

Chapter 2

Biochemical Dynamics

2.1 Single species models

Elementary combinations of enzyme-mediated and simple growth or decay terms can lead to a variety of behaviours. Here we explore some examples and applications of these ideas. We first look at the dynamics of a single species that might be a product of some reaction in the cell, a signaling molecule, or a protein that exists in multiple states. Analogies to single (population) species in ecology will be noted.

First consider continuous (ODE) models of the form

$$\frac{du}{dt} = f(u), \quad u(0) = u_0 \quad (2.1)$$

where u is a concentration (or later a density of some population) of interest. About f we will assume smoothness, so that the derivative $f'(u)$ exists in the range of interest for u ($0 \leq u \leq u_{large}$). In general, the solutions $u(t)$ to Eqn (2.1) can have limited types of behaviour that include:

- The solution approaches some fixed point (also called steady state) as $x \rightarrow +\infty$
- The solution approaches $\pm\infty$ as $t \rightarrow +\infty$.

Because u represents a density or concentration, we rule out negative u values on the grounds that these are nonphysical.

We are interested in exploring the following questions:

- How many steady states can this equation have?
- What are their stability properties?
- How does the system evolve from a given initial condition $u(0) = u_0 \geq 0$?

- How does the behaviour depend on parameters (such as rate constants) that appear in the equation?

For scalar equations (i.e. those involving a single dependent variable), we can find out a lot about the qualitative behaviour of the equation by finding the number, locations, and stability of steady states. This can usually be done by sketching a graph of the rate of change $f(u)$ versus u , and identifying points $u = u_s$ at which there is no change, i.e., where $f(u_s) = 0$. The local slope of f at such points determines the stability. If $f'(u_s) > 0$, then u_s is unstable, whereas if $f'(u_s) < 0$, then u_s is stable.

More specifically, we may consider restating our model equation in terms of rates of production and decay (or source and removal rates) as follows:

$$\frac{du}{dt} = P(u) - R(u), \quad (2.2)$$

where P, R are, respectively the rates of input and removal of the substance. This means that values of u such that $P(u) = R(u)$ will be steady states, i.e. states for which there is no change ($du/dt = 0$). Examples of this type follow.

2.2 Example 1: Michaelian production, linear decay

$$\frac{du}{dt} = \gamma \frac{u}{k + u} - du \quad (2.3)$$

Here u reflects the concentration of some substance that is produced at a saturating concentration-dependent rate. The higher is u , the more it is produced, but the rate of production can be at most γ per unit time. In fact, the first term is a form of autocatalysis (where u contributes to enhancing its own production). It is also removed (or degraded) at rate proportional to its concentration.

It can be seen that Eqn. (2.3) can have at most two steady state, one of which, $u = 0$ is unstable. We can see this result by sketching the functions $P(u), R(u)$ vs u on a common set of axes and observing which function dominates (is largest) over which range of values of u .

Exercise 2.2.1 (Single nontrivial steady state)

Use geometric or algebraic arguments to establish that, aside from $u = 0$, Eqn. (2.3) can have at most one positive steady state. Are there any conditions on the parameters that have to be satisfied for this to be true?

Solution to 2.2.1:

2.3 Example 2: Biological pest control

A similar idea can be applied to a situation in ecology where a pest species (e.g. common garden slugs) are kept under control by introducing a predator that eats this prey (e.g. ducks). Let $u(t)$ now represent the density of slugs in some area, and suppose that slugs reproduce at rate r per unit time.

Then one model for the slug population is

$$\frac{du}{dt} = ru - Pv_c \frac{u}{k + u} \quad (2.4)$$

Here P is the number of predators (of Type II), assumed fixed, v_c the rate of consumption of slugs per predator per unit time. ($P, \alpha \geq 0$).

The behaviour of Eqn. (2.4) is easily understood as a slight variant of Eqn. (2.3). We can show that, under appropriate conditions, the predators will eliminate the prey, provided that prey population is not too large. (We interpret this to mean that biological control of the slugs will work provided enough predators are introduced relative to the size of the prey population.)

However, it is interesting to note that the behaviour of this model changes in an important way if the predators are of type III, i.e. if we consider the modified model

$$\frac{du}{dt} = ru - Pv_c \frac{u^2}{k^2 + u^2} \quad (2.5)$$

Exercise 2.3.2 (Controlling the slugs)

- (a) Verify the above assertions for Eqn. (2.4), and determine how to determine the number of predators needed to eliminate slugs from the area if the initial slug population is $u(0) = u_0$.
- (b) How does the Type III predation model differ from that of the the Type II?

Solution to 2.3.2:

- (a)
- (b)

2.4 Michaelian autocatalysis and removal

Next, we consider whether simple changes in the decay rate (which we took as first-order in Example 1 could increase the number of fixed points or the type of qualitative dynamics observed in that example.

This leads us to explore the equation

$$\frac{du}{dt} = V_1 \frac{u}{k_1 + u} - V_2 \frac{u}{k_2 + u} \quad (2.6)$$

for $V_1, V_2, k_1, k_2 > 0$. We interpret this equation as a production of u by autocatalysis by one enzyme (first term in the equation) and removal by second enzyme (second term). We find that $u = 0$ is again a steady state solution. It is easy to verify using geometric or algebraic arguments that Eqn. (2.6) can have at most one other positive steady state, so that the two saturation terms did not increase the number of steady states.

However, intriguingly, introduction of a third linear decay term, to arrive at the modified equation

$$\frac{du}{dt} = V_1 \frac{u}{k_1 + u} - V_2 \frac{u}{k_2 + u} - du \quad (2.7)$$

changes our conclusions, and introduces the possibility of a third steady state solution. Eqn (2.7) can have up to three steady states (including the trivial one at $u = 0$).

Exercise 2.4.3 (Two or three steady states)

- Verify that Eqn. (2.6) can have at most two steady states, one of which is at $u = 0$.
- Verify that Eqn. (2.7) cannot have more than two steady states if $k_1 = k_2$ or if $V_1 = V_2$ or if $d = 0$.
- Give an argument that supports the fact that Eqn. (2.7) can have up to three steady states. Which states would be stable?

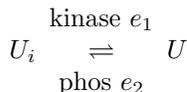
Solution to 2.4.3:

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We refer to dynamics in which there are two stable steady states as “bistability”. An application of this equation to growth of a population of bacteria and removal of those bacteria by neutrophils is due to Prof Vered Rom-Kedar and Roie Malka (Weizmann Institute of Science, Israel).

2.5 Molecular switches

Many biochemical signaling molecules can be found in “on-off” states, i.e. can be in either an active or an inactive form. To convert between one form and another, some small change is made in the molecule, for example, addition of a phosphate side-group. Enzymes that add a phosphate to a protein are called kinases and those that remove a phosphate are called phosphatases.



Here U_i is the inactive protein, U the active protein, and enzymes e_1, e_2 are, respectively, the kinase (adds phosphate) and the phosphatase (removes phosphate). Let u_i, u denote the concentrations of U, U_i . In most cases the total amount of the protein that switches between these forms is conserved so that $u + u_i = T = \text{constant}$. The differential equation satisfied by u resembles one studied earlier, but note carefully that the substrate for the production term is the inactive form.

$$\frac{du}{dt} = V_1 e_1 \frac{u_i}{k_1 + u_i} - V_2 e_2 \frac{u}{k_2 + u} \quad (2.8)$$

Using the conservation statement, we can eliminate u_i from this equation to obtain

$$\frac{du}{dt} = \gamma_1 \frac{(T - u)}{k_1 + (T - u)} - \gamma_2 \frac{u}{k_2 + u} \quad (2.9)$$

where we have also made the substitution $\gamma_i = V_i e_i$ to simplify the notation.

A simple geometric argument can be made to verify that Eqn. (2.9) has no trivial steady state, and only one positive steady state value. Equations of this form were considered by Goldbeter and Koshland and used in models for the cell cycle by Tyson to be discussed shortly.

In cases where an extracellular signal, S causes the activation of the kinases that produce the active form, the equation considered above is modified slightly to read

$$\frac{du}{dt} = \gamma_1 S \frac{(T - u)}{k_1 + (T - u)} - \gamma_2 \frac{u}{k_2 + u} \quad (2.10)$$

The dependence of the steady state u_s of Eqn. (2.10) on the strength of the signal, S is then called a Goldbeter-Koshland function.

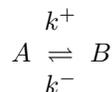
Exercise 2.5.4 (The Goldbeter function)

- Show that Eqn. (2.10) can have at most one biological steady state.
- Find that steady state by solving the equation $du/dt = 0$ to get the so-called Goldbeter-Koshland function.

Solution to 2.5.4:

2.6 Positive feedback and bistability

In some cases the product of a reaction causes an acceleration in its own rate of production by some enzyme. This type of effect is called positive feedback. Negative feedback similarly consists of a decrease in the rate of production caused by the product of a reaction. Both positive and negative feedbacks are ubiquitous in biochemistry and cell biology. As an example, consider



where k^- is a constant, but where k^+ depends on the level of A . We will consider the special case that

$$k^+ = g(A) = k_0 + \frac{\gamma A^2}{k^2 + A^2}.$$

Here k_0 is the basal value of k^+ , i.e., the rate of the reaction that would occur without the feedback. The sigmoidal term represents the feedback. If A is very large, its feedback towards its own production can be at most γ . Then an equation describing the concentration of A would be

$$\frac{dA}{dt} = B \left(k_0 + \frac{\gamma A^2}{k^2 + A^2} \right) - \delta A \quad (2.11)$$

Consider first a simple special case for which $k_0 = 0$, so that there is very little basal production of A . We also assume for now that the level of B is kept fixed, so that B is some constant parameter (unlike previous examples where the total amount of A plus B was kept constant.) Then

$$\frac{dA}{dt} = B \left(\frac{\gamma A^2}{k^2 + A^2} \right) - \delta A \quad (2.12)$$

For this case, we can solve for the steady states of the equation. It is evident that $dA/dt = 0$ is always true for the steady state $A = 0$. If $A \neq 0$ then steady states, if any, satisfy

$$B \left(\frac{\gamma A}{k^2 + A^2} \right) = \delta$$

Exercise 2.6.5 (Bistability)

Find conditions on the parameters such that there are two solutions to the above steady state equation.

Solution to 2.6.5:

2.7 Guide to literature

The effect of predators on prey populations was nicely explained by (8).

The threshold dependence of a response on a signal (“ultrasensitivity”) was in (6). The conditions for a biochemical (or other) system to be bistable have been explored, e.g. by (3; 10), but they are actually much more complicated than first conceived, e.g. see (2). A variety of simple dynamical systems and their behaviour in the context of biochemical systems is discussed in (11). More examples of the variety of dynamics that can be obtained in larger biochemical circuits is given in (7). An artificially designed switch that has been bio-engineered in a bacterial cell is given in (4).

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