Python practical 2

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I. CHEMICAL REACTIONS

Molecules of type A and B are involved in the following chemical reaction

$$2A \; \overset{k_1}{\underset{k_2}{\rightleftharpoons}} \; B \tag{1}$$

The forward and backward reaction rates are k_1 and k_2, respectively. The Ordinary Differential Equations (ODEs) describing this system are given by (using the law of mass action):

$$\frac{dA}{dt} = -2k_1 A^2 + 2k_2 B \tag{2}$$

$$\frac{dB}{dt} = k_1 A^2 - k_2 B \tag{3}$$

Starting with concentrations $A(0) = 1$ and $B(0) = 0$, and using rate constants $k_1 = 0.1$ and $k_2 = 0.3$, we want to numerically obtain $A(t)$ and $B(t)$ for $0 \leq t \leq 10$.

Question 1: Plot $A(t)$ and $B(t)$ vs. t for t from 0 to 10.
This code will help you integrate the ODE to give you the time evolution of the concentrations of $A(t)$ and $B(t)$

```
1  import scipy.integrate
2  import numpy as np
3  def dydt(t,y,k1,k2):
4
5      A , B= y
6      dAdt = -2*k1*A**2 + 2*k2*B
7      dBdt =  k1*A**2-k2*B
8      return (dAdt, dBdt)
9
10 dydt_withks = lambda t,y: dydt(t,y,k1,k2)
11 solution = scipy.integrate.solve_ivp(dydt_withks, t_span=(0,10), y0=(A0,B0), method='RK45', rtol=1e-6)
```

Question 2: What are the equilibrium points of this chemical reaction system? Does this make sense with respect to what you obtained from Question 1?

II. AUTO-ACTIVATION AND BISTABILITY

Consider the following auto-activated gene expression system, including mRNA (m) and its associated protein (P). Transciption is cooperative, requiring two copies of the self-activating protein

$$\frac{dm}{dt} = \frac{P^2}{1 + P^2} - bm, \tag{4}$$

while translation is given by

$$\frac{dP}{dt} = m - aP. \tag{5}$$

The parameters a and b are the (positive) rate constants associated with the degradation of protein and mRNA, respectively.

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Question 1: Compute the equilibrium points of the system. Show that the number of equilibrium points depends on the parameter $c = ab$. Illustrate the dependence of the number of equilibrium points by plotting a bifurcation diagram of the steady-state protein concentration P^* (obtained by setting the time derivatives of m and P to zero) as a function of $c = ab$ with c in a range from 0.1 to 0.5.

Hint: You need to solve a quadratic equation to obtain the steady states other than $P^* = 0$.

Question 2: For $a = 0.7$ and $b = 0.6$, plot the phase portrait, i.e., the vector ($[dm/dt,\ dp/dt]$) in an m versus p plot. Also include on this plot the graphs of $m^* = aP^*$ and $m^* = \frac{1}{b}\frac{P^{*2}}{1+P^{*2}}$ for both mRNA and protein concentrations at steady state. Make sure to plot in a range which includes all steady states. What are the possible steady-state values of the protein and mRNA concentrations? Hint: use the *quiver* command for plotting a vector field.

```
1 fig, ax = plt.subplots()
2 q=ax.quiver(p,m,pdot,mdot)
3 ax.quiverkey(q,X=0.3,Y=2.4, U=5,
4              label='Quiver key, length = 5', labelpos='E')
5 ax.plot(p,np.multiply(a,p))
6 ax.plot(p, np.divide( np.square(p), np.multiply(b,(1+np.square(p)))))
```

Question 3: Complete the script you have written in question 2 by adding the code that allows you to solve the ODE system. Use this approach to simulate the system starting from two different initial conditions $(m_0, P_0) = (2, 2)$ and $(m_0, P_0) = (0, 0.5)$ and add the corresponding phase plane trajectory to the plot you obtained in Question 2.

Question 4 (if you have time): Consider the auto-inhibiting system:

$$\frac{dm}{dt} = \frac{1}{1+P^2} - bm, \tag{6}$$

$$\frac{dP}{dt} = m - aP. \tag{7}$$

To find the equilibrium points (obtained by taking the time derivatives to zero), plot in an m vs p plot the two functions $m^* = aP^*$ and $m^* = \frac{1}{b}\frac{1}{1+P^{*2}}$. The equilibrium points are found at the intersection of these two curves. How many equilibrium points do you obtain? Redo the steps in question 2 for this system: Plot its phase portrait and include the curves $m^* = aP^*$ and $m^* = \frac{1}{b}\frac{1}{1+P^{*2}}$. Looking at the phase portrait what seems to be the stability of the equilibrium point? Solve the ODE system starting from the initial condition $(m_0, P_0) = (2, 2)$ and add to the plot the corresponding phase plane trajectory.

III.   OPTIONAL EXERCISE: EULER INTEGRATION WITH NOISE

Gene expression is noisy as the biochemical reactions involved are random events involving low numbers of molecules. Here we consider mRNA denoted by m and its associated protein denoted by P. When noise is relatively small, e.g., at large concentrations or large reaction volumes, one often makes the Langevin approximation, consisting in considering deterministic differential equations plus small noise terms. As an example, consider the case of constitutive gene expression:

$$\frac{dm}{dt} = a - bm + \eta_m \tag{8}$$

$$\frac{dP}{dt} = cm - dP + \eta_P, \tag{9}$$

where a is the (positive) rate constant of mRNA production, b is the (positive) rate constant of mRNA degradation, c is the (positive) rate constant of protein production, and d is the (positive) rate constant of protein degradation. Also included are noise terms $\eta_m(t)$ for mRNA and $\eta_P(t)$ for protein, consituting so-called Gaussian white noise with the following properties: mean $\langle \eta_m \rangle = 0$ and variance $\langle \eta_m(t), \eta_m(t') \rangle = 2a \cdot \delta(t - t')$ for mRNA, and mean $\langle \eta_P \rangle = 0$ and variance $\langle \eta_P(t), \eta_P(t') \rangle = 2ac/b \cdot \delta(t - t')$ for protein (δ represents the *Dirac* function). The quantities in front of the δ-functions describe the variances of the corresponding Gaussian noise distributions, and are technically valid only at steady state.

Question 1: Obtain the time courses of mRNA and protein by numerically integrating Eqs. (8) and (9) using Euler's method and Gaussian-distributed random numbers. Create plots of the time courses for some initial values of the mRNA and protein numbers. What are their steady states? Use parameters $a = 3$ (unit: M/s), $b = 1$ (unit: /s), $c = 4$ (unit:

/s), and $d = 1$ (unit: /s).

Question 2: Compare with the determinisitic solution in same plot.