Physical Modelling of Complex Systems: Assignment 3

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1 Linear example of quasi steady-state approximation

When dealing with N coupled first-order differential equations, one can use the so-called *quasi-steady-state approximation* (QSSA). This approximation can be applied if one variable evolves much faster than the others. Let us suppose that $x_1(t)$ is this 'fast' variable. We then take $\dot{x}_1 = 0$, from which one obtains $x_1(t)$ as a function of the other $N - 1$ variables. The procedure is known in mathematics as singular perturbation theory.

As an example of this method, we consider the following system of linear differential equations

$$\begin{cases} \dot{x} &= -3x + y \\ \dot{y} &= 100(2x - y) \end{cases}, \tag{1.1}$$

with initial conditions $x(0) = 1$ and $y(0) = 0$. The fast variable can be identified by looking at a plot of the solutions, obtained via numerically solving the above set of differential equations as in the previous assignment. Figure 1.1 below shows the solutions for the given initial conditions. It is clear that y is the fast changing variable in this scenario.

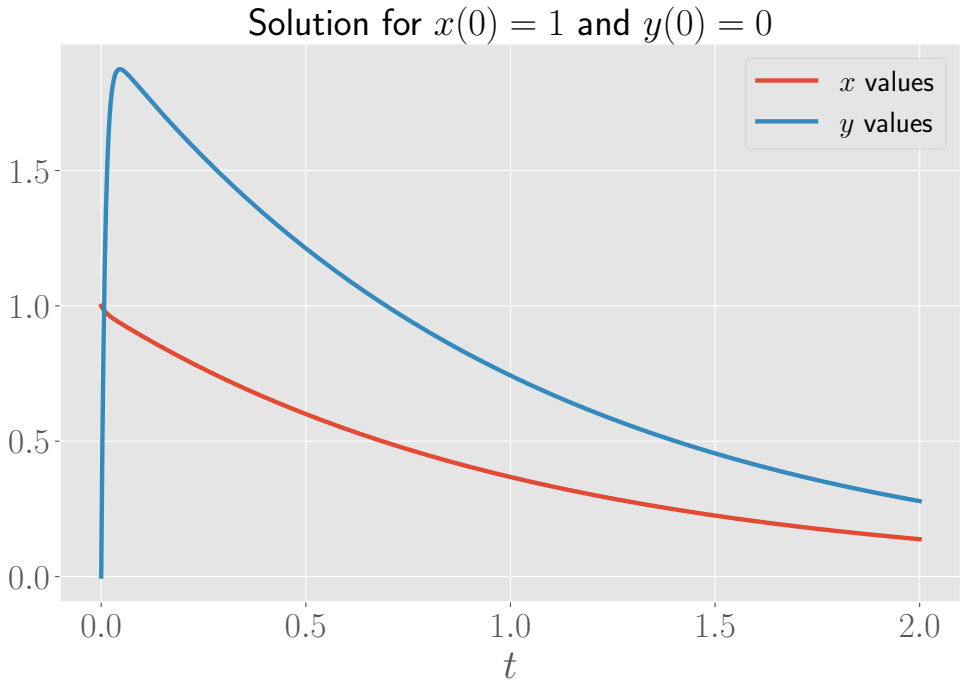

Figure 1.1: Solution to the set of differential equations (1.1) for initial conditions $x(0) = 1$ and $y(0) = 0$. From this, we can identify y as the fast variable.

As a brief side remark, we note that we can rewrite the system of differential equations in a matrix form

$$\dot{\Omega}(t) = M\Omega(t)\,, \quad \Omega(t) = \begin{pmatrix} x(t) \\ y(t) \end{pmatrix}\,, \tag{1.2}$$

where M is a 2×2 matrix. Using this notation, the system can be solved exactly, and the solution can be expressed in terms of the eigenvectors and eigenvalues of M. We will give the general outline of this method. By diagonalising the matrix M, we find an invertible matrix P (of which the columns are the eigenvectors of M) and a diagonal matrix D containing the corresponding eigenvalues λ_1 and λ_2, such that $M = PDP^{-1}$. Substituting this into the above differential equation and multiplying both sides of the equation to the left by P^{-1}, this becomes

$$P^{-1}\dot{\Omega} = DP^{-1}\Omega\,, \tag{1.3}$$

and if we define variables u and v as linear combinations of x and y, via

$$\begin{pmatrix} u \\ v \end{pmatrix} = P^{-1}\Omega\,, \tag{1.4}$$

then the set of differential equations is transformed into the following differential equations

$$\begin{cases} \dot{u} &= \lambda_1 u \\ \dot{v} &= \lambda_2 v \end{cases}\,, \tag{1.5}$$

of which the solutions are exponentials in time. The solutions for x and y are then found by multiplying by P. For our case, the matrix M is

$$M = \begin{pmatrix} -3 & 1 \\ 200 & -100 \end{pmatrix}, \tag{1.6}$$

and its eigenvalues and eigenvectors can easily be computed numerically (as done for example here), and we find

$$P = \begin{pmatrix} \frac{\sqrt{10209}+97}{400} & \frac{-\sqrt{10209}+97}{400} \\ 1 & 1 \end{pmatrix}, \quad D = \begin{pmatrix} \frac{-103+\sqrt{10209}}{2} & 0 \\ 0 & \frac{-103-\sqrt{10209}}{2} \end{pmatrix} \tag{1.7}$$

$$P^{-1} = \begin{pmatrix} \frac{-200}{\sqrt{10209}} & \frac{1}{2} + \frac{97}{2\sqrt{10209}} \\ \frac{200}{\sqrt{10209}} & \frac{1}{2} - \frac{97}{2\sqrt{10209}} \end{pmatrix}. \tag{1.8}$$

Following the general outline given above gives us the exact solutions for x and y. However, the details will not be provided here, since this is a tedious exercise and the expressions become quite cumbersome. Moreover, the numerical solutions to the differential equations are sufficient for us to capture the idea of the QSSA.

We now apply the QSSA to our set of differential equations, by setting $\dot{y} = 0$. This allows us to express $y(t)$ in function of $x(t)$. From equation (1.1), we see that in the QSSA we have $y = 2x$. We will compare the QSSA to the numerical solutions, by reproducing Figure 1.1 and also plotting the curve $y_{\text{QSSA}}(t) = 2x(t)$. The result is shown in Figure 1.2 below, with the QSSA shown as a grey dashed line.

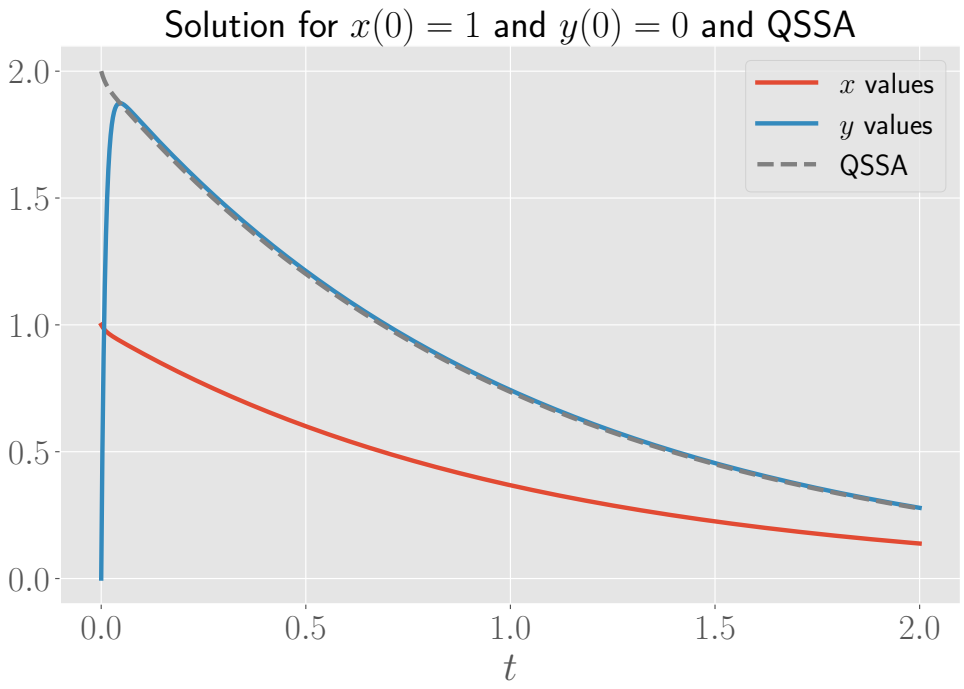

Figure 1.2: Solution to the system of differential equations (1.1) for initial conditions $x(0) = 1$ and $y(0) = 0$, along with the curve showing the QSSA $y = 2x$.

We see that approximation is very close to the exact (i.e., without the QSSA) solution for almost all values of t. However, for small t, the fast variable is varying much, and this variation is not captured by the approximation. Hence we can conclude that while the QSSA is a good approximation if one wants to deduce the long time behaviour of 'fast variables', it does not provide an accurate description of the solutions for times close to zero.

2 Enzymatic degradation

In many situations a chemical X is degradated, meaning that it breaks into fragments which do not participate to the reactions anymore. Spontaneous degradation of X, i.e. a reaction $X \to \emptyset$, is described in the mass action kinetics by a term $-\alpha x$, where x is the concentration of X, and α the degradation rate. Synthesis and degradation of a chemical are described by the equation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \beta - \alpha x\,, \tag{2.1}$$

where β is the creation rate, which can eventually depend on other chemical concentrations.

We consider here a different type of degradation due to the effect of an enzyme E on X.

The enzymatic degradation is described by the following reactions

$$E + X \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EX \xrightarrow{k'} E\,, \tag{2.2}$$

which describe the binding of X to the enzyme E and formation of a complex EX, through a reversible reaction, followed by the irreversible degradation of X. Once degradation has occured, the free enzyme is released.

We will first write down the system of differential equations corresponding to the above scenario. For this, we write the chemical reactions in equation (2.2) in separate chemical reactions.

$$E + X \xrightarrow{k_1} EX \tag{2.3}$$

$$EX \xrightarrow{k_{-1}} E + X \tag{2.4}$$

$$EX \xrightarrow{k'} E\,. \tag{2.5}$$

To find the differential equations governing these chemical reactions, we use mass action kinetics. Define

$$x \equiv [X]\,, \quad e \equiv [E]\,, \quad c \equiv [EX]\,. \tag{2.6}$$

Then we find

$$\begin{cases} \dot{e} &= -k_1 ex + (k_{-1} + k')c \\ \dot{x} &= -k_1 ex + k_{-1} c \\ \dot{c} &= k_1 ex - (k_{-1} + k')c \end{cases}\,. \tag{2.7}$$

As expected, not all these differential equations are independent. Indeed, since X is the only chemical which exhibits degradation, the sum of the concentrations of E and EX should be constant. This is verified by looking at equation (2.7), which shows that

$$\frac{\mathrm{d}(e+c)}{\mathrm{d}t} = 0\,. \tag{2.8}$$

Therefore, we can write $e + c = e_0 \equiv e(0)$ (we assume that at $t = 0$, there are no complex chemicals formed yet) and eliminate e from the above equations. This gives the equivalent set of differential equations

$$\begin{cases} \dot{x} &= -k_1 e_0 x + (k_1 x + k_{-1})c \\ \dot{c} &= k_1 e_0 x - (k_1 x + k_{-1} + k')c \\ e + c &= e_0 \end{cases}\,. \tag{2.9}$$

We will now apply the QSSA, assuming that the complex is rapidly formed and hence c is the fast variable. Therefore, we are allowed to put $\dot{c} = 0$. Then we find that

$$c = \frac{k_1 e_0 x}{k_1 x + k_{-1} + k'} = \frac{e_0 x}{x + K_m}, \quad K_m \equiv \frac{k_{-1} + k'}{k_1}\,, \tag{2.10}$$

where K_m is the so-called Michaelis-Menten constant. Substituting this result for c back into the equation of $\dot{x}$, and doing some straightforward algebraic manipulations, we find

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{-k' e_0 x}{x + K_m} \,. \tag{2.11}$$

We see that in this approximation, the equation for $\dot{x}$ contains a degradation term which is different from the degradation term in equation (2.1), and can be called *enzymatic degradation*. In Figure 2.1 below, we make a plot of this enzymatic degradation curve. As is already clear from the equation in (2.11), this curve has saturation and becomes approximately constant for large x. The concentration of the complex has the same feature and also has a plateau for large x, as seen from equation (2.10). The explanation is that for a large concentration of substrate particles X, all enzymes are bound to the substrate chemicals X. Since the reaction needs an enzyme to occur, there are no additional reactions occurring unless an enzyme becomes free again and available to link with another substrate chemical. Hence the formation of complexes does not speed up beyond this point.

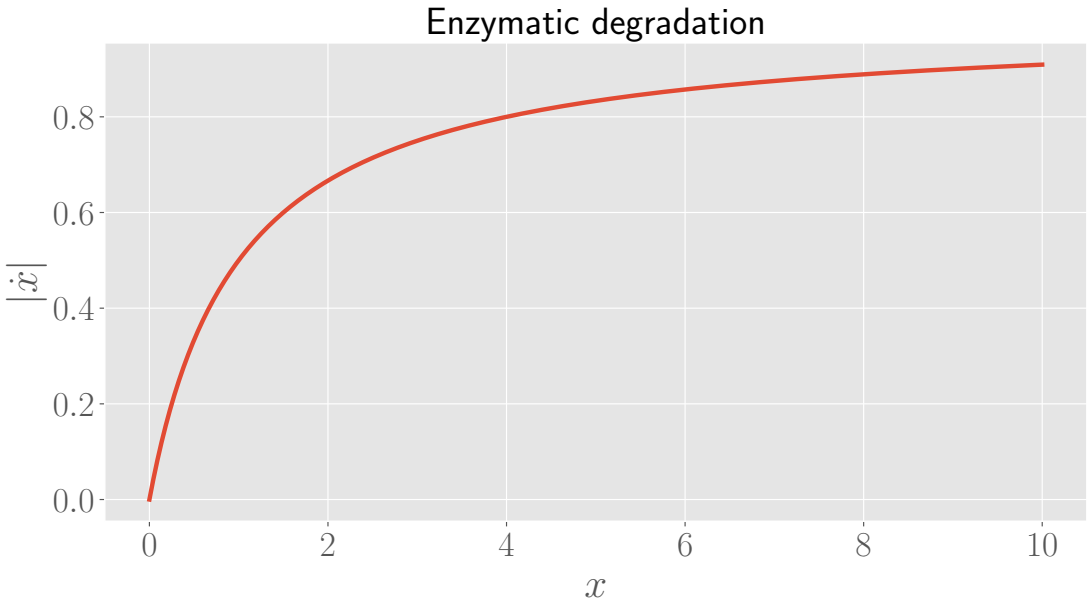

Figure 2.1: Plot of the absolute value of the enzymatic degradation curve, defined in equation (2.11), with all parameters set to 1.

3 Two subunit enzyme

We consider an enzyme which is formed by two subunits and which we denote as EE. Each subunit is capable of transforming a substrate S into a product P. The reactions are

$$EE + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} EES \tag{3.1}$$

$$EES \xrightarrow{k_3} EE + P \tag{3.2}$$

$$EES + S \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} SEES \tag{3.3}$$

$$SEES \xrightarrow{k_4} EES + P\,. \tag{3.4}$$

As before, we will use mass action kinetics to find the relevant differential equations. Define $s \equiv [S]$, $e \equiv [E]$, $c_1 \equiv [EES]$, $c_2 \equiv [SEES]$ and $p = [P]$. The system of equations governing the reactions is

$$\begin{cases} \dot{s} &= -k_1 es + k_{-1}c_1 + k_{-2}c_2 - k_2 c_1 s \\ \dot{e} &= -k_1 es + (k_{-1} + k_3)c_1 \\ \dot{c}_1 &= k_1 es - (k_{-1} + k_3)c_1 - k_2 c_1 s + (k_{-2} + k_4)c_2 \\ \dot{c}_2 &= k_2 c_1 s - (k_{-2} + k_4)c_2 \\ \dot{p} &= k_3 c_1 + k_4 c_2 \end{cases}\,. \tag{3.5}$$

As before, we have a conservation equation

$$\frac{\mathrm{d}(e + c_1 + c_2)}{\mathrm{d}t} = 0\,, \tag{3.6}$$

from which we find that $e + c_1 + c_2 \equiv e_0$ is constant. Again, we assume no complex chemicals are formed at $t = 0$. We now apply the QSSA for c_1 and c_2, and hence set $\dot{c}_1 = 0 = \dot{c}_2$. This gives

$$\begin{cases} 0 &= k_1 es - (k_{-1} + k_3)c_1 - k_2 c_1 s + (k_{-2} + k_4)c_2 \\ 0 &= k_2 c_1 s - (k_{-2} + k_4)c_2\,. \end{cases} \tag{3.7}$$

Define

$$K_{m1} = \frac{k_{-1} + k_3}{k_1}, \quad K_{m2} = \frac{k_{-2} + k_4}{k_2}\,. \tag{3.8}$$

The second condition, $\dot{c}_2 = 0$, can be written as

$$c_2 = \frac{s}{K_{m2}} c_1\,, \tag{3.9}$$

Subsituting this in the equation $\dot{c}_1 = 0$ gives

$$k_1 es = k_1 K_{m1} c_1 - k_2 c_1 s + (k_{-2} + k_4)\frac{s}{K_{m2}} c_1\,, \tag{3.10}$$

and using the definitions of K_{m1} and K_{m2}, this can be further simplified. The outcome is

$$c_1 = \frac{es}{K_{m1}}\,, \quad c_2 = \frac{es^2}{K_{m1}K_{m2}}\,. \tag{3.11}$$

Now we are able to derive the rate of production of the P particles. We will divide the equation for $\dot{p}$ by $e_0 = e + c_1 + c_2$, and get

$$\frac{1}{e_0}\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{k_3 c_1 + k_4 c_2}{e + c_1 + c_2} \tag{3.12}$$

$$= \frac{k_3 \frac{es}{K_{m1}} + \frac{k_4 es^2}{K_{m1}K_{m2}}}{e + \frac{es}{K_{m1}} + \frac{es^2}{K_{m1}K_{m2}}}\,, \tag{3.13}$$

where we used the expressions for c_1 and c_2 found above. We see that the dependence on e cancels in the right hand side. We can further simplify the right hand side, and we end up with

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{k_3 K_{m2} e_0 s + k_4 e_0 s^2}{K_{m1}K_{m2} + K_{m2}s + s^2}\,. \tag{3.14}$$

Now we consider the limit $K_{m1} \to +\infty$, $K_{m2} \to 0$ such that $K_{m1}K_{m2} \to K = \text{cte}$. Inserting these limits in the above equation, this gives

$$\frac{\mathrm{d}p}{\mathrm{d}t} \to \frac{k_4 e_0 s^2}{K + s^2}\,. \tag{3.15}$$

Hence in this limit, the kinetics has the form of Hill kinetics, with the Hill exponent equal to 2.

Up until now, we considered arbitrary values for the rates k_i. Now, we consider the rates to be given by

$$k_1 = 2k_2, \quad k_{-2} = 2k_{-1} \quad k_4 = 2k_3\,. \tag{3.16}$$

This corresponds to the situation where the two subunits of the enzyme work independently from each other. For example, the equality $k_1 = 2k_2$ tells us that the reaction to the right in (3.1) is twice as strong as the reaction going to the right in (3.3): this is because in the former, there are two binding sites available, working independently, whereas in the latter, one of the sites is already occupied and hence only one of the binding sites can participate in the reaction. Hence the former reaction has a probability to occur which is twice as large as the latter. For the equality $k_{-2} = 2k_{-1}$, the substrate S can more easily break off from the complex SEES than from the complex EES, again with twice the probability to occur. This is because the substrate from either side of SEES can break off the complex, and since both sites are independent, this gives a factor two. The same conclusion holds for the equality $k_4 = 2k_3$: both subunits can produce a product particle, and since both work independent from each other, this reaction occurs with a rate equal to twice the rate compared to the case in which only one site is occupied.

Using these rates, we have $K_{m2} = 4K_{m1}$. We can use this in equation (3.14) to find

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{2k_3 e_0 s(2K_{m1} + s)}{4K_{m1}^2 + 4K_{m1}s + s^2}\,. \tag{3.17}$$

In the denominator, we recognise $(2K_{m1} + s)^2$, and this simplifies with the factor in the numerator, yielding

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{2k_3 e_0 s}{2K_{m1} + s} \equiv \frac{v_{\max} s}{K_m + s}\,, \tag{3.18}$$

where we defined the parameters

$$v_{\max} = 2k_3 e_0, \quad K_m = 2K_{m1}\,. \tag{3.19}$$

The equation (3.18) implies that the system follows the usual Michaelis-Menten kinetics for the rates given in equation (3.16).