
Biomolecular Feedback Systems

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Chapter 3

Dynamic Behavior

In this chapter, we describe some of the tools from dynamical systems and feedback control theory that will be used in the rest of the text to analyze and design biological circuits, building on tools already described in AM08. We focus here on deterministic models and the associated analyses; stochastic methods are given in Chapter 4.

Prerequisites. Readers should have a understanding of the tools for analyzing stability of solutions to ordinary differential equations, at the level of Chapter 4 of AM08. We will also make use of linearized input/output models in state space, based on the techniques described in Chapter 5 of AM08, and sensitivity function methods, described in Chapters 11 and 12 of AM08 and building on the frequency domain techniques described in Chapters 8–10.

3.1 Analysis Near Equilibria

As in the case of many other classes of dynamical systems, a great deal of insight into the behavior of a biological system can be obtained by analyzing the dynamics of the system subject to small perturbations around a known solution. We begin by considering the dynamics of the system near an equilibrium point, which is one of the simplest cases and provides a rich set of methods and tools.

Parametric uncertainty

Consider a general nonlinear system of the form

$$\dot{x} = f(x, \theta, w),$$

where $x \in \mathbb{R}^n$ is the system state, $\theta \in \mathbb{R}^p$ are the system parameters and $w \in \mathbb{R}^q$ is a set of external inputs. Let $x_e(\theta_0, w_0)$ represent an equilibrium point for fixed parameters θ_0 and external input w_0 , so that $f(x_e, \theta_0, w_0) = 0$. The stability of the system around the equilibrium point can be analyzed using the tools described in AM08. Here we focus instead on understanding how the location of the equilibrium point and the dynamics near the equilibrium point vary as a function of changes in the parameters θ and external inputs w .

We start by assuming that $w = 0$ and investigating how x_e depends on θ . The simplest approach is to analytically solve the equation $f(x_e, \theta_0) = 0$ for x_e . However,

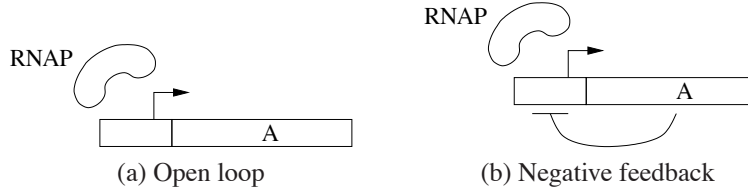


Figure 3.1: Parameter sensitivity in a genetic circuit. The open loop system (a) consists of a constitutive promoter, while the closed loop circuit (b) is self-regulated with negative feedback (repressor).

this is often difficult to do in closed form and so as an alternative we instead look at the linearized response given by $S_{x_e\theta} = dx_e/d\theta$, the (infinitesimal) change in the equilibrium state due to a change in the parameter. To determine $S_{x_e\theta}$ we begin by differentiating the relationship $f(x_e(\theta), \theta) = 0$ with respect to θ :

$$\frac{df}{d\theta} = \frac{\partial f}{\partial x} \frac{\partial x_e}{\partial \theta} + \frac{\partial f}{\partial \theta} = 0 \quad \implies \quad \frac{\partial x_e}{\partial \theta} = - \left(\frac{\partial f}{\partial x} \right)^{-1} \frac{\partial f}{\partial \theta} \Big|_{(x_e, \theta_0)}. \quad (3.1)$$

These quantities can be computed numerically and hence we can evaluate the effect of small (but constant) changes in the parameters θ on the equilibrium state x_e .

A similar analysis can be performed to determine the effects of small (but constant) changes in the external input w . Suppose that x_e depends on both θ and w , with $f(x_e, \theta_0, w_0) = 0$ and θ_0 and w_0 representing the nominal values. Then

$$\frac{\partial x_e}{\partial \theta} = - \left(\frac{\partial f}{\partial x} \right)^{-1} \frac{\partial f}{\partial \theta} \Big|_{(x_e, \theta_0, w_0)}, \quad \frac{\partial x_e}{\partial w} = - \left(\frac{\partial f}{\partial x} \right)^{-1} \frac{\partial f}{\partial w} \Big|_{(x_e, \theta_0, w_0)}.$$

We see that the vector $\partial f / \partial w$ describes how the specific inputs vary and $(\partial f / \partial x)^{-1}$ indicates how the perturbations are reflected in the equilibrium states. If the system is close to instability then some eigenvalues of $\partial f / \partial x$ will be near zero and hence the inverse could be large, resulting in significant changes in the equilibrium point due to variations in the disturbances (or parameters).

Example 3.1 (Transcriptional regulation). Consider a genetic circuit consisting of a single gene. We wish to study the response of the protein concentration to fluctuations in its parameters in two cases: a *constitutive promoter* (no regulation) and self-repression (negative feedback), illustrated in Figure 3.1. The dynamics of the system are given by

$$\frac{dm}{dt} = F(P) - \gamma m, \quad \frac{dP}{dt} = \beta m - \delta P,$$

where m is the mRNA concentration and P is the protein concentration.

For the case of no feedback we have $F(p) = \alpha_0$, and the system has an equilibrium point at $m_e = \alpha_0/\gamma$, $P_e = \beta\alpha_0/(\delta\gamma)$. The parameter vector can be taken as $\theta = (\alpha_0, \gamma, \beta, \delta)$. Since we have a simple expression for the equilibrium concentrations, we can compute the sensitivity to the parameters directly:

$$\frac{\partial x_e}{\partial \theta} = \begin{pmatrix} \frac{1}{\gamma} & -\frac{\alpha_0}{\gamma^2} & 0 & 0 \\ \frac{\beta}{\delta\gamma} & -\frac{\beta\alpha_0}{\delta\gamma^2} & \frac{\alpha_0}{\delta\gamma} & -\frac{\beta\alpha_0}{\gamma\delta^2} \end{pmatrix}$$

If we choose the parameters as $\theta = (0.00138, 0.00578, 0.115, 0.00116)$, then the resulting sensitivity matrix evaluates to

$$S_{x_e, \theta}^{\text{open}} \approx \begin{pmatrix} 170 & -41 & 0 & 0 \\ 17000 & -4100 & 210 & -21000 \end{pmatrix}. \quad (3.2)$$

If we look instead at the scaled sensitivity matrix, then the open loop nature of the system yields a particularly simple form:

$$\bar{S}_{x_e, \theta}^{\text{open}} = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 1 & -1 & 1 & -1 \end{pmatrix}. \quad (3.3)$$

In other words, a 10% change in any of the parameters will lead to a comparable positive or negative change in the equilibrium values.

For the case of negative regulation, we have

$$F(P) = \frac{\alpha}{K + P^n} + \alpha_0,$$

and the equilibrium points satisfy

$$m_e = \frac{\delta}{\beta} P_e, \quad \frac{\alpha}{K + P_e^n} + \alpha_0 = \gamma m_e = \frac{\gamma\delta}{\beta} P_e.$$

Rather than attempt to solve for the equilibrium point in closed form, we instead investigate the sensitivity using the computations in equation (3.1). The state, dynamics and parameters are given by

$$x = \begin{pmatrix} m & P \end{pmatrix}, \quad f(x, \theta) = \begin{pmatrix} F(P) - \gamma m \\ \beta m - \delta P \end{pmatrix}, \quad \theta = (\alpha_0 \quad \gamma \quad \beta \quad \delta \quad \alpha \quad n \quad K).$$

Note that the parameters are ordered such that the first four parameters match the open loop system. The linearizations are given by

$$\frac{\partial f}{\partial x} = \begin{pmatrix} -\gamma & F'(P_e) \\ \beta & -\delta \end{pmatrix}, \quad \frac{\partial f}{\partial \theta} = \begin{pmatrix} 1 & -m & 0 & 0 & \frac{1}{K+P^n} & \frac{\alpha P^n \log(P)}{(K+P^n)^2} & \frac{\alpha}{(K+P^n)^2} \\ 0 & 0 & m & -P & 0 & 0 & 0 \end{pmatrix}$$

from which we can compute the sensitivity as

$$S_{x, \theta} = \begin{pmatrix} -\frac{\delta \frac{\partial \alpha}{\partial \alpha_0}}{\delta\gamma - \beta F'} & \frac{\delta m}{\delta\gamma - \beta F'} & -\frac{m F'}{\delta\gamma - \beta F'} & \frac{P F'}{\delta\gamma - \beta F'} & -\frac{\delta \frac{\partial \alpha}{\partial \alpha_1}}{\delta\gamma - \beta F'} & -\frac{\delta \frac{\partial \alpha}{\partial n}}{\delta\gamma - \beta F'} & -\frac{\delta \frac{\partial \alpha}{\partial K}}{\delta\gamma - \beta F'} \\ -\frac{\beta \frac{\partial \alpha}{\partial \alpha_0}}{\delta\gamma - \beta F'} & \frac{\beta m}{\delta\gamma - \beta F'} & -\frac{\gamma m}{\delta\gamma - \beta F'} & \frac{\gamma P}{\delta\gamma - \beta F'} & -\frac{\beta \frac{\partial \alpha}{\partial \alpha_1}}{\delta\gamma - \beta F'} & -\frac{\beta \frac{\partial \alpha}{\partial n}}{\delta\gamma - \beta F'} & -\frac{\beta \frac{\partial \alpha}{\partial K}}{\delta\gamma - \beta F'} \end{pmatrix},$$

where $F' = \partial F / \partial P$ and all other derivatives of F are evaluated at the nominal parameter values..

We can now evaluate the sensitivity at the same protein concentration as we use in the open loop case. The equilibrium point is given by

$$x_e = \begin{pmatrix} m_e \\ P_e \end{pmatrix} = \begin{pmatrix} \frac{\alpha_0}{\gamma} \\ \frac{\alpha_0 \beta}{\delta \gamma} \end{pmatrix} = \begin{pmatrix} 0.239 \\ 23.9 \end{pmatrix}$$

and the sensitivity matrix is

$$\bar{S}_{x_e, \theta}^{\text{closed}} \approx \begin{pmatrix} 76.1 & -18.2 & -1.16 & 116. & 0.134 & -0.212 & -0.000117 \\ 7610. & -1820. & 90.8 & -9080. & 13.4 & -21.2 & -0.0117 \end{pmatrix}.$$

The scaled sensitivity matrix becomes

$$\bar{S}_{x_e, \theta}^{\text{closed}} \approx \begin{pmatrix} 0.16 & -0.44 & -0.56 & 0.56 & 0.28 & -1.78 & -3.08 \times 10^{-7} \\ 0.16 & -0.44 & 0.44 & -0.44 & 0.28 & -1.78 & -3.08 \times 10^{-7} \end{pmatrix}. \quad (3.4)$$

Comparing this equation with equation (3.3), we see that there is reduction in the sensitivity with respect to most parameters. In particular, we become less sensitive to those parameters that are not part of the feedback (columns 2–4), but there is higher sensitivity with respect to some of the parameters that are part of the feedback mechanisms (particularly n). ∇

More generally, we may wish to evaluate the sensitivity of a (non-constant) solution to parameter changes. This can be done by computing the function $dx(t)/d\theta$, which describes how the state changes at each instant in time as a function of (small) changes in the parameters θ . We assume $w = 0$ for simplicity of exposition.

Let $x(t; x_0, \theta_0)$ be a solution of the dynamics with initial condition x_0 and parameters θ_0 . To compute $dx/d\theta$, we write down a differential equation for how it evolves in time:

$$\begin{aligned} \frac{d}{dt} \left(\frac{dx}{d\theta} \right) &= \frac{d}{d\theta} \left(\frac{dx}{dt} \right) = \frac{d}{d\theta} (f(x, \theta, w)) \\ &= \frac{\partial f}{\partial x} \frac{dx}{d\theta} + \frac{\partial f}{\partial \theta}. \end{aligned}$$

This is a differential equation with $n \times m$ states $S_{ij} = dx_i/d\theta_j$ and with initial condition $S_{ij}(0) = 0$ (since changes to the parameters do not affect the initial conditions).

To solve these equations, we must simultaneously solve for the state x and the sensitivity S (whose dynamics depend on x). Thus, we must solve the set of $n + nm$ coupled differential equations

$$\frac{dx}{dt} = f(x, \theta, w), \quad \frac{dS_{x\theta}}{dt} = \frac{\partial f}{\partial x}(x, \theta, w) S_{x\theta} + \frac{\partial f}{\partial \theta}(x, \theta, w). \quad (3.5)$$

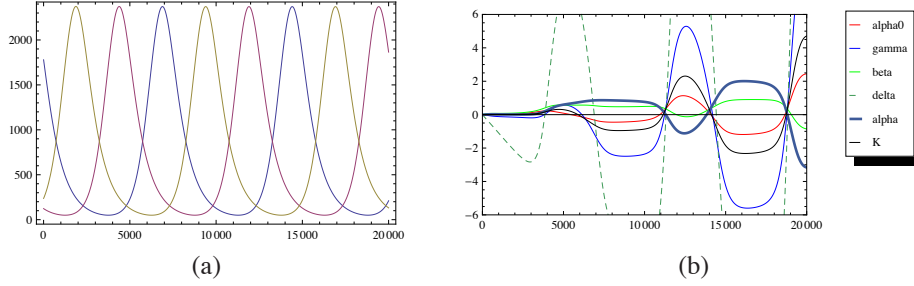


Figure 3.2: Repressilator sensitivity plots

This differential equation generalizes our previous results by allowing us to evaluate the sensitivity around a (non-constant) trajectory. Note that in the special case that we are at an equilibrium point and the dynamics for $S_{x,\theta}$ are stable, the steady state solution of equation (3.5) is identical to that obtained in equation (3.1). However, equation (3.5) is much more general, allowing us to determine the change in the state of the system at a fixed time T , for example. This equation also does not require that our solution stay near an equilibrium point, it only requires that our perturbations in the parameters are sufficiently small.

Example 3.2 (Repressilator). Consider the example of the repressilator, which was described in Example 2.1. The dynamics of this system can be written as

$$\begin{aligned} \frac{dm_1}{dt} &= F_{\text{rep}}(P_3) - \gamma m_1 & \frac{dP_1}{dt} &= \beta m_1 - \delta P_1 \\ \frac{dm_2}{dt} &= F_{\text{rep}}(P_1) - \gamma m_2 & \frac{dP_2}{dt} &= \beta m_2 - \delta P_2 \\ \frac{dm_3}{dt} &= F_{\text{rep}}(P_2) - \gamma m_3 & \frac{dP_3}{dt} &= \beta m_3 - \delta P_3, \end{aligned}$$

where the repressor is modeled using a Hill function

$$F_{\text{rep}}(p) = \frac{\alpha}{K + p^n} + \alpha_0.$$

The dynamics of this system lead to a limit cycle in the protein concentrations, as shown in Figure 3.2a.

We can analyze the sensitivity of the protein concentrations to changes in the parameters using the sensitivity differential equation. Since our solution is periodic, the sensitivity dynamics will satisfy an equation of the form

$$\frac{dS_{x,\theta}}{dt} = A(t)S_{x,\theta} + B(t),$$

where $A(t)$ and $B(t)$ are both periodic in time. Letting $x = (m_1, P_1, m_2, P_2, m_3, P_3)$ and $\theta = (\alpha_0, \gamma, \beta, \delta, \alpha, K)$, we can compute $S_{x,\theta}$ along the limit cycle. If the dynamics

for $S_{x,\theta}$ are stable then the resulting solutions will be periodic, showing how the dynamics around the limit cycle depend on the parameter values. The results are shown in Figure 3.2b, where we plot the steady state sensitivity of P_1 as a function of time. We see, for example, that the limit cycle depends strongly on the protein degradation and dilution rate γ , indicating that changes in this value can lead to (relatively) large variations in the magnitude of the limit cycle.

▽

Several simulation tools include the ability to do sensitivity analysis of this sort, including COPASI.

Frequency domain analysis

Another way to look at the sensitivity of the solutions near equilibria to changes in parameters and inputs is to use frequency domain techniques. Recall that the *frequency response* of a linear system

$$\begin{aligned}\dot{x} &= Ax + Bu \\ y &= Cx + Du\end{aligned}$$

is the response of the system to a sinusoidal input $u = a \sin \omega t$ with input amplitude a and frequency ω . The transfer function for a linear system is given by

$$G_{yu}(s) = C(sI - A)^{-1}B + D$$

and represents the response of a system to an exponential signal of the form $u(t) = e^{st}$ where $s \in \mathbb{C}$. In particular, the response to a sinusoid $u = a \sin \omega t$ is given by $y = Ma \sin(\omega t + \theta)$ where the gain M and phase shift θ can be determined from the transfer function evaluated at $s = i\omega$:

$$G_{yu}(i\omega) = Me^{i\theta}.$$

For finite dimensional linear (or linearized) systems, the transfer function can be written as a ratio of polynomials in s :

$$G(s) = \frac{b(s)}{a(s)}.$$

The values of s at which the numerator vanishes are called the zeros of the transfer function and the values of s at which the denominator vanishes are called the poles.

The transfer function representation of an input/output linear system is essentially equivalent to the state space description, but we reason about the dynamics by looking at the transfer function instead of the state space matrices. For example, it can be shown that the poles of a transfer function correspond to the eigenvalues of the matrix A , and hence the poles determine the stability of the system.

Interconnections between subsystems often have simple representations in terms of transfer functions. Two systems G_1 and G_2 in series (with the output of the first connected to the input of the second) have a combined transfer function $G_{\text{series}}(s) = G_1(s)G_2(s)$ and two systems in parallel (a single input goes to both systems and the outputs are summed) has the transfer function $G_{\text{parallel}}(s) = G_1(s) + G_2(s)$. A common interconnection is two put two systems in feedback form for which the transfer function is given by

$$G_{\text{yr}}(s) = \frac{G_1(s)}{G_1(s) + G_2(s)} = \frac{n_1(s)d_2(s)}{n_1(s)d_2(s) + d_1(s)n_2(s)},$$

where $n_i(s)$ and $d_i(s)$ are the numerator and denominator of the individual transfer function. The ease in which the input/output response for interconnected systems can be computed with transfer functions is one of the main motivations for their widespread use in engineering.

Transfer functions are useful representations of linear systems because the properties of the transfer function can be related to the properties of the dynamics. In particular, the shape of the frequency response describes how the system response to inputs and disturbances, as well as allows us to reason about the stability of interconnected systems. The Bode plot of a transfer function gives the magnitude and phase of the frequency response as a function of frequency and the Nyquist plot can be used to reason about stability of a closed loop system from the open loop frequency response. The transfer function for a system can be determined from experiments by measuring the frequency response and fitting a transfer function to the data. Formally, the transfer function corresponds to the ratio of the Laplace transforms of the output to the input.

Returning to our analysis of biomolecular systems, suppose we have a systems whose dynamics can be written as

$$\dot{x} = f(x, \theta, w)$$

and we wish to understand how the solutions of the system depend on the parameters θ and disturbances w . We focus on the case of an equilibrium solution $x(t; x_0, \theta_0) = x_e$. Let $z = x - x_e$, $\tilde{w} = w - w_0$ and $\tilde{\theta} = \theta - \theta_0$ represent the deviation of the state, input and parameters from their nominal values. We can write the dynamics of the perturbed system using its linearization:

$$\frac{dz}{dt} = \left(\frac{\partial f}{\partial x} \right)_{(x_e, \theta_0, w_0)} \cdot z + \left(\frac{\partial f}{\partial \theta} \right)_{(x_e, \theta_0, w_0)} \cdot \tilde{\theta} + \left(\frac{\partial f}{\partial w} \right)_{(x_e, \theta_0, w_0)} \cdot \tilde{w}.$$

This linear system describes small deviations from $x_e(\theta_0, w_0)$ but allows $\tilde{\theta}$ and \tilde{w} to be time-varying instead of the constant case considered earlier.

To analyze the resulting deviations, it is convenient to look at the system in the frequency domain. Let $y = Cx$ be a set of values of interest. The transfer functions

between $\tilde{\theta}$, \tilde{w} and y are given by

$$H_{y\tilde{\theta}}(s) = C(sI - A)^{-1}B_{\theta}, \quad H_{y\tilde{w}}(s) = C(sI - A)^{-1}B_w,$$

where

$$A = \left. \frac{\partial f}{\partial x} \right|_{(x_e, \theta_0, w_0)}, \quad B_{\theta} = \left. \frac{\partial f}{\partial \theta} \right|_{(x_e, \theta_0, w_0)}, \quad B_w = \left. \frac{\partial f}{\partial w} \right|_{(x_e, \theta_0, w_0)}.$$

Note that if we let $s = 0$, we get the response to small, constant changes in parameters. For example, the change in the outputs y as a function of constant changes in the parameters is given by

$$H_{y\tilde{\theta}}(0) = CA^{-1}B_{\theta} = CS_{x,\theta},$$

which matches our previous parametric analysis.

Example 3.3 (Transcriptional regulation). Consider again the case of transcriptional regulation described in Example 3.1. Suppose that the mRNA degradation rate γ can change as a function of time and that we wish to understand the sensitivity with respect to this (time-varying) parameter. Linearizing the dynamics around an equilibrium point

$$A = \begin{pmatrix} -\gamma & F'(p_e) \\ \beta & -\delta \end{pmatrix}, \quad B_{\gamma} = \begin{pmatrix} -m_e \\ 0 \end{pmatrix}.$$

For the case of no feedback we have $F(P) = \alpha_0$, and the system has an equilibrium point at $m_e = \alpha_0/\gamma$, $P_e = \beta\alpha_0/(\delta\gamma)$. The transfer function from γ to p is given by

$$G_{P\gamma}^{\text{ol}}(s) = \frac{-\beta m_e}{(s + \gamma)(s + \delta)}.$$

For the case of negative regulation, we have

$$F(P) = \frac{\alpha}{K + P^n} + \alpha_0,$$

and the resulting transfer function is given by

$$G_{P\gamma}^{\text{cl}}(s) = \frac{\beta m_e}{(s + \gamma)(s + \delta) + \beta\sigma}, \quad \sigma = F'(P_e) = \frac{n\alpha P_e^{n-1}}{(K + P_e^n)^2}.$$

Figure 3.3 shows the frequency response for the two circuits. We see that the feedback circuit attenuates the response of the system to disturbances with low-frequency content but slightly amplifies disturbances at high frequency (compared to the open loop system). ∇

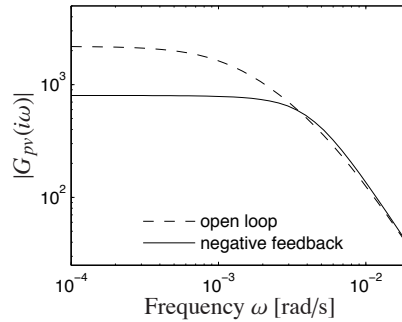


Figure 3.3: Noise attenuation in a genetic circuit.



Robustness analysis

A slightly more general analysis of sensitivity can be accomplished using the control theoretic notions of sensitivity described in AM08, Chapter 12. Rather than just considering static changes to parameter values, we can instead consider the case of *unmodeled dynamics*, in which we allow bounded input/output uncertainties to enter the system dynamics. This can be used to model parameters whose values are unknown and also time-varying, as well as capturing uncertain dynamics that are being ignored or approximated.

To illustrate the basic approach, consider the problem of determining the sensitivity of a set of reactions to a set of additional unmodeled reactions, whose detailed effects are unknown but assumed to be bounded. We set this problem up using the general framework shown in Figure 3.4.

3.2 Analysis of Reaction Rate Equations

The previous section considered analysis techniques for general dynamical systems with small perturbations. In this section, we specialize to the case where the

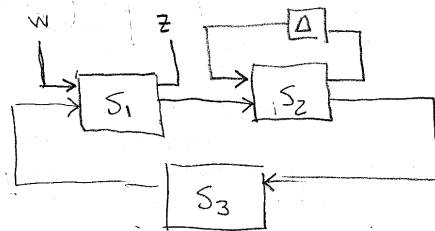


Figure 3.4: Analysis of dynamic uncertainty in a reaction system.

dynamics have the form of a reaction rate equation:

$$\dot{s} = Nv(s, p), \quad (3.6)$$

where s is the vector of species concentrations, p is the vector of reaction parameters, N is the stoichiometry matrix, $v(s, p)$ is the reaction rate (or flux) vector.

Reduced reaction dynamics

When analyzing reaction rate equations, it is often the case that there are conserved quantities in the dynamics. For example, conservation of mass will imply that if all compounds containing a given species are captured by the model, the total mass of that species will be constant. This type of constraint will then give a conserved quantity of the form $c_i = H_i s$ where H_i represents that combinations of species in which the given element appears. Since c_i is constant, it follows that $\dot{c}_i = 0$ and, aggregating the set of all conserved species, we have

$$0 = \dot{c} = H\dot{x} = HNv(s, p) \quad \text{for all } s.$$

If we assume that the vector of fluxes spans \mathbb{R}^m (the range of $v : \mathbb{R}^n \times \mathbb{R}^p \rightarrow \mathbb{R}^m$), then this implies that the conserved quantities correspond to the left null space of the stoichiometry matrix N .

It is often useful to remove the conserved quantities from the description of the dynamics and write the dynamics for a set of independent species. To do this, we transform the state of the system into two sets of variables:

$$\begin{pmatrix} s_i \\ s_d \end{pmatrix} = \begin{pmatrix} P \\ H \end{pmatrix} s. \quad (3.7)$$

The vector $s_i = Ps$ is the set of independent species and is typically chosen as a subset of the original species of the model (so that the rows P consists of all zeros and a single 1 in the column corresponding to the selected species). The matrix H should span the left null space of N , so that s_d represents the set of dependent concentrations. These dependent species do not necessarily correspond to individual species, but instead are often combinations of species (for example, the total concentration of a given element that appears in a number of molecules that participate in the reaction).

Given the decomposition (3.7), we can rewrite the dynamics of the system in terms of the independent variables s_i . We start by noting that given s_i and s_d , we can reconstruct the full set of species s :

$$s = \begin{pmatrix} P \\ H \end{pmatrix}^{-1} \begin{pmatrix} s_i \\ s_d \end{pmatrix} = Ls_i + c_0, \quad L = \begin{pmatrix} P \\ H \end{pmatrix}^{-1} \begin{pmatrix} I \\ 0 \end{pmatrix}, \quad c_0 = \begin{pmatrix} P \\ H \end{pmatrix}^{-1} \begin{pmatrix} 0 \\ c \end{pmatrix}$$

where c_0 represents the conserved quantities. We now write the dynamics for s_i as

$$\dot{s}_i = P\dot{s} = PNv(Ls_i + c_0, p) = N_r v_r(s_i, c_0, p), \quad (3.8)$$

where N_r is the *reduced stoichiometry matrix* and v_r is the rate vector with the conserved quantities separated out as constant parameters.

The reduced order dynamics in equation (3.8) represent the evolution of the independent species in the reaction. Given s_i , we can “lift” the dynamics from the independent species to the full set of species by writing $s = Ls_i + c_0$. The vector c_0 represents the values of the conserved quantities, which must be specified in order to compute the values of the full set of species. In addition, since $s = Ls_i + c_0$, we have that

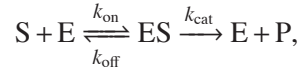
$$\dot{s} = L\dot{s}_i = LN_r v_r(s_i, c_0, p) = LN_r v(s, p),$$

which implies that

$$N = LN_r.$$

Thus, L also “lifts” the reduced stoichiometry matrix from the reduced space to the full space.

Example 3.4 (Enzyme kinetics). Consider an enzymatic reaction



whose full dynamics can be written as

$$\frac{d}{dt} \begin{pmatrix} S \\ E \\ ES \\ P \end{pmatrix} = \begin{pmatrix} -1 & 1 & 0 \\ -1 & 1 & 0 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} k_{\text{on}}E \cdot S \\ k_{\text{off}}ES \\ k_{\text{cat}}ES \end{pmatrix}.$$

The conserved quantities are given by

$$H = \begin{pmatrix} 0 & 1 & 1 & 0 \\ 1 & -1 & 0 & 1 \end{pmatrix}.$$

The first of these is the total enzyme concentration $E_T = E + ES$, while the second asserts that the concentration of product P is equal to the free enzyme concentration E minus the substrate concentration S . If we assume that we start with substrate concentration S_0 , enzyme concentration E_T and no product or bound enzyme, then the conserved quantities are given by

$$c = \begin{pmatrix} E + ES \\ S - E + P \end{pmatrix} = \begin{pmatrix} E_T \\ S_0 - E_T \end{pmatrix}.$$

There are many possible choices for the set of independent species $s_i = Ps$, but since we are interested in the substrate and the product, we choose P as

$$P = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

Once P is chosen then we can compute

$$L = \begin{pmatrix} P \\ H \end{pmatrix}^{-1} \begin{pmatrix} I \\ 0 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 1 & 1 \\ -1 & -1 \\ 0 & 1 \end{pmatrix}, \quad c_0 = \begin{pmatrix} P \\ H \end{pmatrix}^{-1} \begin{pmatrix} 0 \\ c \end{pmatrix} = \begin{pmatrix} 0 \\ E_T - S_0 \\ S_0 \\ 0 \end{pmatrix},$$

The resulting reduced order dynamics can be computed to be

$$\begin{aligned} \frac{d}{dt} \begin{pmatrix} S \\ P \end{pmatrix} &= \begin{pmatrix} -1 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} k_{\text{on}}(P+S+E_T-S_0)S \\ k_{\text{off}}(-P-S+S_0) \\ k_{\text{cat}}(-P-S+S_0) \end{pmatrix} \\ &= \begin{pmatrix} -k_{\text{on}}(P+S+E_T-S_0)S - k_{\text{off}}(P+S-S_0) \\ k_{\text{cat}}(S_0-S-P) \end{pmatrix}. \end{aligned}$$

A simulation of the dynamics is shown in Figure 3.5. We see that the dynamics are very well approximated as being a constant rate of production until we exhaust the substrate (consistent with the Michaelis-Menten approximation).

▽

Metabolic control analysis

Metabolic control analysis (MCA) focuses on the study of the sensitivity of steady state concentrations and fluxes to changes in various system parameters. The basic concepts are equivalent to the sensitivity analysis tools described in Section 3.1, specialized to the case of reaction rate equations. In this section we provide a brief introduction to the key ideas, emphasizing the mapping between the general concepts and MCA terminology (as originally done by Ingalls [22]).

Consider the reduced set of chemical reactions

$$\dot{s}_i = N_r v_r(s_i, p) = N_r v(Ls_i + c_0, p).$$

We wish to compute the sensitivity of the equilibrium concentrations s_e and equilibrium fluxes v_e to the parameters p . We start by linearizing the dynamics around an equilibrium point s_e . Defining $x = s - s_e$, $u = p - p_0$ and $f(x, u) = N_r v(s_e + x, p_0 + u)$, we can write the linearized dynamics as

$$\dot{x} = Ax + Bu, \quad A = \left(N_r \frac{\partial v}{\partial s} L \right), \quad B = \left(N_r \frac{\partial v}{\partial p} \right), \quad (3.9)$$

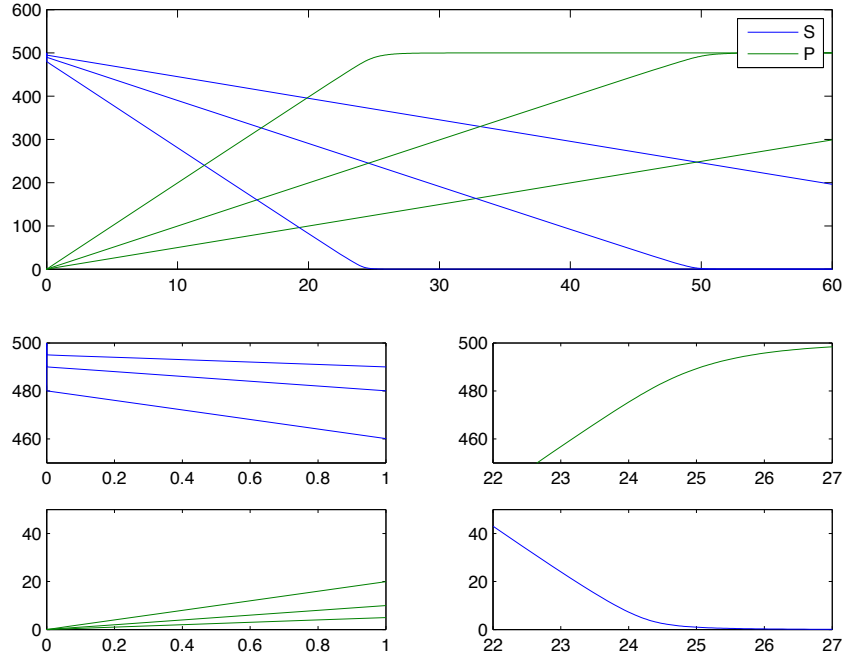


Figure 3.5: Enzyme dynamics. The simulations were carried out $k_{\text{on}} = k_{\text{off}} = 10$, $k_{\text{cat}} = 1$, $S_0 = 500$ and $E_T = 5, 10, 20$. The top plot shows the concentration of substrate S and product P , with the fastest case corresponding to $E_T = 20$. The figures on the lower left zoom in on the substrate and product concentrations at the initial time and the figures on the lower right at one of the transition times.

which has the form of a linear differential equation with state x and input u .

In metabolic control analysis, the following terms are defined:

$$\begin{aligned}
 \bar{\epsilon}_p &= \left. \frac{dv}{dp} \right|_{s_e, p_0} & \bar{\epsilon}_p &= \text{flux control coefficients} \\
 \bar{R}_p^s &= \frac{\partial s_e}{\partial p} = \bar{C}^s \bar{\epsilon}_p & \bar{R}_p^s &= \\
 \bar{R}_p^v &= \frac{\partial v_e}{\partial p} = \bar{C}^v \bar{\epsilon}_p & \bar{C}^s &= \text{concentration control coefficients} \\
 & & \bar{R}_p^v &= \\
 & & \bar{C}^v &= \text{rate control coefficients}
 \end{aligned}$$

These relationships describe how the equilibrium concentration and equilibrium rates change as a function of the perturbations in the parameters. The two control matrices provide a mapping between the variation in the flux vector evaluated at equilibrium,

$$\left(\frac{\partial v}{\partial p} \right)_{s_e, p_0},$$

and the corresponding differential changes in the equilibrium point, $\partial s_e / \partial p$ and

$\partial v_e / \partial p$. Note that

$$\frac{\partial v_e}{\partial p} \neq \left(\frac{\partial v}{\partial p} \right)_{s_e, p_0}.$$

The left side is the relative change in the equilibrium rates, while the right side is the change in the rate function $v(s, p)$ evaluated at an equilibrium point.

To derive the coefficient matrices \bar{C}^s and \bar{C}^v , we simply take the linear equation (3.9) and choose outputs corresponding to s and v :

$$y_s = Ix, \quad y_v = \frac{\partial v}{\partial s} Lx + \frac{\partial v}{\partial p} u.$$

Using these relationships, we can compute the transfer functions

$$H_s(s) = (sI - A)^{-1} B = \left[(sI - N_r \frac{\partial v}{\partial s} L)^{-1} N_r \right] \frac{\partial v}{\partial p},$$

$$H_v(s) = \frac{\partial v}{\partial s} L (sI - A)^{-1} B + \frac{\partial v}{\partial p} = \left[\frac{\partial v}{\partial s} L (sI - N_r \frac{\partial v}{\partial s} L)^{-1} N_r + I \right] \frac{\partial v}{\partial p}.$$

Classical metabolic control analysis considers only the equilibrium concentrations, and so these transfer functions would be evaluated at $s = 0$ to obtain the equilibrium equations.

These equations are often normalized by the equilibrium concentrations and parameter values, so that all quantities are expressed as fractional quantities. If we define

$$D^s = \text{diag}\{s_e\}, \quad D^v = \text{diag}\{v(s_e, p_0)\}, \quad D^p = \text{diag}\{p_0\},$$

the the normalized coefficient matrices (without the overbar) are given by

$$C^s = (D^s)^{-1} \bar{C}^s D^v, \quad C^v = (D^v)^{-1} \bar{C}^v D^v,$$

$$R_p^s = (D^s)^{-1} \bar{R}_p^s D^p, \quad R_p^v = (D^v)^{-1} \bar{R}_p^v D^p.$$

Example 3.5 (Enzyme kinetics). TBA

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Flux balance analysis

Flux balance analysis is a technique for studying the relative rate of different reactions in a complex reaction system. We are most interested in the case where there may be multiple pathways in a system, so that the number of reactions m is greater than the number of species n . The dynamics

$$\dot{s} = Nv(s, p)$$

thus have the property that the matrix N has more columns than rows and hence there are multiple reactions that can produce a given set of species. Flux balance is often applied to pathway analysis in metabolic systems to understand the limiting

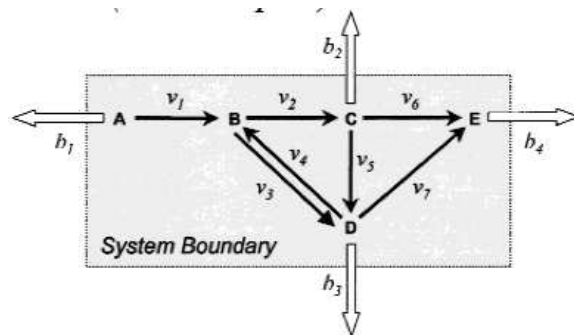


Figure 3.6: Flux balance analysis.

pathways for a given species and the effects of changes in the network (e.g., through gene deletions) to the production capacity.

To perform a flux balance analysis, we begin by separating the reactions of the pathway into internal fluxes v_i versus exchanges flux v_e , as illustrated in Figure 3.6. The dynamics of the resulting system now be written as

$$\dot{s} = Nv(s, p) = N \begin{pmatrix} v_i \\ v_e \end{pmatrix} = Nv_i(s, p) - b_e,$$

where $b_e = -Nv_e$ represents the effects of external fluxes on the species dynamics. Since the matrix N has more columns than rows, it has a *right* null space and hence there are many different internal fluxes that can produce a given change in species.

In particular, we are interested studying the steady state properties of the system. In this case, we have that $\dot{s} = 0$ and we are left with an algebraic system

$$Nv_i = b_e.$$

Power law formalism

Chemical reaction rate equations are nonlinear differential equations whenever two or more species interact. However, the nonlinearities are very structured: they can be decomposed into a stoichiometry matrix and flux rates, and the flux rates typically consist of either polynomial terms or simple ratios of polynomials (e.g., Michaelis-Menten kinetics or Hill functions). In this section we consider power law representations that exploit these properties and attempt to provide simpler techniques for understand the relationships between species concentrations, parameter values and flux rates. This formalism was developed by Savageau [39] and is also called biochemical systems theory (BST).

The general power law formalism describes a set of reaction dynamics using a set of differential equations of the form

$$\frac{dx_i}{dt} = \sum_r E_r \prod_{j=1}^{n+m} x_j^{\epsilon_j^r} - \sum_s E_s \prod_{j=1}^{n+m} x_j^{\epsilon_j^s}, \quad i = 1, \dots, n. \quad (3.10)$$

Here, x_i is the concentration for species i , with $i = 1, \dots, n$ representing internal species and $i = n + 1, \dots, m$ representing external species, and the dynamics are broken into two summations. The first sum is over the set of reactions that produce the species x_i and the second is over the reactions that utilize x_i (and so decrease its concentration). The linear coefficients E_r and E_s are the activity levels and correspond to the rate constants (for metabolic networks the rate constants are often proportional to a fixed enzyme level, hence the use of the symbol E). The exponents ϵ_j^r and ϵ_j^s are the *kinetic orders* of the production and utilization reactions.

In this general form, the power law formalism is able to exactly capture mass action kinetics, but it does not provide any additional structure. If we consider a general rate equation of the form $v_i(x_1, \dots, x_{n+m})$, we can approximate this function in a number of ways. The first is through its linearization,

$$v_i(x_1, \dots, x_{n+m}) \approx v_i(x_{1,e}, \dots, x_{n+m,e}) + \sum \frac{\partial v}{\partial x_j} (x_j - x_{j,e}) + \text{higher order terms.}$$

We have used exactly this approximation in previous sections.

A different approximation can be obtained by taking a Taylor series expansion for $\log v_i$:

$$\log v_i(x_1, \dots, x_{n+m}) \approx \log v_i(x_{1,e}, \dots, x_{n+m,e}) + \sum \frac{\partial \log v_i}{\partial \log x_j} (\log x_j - \log x_{j,e}) + \text{higher order terms.}$$

If we define

$$g_{i,j} = \frac{\partial \log v_i}{\partial \log x_j} = \frac{x_j}{v_i} \cdot \frac{\partial v_i}{\partial x_j}$$

and collect terms, we have

$$\log v_i(x) \approx \log \alpha_i + g_{i,1} \log x_1 + \dots + g_{i,n+m} \log x_{n+m}.$$

Converting this back from log coordinates, we can thus write

$$v_i(x) \approx \alpha_i \prod_{j=1}^{n+m} x_j^{g_{i,j}}.$$

Using this approximation on the sums in equation (3.10), we can approximate the resulting dynamics as

$$\frac{dx_i}{dt} = \alpha_i \prod x_j^{g_{i,j}} - \beta_i \prod x_j^{h_{i,j}},$$

where α_i and $g_{i,j}$ are the rate constant and kinetic orders for the production terms and β_i and $h_{i,j}$ are the rate constant and kinetic orders for reactions that utilize x_i . While this is only an approximation, its form is convenient for performing equilibrium analyses. In particular, if $\dot{x}_i = 0$ then we can equate the production rate to the utilization rate and take the log of this expression to obtain

$$\log \alpha_i + \sum g_{i,j} \log x_j = \log \beta_i + \sum h_{i,j} \log x_j.$$

This is now a linear equation for the logs of the concentrations in terms of the various parameters that enter the system.

3.3 Limit Cycle Behavior

Before studying periodic behavior of systems in \mathbb{R}^n , we study the behavior of systems in \mathbb{R}^2 as several high dimensional systems can be often well approximated by systems in two dimensions by, for example, employing quasi-steady state approximations. For systems in \mathbb{R}^2 , we will see that there are only two types of solutions: those converging (diverging) from steady states and periodic solutions. That is, chaos can be ruled out in two-dimensional systems.

Consider the system $\dot{x} = f(x)$, in which $f(x)$ is often referred to as vector field, and let $x(t, x_0)$ denote its solution starting at x_0 at time $t = 0$, that is, $\dot{x}(t, x_0) = f(x(t, x_0))$ and $x(0, x_0) = x_0$. We say that $x(t, x_0)$ is a *periodic solution* if there is $T > 0$ such that $x(t, x_0) = x(t + T, x_0)$ for all $t \in \mathbb{R}$. Here, we seek to answer two questions: (a) when does a system $\dot{x} = f(x)$ admit periodic solutions? (b) When are these periodic solutions stable or asymptotically stable?

We first tackle these questions for the case $x \in \mathbb{R}^2$. The first result that we next give provides a simple check to rule out periodic solutions for system in \mathbb{R}^2 . Specifically, let $(x, y) \in \mathbb{R}^2$ and consider

$$\begin{aligned} \dot{x} &= f(x, y) \\ \dot{y} &= g(x, y), \end{aligned} \tag{3.11}$$

in which the functions g, f are smooth. Then, we have the following result:

Theorem 3.1 (Bendixson's Criterion). *If on a simply connected region $D \subset \mathbb{R}^2$ (i.e., there are no holes in it) the expression*

$$\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y}$$

is not identically zero and does not change sign, then system (3.11) has no closed orbits that lie entirely in D .

Example 3.6. Consider the system

$$\begin{aligned}\dot{x} &= -y^3 + \delta x^3 \\ \dot{y} &= x^3,\end{aligned}$$

with $\delta \geq 0$. We can compute $\frac{\partial f}{\partial x} + \frac{\partial g}{\partial y} = 3\delta x^2$, which is positive in all \mathbb{R}^2 if $\delta \neq 0$. If $\delta \neq 0$, we can thus conclude from Bendixson's criterion that there are no periodic solutions. Investigate as an exercise what happens when $\delta = 0$. ∇

In order to provide the main result to state the existence of a stable periodic solution, we need the concept of omega-limit set of a point p , denoted $\omega(p)$. Basically, the omega-limit set $\omega(p)$ denotes the set of all points to which the trajectory of the system starting from p tends as time approaches infinity. This is formally defined in the following definition

Definition 3.1. A point $\bar{x} \in \mathbb{R}^n$ is called an *omega-limit point* of $p \in \mathbb{R}^n$ if there is a sequence of times $\{t_i\}$ with $t_i \rightarrow \infty$ for $i \rightarrow \infty$ such that $x(t_i, p) \rightarrow \bar{x}$ as $i \rightarrow \infty$. The *omega limit set* of p , denoted $\omega(p)$, is the set of all omega-limit points of p .

The omega-limit set of a system has several relevant properties, among which the fact that it cannot be empty and that it must be a connected set.

The following theorem, completely characterizes the omega limit set of any point for a system in \mathbb{R}^2 .

Theorem 3.2 (Poincarè-Bendixson). *Let M be a positively invariant region for the system $\dot{x} = f(x)$ with $x \in \mathbb{R}^2$ (i.e., any trajectory that starts in M stays in M for all $t \geq 0$). Let $p \in M$, then one of the following possibilities holds for $\omega(p)$:*

- (i) $\omega(p)$ is a steady state;
- (ii) $\omega(p)$ is a closed orbit;
- (iii) $\omega(p)$ consists of a finite number of steady states and orbits, each starting (for $t = 0$) and ending (for $t \rightarrow \infty$) at one of the fixed points.

This theorem has two important consequences:

1. If the system does not have steady states in M , since $\omega(p)$ is not empty, it must be a periodic solution;
2. If there is only one steady state in M and it is unstable and not a saddle (i.e., the eigenvalues of the linearization at the steady state are both positive), then $\omega(p)$ is a periodic solution.

Example 3.7. Consider the following system in \mathbb{R}^2 :

$$\begin{aligned}\dot{x} &= x - y - (x^2 + y^2)x \\ \dot{y} &= x + y - (x^2 + y^2)y.\end{aligned}$$

Verify as an exercise that this system admits one equilibrium point only (the origin), which is unstable. Also, show that its trajectories are globally bounded (for example, take a set $x^2 + y^2 = c$ for c large enough and demonstrate that the vector field of the system always points inside the circle $x^2 + y^2 = c$). Therefore, by Poincarè-Bendixson Theorem, we can conclude that the omega-limit set of any point in \mathbb{R}^2 different from the origin is a non-zero periodic orbit. ∇

This result holds only for systems in two dimensions. However, there have been recent extensions of this theorem to systems with special structure in \mathbb{R}^n . In particular, we have the following result due to Hastings et al. (1977).

Theorem 3.3 (Hastings et al. 1977). *Consider a system $\dot{x} = f(x)$, which is of the form*

$$\begin{aligned}\dot{x}_1 &= f_1(x_n, x_1) \\ \dot{x}_j &= f_j(x_{j-1}, x_j), \quad 2 \leq j \leq n\end{aligned}$$

on the set M defined by $x_i \geq 0$ for all i with the following inequalities holding in M :

(i) $\frac{\partial f_i}{\partial x_i} < 0$ and $\frac{\partial f_i}{\partial x_{i-1}} > 0$, for $2 \leq i \leq n$, and $\frac{\partial f_1}{\partial x_n} < 0$;

(ii) $f_i(0, 0) \geq 0$ and $f_1(x_n, 0) > 0$ for all $x_n \geq 0$;

(iii) The system has a unique steady state $x^* = (x_1^*, \dots, x_n^*)$ in M such that $f_1(x_n, x_1) < 0$ if $x_n > x_n^*$ and $x_1 > x_1^*$, while $f_1(x_n, x_1) > 0$ if $x_n < x_n^*$ and $x_1 < x_1^*$;

(iv) $\frac{\partial f_1}{\partial x_1}$ is bounded above in M .

Then, if the Jacobian of f at x^* has no repeated eigenvalues and has any eigenvalue with positive real part, then the system has a non-constant periodic solution in M .

This theorem states that for a system with cyclic structure in which the cycle “has negative gain”, the instability of the steady state (under some technical assumption) is equivalent to the existence of a periodic solution. This theorem, however, does not provide information about whether the orbit is attractive or not, that is, of whether it is an omega-limit set of any point in M . This stability result is implied by a more recent theorem due to Mallet-Paret and Smith (1990), for which we provide a simplified statement as follows.

Theorem 3.4 (Mallet-Paret and Smith, 1990). *Consider the system $\dot{x} = f(x)$ with the following cyclic feedback structure*

$$\begin{aligned}\dot{x}_1 &= f_1(x_n, x_1) \\ \dot{x}_j &= f_j(x_{j-1}, x_j), \quad 2 \leq j \leq n\end{aligned}$$

on a set M defined by $x_i \geq 0$ for all i with all trajectories starting in M bounded for $t \geq 0$. Then, the omega-limit set $\omega(p)$ of any point $p \in M$ can be one of the following:

- (a) A steady state;
- (b) A non-constant periodic orbit;
- (c) A set of steady states connected by homoclinic or heteroclinic orbits.

A heteroclinic orbit is an orbit that starts (for $t = 0$) at a steady state and ends (for $t \rightarrow \infty$) into a different steady state. A homoclinic orbit is an orbit that starts and ends at the same steady state. It is thus clear that a steady state whose linearization admits all positive or all negative eigenvalues cannot have a homoclinic orbit. As a consequence of the theorem, then we have that for a system with cyclic feedback structure that admits one steady state only and at which the linearization has all eigenvalues with positive real part, the omega limit set must be a periodic orbit.

Let for some $\delta_i \in \{1, -1\}$ be $\delta_i \frac{\partial f_i(x, x_{i-1})}{\partial x_{i-1}} > 0$ for all $0 \leq i \leq n$ and define $\Delta := \delta_1 \cdot \dots \cdot \delta_n$. One can show that the sign of Δ is related to whether the system has one or multiple steady states.

Therefore, a system with a cyclic feedback structure and a unique equilibrium point at which the linearization has all eigenvalues with positive real part admits a stable periodic orbit.

3.4 Analysis Using Describing Functions

Unlike the case of linear systems, where it is possible to fully characterize the solutions of a model and there are a wide variety of analysis techniques available, the behavior of nonlinear systems is harder to analyze, especially away from equilibrium points (where the linearization gives a good approximation). One of the more useful techniques for studying the behavior of nonlinear systems is the method of harmonic balance, of which a special case is the method of describing functions. This section explores the use of harmonic balance and describing functions for analyzing nonlinear systems, including the detection and analysis of limit cycles and the propagation of noise through nonlinear systems.

Describing functions (AM08)

For special nonlinear systems like the one shown in Figure 3.7a, which consists of a feedback connection between a linear system and a static nonlinearity, it is possible to obtain a generalization of Nyquist's stability criterion based on the idea of *describing functions*. Following the approach of the Nyquist stability condition, we will investigate the conditions for maintaining an oscillation in the system. If the linear subsystem has low-pass character, its output is approximately sinusoidal even if its input is highly irregular. The condition for oscillation can then be found by exploring the propagation of a sinusoid that corresponds to the first harmonic.

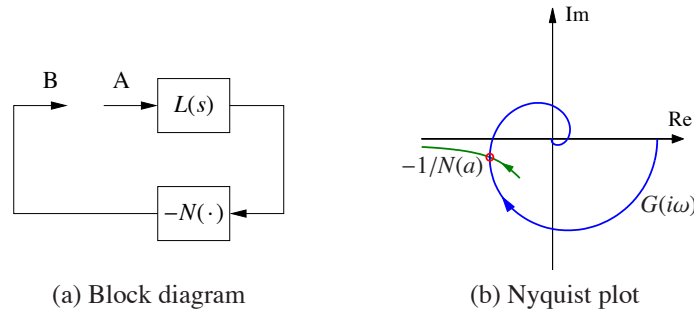


Figure 3.7: Describing function analysis. A feedback connection between a static nonlinearity and a linear system is shown in (a). The linear system is characterized by its transfer function $L(s)$, which depends on frequency, and the nonlinearity by its describing function $N(a)$, which depends on the amplitude a of its input. The Nyquist plot of $L(i\omega)$ and the plot of the $-1/N(a)$ are shown in (b). The intersection of the curves represents a possible limit cycle.

To carry out this analysis, we have to analyze how a sinusoidal signal propagates through a static nonlinear system. In particular we investigate how the first harmonic of the output of the nonlinearity is related to its (sinusoidal) input. Letting F represent the nonlinear function, we expand $F(e^{i\omega t})$ in terms of its harmonics:

$$F(ae^{i\omega t}) = \sum_{n=0}^{\infty} M_n(a)e^{i(n\omega t + \phi_n(a))},$$

where $M_n(a)$ and $\phi_n(a)$ represent the gain and phase of the n th harmonic, which depend on the input amplitude since the function F is nonlinear. We define the describing function to be the complex gain of the first harmonic:

$$N(a) = M_1(a)e^{i\phi_1(a)}. \quad (3.12)$$

The function can also be computed by assuming that the input is a sinusoid and using the first term in the Fourier series of the resulting output.

Arguing as we did when deriving Nyquist's stability criterion, we find that an oscillation can be maintained if

$$L(i\omega)N(a) = -1. \quad (3.13)$$

This equation means that if we inject a sinusoid at A in Figure 3.7, the same signal will appear at B and an oscillation can be maintained by connecting the points. Equation (3.13) gives two conditions for finding the frequency ω of the oscillation and its amplitude a : the phase must be 180° , and the magnitude must be unity. A convenient way to solve the equation is to plot $L(i\omega)$ and $-1/N(a)$ on the same

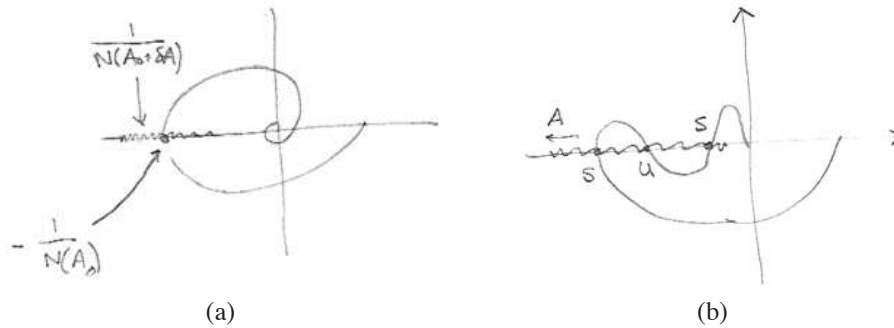


Figure 3.8: Heuristic stability of limit cycles using describing functions. (a) To check if a perturbation from amplitude a_0 to amplitude $a_0 + \delta a$ is stabilizing, we check to see if the Nyquist criterion is satisfied for the original frequency response and the perturbed critical point $P_1 = 1/N(a_0 + \delta a)$. (b) An example of a nonlinear system with multiple limit cycles. Stable limit cycles are labeled 's' and unstable limit cycles are labeled 'u'.

diagram as shown in Figure 3.7b. The diagram is similar to the Nyquist plot where the critical point -1 is replaced by the curve $-1/N(a)$ and a ranges from 0 to ∞ .

It is possible to define describing functions for types of inputs other than sinusoids. Describing function analysis is a simple method, but it is approximate because it assumes that higher harmonics can be neglected. Excellent treatments of describing function techniques can be found in the texts by Atherton [5] and Graham and McRuer [17].

Example 3.8 (Repressilator). ▽

Stability of limit cycles using describing functions

In order to check the stability of a limit cycle, we must reason about how solutions that have initial conditions near the limit cycle evolve in time and whether they move closer to the limit cycle (asymptotic stability) or diverge from the limit cycle (instability).

We begin by arguing heuristically, using the Nyquist plot in Figure 3.7b. Suppose that we were to consider a perturbed limit cycle with amplitude $a_0 + \delta a$, where a_0 is the amplitude of the limit cycle predicted by the describing function method. If we did so, then the point of intersection of the describing function and the frequency response would move from $P_0 = -1/N(a_0)$ to $P_1 = -1/N(a_0 + \delta a)$, as shown in Figure 3.8a. Now evaluate the Nyquist criterion for the frequency response with critical point P_1 . If the criterion indicates that the perturbed system is stable (i.e., no net encirclements of P_1 for a stable process), then intuitively the amplitude of the perturbed solution would decrease and we would return to our original amplitude limit cycle. Conversely, if the Nyquist criterion with critical point P_1 indicates

instability, then the oscillation would grow and hence we can infer that the limit cycle is unstable. Figure 3.8b shows a situation with multiple limit cycles with some stable and some unstable.

While this heuristic method is intuitively appealing, it does not always give the correct answer. Indeed, even the prediction of the existence of a limit cycle using describing functions can be incorrect unless the system satisfies some additional conditions. We present here one such set of conditions, due to Mees [?].

Suppose that (ω_0, a_0) satisfies the describing function balance equation $P(i\omega_0) = -1/N(a_0)$ and that the frequency response curve and the describing function locus are transverse (not tangent) at their intersection. Define

$$\begin{aligned}\rho(\omega)^2 &= \sum_{k=3,5,9,\dots} |P(ik\omega_0)|^2, && \text{“gain of harmonics”} \\ p(a)^2 &= \|n(a \sin t)\|_2^2 - |aN(a)|^2, && \text{“first harmonic error”} \\ q(a, \epsilon) &= \|m(a \sin t, \epsilon)\|_2, && \text{“slope bound”} \\ m(x, \epsilon) &= \max\{|N(x + \epsilon) - N(x)|, |N(x - \epsilon) - N(x)|\}.\end{aligned}$$

Now find an ϵ such that for all (ω, a) near (ω, a_0) ,

$$\rho(\omega)(p(a) + q(a, \epsilon)) \leq \epsilon$$


and let $\Omega \in \mathbb{R}_+^2$ be the set of (ω, a) such that

$$|N(a) + 1/G(i\omega)| \leq q(a, \epsilon)/a.$$

Theorem 3.5. *Suppose Ω is bounded and there exists a unique $(\omega, a_0) \in \Omega$ satisfying the balance equation. Then there exists a periodic solution of the form $y(t) = a \sin(\omega t) + y^*(t)$ with remnant $\|y^*\|_\infty \leq \epsilon$.*

Sketch of proof. Reduced to the contraction mapping theorem, which generates ρ , p and q . □

The basic idea behind this theorem is that if the harmonics around the loop die off sufficiently fast, then we can insure that there is truly a periodic solution and bound the error of the higher harmonics. There is also a graphical version of the stability theorem that checks for “complete intersections” between the describing function locus and the Nyquist curve [?].

Mathematically, the stability of a limit cycle can be analyzed by taking the linearization of the system around the (non-equilibrium) solution. To see how this is done, consider a nonlinear system of the form 

$$\dot{x} = f(x)$$

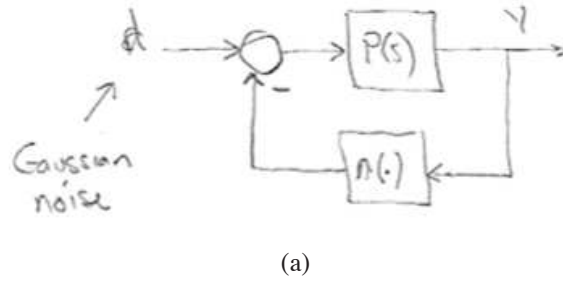


Figure 3.9: Random input describing function analysis.

that has a solution $x_d(t)$ that is periodic with period T . To compute the linearization of the dynamics around the equilibrium point, we compute the dynamics of the error $e = x - x_d$:

$$\dot{e} = f(x) - f(x_d) = F(e, x_d(t)) \approx A(t)e$$

where $A(t)$ is the time-varying linearization given by

$$A(t) = \left. \frac{\partial F}{\partial e}(e, x_d) \right|_{e=0, x_d(t)}.$$

The dynamics matrix $A(t)$ is periodic and so the dynamics of the linearization are given by a periodic, linear ordinary differential equation.

The dynamics of periodic linear systems can be studied using *Floquet* theory, which we briefly review here. Let $\Phi(t, 0)$ be the (T -periodic) fundamental matrix for $\dot{e} = A(t)e$, so that the solution is given by $x(t) = \Phi(t, 0)x(0)$. It can be shown that $\Phi(t, 0)$ has the form $\phi(t, 0) = P(t)e^{Ft}$ where $P(t) = P(t+T) \in \mathbb{R}^{n \times n}$ is a periodic matrix and $F \in \mathbb{R}^{n \times n}$ is a constant matrix. We can now check stability by examining the eigenvalues of the matrix e^{FT} , which corresponds to the “first return” map for the system.

Random input describing functions

In addition to allowing prediction and analysis of limit cycles, describing functions can also be used to analyze the propagation of noise through nonlinear feedback systems. This approach is known as the *random input describing function* method.

As in the single input describing function method, we begin with a system in the form of a linear system with a nonlinear feedback, as shown in Figure 3.9a. To analyze this system, we construct an input that contains both a sinusoid and a random input $r(t)$:

$$y = b + a \sin(\omega t + \phi) + r(t),$$

where b is the bias term, a is the amplitude of the sinusoidal term, ϕ is a uniform random variable and $r(t)$ is a stationary Gaussian random process with variance

σ^2 and correlation $\rho(\tau)$.¹ We approximate the response of the system through the nonlinearity by

$$N(y(t)) \approx N_b b + N_a a \sin(\omega t + \phi) + N_r r(t),$$

where N_b is called the *bias gain*, N_a is the sinusoidal gain and N_r is the stochastic gain. These functions are given by

$$\begin{aligned} N_b(b, a, \sigma) &= \frac{1}{b} E\{f(y)\} = \frac{1}{(2\pi)^{3/2} \sigma b} \int_0^{2\pi} \int_{-\infty}^{\infty} f(b + a \sin \theta + r(t)) e^{-\frac{r^2}{2\sigma^2}} dr d\theta \\ N_a(b, a, \sigma) &= \frac{2}{a} E\{f(y) \sin \theta\} = \frac{2}{(2\pi)^{3/2} \sigma a} \int_0^{2\pi} \int_{-\infty}^{\infty} f(b + a \sin \theta + r(t)) \sin \theta e^{-\frac{r^2}{2\sigma^2}} dr d\theta \\ N_r(b, a, \sigma) &= \frac{1}{\sigma^2} E\{f(y)r\} = \frac{1}{(2\pi)^{3/2} \sigma^3} \int_0^{2\pi} \int_{-\infty}^{\infty} f(b + a \sin \theta + r(t)) r e^{-\frac{r^2}{2\sigma^2}} dr d\theta \end{aligned} \quad (3.14)$$

The random input describing function method has a number of special cases. If we take $\sigma = 0$, then it can be shown that we recover the standard describing function method. If we instead take $a = 0$, we can study how noise propagates through the system. Recall that in the linear case, where the feedback term is given by a constant gain N , the spectral density of the output y is given by

$$S_y(\omega) = H_{yd}(-i\omega) S_d(\omega) H_{yd}(i\omega), \quad \sigma_y = \frac{1}{2\pi} \int_{-\infty}^{\infty} S_y(\omega) d\omega.$$

In the nonlinear case, we replace the feedback gain N with $N_r(\sigma_y)$ so that

$$\tilde{H}_{yd}(s) = \frac{P(s)}{1 + P(s)N_r(\sigma_y)}, \quad \sigma_y = \frac{1}{2\pi} \int_{-\infty}^{\infty} \tilde{H}_{yd}(-i\omega) S_d(\omega) \tilde{H}_{yd}(i\omega) d\omega. \quad (3.15)$$

Note that this equation gives an algebraic relationship for σ_y that can be solved and then used to compute $N_r(\sigma)$ and $S_y(\omega)$.

Consider next the case of both a limit cycle and random noise,

$$y(t) = a \sin(\omega t + \phi) + r(t).$$

We now look for solutions of the coupled equations

$$\begin{aligned} \tilde{H}_{yd}(s) &= \frac{P(s)}{1 + P(s)N_r(\sigma_y)}, \quad \sigma_y = \frac{1}{2\pi} \int_{-\infty}^{\infty} \tilde{H}_{yd}(-i\omega) S_d(\omega) \tilde{H}_{yd}(i\omega) d\omega, \\ N_a(a, \sigma_y) P(i\omega_0) &= -1. \end{aligned} \quad (3.16)$$

If we can find a , σ_y and ω_0 that satisfy all of the equations, then we get a description of $y(t)$.

It is interesting to note that it can sometimes happen that $S_d(\omega)$ can cause an unstable (noiseless) system to be stable. Similarly, we can get a system with $N_r(0, \sigma_y)$ that destabilizes and otherwise stable system.

¹These are described in more detail in Chapter 4.

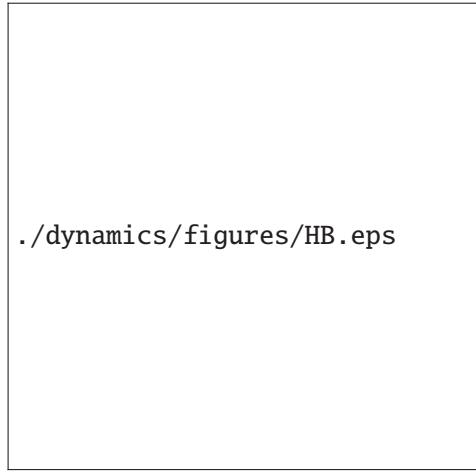


Figure 3.10: Hopf Bifurcation.

3.5 Bifurcations

Hopf bifurcation is a technique that is often used to understand whether a system admits a periodic orbit when some parameter is varied. Usually, such an orbit is a small amplitude periodic orbit that is present in the close vicinity of an unstable steady state.

Consider the system dependent on a parameter α :

$$\dot{x} = g(x, \alpha), x \in \mathbb{R}^n, \alpha \in \mathbb{R},$$

and assume that at the steady state \bar{x} corresponding to $\alpha = \bar{\alpha}$ (i.e., $g(\bar{x}, \bar{\alpha}) = 0$), the linearization $\frac{\partial g}{\partial x}(\bar{x}, \bar{\alpha})$ has a pair of (non zero) imaginary eigenvalues with the remaining \mathbb{R}^{n-2} eigenvalues having negative real parts. Define the new parameter $\mu := \alpha - \bar{\alpha}$ and re-define the system as

$$\dot{x} = f(x, \mu) := g(x, \mu + \bar{\alpha}),$$

so that the linearization $\frac{\partial f}{\partial x}(\bar{x}, 0)$ has a pair of (non zero) imaginary eigenvalues with the remaining \mathbb{R}^{n-2} eigenvalues having negative real parts. Denote by $\lambda(\mu) = \beta(\mu) + i\omega(\mu)$ the eigenvalue such that $\beta(0) = 0$. Then, if $\frac{\partial \beta}{\partial \mu}(\mu = 0) \neq 0$ the system admits a small amplitude almost sinusoidal periodic orbit for μ small enough and the system is said to go through a Hopf bifurcation at $\mu = 0$. If the small amplitude periodic orbit is stable, the Hopf bifurcation is said *supercritical*, while if it is unstable it is said *subcritical*. Figure 3.10 shows diagrams corresponding to these bifurcations.

In order to determine whether a Hopf bifurcation is supercritical or subcritical, it is necessary to calculate a “curvature” coefficient, for which there are formulas (Marsden and McCracken, 1976) and available bifurcation software, such as

AUTO. In practice, it is often enough to calculate the value $\bar{\alpha}$ of the parameter at which Hopf bifurcation occurs and simulate the system for values of the parameter α close to $\bar{\alpha}$. If a small amplitude limit cycle appears, then the bifurcation must be supercritical.

The Hopf bifurcation result is based on the center manifold theory for nonlinear dynamical systems. For a rigorous treatment of Hopf bifurcation is thus necessary to study center manifold theory first, which is outside the scope of this text. For details, the reader is referred to Wiggins book on dynamical systems and chaos.

3.6 Model Reduction Techniques

The techniques that we have developed in this chapter can be applied to a wide variety of dynamical systems. However, many of the methods require significant computation and hence we would like to reduce the complexity of the models as much as possible before applying them. In this section we review methods for doing such a reduction in the complexity of the models. Most of the techniques are based on the common idea that if we are interested in the slower time scale dynamics of a system, the fast time scale dynamics can be approximated by their equilibrium solutions. This idea was introduced in Chapter 2 in the context of reduced order mechanisms; we present a more mathematical analysis of such systems here.

Singular Perturbation

Let $(x, y) \in D := D_x \times D_y \subset \mathbb{R}^n \times \mathbb{R}^m$ and consider the vector field

$$\dot{x} = f(x, y), \quad \epsilon \dot{y} = g(x, y), \quad (x(0), y(0)) = (x_0, y_0)$$

in which $0 < \epsilon \ll 1$ is a small parameter. Since $\epsilon \ll 1$, the absolute value of the time derivative of y can be much larger than the time derivative of x , resulting in y dynamics that are much faster than the x dynamics. That is, this system has a slow time scale evolution (in x) and a fast time-scale evolution (in y). If we are interested only in the slower time scale, then the above system can be approximated (under suitable conditions) by the *reduced system*

$$\dot{\bar{x}} = f(\bar{x}, \bar{y}), \quad 0 = g(\bar{x}, \bar{y}), \quad \bar{x}(0) = x_0.$$

Letting $y = \gamma(x)$ (called the *slow manifold*) be the locally unique solution of $g(x, y) = 0$, we can approximate the dynamics in x as

$$\dot{\bar{x}} = f(\bar{x}, \gamma(\bar{x})), \quad \bar{x}(0) = x_0.$$

We seek to determine under what conditions the solution $x(t)$ is “close” to the solution $\bar{x}(t)$ of the reduced system. This problem can be addressed by analyzing

the fast dynamics. Letting $\tau = t/\epsilon$ be the fast time scale, we have that

$$\frac{dx}{d\tau} = \epsilon f(x, y), \quad \frac{dy}{d\tau} = g(x, y), \quad (x(0), y(0)) = (x_0, y_0),$$

so that when $\epsilon \ll 1$, $x(\tau)$ does not appreciably change. Therefore, the above system in the τ time scale can be approximated by

$$\frac{dy}{d\tau} = g(x_0, y), \quad y(0) = y_0,$$

in which x is “frozen” at the initial condition. This system is usually referred to as the *boundary layer* system. If for all x_0 , we have that $y(\tau)$ converges to $\gamma(x_0)$, then for $t > 0$ we will have that the solution $x(t)$ is well approximated by the solution $\bar{x}(t)$ to the reduced system. This qualitative explanation is more precisely captured by the following theorem (originally due to Tikonov).

Theorem 3.6. *Assume that*

$$\left. \frac{\partial}{\partial y} g(x, y) \right|_{y=\gamma(x)} < 0$$

uniformly for $x \in D_x$. Let the solution of the reduced system be uniquely defined for $t \in [0, t_f]$. Then, for all $t_b \in (0, t_f]$ there is a constant $\epsilon^ > 0$ and set $\Omega \subseteq D$ such that*

$$\begin{aligned} x(t) - \bar{x}(t) &= O(\epsilon) \text{ uniformly for } t \in [0, t_f], \\ y(t) - \gamma(\bar{x}(t)) &= O(\epsilon) \text{ uniformly for } t \in [t_b, t_f], \end{aligned}$$

provided $\epsilon < \epsilon^$ and $(x_0, y_0) \in \Omega$.*

Example 3.9 (Linear system). Consider the following linear system

$$\begin{aligned} \dot{x}_1 &= -x_1 \\ \dot{x}_2 &= -\frac{1}{\epsilon}x_2 + \frac{1}{\epsilon}x_1, \quad \epsilon > 0, \end{aligned} \tag{3.17}$$

in which ϵ is very small. This system has two eigenvalues equal to -1 and $-1/\epsilon$ with corresponding eigenvectors $(1 - \epsilon, 1)$ and $(0, 1)$, respectively. The slow manifold, obtained by multiplying both sides of the second equation in system (3.17) by ϵ and setting $\epsilon = 0$, is given by $x_2 = x_1$ and the boundary layer system is exponentially stable. The reduced system is just given by

$$\dot{\bar{x}}_1 = -\bar{x}_1, \text{ and } \bar{x}_2(t) = \bar{x}_1(t).$$

The trajectories of the system along with the slow manifold are represented in Figure 3.11. The initial conditions that are not on the slow manifold quickly converge to the slow manifold and then they converge to the origin. ∇

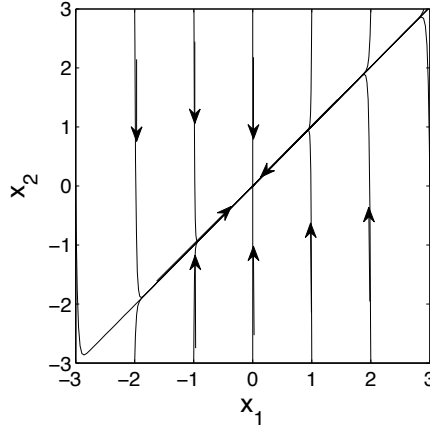
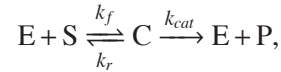


Figure 3.11: Simulation results for the system in equations (3.17). Trajectories in the x_1, x_2 plane.

Example 3.10 (Enzymatic reaction). Let's go back to the enzymatic reaction



in which E is an enzyme, S is the substrate to which the enzyme binds to form the complex C, and P is the product resulting from the modification of the substrate S due to the binding with the enzyme E. The rate k_f is referred to as association constant, k_r as dissociation constant, and k_{cat} as the catalytic rate. The corresponding ODE system is given by

$$\begin{aligned} \frac{dE}{dt} &= -k_f E \cdot S + k_r C + k_{cat} C \\ \frac{dS}{dt} &= -k_f E \cdot S + k_r C \\ \frac{dC}{dt} &= k_f E \cdot S - (k_r + k_{cat}) C \\ \frac{dP}{dt} &= k_{cat} C. \end{aligned}$$

By assuming that $k_r, k_f \gg k_{cat}$, we obtained that approximately $\frac{dC}{dt} = 0$ and thus that $C = \frac{E_{tot} S}{S + K_m}$, with $K_m = \frac{k_r + k_{cat}}{k_f}$ and $\frac{dP}{dt} = \frac{V_{max} S}{S + K_m}$ with $V_{max} = k_{cat} E_{tot}$. From this, it also follows that

$$\frac{dE}{dt} \approx 0 \text{ and } \frac{dS}{dt} \approx -\frac{dP}{dt}. \quad (3.18)$$

How good is this approximation? By applying the singular perturbation method, we will obtain a clear answer to this question. Specifically, define $a := k_f/k_r$ and

take the system to standard singular perturbation form by defining the small parameter as $\epsilon := \frac{k_{cat}}{k_r}$, so that $k_f = \frac{k_{cat}}{\epsilon} a$, $k_r = \frac{k_{cat}}{\epsilon}$, and the system becomes

$$\begin{aligned}\epsilon \frac{dE}{dt} &= -ak_{cat}E \cdot S + k_{cat}C + \epsilon k_{cat}C \\ \epsilon \frac{dS}{dt} &= -ak_{cat}E \cdot S + k_{cat}C \\ \epsilon \frac{dC}{dt} &= ak_{cat}E \cdot S - k_{cat}C - \epsilon k_{cat}C \\ \frac{dP}{dt} &= k_{cat}C.\end{aligned}$$

One cannot directly apply singular perturbation theory on this system because one can verify from the linearization of the first three equations that the boundary layer dynamics is not locally exponentially stable as there are two zero eigenvalues. This is because the three variables E, S, C are not independent. Specifically, $E = E_{tot} - C$ and $S + C + P = S(0) = S_{tot}$, assuming that initially we have S in amount $S(0)$ and no amount of P and C in the system. Given these conservation laws, the system can be re-written as

$$\begin{aligned}\epsilon \frac{dC}{dt} &= ak_{cat}(E_{tot} - C) \cdot (S_{tot} - C - P) - k_{cat}C - \epsilon k_{cat}C \\ \frac{dP}{dt} &= k_{cat}C.\end{aligned}$$

Under the assumption made in the analysis of the enzymatic reaction that $S_{tot} \gg E_{tot}$, we have that $C \ll S_{tot}$ so that the equations finally become

$$\begin{aligned}\epsilon \frac{dC}{dt} &= ak_{cat}(E_{tot} - C) \cdot (S_{tot} - P) - k_{cat}C - \epsilon k_{cat}C \\ \frac{dP}{dt} &= k_{cat}C.\end{aligned}$$

One can verify (show as an exercise) that in this system, the boundary layer dynamics is locally exponentially stable, so that setting $\epsilon = 0$ one obtains $\bar{C} = \frac{E_{tot}(S_{tot} - \bar{P})}{(S_{tot} - \bar{P}) + K_m} =: g(\bar{P})$ and thus that the slow dynamics of the system are given by

$$\frac{d\bar{P}}{dt} = V_{max} \frac{(S_{tot} - \bar{P})}{(S_{tot} - \bar{P}) + K_m}.$$

From the conservation law $\bar{S} + \bar{C} + \bar{P} = S(0) = S_{tot}$, we obtain that $\frac{d\bar{S}}{dt} = -\frac{d\bar{P}}{dt} - \frac{d\bar{C}}{dt}$, in which now $\frac{d\bar{C}}{dt} = \frac{\partial g}{\partial \bar{P}}(\bar{P}) \cdot \frac{d\bar{P}}{dt}$. Therefore

$$\frac{d\bar{S}}{dt} = -\frac{d\bar{P}}{dt} \left(1 + \frac{\partial g}{\partial \bar{P}}(\bar{P})\right), \quad \bar{S}(0) = S_{tot} - g(\bar{P}(0)) - \bar{P}(0) \quad (3.19)$$

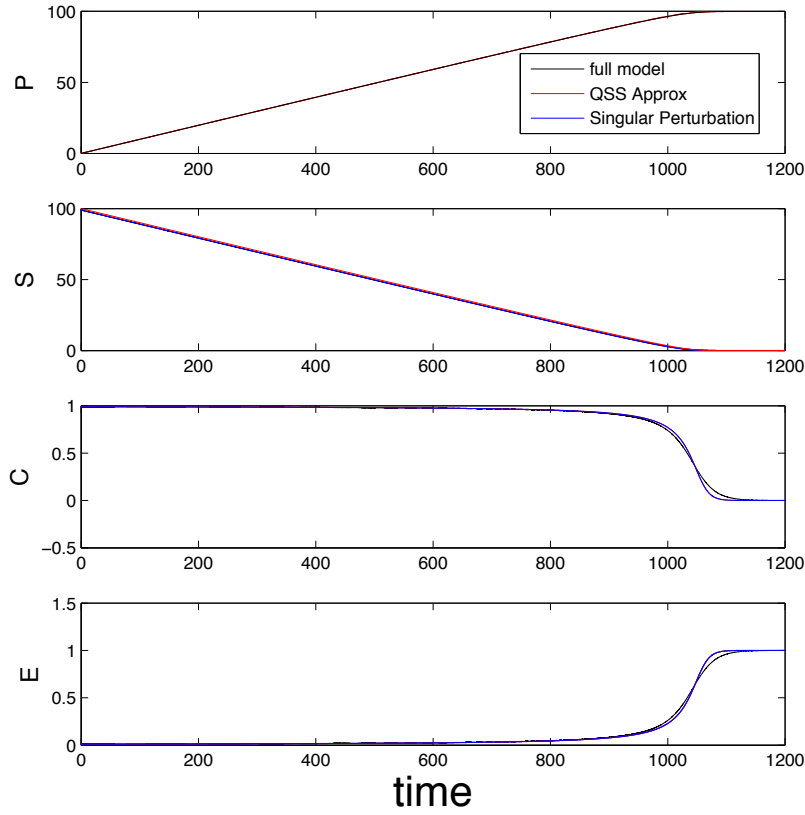


Figure 3.12: Simulation results for the enzymatic reaction comparing the approximations from singular perturbation and from the quasi-steady state approximation. Here, we have $S_{tot} = 100$, $E_{tot} = 1$, $k_r = k_f = 10$, and $k_{cat} = 0.1$.

and

$$\frac{d\bar{E}}{dt} = -\frac{d\bar{C}}{dt} = -\frac{\partial g}{\partial P}(\bar{P}) \frac{d\bar{P}}{dt}, \quad E(0) = E_{tot} - g(\bar{P}(0)), \quad (3.20)$$

which are different from expressions (3.18). Specifically, these expressions are close to those in (3.18) only when $\frac{\partial g}{\partial P}(\bar{P})$ is small enough. In the plots of Figure 3.12, we show the time trajectories of the original system, of the Michaelis-Menten quasi-steady state approximation, and of the singular perturbation approximation. The trajectories of $E(t)$ and of $S(t)$ for the quasi-steady state approximation have been obtained from the conservation laws once $P(t)$ and $C(t)$ are determined. The trajectories of these variables for the singular perturbation approximation have been obtained directly integrating equations (3.19) and (3.20). Notice that the quasi-steady state approximations $\frac{d\bar{C}}{dt} \approx 0$ and $\frac{d\bar{E}}{dt} \approx 0$ are well representing the

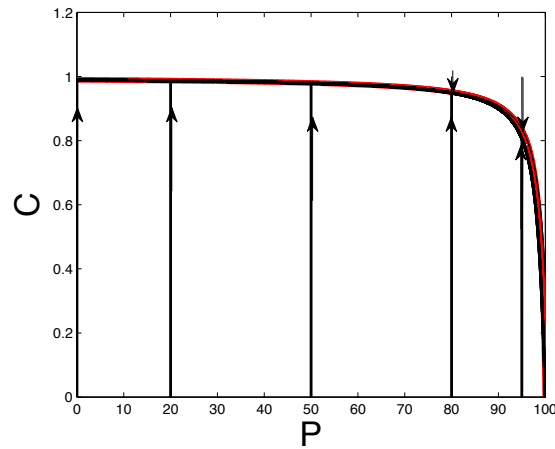


Figure 3.13: The slow manifold of the system $C = g(P)$ is shown in red. In black, we show the trajectories of the the full system. These trajectories collapse into an ϵ -neighbor of the slow manifold. Here, we have $S_{tot} = 100$, $E_{tot} = 1$, $k_r = k_f = 10$, and $k_{cat} = 0.1$.

dynamics of the C and E variables only while $S(t)$ is large enough. By contrast, equations (3.19-3.20) well represent the system even when the substrate goes to zero. In Figure 3.13, we show the curve $C = g(P)$ (in red) and the trajectories of the full system in black. All of the trajectories of the system immediately collapse into an ϵ -neighbor of the curve $C = g(P)$. ∇

Balanced truncation

Principle component analysis (PCA)