions from this *Ansatz*. If you cannot obtain such conditions, at least come up with an example that satisfies the condition of constancy. Confirm your solution with a simulation. To assess robustness, slightly change a parameter and study the response.
- 14.12. Simulating this situation is relatively straightforward, but you can no longer use powers of matrices (confirm why). As an example, you could start with a regular Leslie matrix and replace all α_8 with $(1/n) \alpha_8$ or with $\alpha_8 - 0.1 e^{-n}$, where n is the iteration number that is a substitute for time. Try something similar for the survival parameters σ_8 . Interpret what a specific form of time dependence in these parameters means.
- 14.14. To address this question, it is probably the easiest to forget about men and set up a Leslie process that exclusively considers women; the total population size then is roughly twice the women

population. Use 5 or 10 equally sized age classes and think about how a delay in childbirth would be mapped on the Leslie matrix. Do comparative simulations.

- 14.16. This is an exercise in matrix algebra. Your results should be equivalent when multiplied out, which means that your Leslie matrix will need to be transposed accordingly.
- 14.17. Do simple math or use simulations. Check how often two exponential functions intersect. Interpret your findings. Without death, who will win the population size race? The initially bigger population? The faster growing population? Depends? If so, on what?
- 14.19. Initially, consider only a positive multiplier. Try to imagine or visualize what it means if the entire system is multiplied with the same positive factor, such as 2. Then think about what a phase-plane plot shows. How is time represented? Once you have a good feel for this part, consider multiplication with -1 or -2 .
- 14.21. Look at the equations and determine how they become simpler when either one variable is zero. Analyze the simplified equation(s) with thought, math, and/or simulation.
- 14.23. Recall what the phase-plane plot shows and what a typical simulation of a system of ODEs produces. If you use PLAS, check out the 2D plotting option.
- 14.25. Begin with the steady states. Then determine the nullclines. The results may surprise you. Do simulations. Look at the hint to Exercise 14.23.
- 14.27. Implement the system in PLAS. Change the initial value of X_1 over a wide range. You should see that even small changes in $X_4(0)$ lead to different trajectories. However, some features are predictable. For instance, the system remains bounded between zero and one. In cases of high $X_4(0)$, the simulation results may actually become regular.
- 14.29. Draw nullclines and compute steady states. Don't forget the trivial solutions. Discuss the stability of all steady states in terms of the values of N_1' and N_2' . Sketch trajectories or vectors in different areas of the plot.
- 14.31. Note that, in contrast to the example in the book, the first trajectory in this case is nonlinear. Nonetheless, all trajectories must cross the nullclines in horizontal (N_2') or vertical (N_1') direction. Also note that these directions change at the internal steady state. Draw nullclines and compute steady states. Don't forget the trivial solutions. Discuss their stability in terms of the values of N_1' and N_2' or system trajectories.
- 14.33. One can plot multiple N_1 nullclines on the same phase plane to visualize the impact of the fishing rate on the feasibility of achieving a stable system with the two species. Because the N_1 nullcline is

linear with the same slope, the fishing rates result in parallel nullclines in the phase plane.

- 14.34. A comprehensive answer to this question would be very difficult to develop. List some reasons why that is. Then determine how mathematicians often deal with spatial phenomena in much

simpler settings, such as an ink drop spreading out on a surface. Also look into “agent-based models” for a computational alternative (Chapter 11). List the data needs of each method. Discuss advantages and drawbacks of different methods.

