Chapter 4:
Modelling procedures
Sections: continuous time description and multi-level modelling

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1 Multi-scale modelling: Understanding the interplay between regulatory networks and the micro-environment

In this section, we explore mathematical tools to analyse biological systems with multiple time scales. Specifically, we consider the interplay between biological processes occurring at two time scales: Fast biochemical processes that regulate the phenotypic decision-making of cells in response to micro-environmental conditions, and the slow, tissue level processes regulating the dynamics of the micro-environment (the "bifurcation parameter" in section **??**). As discussed in chapter **??**, the clinical relevance of considering such multi-scale systems comes from the fact that the characteristic gradual aggravation of the chronic degenerative diseases emerges from aberrations in the phenotype-micro-environment interactions (figs. **??** and **??**).

In previous sections, we saw that phenotypes can be mathematically represented as attractors of the underlying regulatory networks, and that transitions between these attractors can be driven not only by stochastic fluctuations (section **??**, but also by changes in the micro-environmental conditions (subsection **??**). In this section, we want to pose the following question: what if these environmental fluctuations are actually changing *as a consequence* of the phenotype changes driven by the individual cells in the tissue (fig. **??**? How to account for tissue-level risk factors, which might propagate across this multi-scale regulatory network, giving rise to the gradual phenotypic deterioration (fig. **??**)?

To model these kind of systems, we will simultaneously consider the changes in the activation state of biochemical reaction networks controlling phenotypic decisions, a the tissue-level processes underlying micro-environmental fluctuations. While the biochemical reactions are fast, in the time-scale of minutes to hours, the dynamics of the surrounding tissue-level conditions stabilize within days to weeks. To account for these two different time-scales, we will perform a *time scale separation*, also known as Quasi-Steady-State Assumption (QSSA): The relation between the micro-environmental factor and the phenotype is described algebraically, by the mapping of the bifurcation parameter S to the stationary solution $\hat{X}_{ss}(S)$ of eq. $\dot{\hat{X}}(t,S) = 0$. The bifurcation parameter S, in turn, is dynamically described by $\dot{\hat{S}} = F(\tau, \hat{X}_{ss}(S))$, with t and τ the time-scales of the fast and the slow system, respectively. Note that the governing function $F(\tau, \hat{X}_{ss}(S))$ for the dynamics of S explicitly considers the algebraic variable $\hat{X}_{ss}(S)$. In other words, in such a model the changes in the bifurcation parameter depend on the proportion of phenotypes within the tissue.

Assuming such differences in time-scales in fact greatly simplifies the analysis of such multi-dimensional systems, described by the coupling between $\dot{\hat{X}}$ and $\dot{\hat{S}}$, with $\hat{X}$ and $\hat{S}$ n and m dimensional vectors, respectively. To illustrate this, let's consider the typical example of a biochemical network described by a

system of ODEs and simplified by the QSSA: The Briggs-Haldane version of the Michaelis-Menten equations [1, 2]).

The system of equations:

$$\frac{d[E]}{dt} = -k_{\mathrm{f}}[E][S] + k_{\mathrm{r}}[ES] + k_{\mathrm{cat}}[ES], \tag{1a}$$
$$\frac{d[S]}{dt} = -k_{\mathrm{f}}[E][S] + k_{\mathrm{r}}[ES], \tag{1b}$$
$$\frac{d[ES]}{dt} = k_{\mathrm{f}}[E][S] - k_{\mathrm{r}}[ES] - k_{\mathrm{cat}}[ES], \tag{1c}$$
$$\frac{d[P]}{dt} = k_{\mathrm{cat}}[ES], \tag{1d}$$

represents the dynamic interactions between the catalysing enzyme E, the substrate S, the enzyme-substrate complex ES, and the product of the enzymatic reaction, P, represented in the reaction network in figure 1. In these equations, it is considered that the total amount of enzymes is conserved (i.e., no *de novo* production of E), which can be seen directly from the conservation equations:

$$\frac{d[E]}{dt} + \frac{d[ES]}{dt} = 0,$$

which imply

$$[E] + [ES] = [E]_0 \tag{2}$$

The key assumption to simplify equations 1 is that the enzyme-substrate formation $[ES]$ is infinitely fast respect to the rest of the dynamics i.e. $\frac{d[ES]}{dt} = 0$. From this QSSA, it follows that

$$k_{\mathrm{f}}[E][S] = [ES](k_{\mathrm{r}} + k_{\mathrm{cat}})$$

. Using the conservation equation 2, $k_{\mathrm{f}}[E][S]$ can be rewritten as:

$$k_{\mathrm{f}}[E]_0[S] - k_{\mathrm{f}}[ES][S] = [ES](k_{\mathrm{r}} + k_{\mathrm{cat}})$$

, from which one can isolate the variable $[ES]$ as

$$[ES] = \frac{k_{\mathrm{f}}[E]_0[S]}{((k_{\mathrm{r}} + k_{\mathrm{cat}}) + k_{\mathrm{f}}[S])},$$

which can be used to rewrite $\frac{d[P]}{dt}$ as

$$\frac{d[P]}{dt} = k_{\mathrm{cat}} \frac{k_{\mathrm{f}}[E]_0[S]}{((k_{\mathrm{r}} + k_{\mathrm{cat}}) + k_{\mathrm{f}}[S])}$$

.

Defining

$$K_{\mathrm{M}} = \frac{k_{\mathrm{r}} + k_{\mathrm{cat}}}{k_{\mathrm{f}}}$$

, one can recognize the simple, one dimensional system representing the dynamics of product formation, known as Michaelis -Menten equation:

$$\frac{d[P]}{dt} = k_{\mathrm{cat}} \frac{[E]_0[S]}{K_{\mathrm{M}+}[S]}$$

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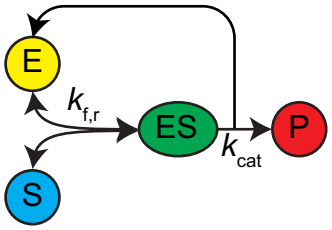

Figure 1: Reaction network of the dynamic interactions between enzyme (E), substrate (S), enzyme-substrate complex (ES) and product of the enzymatic reaction (P) represented in equations 1.

So, using QSSA we were able to reduce a 4-dimensional dynamical system to a one dimensional ODE!

Back to our original problem of coupling phenotypic decisions to micro-environmental changes. Let's consider the simplest multi-stable system in which gradual environmental conditions drive abrupt phenotype changes, namely a bistable system (fig. **??**). As discussed in section **??**, mapping the relation between the bifurcation parameter and the stable steady state solutions can be tricky, since analytical steady solutions for high-order non-linear systems rarely exist (since they are roots of high order polynomials), and numerical methods require exhaustive explorations of the parameter space (including initial conditions) and are often stuck in local solutions. Thus, iteratively solving such multi-scale problems during the numerical integration of slow variables can be computationally very intensive, and might often even fail to find the desired steady state solutions. To overcome this difficulty, it is possible to phenomenologically as opposed to mechanistic, corresponding to algebraic relations of steady state solutions of ODEs as functions of bifurcation diagrams) describe the previously characterized bistable switch by by a piecewise-affine (PWA) functions [3]. Such PWA approximation provides a rule that maps the input (stimulus) to the output (effector) (figure **??**). For example, assuming a perfect switch, the effector can be approximated by two constant values, E_{low} and E_{high}, representing the "low" or "high" branches of the bifurcation diagram, respectively. Now, let's consider that our bifurcation parameter, this is, the input, changes dynamically in the time-scale τ. Then the relation describing how the output $E(\tau)$ is determined by the input $S(\tau)$ and by the previous output values $E(x<\tau)$ can be approximated as follows:

- If $S(\tau) < S^-$, then $E(\tau) = E_{low}$ (effector is low if the stimulus concentration is low).
- If $S(\tau) > S^-$, then $E(\tau) = E_{high}$ (effector is high if the stimulus concentration is high).
- If $S(\tau) \in [S^-, S^+]$, then:
  - if $E(x<\tau) = E_{low}$, then $E(\tau) = E_{low}$, or
  - if $E(x<\tau) = E_{high}$, then $E(\tau) = E_{high}$,

  corresponding to the history-dependent determination of the effector value when the stimulus is in the bistable region.

More formally, these conditions can be represented by the PWA given in equation 3 (adapted from [4]):

$$E(\tau) = \begin{cases} E_{low} & \text{if } (S(\tau) < S^-) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x<\tau) = E_{\text{low}}\} \\ E_{high} & \text{if } (S(\tau) > S^+) \text{ or } \left\{S(\tau) \in [S^-, S^+] \text{ and } E(x<\tau) = E_{\text{high}}\right\}. \end{cases} \tag{3}$$

Note that equation 3 implicitly assumes two time-scales:

- A **fast** time-scale t that governs the stabilized biochemical interactions that underlie the bistable dose-response behaviour. These biochemical reactions can be represented by a system of ODEs $\dot{\mathbf{E}}(t,S,\mathbf{E})$ that operates at time-scale t and has a input S that does not change significantly ($S(t) \approx constant$) while $E(t)$ reaches its equilibrium value (given by E_{low} or E_{high}, respectively).
- A **slow** time-scale τ that determines the dynamics of the input $S(\tau)$ by the governing equation $\dot{S}(\tau) = F(\tau,S)$.

A special case of the system 3, which is of particular interest here, when considering the complex **interplays** between phenotype decisions (described by the different states of the bifurcation diagram) and microenvironmental conditions, occurs when the slowly changing input $S(\tau)$ is itself determined by its quickly stabilizing output $E(t)$ (and vice-versa). In such a case, also the dynamics of $S(\tau)$ (that depend on $E(\tau)$) can be descried by the PWA given in equation 4 (adapted from [4]):

$$\dot{S}(\tau) = \begin{cases} F_{low}(S) & \text{if } E(\tau) = E_{low} \\ F_{high}(S) & \text{if } E(\tau) = E_{high}, \end{cases} \tag{4}$$

where F_{low} and F_{high} are the two *governing equations* that determine the dynamics of S when $E(\tau) = E_{low}$ or $E(\tau) = E_{high}$, respectively.
Accordingly, the long term behaviour of S is given by the *focal points* S_{ss}^{low} and S_{ss}^{high}, corresponding to the steady state values given by the solution to $F_{low} = 0$ and $F_{high} = 0$, respectively [4].
The coupling between equations 3 and 4 represents a hybrid system that has been extensively discussed and analysed in [3, 4]. The long term behaviour of the coupled variable $S(\tau)$ and $E(t)$ is determined by the relative position of the focal points S_{ss}^{low} and S_{ss}^{high} respect to the threshold values S^- and S^+, as follows (figure 2):

- A resting, homeostatic ("low") steady state occurs when $S_{\text{ss}}^{low} \leq S^+$ and $S_{\text{ss}}^{high} < S^-$.
- A chronically inflamed steady state occurs when $S_{\text{ss}}^{low} > S^+$ and $S_{\text{ss}}^{high} \geq S^-$.
- Bistability in the two-time-scale dynamical system occurs when $S_{\text{ss}}^{low} \leq S^+$ but $S_{\text{ss}}^{high} \geq S^-$.
- Oscillations occur when $S_{\text{ss}}^{low} > S^+$ and $S_{\text{ss}}^{high} < S^-$.

In conclusion, this methodology allows the derivation of analytical conditions required for different qualitative behaviours of a complex dynamical system that operates in two time-scales, reducing the need for numerical methods. Note however that the agreement between the dynamical behaviour that is analytically derived from the hybrid system representation and the numerical simulations of the model must be verified for the particular mathematical model that is analysed using this approach, to ensure that neither the discontinuities of the hybrid representation of the system, nor the transient behaviour that is not captured by the focal point analysis detailed above, affect the dynamics of the unsimplified mathematical model.

The model described in section **??** provides an example in which this focal point analysis is used to systematically determine the effects of risk factors affecting tissue level processes on the development of early phases of AD. Such framework can be applied not only to micro-environment - phenotype interactions discussed here, but in general to model (biological) systems in which there is a co-existence and inter-dependence of processes operating at different time-scales, such as metabolism- signalling [5] (although this reference actually uses a numerical method, based on parameter fitting, to uncover the slow changes /adaptations in the signalling pathways that account for the fast metabolic reactions) and metabolism-gene expression [4], among many others.

Multi-scale systems coupling cellular level population dynamics with biochemical processes have been assessed mainly in spatially explicit models (eg. wound healing PDEs models [6], agent based models to understand epidermal homeostasis [7, 8, 9]) which will be discussed in the next chapter

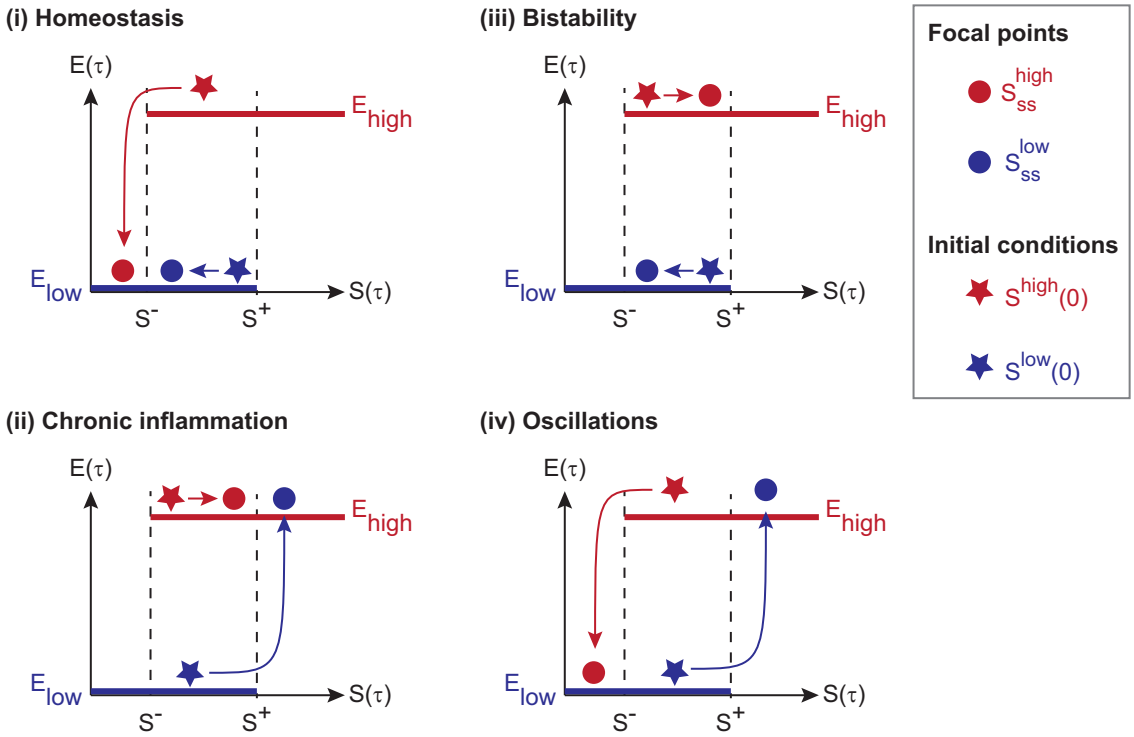

Figure 2: **Schematic representation of the qualitative dynamic behaviours of the hybrid system described in the coupled equations 3 and 4.** The long term dynamical behaviour of the hybrid system 3 and 4 is determined by the position of the focal points S_{ss}^{low} and S_{ss}^{high} respect to the threshold values S^- and S^+. (i) $S_{ss}^{low} \leq S^+$ and $S_{ss}^{high} < S^-$ lead to homeostasis, (ii) chronic inflammation occurs when $S_{ss}^{low} > S^+$ and $S_{ss}^{high} \geq S^-$, (iii) Bistability arises from $S_{ss}^{low} \leq S^+$ but $S_{ss}^{high} \geq S^-$, and (iv) Oscillations result from $S_{ss}^{low} > S^+$ and $S_{ss}^{high} < S^-$.

References

[1] Mark K. Transtrum and Peng Qiu. Bridging Mechanistic and Phenomenological Models of Complex Biological Systems. *PLoS Comput. Biol.*, pages 1–10, 2015.

[2] John Burdon and Sanderson Haldane. A note on the kinetics of Enzyme Action. *Biochem J*, 19(2):338–339, 1925.

[3] Madalena Chaves and Jean-Luc Gouzé. Exact control of genetic networks in a qualitative framework: The bistable switch example. *Automatica*, 47(6):1105–1112, jun 2011.

[4] Diego Oyarzún, Madalena Chaves, and Marit Hoff-Hoffmeyer-Zlotnik. Multistability and oscillations in genetic control of metabolism. *J. Theor. Biol.*, 295:139–53, feb 2012.

[5] Christian a Tiemann, Joep Vanlier, Peter Aj Hilbers, and Natal Aw van Riel. Parameter adaptations during phenotype transitions in progressive diseases. *BMC Syst. Biol.*, 5(1):174, 2011.

[6] L Olsen, J a Sherratt, and Philip K Maini. A mathematical model for fibro-proliferative wound healing disorders. *Bull. Math. Biol.*, 58(4):787–808, jul 1996.

[7] Niels Grabe and Karsten Neuber. A multicellular systems biology model predicts epidermal morphology, kinetics and Ca2+ flow. *Bioinformatics*, 21(17):3541–3547, sep 2005.

[8] Thomas Sütterlin, Simone Huber, Hartmut Dickhaus, and Niels Grabe. Modeling multi-cellular behavior in epidermal tissue homeostasis via finite state machines in multi-agent systems. *Bioinformatics*, 25(16):2057–2063, aug 2009.

[9] Thomas Sütterlin, Christoph Kolb, Hartmut Dickhaus, Dirk Jäger, and Niels Grabe. Bridging the scales: semantic integration of quantitative SBML in graphical multi-cellular models and simulations with EPISIM and COPASI. *Bioinformatics*, 29(2):223–9, jan 2013.