Systems Biology Exercises

What is the difference between a live cat and a dead cat? A dead cat is a collection of its component parts. A live cat is the emergent behavior of the systems incorporating those parts. In pursuit of systems. Nature 435, 1 (2005).

London 2005
ANONYMOUS

Herbert M Sauro
Bioengineering
hsauro@uw.edu

Exercises and Solutions for Modeling Systems Biology: Introduction to Pathway Modeling

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1 Biology

In the following exercises use the data given in the main text along with Tables 1.3, 1.4, 1.5 and 1.6 of the textbook.

1. EXERCISE

How many *E. coli* cells laid end to end would fit across the full stop at the end of this sentence? Assume the diameter of the full stop is 0.5 mm.

2. EXERCISE

Estimate the volume of an *E. coli* cell.

3. EXERCISE

a) Calculate the surface area of an *E. coli* cell assuming its a cylinder.

b) If a typical membrane protein is 5 nm in diameter, estimate the number of membrane proteins that can be laid out on the membrane if the center-center distance between each protein is 6 nm.

4. EXERCISE

Show that a 1 nM concentration is roughly equivalent to 1 molecule in a volume of 1 *E. coli* cell.

5. EXERCISE

Estimate the number of protein molecules a typical *E. coli* cell can make per second assuming the average protein is 360 amino acids long. Assume that the number of proteins in a cell is 3,000,000. How long would it take to make 3,000,000 proteins?

6. **EXERCISE**

If it takes 1,500 ATP molecules to make an average protein, how long would it take before all the ATP is used up? Assume the ATP is not being replaced.

7. **EXERCISE**

E. coli can be considered a cylindrical volume with length 2 μm and diameter 1 μm. A reaction is known to occur in *E. coli* with an intensive rate of 0.5 mmol s^{-1} l^{-1}.

a) What is the rate of reaction per volume of *E. coli*?

b) If Avogadro's number is 6.022×10^{23}, express the rate in terms of molecules converted per second per *E. coli*.

8. **EXERCISE**

What are the visual symbols often used to represent activation and repression in biochemical networks?

9. **EXERCISE**

Draw a similar diagram to the glycolysis regulatory diagram (Figure 1.4) but for the lysine, threonine and methionine biosynthesis pathway from *E. coli*.

10. **EXERCISE**

Why is the size of an organism's genome a poor indicator of the organism's complexity?

11. **EXERCISE**

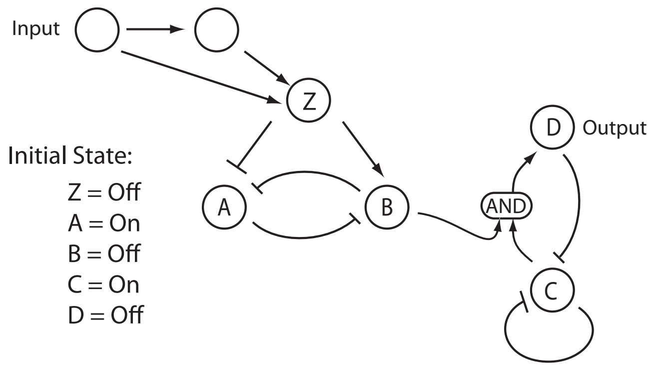
Describe the basic approach used to find network motifs.

12. **EXERCISE**

Looking at motif c) in Figure 1.23 in the textbook, try to explain how it might operate as a memory unit.

13. **EXERCISE**

Study the network shown below and try to figure out its function. Use Figures 1.22, 1.23, and 1.24 in the textbook as guides.



The AND block on the left of the network represents an AND gate, that is the output of the block is only active if *both* inputs are also active.

Solutions

1. Solution

Assuming the length of cell is $2\mu m$ the answer will be 250 cells.

2. Solution

Assume *E. coli* is a cylinder: volume = $1.57\mu m^3$ or 1.57×10^{-15} L

3. Solution

a) Assume *E. coli* is a cylinder: Area = 7.85 μm^2

b) Approximately 218,000 proteins

4. Solution

The volume of an *E. coli* cell is approximately 1.5×10^{-15} L. 1 nM represents approximately $10^{-9} \times 1.5 \times 10^{-15}$ moles in a cell. Multiply by avogadro's number to get the number of molecules: $6 \times 10^{23} = 0.9$. This is roughly one molecule per *E. coli* cell.

5. Solution

25 minutes (1500 seconds)

6. Solution

0.67 seconds

7. Solution

a) 5×10^{-16} mmoles per second per volume of *E. coli*

b) 3×10^{5} per second per *E. coli*

8. Solution

Repression or inhibition is often depicted using a blunt end: $A \dashv B$ where as activation often uses a simple arrow $A \rightarrow B$ or a filled circle end: $A \multimap\!\!\!\bullet\; B$.

9. Solution

Research amino acid biosynthesis pathways online. You will discover that these pathways have a number of negative feedback loops that go form the end product to the start of the pathway. You may also notice that there are nested feedback loops.

10. Solution

Many expressed proteins are covalently modified or form complexes. This is particularly the case for mammalian systems where covalent modifications is endemic amount proteins. This means that the number of states far exceeds the number of gene encoded on a genome.

11. Solution

See page section 1.8 of the textbook

12. Solution

The two inhibitory arcs around the two lower nodes ensurers that only one can be active at anyone time. The z node can be used to flip that state to the other node. For example, if the right-hand node is active then the left-hand node will be inactive. If z is brought to a high value, this will inhibit the right-node and activate the left-node thus changing the state. If the z node is now brought low, the state of the two nodes remains unchanged. In this sense the network has recorded the z event and thus acts as a memory unit.

13. Solution

The first part of the network is a noise filter so that node z is only active when the input has a sufficiently long duration. When z rises it flips the state of nodes A and B so that B becomes active. Note that when the input signal returns to its quiescent state, the state of B remains high because of the two inhibitory arcs between A and B. With B active, it turns on the output D via the AND gate. This last motif is a relaxation oscillator and and as result it will start to oscillate. The 'function' of the entire network is to detect a signal on the input and use that signal to permanently activate an oscillator.

2 Kinetics

14. Exercise

Define the following terms:

a) Stoichiometric amount

b) Stoichiometric coefficient

c) Rate of change

d) Rate of reaction

15. Exercise

What are the stoichiometric amounts and stoichiometric coefficients for each species in the following reactions:

$$\begin{aligned}
\mathrm{A} &\longrightarrow \mathrm{B} \\
\mathrm{A + B} &\longrightarrow \mathrm{C} \\
\mathrm{A} &\longrightarrow \mathrm{B + C} \\
\mathrm{2A} &\longrightarrow \mathrm{B} \\
\mathrm{3A + 4B} &\longrightarrow \mathrm{2C + D} \\
\mathrm{A + B} &\longrightarrow \mathrm{A + C} \\
\mathrm{A + 2B} &\longrightarrow \mathrm{3B + C}
\end{aligned}$$

16. Exercise

Write out the mass-action rate laws for the following elementary reactions:

a) $A \rightarrow$

b) $A + B \rightarrow$

c) $A + 2B \rightarrow$

d) $2A \rightarrow$

17. EXERCISE

Write out the reversible mass-action rate laws for the following reactions:

1. $A \to B$
2. $A + B \to C + D$
3. $2A + B \to 2C$
4. $A \to 2B$

18. EXERCISE

A reversible reaction $A \rightleftharpoons B$ has an equilibrium constant of 5.0. If at equilibrium the concentration of A is 2 mM, what is the equilibrium concentration of B?

19. EXERCISE

Define the following terms:

a) Mass-action ratio

b) Disequilibrium ratio

Solutions

14. SOLUTION

1. The stoichiometric amount is the number of molecules a particular reactant or product takes part in a given reaction
2. c_i = molar amount of product - molar amount of reactant. In reactions where the species only appears on the reactant side, the stoichiometric coefficient is the negative of the stoichiometric amount of the reactant. In reactions where the species only appears on the product side, the stoichiometric coefficient is the stoichiometric amount of the product.
3. The rate of change is defined as the rate of change in concentration or amount of a designated molecular species.
4. The rate of reaction is the rate of change of a given species normalized by its stoichiometric coefficient.

15. SOLUTION

1. 1, 1; -1, 1
2. 1, 1, 1; -1, -1, 1
3. 1, 1, 1; -1, 1, 1
4. 2, 1; -2, 1
5. 3, 4, 2, 1; -3, -3, 2, 1
6. 1, 1, 1, 1; 0, -1, 1
7. 1, 2, 3, 1; -1, 1, 1

16. SOLUTION

a) $v = kA$

b) $v = kAB$

c) $v = kAB^2$

d) $v = kA^2$

17. SOLUTION

a) $k_1 A - k_2 B$; b) $k_1 AB$ - k_2 C D; c) $k_1 A^2 B - k_2 C^2$; d) $k_1 A^2 - k_2 B^2$

18. SOLUTION

Since $K_{eq} = B/A = 5$, and $A = 2$, therefore $B = A \times K_{eq} = 10$ mM

19. SOLUTION

a) The mass-action ratio, Γ, is the ratio of products to the reactants *in vivo*. At equilibrium $\Gamma = K_{eq}$.

b) The disequilibrium ratio, ρ, is the ratio of the mass-action ratio and equilibrium constant.

3 Networks

20. Exercise

Derive a set of differential equations for the following model in terms of the rate of reaction, v_1, v_2, and v_3:

$$\begin{aligned} A &\xrightarrow{v_1} 2B \\ B &\xrightarrow{v_2} 2C \\ C &\xrightarrow{v_3} \emptyset \end{aligned}$$

21. Exercise

Derive the stoichiometry matrix for the previous model.

22. Exercise

Derive the set of differential equations for the following model in terms of the rate of reaction, v_1, v_2 and v_3:

$$\begin{aligned} A &\xrightarrow{v_1} B \\ 2B + C &\xrightarrow{v_2} B + D \\ D &\xrightarrow{v_3} C + A \end{aligned}$$

23. Exercise

Derive the stoichiometry matrix for the previous model.

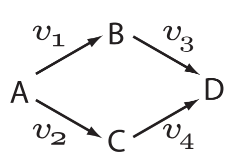
24. Exercise

Enter the previous models, 3 and 4, into Tellurium and confirm that the stoichiometry matrices are the same as those derived manually in the previous question.

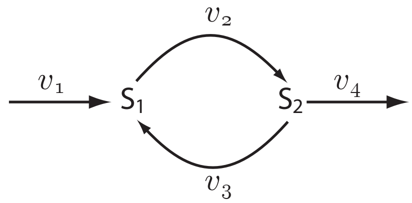
25. Exercise

Derive the stoichiometry matrix for each of the following networks. In addition, write out the mass-balance equations in each case.

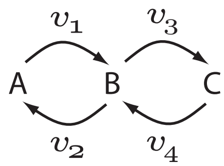
(a)



(b)



(c)



(d)

$$
\begin{aligned}
&A + X \xrightarrow{v_1} B + Y && B + X \xrightarrow{v_2} Y \\
&B \xrightarrow{v_3} C && C + X \xrightarrow{v_4} D + Y \\
&D + Y \xrightarrow{v_5} X && X \xrightarrow{v_6} Y \\
&X + W \xrightarrow{v_7} 2Y && 2Y \xrightarrow{v_8} X + W
\end{aligned}
$$

26. Exercise

For the irreversible enzyme catalyzed reaction, $A \rightarrow B$:

a) Write out the stoichiometry matrix.

b) Write out the stoichiometry matrix in terms of the elementary reactions that make up the enzyme mechanism.

27. Exercise

A gene G_1 expresses a protein p_1 at a rate v_1. p_1 forms a tetramer (4 subunits), called p_1^4 at a rate v_2. The tetramer negatively regulates a gene G_2. p_1 degrades at a rate v_3. G_2 expresses a protein, p_2 at a rate v_9. p_2 is cleaved by an enzyme at a rate v_4 to form two protein domains, p_2^1 and p_2^2. p_2^1 degrades at a rate v_5. Gene G_3 expresses a protein, p_3 at a rate v_6. p_3 binds to p_2^2 forming an active complex, p_4 at a rate v_{10}, which can bind to gene G_1 and activate G_1. p_4 degrades at a rate v_7. Finally, p_2^1 can form a dead-end complex, p_5, with p_4 at a rate v_8.

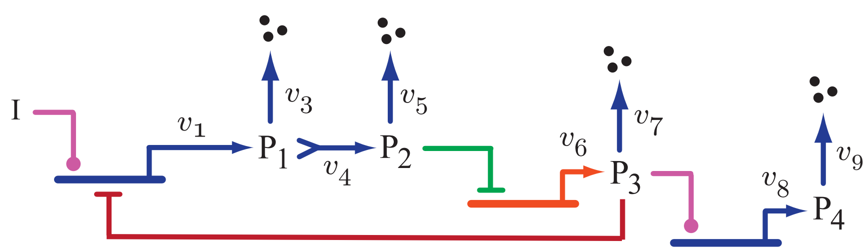
28. **EXERCISE**

Given the following stoichiometry matrix, write out the corresponding network diagram. Why might this process not fully recover the original network from which the stoichiometry matrix was derived?

$$\begin{array}{c} \\ \text{A} \\ \text{B} \\ \text{C} \\ \text{D} \\ \text{E} \\ \text{F} \\ \text{G} \end{array} \begin{array}{c} \begin{array}{ccccc} v_1 & v_2 & v_3 & v_4 & v_5 \end{array} \\ \begin{bmatrix} -1 & 0 & -1 & 0 & 0 \\ 1 & -1 & 0 & 0 & 3 \\ 0 & 2 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 1 & -1 \\ 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & -1 & 0 \end{bmatrix} \end{array} \tag{1}$$

29. **EXERCISE**

Derive the mass-balance equations for the following gene regulatory network:



30. **EXERCISE**

Why is it better to store a model as a list of reactions rather than a set of differential equations?

Solutions

20. **SOLUTION**

$$\frac{dA}{dt} = -v_1; \qquad \frac{dB}{dt} = 2v_1 - v_2; \qquad \frac{dC}{dt} = 2v_2 - v_3$$

21. **SOLUTION**

$$\begin{bmatrix} -1 & 0 & 0 \\ 2 & -1 & 0 \\ 0 & 2 & -1 \end{bmatrix}$$

22. SOLUTION

$$\frac{dA}{dt} = v_3 - v_1; \qquad \frac{dB}{dt} = v_1 - 2v_2 + v_2 = v_1 - v_2$$

$$\frac{dC}{dt} = v_3 - v_2; \qquad \frac{dD}{dt} = v_2 - v_3$$

23. SOLUTION

$$\begin{bmatrix} -1 & 0 & 1 \\ 1 & -1 & 0 \\ 0 & -1 & 1 \\ 0 & 1 & -1 \end{bmatrix}$$

24. SOLUTION

a)
```
import tellurium as te

r = te.loada('''
   A -> 2B; v1;
   B -> 2C; v2;
   C ->; v3
   v1 = 0; v2 = 0; v3 = 0
''')
print (r.getFullStoichiometryMatrix())

     _J0, _J1, _J2
A [[  -1,   0,   0],
B  [   2,  -1,   0],
C  [   0,   2,  -1]]
```

b)
```
import tellurium as te

r = te.loada('''
   A -> B; v1;
   2B + C -> B + D; v2;
   D -> C + A; v3
   v1 = 0; v2 = 0; v3 = 0
''')
print (r.getFullStoichiometryMatrix())

     _J0, _J1, _J2
A [[  -1,   0,   1],
B  [   1,  -1,   0],
C  [   0,  -1,   1],
```

```
D  [   0,    1,  -1]]
```

25. **Solution**

a)

$$\begin{bmatrix} -1 & -1 & 0 & 0 \\ 1 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 \\ 0 & 0 & 1 & 1 \end{bmatrix}$$

$$\frac{dA}{dt} = -v_1 - v_2; \quad \frac{dB}{dt} = v_1 - v_3; \quad \frac{dC}{dt} = v_2 - v_4; \quad = v_3 + v_4$$

b)

$$\begin{bmatrix} 1 & -1 & 1 & 0 \\ 0 & 1 & -1 & -1 \end{bmatrix}$$

$$\frac{dS_1}{dt} = v_1 - v_2 + v_3; \quad \frac{dS2}{dt} = v_2 - v_3 - v_4$$

c)

$$\begin{bmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix}$$

$$\frac{dA}{dt} = -v_1 + v_2; \quad \frac{dB}{dt} = v_1 - v_2 - v_3 + v_4; \quad \frac{dC}{dt} = v_3 - v_4$$

d)

```
      vo,  v1,  v2,  v2,  v4,  v5,  v6,  v7
A [[  -1,   0,   0,   0,   0,   0,   0,   0],
X  [  -1,  -1,   0,  -1,   1,  -1,  -1,   1],
B  [   1,  -1,  -1,   0,   0,   0,   0,   0],
Y  [   1,   1,   0,   1,  -1,   1,   2,  -2],
C  [   0,   0,   1,  -1,   0,   0,   0,   0],
D  [   0,   0,   0,   1,  -1,   0,   0,   0],
W  [   0,   0,   0,   0,   0,   0,  -1,   1]]

dA/dt = -v0
dX/dt = -v0 - v1 - v3 + v4 - v5 - _6 + v7
dB/dt = v0 - v1 - v2
dY/dt = v0 + v1 + v3 - v4 + v5 + 2.0*v6 - 2.0*v7
dC/dt = v2 - v3
dD/dt = v3 - v4
dW/dt = -v6 + v7
```

26. **Solution**

a)

$$\begin{bmatrix} -1 & 1 \end{bmatrix}$$

b) Species order A, E, ES, P

$$\begin{bmatrix} -1 & 1 & 0 \\ -1 & 1 & 1 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{bmatrix}$$

27. **Solution**

NA

28. **Solution**

There may be stoichiometry calculations due to the same reactants and products appearing on both sides of a reaction.

29. **Solution**

$$\frac{dP_1}{dt} = v_1 + v_3 - 2v_4; \quad \frac{dP_2}{dt} = v_4 - v_5$$

$$\frac{dP_3}{dt} = v_6 - v_7; \quad \frac{dP_4}{dt} = v_8 - v_9$$

30. **Solution**

Storing a model as a list of reactions preserves any stoichiometries that might cancel when converting the scheme to a stoichiometry matrix.

4 Modeling

31. **Exercise**

Which of the following best describes what a model is:

a) an attempt to form an exact replica of reality.

b) the truth about the real system.

c) a simplification of the real world.

32. EXERCISE

State the difference between a deterministic and stochastic model.

33. EXERCISE

State the difference between a discrete and continuous model.

34. EXERCISE

Suggest what modeling approach you would use for the following systems, i.e. continuous or discrete and determisititic or stochastic:

a) The spread of a forest fire.

b) Growth and spread of sand dunes.

c) A line of people waiting at cash tills in a store.

d) AM radio electrical circuit.

e) A chess game where both players are computer programs.

f) A tumor where individual cells secrete growth factors.

35. EXERCISE

Figure 1 shows three water tanks connected via outflows. Derive the differential equations that describes the rate of change of the heights, h_1, h_2, and h_3. You can assume that the flow rate out of a tank is proportional to the height of water.

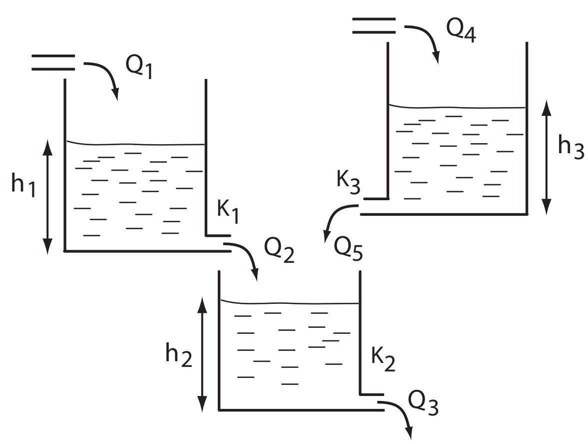


Figure 1: Three tank model.

36. EXERCISE

State any assumptions or approximations you made in the previous question relating to the water tank model.

37. EXERCISE

List the three most desirable attributes of a model.

38. EXERCISE

When we “validate” a model, which of the following do we most likely mean:

a) We show that the model represents the truth about the real system.

b) We increase our confidence in the model’s predictive power.

c) We prove that the model is correct.

39. EXERCISE

Two scientists are arguing about a model, one claims that the model is correct but the other suggests that it is the best so far. Who is making the most reasonable claim and why?

40. EXERCISE

Explain the difference between accuracy and predictability of a model.

41. EXERCISE

The authors of a published biochemical model claim that their model has been validated. What do they mean by this?

42. EXERCISE

The author George Box is said to made a statement similar to: “all models are wrong, but some are useful.”. What does he mean by this?

43. EXERCISE

The transport of a solute across a membrane is given by the equation $J = P_A(S_{\text{in}} - S_{\text{out}})$. If P_A is expressed in cm s^{-1} and the transport rate in moles cm$^{-2}s^{-1}$, what should the concentrations, S_{in} and S_{out} be expressed in?

44. EXERCISE

What is the difference between a state variable and a boundary variable in a biochemical model?

45. EXERCISE

Describe the state variables and types of parameter in the following model of a biochemical pathway:

$$\frac{dS_1}{dt} = k_1 X_o - k_2 S_1$$

$$\frac{dS_2}{dt} = k_2 S_1 - (k_3 S_2 - k_4 X_1)$$

46. EXERCISE

Show that the following functions are nonlinear with respect to x:

a) $\sin(x)$

b) e^x

c) $V_m x/(x + K_m)$

47. EXERCISE

Linearize the following functions:

a) $4x^2 + 6x - 10$ at $x = 1$

b) $V_m x/(x + K_m)$ at $x = 0$ and $x = K_m$

48. EXERCISE

In the equation $v = V_m S/(K_m + S)$ where S is expressed in units of mol l^{-1}, V_m in mol l^{-1} s^{-1}, and the reaction velocity, v in mol l^{-1} s^{-1} what are the units for K_m?

49. EXERCISE

In the previous question, if only the units for S are known, what can one say about the units of K_m?

Solutions

31. SOLUTION

c)

32. SOLUTION

A deterministic model is one where a given input will always produce the same output. For example, in the equation $y = x^2$, setting x to 2 will always yield the output 4. A stochastic model is one where the processes described by the model include a random element. This means that repeated runs of a model will yield slightly different outcomes.

33. SOLUTION

a) Discrete, stochastic

b) Although a sand dune is made up of discrete sand particles that appear to move randomly, given the large number of particles and their size, it is more likely one would use a deterministic and continuous model.

c) Discrete, stochastic.

d) Continuous, deterministic.

e) Discrete, deterministic

f) Discrete model for the individual cells but a continuous model for the growth factors.

34. SOLUTION

$$\frac{dh_1}{dt} = (Q_1 - K_1 h_1)/A$$
$$\frac{dh_2}{dt} = (K_1 h_1 + K_3 h_3)/A$$
$$\frac{dh_3}{dt} = (Q_4 - K_3 h_3)/A$$

35. SOLUTION

$$\frac{dh_1}{dt} = (Q_1 - K_1 h_1)/A$$
$$\frac{dh_2}{dt} = (K_1 h_1 + K_3 h_3)/A$$
$$\frac{dh_3}{dt} = (Q_4 - K_3 h_3)/A$$

36. SOLUTION

a) Assumed that the rate of flow out of a tank was proportional tot eh height of water instead of using Torricelli's law. A low water heights a direct proportionality law is approximately true. b) Constant temperature

37. SOLUTION

Accuracy, predicability and falsifiability.

38. SOLUTION

b)

39. SOLUTION

The second scientist is making the more reasonable statement that the model is the best so far.

40. SOLUTION

An accurate model is one that can recapitulate the current knowledge about a system. predictive model is one that can predict new information about a system that is currently not yet known.

41. SOLUTION

The authors claiming that their model has been validated means that the model has been shown to correctly predict one or more new experimental data.

42. SOLUTION

George Box meant that it is not possible to produce a model that is an exact replica of reality (or even desirable), but that simplified models can still generate useful predictions and hence nevertheless useful.

43. SOLUTION

moles cm^{-3}

44. SOLUTION

A boundary variable is a quantity of a model that does not change as a result of the action of the model. For a model that uses differential equations, a boundary species does not have a differential equation describing its change. A state variable is a variable that does change as a result of the action of the model.

45. **SOLUTION**

State Variables: S_1 and S_2. Parameters, k_1, k_2, k_3 and k_4. Boundary species: X_o and X_1.

46. **SOLUTION**

1. $\sin(x_1) + \sin(x_2) \neq \sin(x_1 + x_2))$
2. $e^{x_1} + e^{x+2} \neq e^{x_1+x_2}$
3. $V_m x_1/(K_m + x_1) + V_m x_2/(K_m + x_2) \neq V_m(x_1 + x_2)/(K_m + x_1 + x_2)$

47. **SOLUTION**

1. Let $f(x)$ be the function to linearise. $\frac{df}{dx} = 8x + 6$, therefore at x_o = 1, $y = f(x) + (8x + 6)(x - 1)$, or $y = 14x - 14$
2. Let $f(x)$ be the function to linearise. $\frac{df}{dx} = K_m V_m/(Km + x)^2$. At $x_o = K_m$, $\frac{df}{dx} = V_m/(4K_m)$, therefore at $x_o = K_m$, $y = f(Km) + V_m/(4K_m)(x - Km)$. Simplifying this equation yields: $y = V_m/4 + V_m x(4K_m) = V_m(K_m + x)/(4K_m)$

48. **SOLUTION**

mol l^{-l}

49. **SOLUTION**

The units for K_m and S are the same, hence know the units for S automatically gives you the units for K_m.

5 Differential Equations

50. **EXERCISE**

Implement the Euler method in your favorite computer language and use the code to solve the following two problems. Set initial conditions: $S_1 = 10, S_2 = 0$. Set the rate constants to $k_1 = 0.1; k_2 = 0.25$. Investigate the effect of different steps sizes, h, on the simulation results.

a) $dS_1/dt = -k_1 S_1$

b) $dS_1/dt = -k_1 S_1$; $dS_2/dt = k_1 S_1 - k_2 S_2$

51. Exercise

The following model shows oscillations in S_1 and S_2 at a step size of $h = 0.044$ when using the Euler method. Note that species names with a dollar in front are fixed species. By using simulation, show that these oscillations are in fact an artifact.

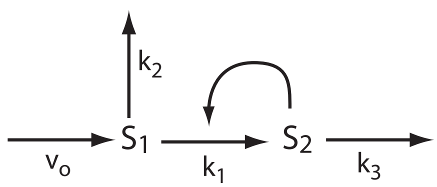
```
$Xo -> S1; k1*Xo;
 S1 -> S2; k2*S1;
 S2 ->;    k3*S2;

 Xo = 10; S1 = 0; S2 = 0;
 k1 = 23.4; k2 = 45.6; k3 = 12.3;
```

52. Exercise

Find out what differential equation solvers the Python SciPy Package supports.

53. Exercise

Construct a model of the following system using Tellurium.



Let the reaction associated with the positive feedback (k_1) be governed by the following rate law:

$$k_1 S_1 (1 + c S_2^q)$$

All other reactions are governed by first-order kinetics except the first reaction which has a constant rate of v_o. Set the constants to the following values: $v_o = 8; c = 1.0; k_1 = 1; k_2 = 1; k_3 = 5$ and $q = 3$. Study the effect of changing v_o on the dynamics of the system.

54. Exercise

Download the model `BIOMD0000000010` from Biomodels ("Kholodenko2000 - Ultrasensitivity and negative feedback bring oscillations in MAPK cascade") and load it into Tellurium. Run a simulation of the model. Make sure the model is in your current directory. Use `loads` to load a SBML model.

55. Exercise

Given a system at equilibrium, $A \rightleftharpoons B$, with equilibrium constant, K_{eq}, and total mass in the system to be $T = A + B$, show that a change δT in the total results in equal proportional changes to A and B.

50. Solution

```
import matplotlib.pyplot as plt

# Problem a)

h = 0.1
for k in range (5):
    k1 =0.1; s1 = 10; t = 0
    x = []; y = []
    for i in range (15):
        x.append (t); y.append (s1)
        ds1 = -k1*s1
        s1 = s1 + h*ds1
        t = t + h

    plt.plot (x, y)
    h = h + 4
plt.show()

# Problem b)

h = 0.1
for k in range (5):
    k1 =0.1; k2 = 0.25; s1 = 10; s2 = 0; t = 0
    x = []; y1 = []; y2 = []
    for i in range (15):
        x.append (t);
        y1.append (s1); y2.append (s2)
        ds1 = -k1*s1
        ds2 = k1*s1 - k2*s2
        s1 = s1 + h*ds1
        s2 = s2 + h*ds2
        t = t + h

    plt.plot (x, y1)
    plt.plot (x, y2)
    h = h + 2
```

51. Solution

```
h = 0.044
k1 = 23.4; k2 = 45.6; k3 = 12.3
```

```
Xo = 10; s1 = 0; s2 = 0
t = 0
x = []; y1 = []; y2 = []
for i in range (15):
    x.append (t);
    y1.append (s1); y2.append (s2)
    ds1 = k1*Xo - k2*s1
    ds2 = k1*s1 - k3*s2
    s1 = s1 + h*ds1
    s2 = s2 + h*ds2
    t = t + h

plt.plot (x, y1)
plt.plot (x, y2)

Set h = 0.001 and the oscillations disappear.
```

52. SOLUTION

Python Scipy 1.71 supports the following ODE algorithms: rk23, rk45, rk8, LSODA, Radau, etc.

53. SOLUTION

```
import tellurium as te
import matplotlib.pyplot as plt

r = te.loada("""
     J1:     -> S1;   vo;
     J2:   S1 -> ;    S1*k2;
     J3:   S1 -> S2;  (k1*S1-k_1*S2)*(1+c*S2^q);
     J4:   S2 -> ;    S2*k3;

     S1 = 0; S2 = 0;

    k1 = 1; k2 = 1; k3 = 5;
    q = 3; c = 1; k_1 = 0;  vo = 7;
""")

for i in range (10):
    r.reset()
    m = r.simulate (0, 10, 100)
    plt.plot (m['time'], m['[S1]'])
    r.vo = r.vo + 0.1
plt.show()
```

54. SOLUTION

```
r = te.loads ('BIOMD0000000010.xml')
m = r.simulate (0, 5000, 1000)
r.plot()
```

55. SOLUTION

At equilibrium $K_{eq} = B/A$ and $T = A + B$. Therefore $B = T - A$. Solving for B yields: $B = K_{eq}T/(1 + K_{eq})$. If we make a δT change in T, we can compute dB/dT which equals $dB/dT = K_{eq}/(1 + K_{eq})$. To get the proportional change we multiply by T and divide by B which yields one, i.e a change in T yields a proportional change in B and hence also A.

6 Stochastic Models

56. EXERCISE

Define the following terms:

a) c

b) h

c) $hc\delta t$

57. EXERCISE

Given a reaction of the form $X + X \rightarrow$, what is value of h

58. EXERCISE

The deterministic rate constant for the reaction $2X \rightarrow$ is equal to 0.5 $\text{mM}^{-1}\ \text{s}^{-1}$. If the volume of the compartment in which the reaction takes place is 10 mm^3, what is the value for the equivalent stochastic rate constant?

59. EXERCISE

Given the system:

```
s1 -> s2; k1*s1
s2 -> s3 + s4; k2*s2
s4 -> s5; k3*s4

k1 = 0.1; k2 = 0.34; k3 = 0.02
s1 = 100
```

Write a Tellurium script to run a stochastic simulation from time 0 to time 80. Repeat this 10 times and overlay the results on to one graph.

Solutions

56. Solution

a) c is the average probability that a reactant molecule will react per unit time

b) h is the number of distinct molecular reactant combinations for a given reaction

c) $hc\delta t$ is the probability that a reaction will occur in a population of molecules in the next time interval δt.

57. Solution

$x_a(x_a - 1)/2$ where x_a is the number of molecules.

58. Solution

We've first convert the units to moles and liters. With that, the value for the deterministic rate constant will be 0.5×10^{-3} M s^{-1}. The volume, 10 mm^3 is converted to 10×10^{-6}L. To convert we use the expression $2k/(N_A V)$ where N_A is Avogadro's number of 6.022×10^{23}. Hence: $c = 2 \times 0.5 \times 10^{-3}/(6.022 \times 10^{23} \times 10 \times 10^{-6}) = 1.66 \times 10^{-22}$ molecules^{-1} s^{-1}.

59. Solution

```
import tellurium as te

r = te.loada ('''
    s1 -> s2; k1*s1
    s2 -> s3 + s4; k2*s2
    s4 -> s5; k3*s4

    k1 = 0.1; k2 = 0.34; k3 = 0.02
    s1 = 100
''')

for i in range(10):
   m = r.gillespie (0, 80)
   r.plot(m, show=False, alpha=0.8)
   r.reset()

te.show()
```

7 System Behavior

60. EXERCISE

Describe the difference between thermodynamic equilibrium and a steady state.

61. EXERCISE

Write out the differential equations for the system $A \rightarrow B \rightarrow C$ where the reactions rates are given by:

$$\begin{aligned} v_1 &= k_1 A - k_2 B \\ v_2 &= k_3 B - k_4 C \end{aligned}$$

Find the concentrations of A, B, and C when the rates of change are zero: $dA/dt = 0, dB/dt = 0, dC/dt = 0$. Show that this system is at thermodynamic equilibrium when the rates of change are zero.

62. EXERCISE

What do we mean by the phrase quasi-equilibrium?

63. EXERCISE

Find the mathematical expression that gives the steady state levels of A and B in the following network:

$$\mathrm{X}_o \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{A} \overset{k_3}{\rightarrow} \mathrm{B} \overset{k_4}{\rightarrow} \varnothing \tag{2}$$

Assume that X_o is fixed, and that all reactions are governed by simple mass-action kinetics.

64. EXERCISE

Consider the following model, use a software tool of your choice to visualize the time evolution for the following system, simulate for 5 time units. At time zero, set $x = 1$ and $y = 2$. Simulate for 30 time units.

$$\begin{aligned} \frac{dx}{dt} &= 0.1 - 0.3x - 0.4y \\ \frac{dy}{dt} &= 0.5x + 0.1y \end{aligned}$$

Given the model from the previous question, compute the steady state in two ways: 1) Simulating the model for a very long time; 2) Determine algebraically the steady state. Compare the two solutions.

65. Exercise

Given the model from the previous question, explore how perturbations in x and y at steady state behave.

66. Exercise

Use a software tool of your choice to visualize the time evolution for the following system, simulate for 5 time units.

$$\frac{dx}{dt} = 2.55x - 4.4y$$
$$\frac{dy}{dt} = 5x + 2.15y$$

Solutions

60. Solution

Thermodynamic equilibrium is when a system no longer dissipates energy. That is all thermodynamic gradients are at zero, all net fluxes are zero. In steady state, the system dissipates energy at a constant rate (assuming the boundaries of the system are constant).

61. Solution

$$\frac{dA}{dt} = -v_1$$
$$\frac{dB}{dt} = v_1 - v_2$$
$$\frac{dC}{dt} = v_2$$

The first thing to realize about this systems is that its closed. This means there is an additional constraint on the system which is that the total mass is fixed, we'll call it $T = A + B + C$. Setting the rates of change to zero and solving for A, B and C, and noting that $A = T - B - C$, yields:

$$A = \frac{k_2 k_4 T}{k_1 k_3 + k_1 k_4 + k_2 k_4}$$
$$B = \frac{k_1 k_4 T}{k_1 k_3 + k_1 k_4 + k_2 k_4}$$
$$C = \frac{k_1 k_3 T}{k_1 k_3 + k_1 k_4 + k_2 k_4}$$

Since the system is closed, the solution to the system, must be at thermodynamic equilibrium. Another way to look at this is to see if the system is dissipating any energy. We can check this by looking at the network fluxes on the first and second steps. For example, substituting the solution for A and B into v_1 yields a reaction rate of zero. The same applies to v_2.

62. Solution

Quasi-equilibrium is a phrase that is used to indicate that a subpart of a reaction network is at steady state.

63. Solution

The differential equations for this system are:

$$\frac{dA}{dt} = k_1 X_o - k_2 A - k_3 B$$
$$\frac{dB}{dt} = k_3 A - k_4 B$$

$$A = \frac{k_1 k_4 X_o}{k_2 k_4 + (k^3)^2}$$
$$B = \frac{k_1 k_3 X_o}{k_2 k_4 + (k_3)^2}$$

64. Solution

```
import tellurium as te
r = te.loada('''
  x' = 0.1 -0.3*x - 0.4*y
  y' = 0.5*x - 0.1*y
  x = 1; y = 2
''')
m = r.simulate (0, 5, 100) # Then change to 30
r.plot()
```

At $t = 5$, $x = 0.433$, $y = 0.223$, at $t = 30$, $x = 0.0435$, $y = 0.217$
Solving the equation algebraically by setting the differential equations to zero yields solutions: $x = 0.0434783$ and $y = 0.217391$.

65. Solution

```
import tellurium as te
r = te.loada('''
  x' = 0.1 -0.3*x - 0.4*y
  y' = 0.5*x - 0.1*y
  x = 0.043478; y = 0.21739
```

```
  at time > 10:
      x = x + 1

  at time > 60:
      y = y + 1
''')

m = r.simulate (0, 100, 200)
r.plot()
```

66. SOLUTION

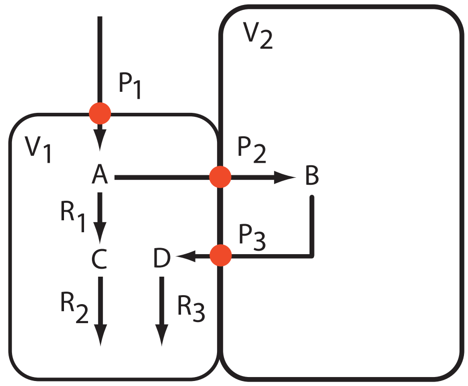
```
import tellurium as te
r = te.loada('''
   x' = 2.55*x - 4.4*y
   y'= 5*x + 2.15*y
   x = 1; y = 1
''')

m = r.simulate (0, 5, 200)
r.plot()
```

The system starts to oscillate uncontrollably.

8 Multicompartment systems

67. EXERCISE

The figure below shows a system of two compartments with volumes V_1 and V_2. There are three membrane transporters, P_1, P_2, and P_3 and three cytosolic reactions, R_1, R_2, and R_3. Write out the differential equations that describe the changes in amounts of A, B, C, and D. Assume simple facilitated diffusion for the transporters and irreversible first-order kinetics for the reactions. Build a computer model of the system and investigate how the output fluxes at R_2 and R_3 are influenced by the difference in volume between V_1 and V_2.



For example, assign reasonable values to all the rate constants in the model, set the two volumes to unity ($V_1 = V_2 = 1$), and compute the two output fluxes. Now increase V_2 ten fold while keeping all other parameters the same. What happens to the R_2 and R_3?

Solutions

67. SOLUTION

```
import tellurium as te
r = te.loada('''
    compartment V1, V2
    var A in V1, C in V1, D in V1
    var B in V2
    ext Out

    P1: -> A; P1_d*(Out - A);
    R1: A -> C; k1*A
    R2: C ->; k2*C

    P2: A -> B; P2_d*(A - B)
    P3: B -> D; P3_d*(B - D)

    R3: D ->; k3*D

    P1_d = 0.1; P2_d = 0.34; P3_d = 0.26
    Out = 1
    k1 = 0.67; k2 = 0.87; k3 = 0.56
    A = 0; B = 0; C = 0; D = 0;

    V2 = 10
''')
```

```
m = r.simulate (0, 10, 100)
r.plot()
```

9 Fitting Models

68. EXERCISE

What are the:

1. Chi-square sum of squares
2. Weighted sum of squares
3. Reduced chi-square

69. EXERCISE

Implement a simple gradient descent using Python to find the minimum for $f(x) = 3 * x^2 - 4 * x + 7$. Use algorithm 4 in Chapter 9 of the textbook

70. EXERCISE

Implement a simple gradient descent with a linear search using Python to find the minimum for $f(x) = 3 * x^2 - 4 * x + 7$. Use algorithm 5 in Chapter 9 of the textbook

71. EXERCISE

The Levenberg-Marquardt optimization method combines which two simpler methods?

72. EXERCISE

Name two global optimizer algorithms

73. EXERCISE

What two factors does a chi-square test try to distinguish?

74. EXERCISE

Students who are new to model fitting are often tempted to fit polynomial functions through data. A typical example is when using Excel to analyse some data where the trend line option gives a variety of fitting functions. A typical plot found in students report is show below:

1. What problem is being highlighted by the fitted plot?
2. Name two statistical test that can be used to help ensure the problem does arise.

75. Exercise

Four models were fitted to the same data. all models appear to fit reasonably well. An AIC value were computed for each model to be 0.8, 15.3, 7.6, and -1.5.
Based on the AIC values which of the four models should we pick for further investigation.

76. Exercise

The classical approach to estimating confidence limits in fitted parameters is to compute the covariance matrix. What are some of the problems associated with this method?

Solutions

68. Solution

1. $\sum_{i=1}^{N}(y_i - f(x_i; p_1 \ldots p_m))^2$
2. $\chi^2 \equiv \sum_{i=1}^{N} \frac{1}{\sigma_i^2}(y_i - f(x_i; p_1 \ldots p_m))^2$
3. $\chi^2_{\text{reduced}} \equiv \frac{1}{N-P} \sum_{i=1}^{N} \frac{1}{\sigma_i^2}(y_i - f(x_i; p_1 \ldots p_m))^2$

69. **Solution**

```
def fcn (x):
    return 3*x**2 - 4*x + 7

def dfcn (x):
    return 6*x - 4

print ("Gradient Descent")
x = 10; niter = 0
alpha = 0.3

while abs (dfcn (x)) > 1E-4:
    df = dfcn (x)
    x = x - alpha*dfcn (x)
    niter += 1
print (niter, ", x = ", x)
```

70. **Solution**

```
def fcn (x):
    return 3*x**2 - 4*x + 7

def dfcn (x):
    return 6*x - 4

print ("Gradient Descent with line search")
x = 10
alpha = 1; niter = 0

while abs (dfcn (x)) > 1E-4:
#for i in range (20):
    df = dfcn (x)
    alpha = 1;
    while fcn (x - alpha*df) > fcn (x):
      alpha /= 2
    x = x - alpha*df
    niter += 1
print (niter, ", x = ", x)
```

71. Solution

It combines a basic gradient descent method with the Guess-Newton method.

72. Solution

Differential evolution, simulated annealing, genetic algorithms

73. Solution

1. The normally distributed errors in the experimental data.
2. The choice of model used in the fitting.

74. Solution

1. The student has overfitted the data
2. F-test and AIC values

75. Solution

We would pick the 4th model because it has the lowest AIC value.

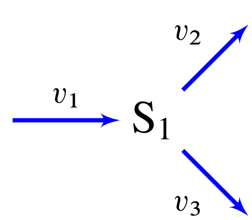
76. Solution

The main problem is that the estimates from the covariance matrix are approximations based on linearising the region around the minimum. This can give a false impression of the actual dimensions of the space around the minimum. In addition it assumes that the experimental noise is normally distritbuted and independent.

10 Steady-State

77. Exercise

Consider the following simple branched network:



where $v_1 = v_o$, $v_2 = k_1 S_1$ and $v_3 = k_2 S_1$.

a) Write the differential equation for S_1.

b) Derive the equation that describes the steady state concentration for S_1.

c) Derive the equations for the steady state fluxes through v_1 and v_2.

d) Determine algebraically the scaled sensitivity (See equation **??**) of the steady state concentration of S_1 with respect to v_o and k_1.

e) Explain why the signs of the sensitivity with respect to v_o and k_1 are positive and negative, respectively?

f) Assuming values for $v_o = 1; k_1 = 0.5$ and $k_2 = 2.5$, compute the values for the sensitivities with respect to k_1 and k_2.

g) What happens to the sensitivity with respect to k_1 as k_1 increases?

78. Exercise

Given the equation:

$$x^2 - a = 0$$

Apply the Newton formula:

$$x_{k+1} = x_k - \frac{f(x_k)}{\partial f / \partial x_k}$$

Show that the iterative solution to x is given by:

$$x_{k+1} = \frac{1}{2}\left(x_k + \frac{a}{x_k}\right) \tag{3}$$

79. Exercise

Implement the Newton-Raphson algorithm and use it to find **one** solution to the quadratic equation: $4x^2 + 6x - 8 = 0$.

80. Exercise

By changing the initial starting point of the Newton-Raphson algorithm, find the second solution to the quadratic equation from the previous question.

81. Exercise

Using Tellurium, find the steady state for the following model:
`Xo -> S1; k1*Xo; S1 -> X1; k2*S1; S1 -> X2; k3*S1;`
Assume that `Xo`, `X1` and `X2` have fixed concentrations with values $Xo = 1; X_1 = 0; X_2 = 0$ and rate constants $k_1 = 0.1; k_2 = 0.35; k_3 = 0.45$. Compute the steady state concentration of `S1`.

82. EXERCISE

Write a Tellurium script to perturb the value of `Xo` in the above model. Apply the perturbation as a square pulse; that is, the concentration of `Xo` rises, stays constant, then falls back to its original value. Make sure the system is at steady state before you apply the perturbation.

83. EXERCISE

Explain what is meant by a stable and unstable steady state.

84. EXERCISE

The steady state of a given pathway is stable. Explain the effect in general terms on the steady state if:
a) A bolus of floating species is injected into the pathway.
b) A permanent change is applied to a kinetic constant.

85. EXERCISE

Why are scaled sensitivities sometimes more advantageous that unscaled sensitivities?

86. EXERCISE

Construct a simple linear pathway with four enzymes as shown below:

$$X_o \xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3} S_3 \xrightarrow{v_4} X_1$$

Assume that the edge metabolites, X_o and X_1, are fixed. Assign reversible Michaelis-Menten kinetics to each step and arbitrary values to the kinetics constants. Assign a modest value to the boundary metabolite, X_o, of 10 mM. Compute the steady state for your pathway. If the software fails to find a steady state, adjust the parameters. Once you have the steady state, use the model to compute the sensitivity of the steady state flux with respect to each of the enzyme maximal activities. You can compute each sensitivity by perturbing each maximal activity and observing what this does to the steady state flux.
How might you use the flux sensitivities in a practical application? Compute the sum of the four sensitivities, what value do you get? Can you make a statement about the sum?

Solutions

77. SOLUTION

a)

$$\frac{dS_1}{dt} = v_o - k1 S_1 - k_2 S_1$$

b)

$$S_1 = \frac{v_o}{k_1 + k_2}$$

c)

$$v_1 = vo,\ v_2 = \frac{k_1 v_o}{k_1 + k_2}$$

$$\frac{dS_1}{dv_o}\frac{v_o}{S_1} = 1$$

$$\frac{dS_1}{dk_1}\frac{k_1}{S_1} = -\frac{k_1}{k_1 + k_2}$$

d) In v_o increases then this increases the rate of production of S_1, therefore S_1 rises, hence the sensitivity is positive. With respect to k_1, if we increase k_1, that causes the rate of v_2 increase, which in turn reduces the concentration of S_1. Hence the sensitivity is negative.

e)

$$\frac{dS_1}{dk_1}\frac{k_1}{S_1} = -\frac{k_1}{k_1 + k_2} = -0.5/3 = -0.1666$$

$$\frac{dS_1}{dk_2}\frac{k_2}{S_1} = -\frac{k_2}{k_1 + k_2} = 2.5/3 = 0.8333$$

f) If k_1 is increased then the sensitivity $-\frac{k_1}{k_1+k_2}$ decreases.

78. SOLUTION

We apply the algorithm in equation (**??**) to the problem $x^2 - a = 0$. This leads to:

$$x_{k+1} = x_k - \frac{x_k^2 - a}{2x_k}$$

Simplified, gives:

$$x_{k+1} = \frac{1}{2}\left(x_k + \frac{a}{x_k}\right)$$

79. SOLUTION

Software project. The solutions to $4x^2 + 6x - 8 = 0$ are $1/4(-3 - sqrt41)$ and $1/4(-3 + sqrt41)$ or 0.851 and -2.35

80. SOLUTION

Programming project.

81. SOLUTION

```
r = te.loada ('''
   $Xo -> S1; k1*Xo
   S1 -> $X1; k2*S1
   S1 -> $X2; k3*S1
   k1 = 0.1; k2 = 0.35; k3 = 0.45
   Xo = 1
  ''')

r.steadyState()
print (r.S1)
```

82. SOLUTION

```
r = te.loada ('''
   $Xo -> S1; k1*Xo
   S1 -> $X1; k2*S1
   S1 -> $X2; k3*S1
   k1 = 0.1; k2 = 0.35; k3 = 0.45
   Xo = 1

   at time > 30:
       Xo = Xo + 1
   at time > 50:
       Xo = Xo - 1
''')

m = r.simulate (0, 100, 200)
r.plot()
```

83. SOLUTION

A stable steady state is one where a perturbed species relaxes back to the ordinal steady state. If the steady state is unstable, and perturbation will not recover and will evolve to a new value.

84. SOLUTION

a) The floating species will initially rise but will in time fall back to it original steady state value.

b) The rate constant is increased, this will result in the steady state change to a new state.

85. **SOLUTION**

Scaled sensitivities are more useful because they are unit less and can be approximated as a ration of percentage changes. Such changes are more easily measured than absolute values.

86. **SOLUTION**

Programming project

11 Stability

87. **EXERCISE**

Determine the Jacobian matrix for the following system that describes a branched pathway:

$$\frac{dS_1}{dt} = v_o - k_1 S_1 - k_2 S_1$$
$$\frac{dS_2}{dt} = k_2 S_1 - k_3 S_2 - k_4 S_2$$

88. **EXERCISE**

Determine the Jacobian matrix for the following two systems:

$$\text{a)}\ \frac{dx}{dt} = x^2 - y^2 \quad \frac{dy}{dt} = x(1-y)$$

$$\text{b)}\ \frac{dx}{dt} = y - xy \quad \frac{dy}{dt} = xy$$

89. **EXERCISE**

Determine the Jacobian in terms of the unscaled elasticities and stoichiometry matrix for the following three systems. Assume all reactions are product insensitive, X_i species are fixed, and in c) S_3 regulates the first step, $S_1 \to S_2$.

$$\text{a)}\ X_o \to S_1;\ S_1 \to S_2;\ S_2 \to S_3; S_3 \to X_1$$
$$\text{b)}\ X_o \to S_1;\ S_1 \to S_2;\ S_2 \to S_1;\ S_2 \to X_1$$
$$\text{c)}\ S_1 \to S_2;\ S_2 \to S_3$$

90. Exercise

Show that the following system is stable to perturbations in S_1 and S_2 by computing the eigenvalues at steady state (See Listing **??**):

$$X_o \xrightarrow{v_1} S_1 \xrightarrow{v_2} S_2 \xrightarrow{v_3} X_1$$

The three rate laws are given by:

$$v_1 = \frac{V_{m_1} X_o}{Km_1 + X_o + S_1/K_1}$$

$$v_2 = \frac{V_{m_2} S_1}{Km_2 + S_1 + S_2/K_2}$$

$$v_3 = \frac{V_{m_3} S_2}{Km_3 + S_2}$$

Assign the following values to the parameters: $X_o = 1; X_1 = 0; V_{m_1} = 1.5; V_{m_2} = 2.3; V_{m_3} = 1.9; K_{m_1} = 0.5; K_{m_2} = 0.6; K_{m_3} = 0.45; K_1 = 0.1; K_2 = 0.2.$

91. Exercise

Given the Jacobian matrix you evaluated in first question of this section, do you think the system will stable or unstable? Hint: The eigenvalues of a triangular matrix are equal to the elements of the main diagonal.

92. Exercise

Show that the following system is unstable. What kind of unstable dynamics does it have?

```
import tellurium as te

r = te.loada ('''
    J0: $X0 -> S1; VM1*(X0-S1/Keq1)/(1+X0+S1+pow(S4,h));
    J1: S1 -> S2; (10*S1-2*S2)/(1+S1+S2);
    J2: S2 -> S3; (10*S2-2*S3)/(1+S2+S3);
    J3: S3 -> S4; (10*S3-2*S4)/(1+S3+S4);
    J4: S4 -> $X1; Vm4*S4/(KS4+S4);

    X0 = 10;        X1 = 0;
    S1 = 0.973182; S2 = 1.15274;
    S3 = 1.22721;  S4 = 1.5635;
    VM1 = 10;      Keq1 = 10;
    h = 4;        Vm4 = 2.5;
    KS4 = 0.5;
''')
```

93. Exercise

Show that the following system is unstable. What kind of unstable dynamics does it have?

```
import tellurium as te

r = te.loada ('''
    J0:  $src -> X;     k1*S;
    J1:  X -> R;        (kop + ko*EP)*X;
    J2:  R -> $waste;   k2*R;
    J3:  E -> EP;       Vmax_1*R*E/(Km_1 + E);
    J4:  EP -> E;       Vmax_2*EP/(Km_2 + EP);

    src = 0;       kop = 0.01;
    ko =  0.4;     k1 = 1;
    k2 = 1;        R = 1;
    EP = 1;        S = 0.2;
    Km_1 = 0.05;  Km_2 = 0.05;
    Vmax_2 = 0.3; Vmax_1 = 1;
    KS4 = 0.5;
''')

result = r.simulate(0, 500, 1000)
r.plot()
```

Solutions

87. Solution

$$\begin{bmatrix} -k_1 & -k_2 \\ k_2 & -(k_3 + k_4) \end{bmatrix}$$

88. Solution

a)

$$\begin{bmatrix} 2x & -2y \\ 1 - y & -x \end{bmatrix}$$

b)

$$\begin{bmatrix} -y & 1 - x \\ y & x \end{bmatrix}$$

89. SOLUTION

Stable

```
import telluirum as te
r = te.loada ('''
    $Xo -> S1;  Vm1*Xo/(Km1 + Xo + S1/K1);
    S1 -> S2; Vm2*S1/(Km2 + S1 + S2/K2)
    S2 -> $X1; Vm3*S2/(Km3 + S2)

    // Set up the model initial conditions
    Xo = 1; X1 = 0
    Vm1 = 1.5; Vm2 = 2.3; Vm3 = 1.9
    Km1 = 0.5; Km2 = 0.6; Km3 = 0.45
    K1 = 0.1; K2 = 0.2
''')

# Evaluation of the steady state
print (r.getSteadyStateValues())
# print the eigenvalues of the full Jacobian matrix
print (r.getFullEigenValues())
```

```
[0.23769588 0.11506555]
[-1.5956469 +0.j -4.80299766+0.j]
```

Both eigenvalues have negative real parts hence the system is stable.

90. SOLUTION

a)

$$\begin{bmatrix} -\varepsilon_1^2 & 0 & 0 \\ \varepsilon_1^2 & -\varepsilon_2^3 & 0 \\ 0 & \varepsilon_2^3 & -\varepsilon_3^4 \end{bmatrix}$$

b)

$$\begin{bmatrix} -\varepsilon_1^2 & \varepsilon_2^3 \\ \varepsilon_1^2 & -\varepsilon_2^3 - \varepsilon_2^4 \end{bmatrix}$$

c)

$$\begin{bmatrix} -\varepsilon_1^1 & 0 & -\varepsilon_3^1 \\ \varepsilon_1^1 & -\varepsilon_2^2 & 0 \\ 0 & \varepsilon_2^2 & 0 \end{bmatrix}$$

91. SOLUTION

The Jacobian has a triangular form, hence the eigenvalues are the values on the main diagonal, which in this case are $-k_1$ and $-(k_3 + k_4)$. Since rate constants are positive, the eigenvalues must be negative. Hence the system is stable.

92. SOLUTION

Using the commands:

```
# Evaluation of the steady state
print (r.getSteadyStateValues())
# print the eigenvalues of the full Jacobian matrix
print (r.getFullEigenValues())
```

to compute the eigenvalues for the system. Running this code yields:

```
-0.24875048+1.04230509j, -0.24875048-1.04230509j,
 -4.35227266+0.j -,5.35539319+0.j
```

This includes two eigenvalues with negative real parts and a conjugate pair also with negative real parts. This corresponds to a stable spiral. that is a damped oscillation.

93. SOLUTION

The system shows sustained oscillations with an alternation of rapid and slow dynamics.

12 Feedforward Networks

94. EXERCISE

Study the behavior of an Incoherent Type I FFL by using a competitive model for the activator/repression step. In a competitive model both the repressor and activator bind to the same operator site.

Solutions

94. SOLUTION

The competitive model (taken from Enzyme Kinetics for Systems Biology) is of the form:

$$v = V_f \frac{K_1 A^n}{1 + K_1 A^n + K_2 A^B}$$

Use the script shown in listing **??**.
Study the effect of pulses and step inputs on the dynamics of the feed forward network

13 Behavior of Stochastic Models

95. Exercise

The following modified model is taken from the work of Ribeiro and Lloyd-Price [**?**]. Run a simulation of the model using the given parameters. Explain why this model shows bimodal behavior.

```
import tellurium as te

r = te.loada ('''
    ProA -> A + ProA; g*ProA;
    ProB -> B + ProB; g*ProB;
    A + ProB -> ProBA; a0*A*ProB;
    B + ProA -> ProAB; a0*B*ProA;
    ProBA -> ProB + A; a1*ProBA;
    ProAB -> ProA + B; a1*ProAB;
    A -> $w; d*A;
    B -> $w; d*B;

    g = 0.2;   d = 0.01;
    a0= 0.3;   a1 = 0.05;
    A = 0;     B = 0;
    ProA = 1;  ProB = 1;
''')

r.setSeed(random.randint (1, 1000000))
result = r.gillespie(0, 2000000, ["Time", "A"]);
r.plot()
```

96. Exercise

The following model should be simulated as a deterministic model (i.e. using ODEs) and as a stochastic model.

a) Enter the model into Tellurium and run a deterministic simulation. Show the graphs for S_1, S_2, and S_3 over a time period of 800 time units.

b) Next run the same model as a stochastic model (use gillespie() instead of simulate()) Use the same values for the rate constants and initial conditions. Plot S_1 and S_3 on one graph and S_2 on another graph. As with the deterministic model, simulate for 800 time units.

c) Observe the significant difference between the deterministic and stochastic simulations. Why is this the case? Explain why the dynamics of the stochastic simulation are so different considering the number of molecules involved and the kind of reactions in the models.

d) Given your answer in (c), provide one situation where you think it is important to use a stochastic model rather than a deterministic one.

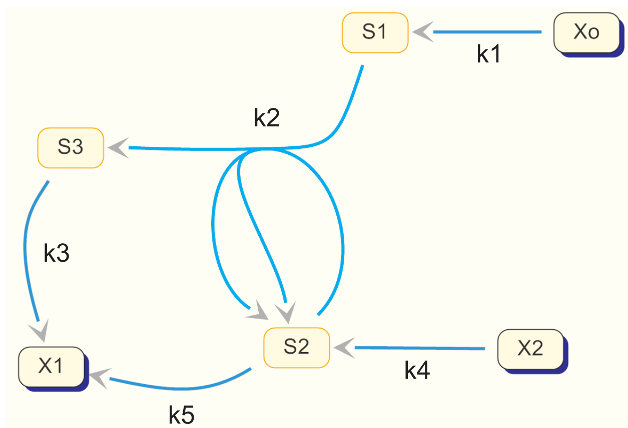


Figure 2: Reaction Scheme: Xo, X1, and X2 are boundary species. Be very careful that you replicate this model exactly as given. Assume all reactions are simple irreversible mass-action. Parameter values are as follows: $k_1 = 0.1; k_2 = 0.1; k_3 = 0.01; k_4 = 0.05; k_5 = 10.1; Xo = 10; X_1 = 0; X_2 = 1$. Note that the k_2 reaction is `S1 + S2 -> S3 + 2 S3`