1. Take the SIRS model, and suppose that the parameters are so that a positive steady state exists. Now assume that a new medication is discovered, which multiplies by 20 the rate at which people get cured (that is, become “removed” from the infectives). However, at the same time, a mutation in the virus which causes this disease makes the disease 5 times as easily transmitted as earlier. How does the steady state number of susceptibles change? (The answer should be stated as something like “it is doubled” or “it is cut in half”.)

Answering this question should only take a couple of lines. You may use any formula from the notes that you want to.

2. Consider the following chemical reaction network, which involves 4 substances called $M, E, C, P$:

\[ 3M + 2E \xrightarrow{\frac{1}{1}} C \xrightarrow{\frac{1}{2}} 2E + P. \]

(a) Find the species vector $S$ and the reaction vector $R(S)$ (assuming mass action kinetics).
(b) Find the stoichiometry matrix $\Gamma$.
(c) Compute the product $\Gamma R(S)$ and show the set of 4 differential equations for $M, E, C, P$.
(d) Find the rank of $\Gamma$.
(e) What is the dimension of the left nullspace of $\Gamma$?
(f) Find a basis of the left nullspace of $\Gamma$ (conservation laws).

3. As in the notes, we study a virus that can only be passed on by heterosexual sex. There are two separate populations, male and female: we use $\bar{S}$ to indicate the susceptible males and $S$ for the females, and similarly for $I$ and $R$.

The equations analogous to the SIRS model are:

\[
\begin{align*}
\frac{d\bar{S}}{dt} &= -\beta \bar{S}I + \gamma \bar{R} \\
\frac{dI}{dt} &= -\beta \bar{S}I - \nu I \\
\frac{d\bar{R}}{dt} &= \nu I - \gamma \bar{R} \\
\frac{dS}{dt} &= -\beta S\bar{I} + \gamma R \\
\frac{dI}{dt} &= \beta S\bar{I} - \nu I \\
\frac{dR}{dt} &= \nu I - \gamma R.
\end{align*}
\]
This model is a little difficult to study, but in many STD’s (especially asymptomatic), there is no “removed” class, but instead the infecteds get back into the susceptible population. This gives:

\[
\begin{align*}
\frac{d\bar{S}}{dt} &= -\bar{\beta}\bar{SI} + \bar{\nu}\bar{I} \\
\frac{d\bar{I}}{dt} &= \bar{\beta}\bar{SI} - \bar{\nu}\bar{I} \\
\frac{d\bar{S}}{dt} &= -\beta\bar{SI} + \nu\bar{I} \\
\frac{d\bar{I}}{dt} &= \beta\bar{SI} - \nu\bar{I}.
\end{align*}
\]

Writing \( \bar{N} = \bar{S}(t) + \bar{I}(t) \) and \( N = S(t) + I(t) \) for the total numbers of males and females, and using these two conservation laws, we then concluded that one may just study the following set of two ODE’s:

\[
\begin{align*}
\frac{d\bar{I}}{dt} &= \bar{\beta}(\bar{N} - \bar{I})\bar{I} - \bar{\nu}\bar{I} \\
\frac{d\bar{I}}{dt} &= \beta(N - I)\bar{I} - \nu I.
\end{align*}
\]

Parts (a)-(c) refer to this reduced model.

(a) Prove that there are two equilibria, the first of which is \( \bar{I} = I = 0 \) and a second one, which exists provided that:

\[
\sigma\bar{\sigma} = \left( \frac{N\bar{\beta}}{\nu} \right) \left( \frac{\bar{N}\bar{\beta}}{\bar{\nu}} \right) > 1
\]

and is given by \( \bar{I} = \frac{N\bar{N} - (\nu\bar{\beta})/(\beta\bar{\nu})}{\nu/\beta + \bar{N}} \).

(b) Prove that the first equilibrium is unstable, and the second one stable.

(c) What vaccination strategies could be used to eradicate the disease?

(d) Now consider the full model (six dimensional, with removeds). How many linearly independent conservation laws are there?

(e) Again for the full model. Reduce by conservation to a system of 5 or less equations (how many, depends on how many conservation laws you found in (d)). Pick some set of numerical parameters (any you want) such that \( \sigma\bar{\sigma} = 2 \). Determine, using computer simulations, what the solutions look like. (You may be able to find the steady states algebraically, too.)

For your answer, attach some plots of solutions \( I(t) \) and \( \bar{I}(t) \) as a function of time.

4. We discussed the chemical kinetics formulation of an example that may be represented as in Figure 1(a).

Many cell signaling processes involve double instead of single transformations such as addition of phosphate groups. A model for a double-phosphorylation as in Figure 1(b) corresponds to reactions as follows (we use double arrows for simplicity, to indicate reversible reactions):

\[
\begin{align*}
E + S_0 &\leftrightarrow ES_0 \rightarrow E + S_1 \leftrightarrow ES_1 \rightarrow E + S_2 \\
F + S_2 &\leftrightarrow FS_2 \rightarrow F + S_1 \leftrightarrow FS_1 \rightarrow F + S_0
\end{align*}
\]

where “\( ES_0 \)” represents the complex consisting of \( E \) bound to \( S_0 \) and so forth.
(a) Find the stoichiometry matrix and write a corresponding system of ODE’s.
(b) Show that there is a basis of conservation laws consisting of three vectors.

5. In the quasi-steady state derivations, suppose that, instead of \( e_0 \ll s_0 \), we know only the weaker condition:

\[
e_0 \ll (s_0 + K_m)
\]

Show that the same formula for product formation is obtained. Specifically, now pick:

\[
x = \frac{s}{s_0 + K_m}, \quad y = \frac{c}{e_0}, \quad \varepsilon = \frac{e_0}{s_0 + K_m}
\]

and show that the equations become:

\[
\frac{dx}{dt} = \varepsilon \left[ k_{-1} y - k_1 (s_0 + K_m) x (1 - y) \right]
\]
\[
\frac{dy}{dt} = k_1 \left[ (s_0 + K_m) x - (K_m + (s_0 + K_m) x) y \right].
\]

Now set \( \varepsilon = 0 \). In conclusion, one doesn’t need \( e_0 \ll s_0 \) for the QSS approximation to hold. It is enough that \( K_m \) be very large, that is to say, for the rate of formation of complex \( k_1 \) to be very small compared to \( k_{-1} + k_2 \) (sum of dissociation rates).

6. We consider a simplification of allosteric inhibition, in which binding of substrate can always occur, but product can only be formed (and released) if \( I \) is not bound. In addition, we will also assume that binding of \( S \) or \( I \) to \( E \) are independent of each other. (If we don’t assume this, the equations are still the same, but we need to introduce some more kinetic constants \( k’ \)s.)

A reasonable chemical model is, then:

\[
E + S \xrightleftharpoons[k_{-1}]{k_1} ES \xrightarrow{k_2} P + E
\]
\[
EI + S \xrightleftharpoons[k_{-1}]{k_3} EIS
\]
\[
E + I \xrightleftharpoons[k_{-3}]{k_3} EI
\]
\[
ES + I \xrightleftharpoons[k_{-3}]{k_3} EIS
\]
where “EI” denotes the complex of enzyme and inhibitor, etc.

Prove that there results under quasi-steady state approximation a rate

\[
\frac{dp}{dt} = \frac{V_{\text{max}}}{1 + i/K_i} \cdot \frac{s^2 + as + b}{s^2 + cx + d}
\]

for some suitable numbers \(a = a(i), \ldots\) and a suitably defined \(K_i\).

7. Do this problem:
http://www.math.rutgers.edu/~sontag/JODE/gardner_cantor_collins_toggle.html

8. This problem deals with the material in the section entitled “A digression on gene expression”.

(a) Consider the full model with repression: write the stoichiometry matrix and the differential equations, and analyze solutions.

(b) Formulate a model with activation instead of repression. (No need to analyze the model.)

9. This problem deals with the material on cell differentiation. We consider a toy “1-d organism”, with cells are arranged on a line. Each cell expresses a certain gene \(X\) according to the same differential equation

\[
\frac{dx}{dt} = f(x) + a
\]

but the cells toward the left end receive a low signal \(a \approx 0\), while those toward the right end see a high signal \(a\) (and the signal changes continuously in between). The level of expression starts at \(x(0) = 0\) for every cell.

This is what \(f + a\) looks like, for low, intermediate, and high values of \(a\) respectively:

We let the system settle to steady state.

After the system has so settled, we next suddenly change the level of the signal \(a\), so that from now on every cell sees the same value of \(a\). The value of \(a\) that every cell is exposed to, in the second part of the experiment, corresponds to an intermediate value that gives a graph like the second (right) one above.

Like in the example worked out above, we ask what the patterns will be after the first and second experiments.

Here are a few possibilities of what will be seen after the first and the second parts of the experiment. Circle the correct one (no need to explain).

(a) 000000000000 → AAAAABBBBCCCC → AAAAAABBBBB
(b) 000000000000 → AAAAAABBBBB → BBBB BBBB BBBB
10. For the van der Pol oscillator:

(a) Show that there are no periodic orbits contained entirely inside the half-plane \( \{(x, y), x > 1\} \).

(b) Show that there are no periodic orbits contained entirely inside the half-plane \( \{(x, y), x < 1\} \).

(Use Bendixon’s criterion to rule out such orbits.)

These next few problems deal with steady-states as function of input: hyperbolic and sigmoidal responses, adaptation:

11. Consider this reaction:

\[
A \xrightleftharpoons{s} B
\]

which describes for example a phosphorylation of \( A \) into \( B \) with rate constant \( s \), and a reverse de-phosphorylation with rate constant 1.

One may think of \( s \) as the concentration of an enzyme that drives the reaction forward.

(a) Write equations for this reaction (assuming mass action kinetics; for example \( da/dt = -sa + b \)).

(b) Observe that \( a(t) + b(t) \) is constant. From now on, assume that \( a(0)=1 \) and \( b(0)=0 \). What is the constant, then?

(c) (Still assuming \( a(0)=1 \) and \( b(0)=0 \).) Use the conservation law from (b) to eliminate \( a \) and write just one equation for \( b \).

(d) Find the steady state \( b(\infty) \) of this equation for \( b \) and think of it as a function of \( s \). Answer this: is \( b(\infty) \) a hyperbolic or sigmoidal function of \( s \)?

(e) Find the solution \( b(t) \) (this is just to practice ODE’s).

12. Consider this reaction:

\[
A \xrightleftharpoons{s} B \xrightleftharpoons{s} C
\]

which describes for example a phosphorylation of \( A \) into \( B \), and then of \( B \) into \( C \), with rate constant \( s \), and reverse de-phosphorylations with rate constant 1.

(a) Write equations for this reaction (assuming mass action kinetics).
(b) Find a conservation law, assuming that $a(0)=1$ and $b(0)=c(0)=0$, and, using this law, eliminate $b$ and write a system of equations for just $a$ and $c$.

(c) Find the steady state $(a(\infty), c(\infty))$ of this equation for $a, c$ and think of $c(\infty)$ as a function of $s$. Answer this: is $c(\infty)$ a hyperbolic or sigmoidal function of $s$?

13. Consider this reaction:

\[ \begin{align*}
    l & \xrightarrow{q} 0 \\
    s & \xrightarrow{p} 0 \\
    l & \xrightarrow{\text{dashed}} p
\end{align*} \]

where the dashed lines mean that $s$ and $q$ do not get consumed in the corresponding reactions (they both behave as enzymes). There are also constants $k_i$ for each of the rates (not shown). Make sure that you understand then why these are the reasonable mass-action equations to describe the system:

\[ \begin{align*}
    \frac{dp}{dt} &= k_1 s - k_2pq \\
    \frac{dq}{dt} &= k_3 s - k_4q
\end{align*} \]

(or one could have used, instead, a more complicated Michaelis-Menten model).

(a) Find the steady state, written as a function of $s$.

(b) Note that $p(\infty)$ (though not $q(\infty)$) is independent of $s$.

This is an example of adaptation, meaning that the system transiently responds to a “signal” $s$ (assumed a constant), but, after a while, it returns to some “default” value which is independent of the stimulus $s$ (and hence the system is ready to react to other signals).

(c) Graph (using for instance JOde) the plot of $p(t)$ versus $t$, assuming that $k_1=k_2=2$ and $k_3=k_4=1$, and $p(0)=q(0)=0$, for each of the following three values of $s$: $s = 0.5, 3, 20$.

You should see that $p(t) \to 1$ as $t \to \infty$ (which should be consistent to your answer to part (b)) but that the system initially reacts quite differently (in terms of “overshoot”) for different values of $s$.

14. Consider a system with equations:

\[ \begin{align*}
    \dot{x} &= f(x) - y \\
    \dot{y} &= \varepsilon(g(x) - y).
\end{align*} \]

Consider these 4 possibilities for the nullclines $y = f(x)$ and $y = g(x)$:
(a) What can you say about stability of the steady states?
(b) Sketch directions of movement in each; use large or small arrows and use this info to sketch what trajectories should look like.
(c) Sketch what solutions \(x(t), y(t)\) look like, for each of the examples.

15. Suppose that \(p(t)\) satisfies the CME. Show that if \(\sum_{k \in \mathbb{Z}_{\geq 0}} p_k(0) = 1\) then \(\sum_{k \in \mathbb{Z}_{\geq 0}} p_k(t) = 1\) for all \(t \geq 0\). (Hint: first, using that \(\rho_j^\sigma (k - \gamma_j) = 0\) unless \(k \geq \gamma_j\), observe that, for each \(j \in \{1, \ldots, m\}\):

\[
\sum_{k \in \mathbb{Z}_{\geq 0}} \rho_j^\sigma (k - \gamma_j)p_{k - \gamma_j} = \sum_{k \in \mathbb{Z}_{\geq 0}} \rho_j^\sigma (k)p_k
\]

and use this to conclude that \(\sum_{k \in \mathbb{Z}_{\geq 0}} p_k(t)\) must be constant. You may use without proof that the derivative of \(\sum_{k \in \mathbb{Z}_{\geq 0}} p_k(t)\) with respect to time is obtained by term-by-term differentiation.)

16. Show, using induction on \(k\), that, as claimed in the notes, \(\pi_k = e^{-\lambda k} \frac{k!}{\beta^k}\), where \(\lambda = \frac{\alpha}{\beta}\), solves

\[
\alpha \pi_{k-1} + (k+1)\beta \pi_{k+1} - \alpha \pi_k - k\beta \pi_k = 0, \quad k = 0, 1, 2, \ldots
\]

(the first term is not there if \(k = 0\)).

17. Write the CME for the bursting model.

18. Write the CME for the dimerization model.

19. Write the CME for the transcription/translation model. (Remember that now “\(k\)” is a vector \((k_1, k_2)\).)

20. This is a problem regarding the SSA.

Implement the SSA in your favorite programming system (MATLAB, Maple, Mathematica).
(b) Take the mRNA/protein model described in the notes, pick some parameters, and an initial state; now plot many sample paths, averaging to get means and variances as a function of time, as well as steady state means and variances.

(c) Compare the latter with the numbers obtained by using theory as described in the notes.

21. Show that an alternative way of writing the diffusion term in the FD equation is as follows:

$$\Gamma \text{diag} \left( \mathbb{E} \left[ \rho_1^2(X(t)) \right], \ldots, \mathbb{E} \left[ \rho_m^2(X(t)) \right] \right) \Gamma'$$

(where “diag \((r_1, \ldots, r_m)\)” means a diagonal matrix with entries \(r_i\) in the diagonal).

22. Prove that, for the probability generating function \(P\):

$$\left. \frac{\partial^2 P(z,t)}{\partial z_i \partial z_j} \right|_{z=1} = \begin{cases} \mathbb{E} \left[ X_i(t) X_j(t) \right] & \text{if } i \neq j \\ \mathbb{E} \left[ X_i(t)^2 \right] - \mathbb{E} \left[ X_i(t) \right] & \text{if } i = j. \end{cases}$$

23. For the mRNA example, derive the variance equation from the probability generating function, and show that the same result is obtained as in the notes.

24. For the mRNA example, solve explicitly the FD differential equations shown in the notes. (You may use matrix exponentials and variation of parameters, Laplace transforms, or whatever method you prefer.)

25. For the dimerization example, obtain an equation for \(\dot{\Sigma}\) (which will depend on moments of order three).

26. For the transcription/translation example:

   (a) prove this formula for the squared coefficient of variation for protein numbers:

   $$\text{cv} [P]^2 = \Sigma_{PP} \mu^2 P = \frac{(\theta + \beta + \delta) \beta \delta}{\alpha \theta (\beta + \delta)} = \frac{1}{\mu P} + \frac{1}{\mu M} \frac{\delta}{\beta + \delta}.$$

   (b) Show that \(\Sigma_{MP} = \frac{\theta \alpha}{\beta (\beta + \delta)}\).

27. Suppose that, in the reaction network \(A \xrightarrow{\mu} B, B \xrightarrow{\nu} A\), we know that initially, there are just \(r\) units of \(A\), that is, \(X(0) = (A(0), B(0)) = (r, 0)\). Show how to reduce the CME to a Markov chain on \(s+1\) states, and that the steady-state probability distribution is a binomial distribution.

28. The example of \(A \xrightarrow{\mu} B, B \xrightarrow{\nu} A\) with \(X(0) = (A(0), B(0)) = (r, 0)\) can be thought of as follows: \(A\) is the inactive form of a gene, and \(B\) is its active form. There are a total of \(r\) copies of the same gene, and the activity of each switches randomly and independently. Suppose that we now consider transcription and translation, where transcription is only possible when one of these copies of the gene is active. This leads to the following system:

$$A \xrightarrow{\mu} B, B \xrightarrow{\nu} A, B \xrightarrow{\alpha} M + B, M \xrightarrow{\beta} 0, M \xrightarrow{\theta} M + P, P \xrightarrow{\delta} 0.$$  

(a) Write down the CME for this system.

(b) Assuming only one copy of the gene, \(r = 1\), compute (using the FD method or generating functions) the steady-state mean and standard deviation of \(M\).

(c) Optional (very tedious computation): again with \(r = 1\), use the FD formula to compute the steady-state mean and standard deviation of \(P\).

(d) Optional: repeat the calculations with an arbitrary copy number \(r\).