Notes on time-scaling analysis

1   Introduction

Mass action modeling permits to construct articulated mathematical descriptions of biological systems with direct interpretation at the level of the individual system components (*i-level* dynamics). The drawback is that when the number of components (or species) in the system or the number of reactions among them grows, mass action leads to large system of ODE's which become rapidly very difficult to analyze. In order to cope with this difficulty, it is expedient to introduce techniques enabling us to reduce the number of degrees of freedom in the analysis at the level of the population dynamics (*p-level* dynamics). An effective way to proceed is to discriminate processes according to the relative speed with which they occur. If the ratios of rates of the involved processes are separated by order of magnitudes, we can decouple the p-level dynamics into *fast* and *slow* degrees of freedom which can be afterward analyzed separately. The scope of these notes is to introduce some mathematical techniques adapted to the systematic inquire of *fast-slow* dynamical systems.

2   Enzyme kinetics

Consider the following *i-level* system with states

1. S substrate

2. E enzyme

3. X enzyme-substrate complex

4. P product

The *i-level* elementary reactions between the system components are described by the diagram

$$S + E \;\; \underset{\beta}{\overset{\alpha}{\rightleftarrows}} \;\; X \overset{\gamma}{\to} P + E \tag{2.1}$$

From the diagram it is straightforward to derive the *p-level* dynamics according to the principles of mass-action modeling:

$$
\begin{aligned}
\frac{ds}{dt} &= -\alpha\, s\, e + \beta\, x \\
\frac{de}{dt} &= -\alpha\, s\, e + \beta\, x + \gamma\, x \\
\frac{dx}{dt} &= \alpha\, s\, e - \beta\, x - \gamma\, x \\
\frac{dp}{dt} &= \gamma\, x
\end{aligned}
\tag{2.2}
$$

The system involves four degrees of freedom. In order to describe the state of the system we do not need to solve four differential equations. The evolution of the system preserves in time two quantities:

1. $s_o := s + x + p$:

$$\frac{d}{dt}(s + x + p) = (-\alpha\,s\,e + \beta\,x) + (\alpha\,s\,e - \beta\,x - \gamma\,x) + \gamma\,x = 0 \tag{2.3}$$

2. $e_o := e + x$:

$$\frac{d}{dt}(e + x) = (-\alpha\,s\,e + \beta\,x + \gamma\,x) + (+\alpha\,s\,e - \beta\,x - \gamma\,x) = 0 \tag{2.4}$$

Thus, we can eliminate x and p from the dynamics in favor of e_o and s_o and write

$$\begin{aligned}
\frac{ds}{dt} &= -\alpha\,s\,e + \beta\,(e_0 - e) \\
\frac{de}{dt} &= -\alpha\,s\,e + (\beta + \gamma)(e_o - e)
\end{aligned} \tag{2.5}$$

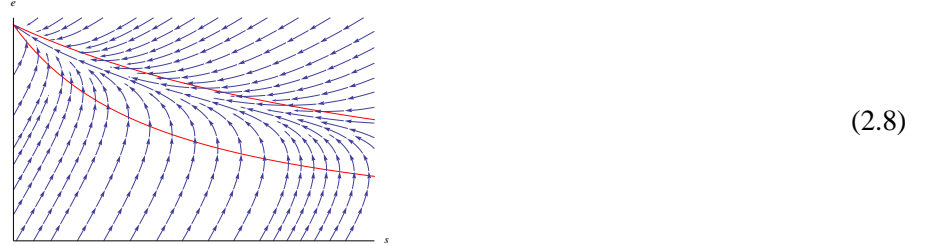The phase plane analysis of the reduced system proceeds as usual from the knowledge of the isoclines

1. $ds/dt = 0$:

$$e = \frac{\beta\,e_o}{\beta + \alpha\,s} \quad \Rightarrow \quad \frac{de}{dt} = \frac{e_o\,s\,\alpha\,\gamma}{\beta + \alpha\,s} > 0 \tag{2.6}$$

2. $de/dt = 0$

$$e = \frac{(\beta + \gamma)\,e_o}{\beta + \gamma + \alpha\,s} \quad \Rightarrow \quad \frac{ds}{dt} = -\frac{e_o\,s\,\alpha\,\gamma}{\beta + \gamma + \alpha\,s} < 0 \tag{2.7}$$

The corresponding phase plane diagram is

$$\tag{2.8}$$

All the orbits converge to the fixed point for $(s\,,e) = (0\,,e_o)$.

2.1 Reduction by decoupling of the degrees of freedom.

A further reduction of the dynamics is possible if we introduce some further hypothesis about the processes involved. In particular the conserved quantities s_o and e_o differ in magnitude in typical situation by several orders

$$\varepsilon := \frac{e_o}{s_o} \ll 1 \tag{2.9}$$

Thus, if the dynamics satisfies the initial conditions

$$s(0) = s_o \quad \& \quad e(0) = e_o \tag{2.10}$$

the we expect that at least for a long time interval

$$\frac{e(t)}{s(t)} \ll 1 \tag{2.11}$$

holds true. We can use the above considerations to extricate some asymptotic behavior of (2.5). To this scope we re-write (2.5) as

$$\frac{1}{s}\frac{ds}{dt} = -\alpha\, e + \beta\, \frac{e_o - e}{s}$$
$$\frac{1}{e}\frac{de}{dt} = -\alpha\, s + (\beta + \gamma)\, \frac{e_o - e}{e} \tag{2.12}$$

Since we expect

$$\frac{e_o - e}{s} \ll 1 \quad \& \quad \frac{e_o - e}{e} \sim O(1) \tag{2.13}$$

it is expedient to introduce the rescaled variables

$$x := \frac{s}{s_o} \quad \& \quad y := \frac{e}{e_o} \tag{2.14}$$

and the parameter

$$\omega := \alpha\, s_o \tag{2.15}$$

so that we can recast (2.5) in to the form

$$\frac{dx}{dt} = -\varepsilon\, \omega\, y\, x + \varepsilon\, \beta\, (1 - y)$$
$$\frac{dy}{dt} = -\omega\, y\, x + (\beta + \gamma)\, (1 - y) \tag{2.16}$$

As ε tends to zero we get into the limit result

$$\frac{dx}{dt} = 0$$
$$\frac{dy}{dt} = -\omega\, y\, x + (\beta + \gamma)\, (1 - y) \tag{2.17}$$

The rescaled substrate variable y is conserved in the limit. We are left with the one dimensional dynamics governing the evolution of the rescaled enzyme density. Plotting the vector field driving the reduced dynamics we see that there exists an attracting fixed point

$$\tag{2.18}$$

for

$$y^\star = \frac{\beta + \gamma}{\beta + \gamma + \omega\, x} \tag{2.19}$$

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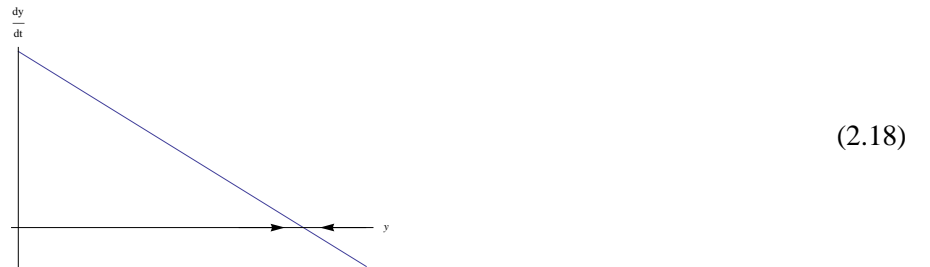
Such fixed point defines a *quasi-steady state* for the full dynamics. In other words in the limit of vanishing ε we expect the dynamics to tend asymptotics to the phase plane diagrams

(2.20)
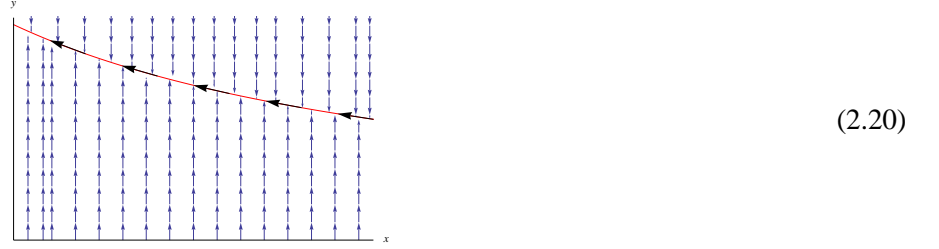
The dynamics along the y-axis contracts towards the isocline (2.19) which specifies the *slow-manifold* of the dynamics. A different rescaling of the variables allows us to describe the behavior of trajectories along the slow manifold. This is done by introducing the *slow time*

$$u = \varepsilon\,t \tag{2.21}$$

and observe that when derivatives are expressed in terms of the slow time we get into

$$\frac{dx}{du} = -\varepsilon\,\omega\,y\,x + \varepsilon\,\beta\,(1-y)$$
$$\varepsilon\,\frac{dy}{du} = -\omega\,y\,x + (\beta+\gamma)\,(1-y) \tag{2.22}$$

The limit ε tending to zero now gives

$$\frac{dx}{du} = -\varepsilon\,\omega\,y\,x + \varepsilon\,\beta\,(1-y)$$
$$0 = -\omega\,y\,x + (\beta+\gamma)\,(1-y) \tag{2.23}$$

This means that the first equation holds true only when the algebraic condition between x and y is satisfied. In other words, along the slow manifold we have

$$\frac{dx}{du} = -\frac{\gamma\,x}{\frac{\beta+\gamma}{\omega} + x} \tag{2.24}$$

We can re-write the above result in terms of the original variables. The enzyme density quickly relaxes to the slow manifold

$$e \to e(s) = \frac{(\beta+\gamma)\,e_o}{\beta+\gamma+\alpha\,s} \tag{2.25}$$

Along the slow manifold the evolution is governed by the one dimensional equation

$$\frac{ds}{du} = -\frac{\gamma\,e_o\,s}{\frac{\beta+\gamma}{\alpha} + s} \tag{2.26}$$

Two remarks are in order

   i The time scale separation, breaks down once s decreases to the order of e i.e. in the neighborhood of the fixed point of $(0, e_o)$.

   ii For large s, we have

$$\frac{ds}{dt} = -\gamma\,e_o = \text{constant} \tag{2.27}$$

   For large s the reaction behaves like a *zeroth order reaction*.

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3 Digression: the order of a reaction

For any $k \in \mathbb{N}$, the reaction

$$A_1 + \cdots + A_k \rightarrow \text{products} \tag{3.1}$$

is called a nth-order reaction if

$$\left| \frac{dA_1}{dt} \right| = \cdots = \left| \frac{dA_k}{dt} \right| = c\, A_1^{m_1} \times \cdots \times A_k^{m_k} \tag{3.2}$$

for some *strictly positive* constant c (i.e. $c > 0$), and provided the condition

$$\sum_{i=1}^{k} m_i = n \tag{3.3}$$

Thus, the overall reaction $S \rightarrow P$ in the reaction chain

$$S + E \underset{\beta}{\overset{\alpha}{\rightleftarrows}} X \overset{\gamma}{\rightarrow} P \tag{3.4}$$

with $s \gg e$ behaves like a zeroth-order reaction because

$$\frac{ds}{dt} \rightarrow \text{constant} \tag{3.5}$$

as $s \uparrow \infty$.

4 Enzyme kinetics: different asymptotics by different time-scaling

If the substrate S and the enzyme E densities are of comparable magnitude, we need a different approach. Let us introduce the quantity

$$g = s - e \tag{4.1}$$

then (2.5) becomes

$$\begin{aligned} \frac{ds}{dt} &= -\alpha\, s\, (s - g) + \beta\, (e_o - s + g) \\ \frac{dg}{dt} &= -\gamma\, (e_o - s + g) \end{aligned} \tag{4.2}$$

As in section 2 we denote by ε an arbitrary dimensionless scaling parameter and assume

$$\alpha, \beta \sim O(1) \quad \& \quad \gamma = O(\varepsilon) \tag{4.3}$$

as $\varepsilon \downarrow 0$. In other words, if $\gamma_o \sim O(1)$ we set
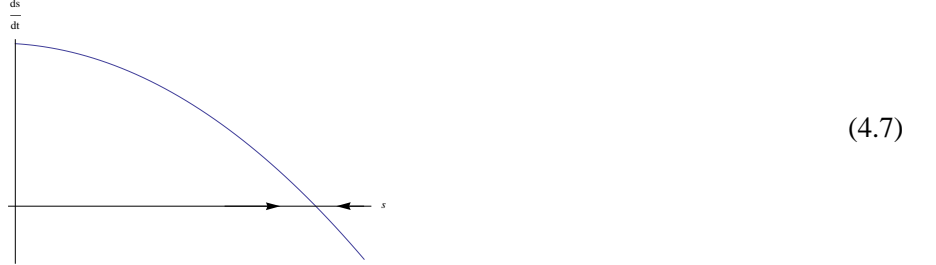
$$\gamma = \varepsilon\, \gamma_o \tag{4.4}$$

and write

$$\begin{aligned} \frac{ds}{dt} &= -\alpha\, s\, (s - g) + \beta\, (e_o - s + g) \\ \frac{dg}{dt} &= -\varepsilon\, \gamma_o\, (e_o - s + g) \end{aligned} \tag{4.5}$$

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Again, the limit ε reduces the system evolution law to a one equation

$$
\begin{aligned}
\frac{ds}{dt} &= -\alpha\, s\,(s-g) + \beta\,(e_o - s + g) \\
\frac{dg}{dt} &= -\varepsilon\,\gamma_o\,(e_o - s + g)
\end{aligned}
\tag{4.6}
$$

as g becomes asymptotically a conserved quantity. The effective vector field governing the fast substrate evolution

$$\tag{4.7}$$

exhibits now an attracting fixed point for

$$
s(g) = \frac{\alpha\, g - \beta + \sqrt{(\alpha\, g + \beta)^2 + 4\, e_o\, \alpha\, \beta}}{2\,\alpha} > 0
\tag{4.8}
$$

which specifies a *quasi-equilibrium* (or quasi steady-state) for the substrate. After a fast relaxation to the quasi-equilibrium, the evolution of the system is determined by the slow change of the difference g between the substrate and the enzyme densities. We can set the focus on the slow dynamics by evaluating time derivatives in units of the *slow-time*

$$
u = \varepsilon\, t
\tag{4.9}
$$

as we did in section 2.1. We get into the equation

$$
\begin{aligned}
\varepsilon\,\frac{ds}{du} &= -\alpha\, s\,(s-g) + \beta\,(e_o - s + g) \\
\frac{dg}{du} &= -\gamma_o\,(e_o - s + g)
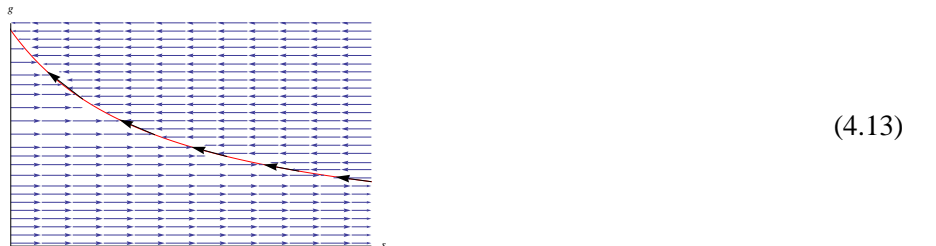\end{aligned}
\tag{4.10}
$$

Letting $\varepsilon \downarrow 0$, we get into

$$
\begin{aligned}
0 &= -\alpha\, s\,(s-g) + \beta\,(e_o - s + g) \\
\frac{dg}{du} &= -\gamma_o\,(e_o - s + g)
\end{aligned}
\tag{4.11}
$$

The asymptotic evolution occurs again the slow manifold now specified by (4.8). We summarize the result as

$$
\begin{aligned}
s &\to s(g) & \text{fast kinetics} \\
\frac{dg}{dt} &= -\gamma\,(e_o - s + g) & \text{fast kinetics}
\end{aligned}
\tag{4.12}
$$

On the (s, g)-plane we have the phase-plane plot

$$\tag{4.13}$$

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Observation: whenever the substrate density relaxes to the slow manifold the time derivative vanishes

$$\frac{ds}{dt} = 0 \tag{4.14}$$

this condition is *equivalent* to writing

$$e = \frac{\beta \, e_o}{\beta + \alpha \, s} \tag{4.15}$$

In the original variables the fast evolution keeps $g = s - e$ constant. Finally a straightforward calculation yields

$$\frac{ds(g)}{dt} = -\frac{\alpha \, \gamma \, s(g) \, e_o \, [s(g) + \beta]}{\alpha \, \beta \, e_o + [s(g) + \beta]^2} \tag{4.16}$$

so that the overall reaction $S \to P$ at quasi-equilibrium has no well-defined order.

5   Yet another possible time scaling

Suppose now that the reaction (2.1) occurs with rates

$$\alpha \, , \beta \, , \sim \, O(\varepsilon) \quad \& \quad \gamma \sim O(1) \tag{5.1}$$

i.e. we suppose

$$\alpha = \varepsilon \, \alpha_o \quad \& \quad \beta = \varepsilon \, \beta_o \quad \alpha_o \, , \beta_o \, \sim O(1) \tag{5.2}$$

Proceeding as in the previous section we find in such a case

$$\begin{aligned} \frac{ds}{dt} &= 0 \\ \frac{dg}{dt} &= -\gamma_o \, (e_o - s + g) \end{aligned} \tag{5.3}$$

Again the quasi-equilibrium point is attracting and is reached for

$$g(s) = s - e_o \tag{5.4}$$

Introducing a slow-time $u = \varepsilon \, t$ we find for the asymptotic evolution on the slow-manifold the equations

$$\begin{aligned} \frac{ds}{du} &= -\alpha_o \, s \, (s - g) + \beta_o (e_o - s + g) \\ 0 &= -\gamma_o \, (e_o - s + g) \end{aligned} \tag{5.5}$$

which reduce to

$$\frac{ds}{du} = -\alpha_o \, s \, e_o \tag{5.6}$$

We thus see that the slow dynamics describes in this case the overall process $S \to P$ as a first order reaction.