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APPLICATION OF p-DOMINANCE THEORY TO BIOCHEMICAL REACTIONS

Internship report after a placement at the University of Cambridge with a view to obtaining the Masters degree in mathematics, with research focus

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Abstract

Nowadays, mathematics explain most biological and natural phenomena. Amongst them, chemical reactions in particular remain a field of research that mathematicians have studied for ages. The chemical reaction networks theory was developed in the twentieth century, and allows to understand how reactions work. The stoichiometric compatibility classes especially provide the subspace in which species circulate. Therefore, each initial condition of species concentrations matches with a class. Thus, the initial dimension of the system can be reduced. This theory can especially be applied to enzymatic reactions, glycolysis being one of the most famous examples of them. In parallel with this theory, F. Forni developed the theory of p-dominance a few years ago. This new tool provides the dimension of the asymptotic behaviour of any dynamical system, which reduces the initial dimension of the system as well. The main advantage of this theory lies in the fact that an algorithmic approach has been developed. Both theories can then be applied to reduce the dimension of the system.

This work aims to use both theories to reduce the initial dimension of the system as much as possible. This amounts to computing the p-dominance of the system within each stoichiometric compatibility class. This new theory is applied to several enzymatic reactions, and a preliminary analysis of the glycolysis is provided.

Keywords: p-dominance theory, algorithmic test, differential equations, chemical reactions, enzymatic reactions, glycolysis, glycolic oscillations

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Introduction

Natural, biological or even astronomical phenomena happen in everyday life. Fortunately, chemistry and physics can help us understand most of them. Chemical reactions in particular appear to be the key to all processes that occur in the body. We can for example mention the digestion, i.e. the metabolism of food in the body, during which a lot of chemical reactions occur. Furthermore, everybody knows that mathematics is used as a powerful tool to explain a lot of phenomena in the world and beyond. Then it could be interesting to take into account these both spheres of competence to improve the knowledge. In this work, we introduce and develop two theories: a chemical theory that constraints the concentration of the species in the reaction, and the p-dominance theory that constraints the asymptotic behaviour of a dynamical system.

The three first sections of this work focus on chemical theory, and are mainly based on Martin Feinberg's lectures [1] and on James keener and James Sneyd's book [7] called *Mathematical Physiology*. Some other references [2], [6], [8], [9], [10] and [11] are used to better understand all the notions. First, we have to introduce and explain what kind of reaction we deal with, and develop some famous theorems about them, i.e. the deficiency theorems. Among all the notions introduced in the first chapter, the stoichiometric compatibility classes particularly interest us since they describe the subspace in which the concentration of each species of the reaction wanders. This can be useful when the dimension of this subspace is much smaller than the initial dimension of the system. In the second chapter, our study will be confined on the enzymatic reactions, i.e. reactions that are accelerated thanks to molecules called enzymes. Different reactions are then studied, and we apply the theory of the first chapter to each of them. Finally, the third chapter describes one of the most studied metabolic pathway that provides energy (ATP) from glucose, which means the glycolysis and it is regulated by enzymes.

The fourth section of this report defines what p-dominance theory is. This theory is used to understand the asymptotic behaviour of a dynamical system by finding the dimension p of this behaviour. For example, a 0-dominant system admits a unique fixed point since the asymptotic behaviour is 0-dimensional. This concept can be extended to a p-dimensional behaviour for any $p \geq 0$. The p-dominance is described via a dissipation inequality and it can be proved by using linear matrix inequalities. An algorithmic test is besides provided in the second section of the fourth chapter with some examples. This chapter is mainly based on Fulvio Forni's publications [3], [4] and [5].

Both theories can severally be used to better understand and study a system since stoichiometric classes can reduce the dimension of the system, and p-dominance as well. The purpose of this work consists of mixing both theories to know the asymptotic behaviour inside each stoichiometric class. The fifth and last chapter focuses on this goal, and we apply this new theory on different examples that we have introduced in the previous chapters. A preliminary analysis is also performed for glycolysis.

Chapter 1

Chemical reaction networks theory

In this section, we provide a formal frame to study chemical reactions daily used by chemists. Everything is based on lectures [1] delivered by Martin Feinberg and on the first volume of James Keener and James Sneyd's book [7] *Mathematical Physiology*. First of all, we should clarify which type of reaction we deal with and what we mean by chemical reaction network. First of all, let us use an example to introduce some notions. Given the following chemical reaction diagram:

$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{C}. \tag{1.1}$$

This reaction diagram shows that one mole of the species A can react with one mole of the species B to form one mole of the species C. This reaction generally involves three different species: A, B and C. Thanks to these species, it is possible to form some complexes, i.e. some linear combinations that appear in the diagram, either on the right of the arrow or on the left. For example, the reaction (1.1) involves two complexes: $A + B$ and C. However, they play two distinct roles. The complex $A + B$ will be defined as the reactant of the reaction and C as the product since A and B react to finally form C. Let us define formally what a chemical reaction network is.

Definition 1.1

A **chemical reaction network** consists of three sets:

1. a finite set $\mathcal{S}$ of m elements which are called **species** of the network;
2. a finite set $\mathcal{C}$ of n distinct vectors in $\mathbb{R}^m$ such that

$$\bigcup_{y \in \mathcal{C}} supp(y) \;=\; \mathcal{S},$$

   where $supp(y)$ means the set of the species involved in the complex y. Elements of $\mathcal{C}$ are called the **complexes** of the network;
3. a relation $\mathcal{R} \subset \mathcal{C} \times \mathcal{C}$ such that
   (a) no complex reacts to itself, i.e. $\forall\, y \in \mathcal{C},\ (y, y) \notin \mathcal{R}$,
   (b) no complex is isolated, i.e. for each $y \in \mathcal{C}$, $\exists\, y' \in \mathcal{C}$ such that $(y', y) \in \mathcal{R}$ or $(y, y') \in \mathcal{R}$.

   Elements of $\mathcal{R}$ are called **reactions** and $(y', y) \equiv y \to y'$, where y is the **reactant** complex and y' is the **product** complex.

In other words, this definition means that each element of each complex has to belong to the set of species and each complex of the set $\mathcal{C}$ has to interact with another complex, either being the reactant of the reaction or the product. Let us also notice that we have introduced the notion of *supp* of a complex y through the definition of chemical reaction network as the set of all the species involved in the complex y. So, if we denote by y_s the number of species s involved in y, the support of a complex can easily be defined as

$$supp(y) \;=\; \{s \in \mathcal{S} \mid y_s \neq 0\}\,. \tag{1.2}$$

For example, we have that $supp(A+B) = \{A, B\}$. In this report, we can either use y_s with $s \in \mathcal{S}$, or the notation y_i with $i = 1, \cdots, m$ to appoint the ith component of the vector complex $y \in \mathcal{C}$ which is associated to the species s. In other words, we can express a concentration vector or a complex in two different ways: either a combination of the species $s \in \mathcal{S}$, or a m-dimensional vector for which we have defined an order and one component is associated to one species.

Example 1.1. *Let us consider a reaction diagram similar to the diagram (1.1), given by*

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C}. \tag{1.3}$$

We can define each of the sets defined in the previous definition. First, the set of species $\mathcal{S}$ is given by $\{A, B, C\}$, so $m = 3$. Secondly, the set of complexes $\mathcal{C}$ is $\{A + B, C\}$ and $n = 2$. Each complex here is expressed with a combination of species but we can also express them with vectors of three components. If we consider that the first component is associated with the species A, the second component with B and the third one with C, then the complex $A + B$ is equivalent to the vector $(1, 1, 0)^t$ and the complex C is related to $(0, 0, 1)^t$. Finally, the set of reactions $\mathcal{R}$ is given by $\{A+B \to C, C \to A+B\}$.

Let us mention that the definition of chemical reaction network enables to write open systems. For example, it includes network with supply of a species, so that we will have a reaction given by

$$0 \longrightarrow \mathrm{A}.$$

If we remove one species from the network, we can also formalize it, and then write

$$\mathrm{A} \longrightarrow 0.$$

This kind of networks are particularly studied at the end of the second lecture of [1].

Within this chapter, we would like to study the evolution of the concentration of each species of the chemical reaction network over time. This means that, assuming that we put some molecules into a test tube, we wonder what the result product could be, whether there will be an equilibrium or whether the solution will always oscillate, and so on. To do this we will first induce differential equations from a diagram and a kinetics, i.e. the way that species react and reactions occur. We will particularly focus on one kinetics: the law of mass action. Then, we will show that the diagram implies restrictions on trajectories of concentration by limiting movement inside a subset, called a stoichiometric class.

1.1 Differential equations

As we said before, we want to investigate the evolution of the concentration of each species, knowing that these concentrations change with the chemical reactions. Therefore, if we want to write the differential equations induced from the diagram, we have to know how rapidly these reactions occur. This idea leads to the following concept.

Definition 1.2

A **kinetics** for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is an assignment to each reaction $y \to y'$ in $\mathcal{R}$ of a continuous rate function, denoted by $\mathcal{K}_{y\to y'} : \mathbb{R}_+^m \to \mathbb{R}_+$, such that

$$\mathcal{K}_{y\to y'}(c(t)) > 0 \;\Leftrightarrow\; supp(y) \subset supp(c(t)). \tag{1.4}$$

Then, we will call a **reaction system** $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ endowed with a kinetics $\mathcal{K}$.

The equivalence (1.4) means that the reaction $y \to y'$ can happen if and only if at that time its reactants are present in the composition $c(t)$, which means that the non-null components of the complex y are also different from 0 in the concentration vector $c(t)$. However, we still have to define some things to be able to write down the differential equations.

Definition 1.3

The **species formation rate function** $f : \mathbb{R}_+^m \to \mathbb{R}^m$ is defined by

$$f(c) \;\equiv\; \sum_{y\to y'\in\mathcal{R}} \mathcal{K}_{y\to y'}(c)\,(y' - y), \tag{1.5}$$

where the vector $y' - y$ is called the **reaction vector**.

The differential equation for a reaction system is given by $\dot{c} = f(c)$, and then, for a species $s \in \mathcal{S}$, the equation is

$$\dot{c}_s \;=\; \sum_{y\to y'\in\mathcal{R}} \mathcal{K}_{y\to y'}(y'_s - y_s).$$

Let us take an example to see exactly how it works.

Example 1.2. *Given the previous example (1.3), we can write down the differential equations. For the concentration of A, B and C, we have*

$$\begin{aligned}
\dot{c}_A &= \sum_{y\to y'\in\mathcal{R}} \mathcal{K}_{y\to y'}\,(y'_A - y_A)\,, \\
&= \mathcal{K}_{C\to A+B}(1-0) + \mathcal{K}_{A+B\to C}(0-1), \\
\dot{c}_B &= \mathcal{K}_{C\to A+B}(1-0) + \mathcal{K}_{A+B\to C}(0-1), \\
\dot{c}_C &= \mathcal{K}_{A+B\to C}(1-0) + \mathcal{K}_{C\to A+B}(0-1).
\end{aligned} \tag{1.6}$$

What we need to find out now is the nature of the kinetics function. Most of the times, we assume that the kinetics is of mass action type.

Definition 1.4

A kinetics $\mathcal{K}$ for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ is **mass action** if, for each reaction $y \to y' \in \mathcal{R}$, there exists a positive number $k_{y\to y'}$ such that

$$\mathcal{K}_{y\to y'}(c) \equiv k_{y\to y'} \underbrace{\prod_{s\in\mathcal{S}} c_s{}^{y_s}}_{\underset{\text{not}}{:=} c^y},$$

where the numbers $k_{y\to y'}$ are called the **rate constants**. We will then talk about **elementary reactions** and we will denote this reaction system by $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$.

This comes from the fact that for each reaction, the rate of the reaction is the product of the number of collisions per unit time, and the probability that a collision is sufficiently energetic to overcome the free energy of activation. This probability is proportional to the product of each reactant. If we consider the previous example and we denote the forward and backward rate constants by k^+ and k^- respectively, we can find that at the equilibrium,

$$\frac{k^-}{k^+} = \frac{c_A c_B}{c_C} := K_{eq},$$

where K_{eq} is called the equilibrium constant. If K_{eq} is small, this means that at steady-state, the forward reaction is preferred and most of A and B are transformed to give the product C. This constant can be related to Free Gibbs energy via the formula of ideal dilute solutions, which is

$$G = G_0 + RT\ln(c),$$

where T is the temperature and R is the ideal gas constant. The change in chemical potential ΔG is the difference between G_C and the sum of G_A and G_B, i.e.

$$\begin{aligned} \Delta G &= G_C - (G_B + G_A), \\ &= \Delta G_0 + RT\ln\left(\frac{c_C}{c_B c_A}\right). \end{aligned}$$

We can easily show that

$$K_{eq} = e^{\Delta G_0/RT}. \tag{1.7}$$

This relation is logical as the more negative ΔG_0 is, the greater the reaction goes from left to right, and the smaller the equilibrium constant is. This relation can be generalized to a more complex reaction diagram given by

$$\alpha\mathrm{A} + \beta\mathrm{B} \rightleftharpoons \gamma\mathrm{C} + \delta\mathrm{D}$$

for which the relation is the same as before (1.7).

1.2 Network restrictions

Now that we have differential equations, we can compute the concentration trajectories from an initial condition. In this section, we will see that these trajectories cannot wander in $\mathbb{R}^m_+$; only some directions are allowed to go through. If we look at the definition (1.5) of the species formation rate function, we can see that this is a combination of the reaction vectors $(y - y')$. It motivates us to define the following concept.

Definition 1.5

The **stoichiometric subspace** S is the linear subspace of $\mathbb{R}^m$ defined by

$$S \;=\; span\,\{y' - y \text{ such that } y \to y' \in \mathcal{R}\}\,. \tag{1.8}$$

The dimension s of this subspace is called the **rank of the reaction network**.

We can now establish a lemma that constraints the concentration trajectories.

Lemma 1.1.
Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ be a reaction system, and let $c : I \to I\!R^m$ be the solution of the differential equation

$$\dot{c} \;=\; \sum_{\mathcal{R}} \mathcal{K}_{y\to y'}(c)(y' - y),$$

where $I \subset I\!R$ is an interval. Then, for each time $t_1 < t_2 \in I$, there exists $\alpha : \mathcal{R} \to I\!R_+$ such that

$$c(t_2) - c(t_1) \;=\; \sum_{\mathcal{R}} \alpha_{y\to y'}(y' - y). \tag{1.9}$$

⌟

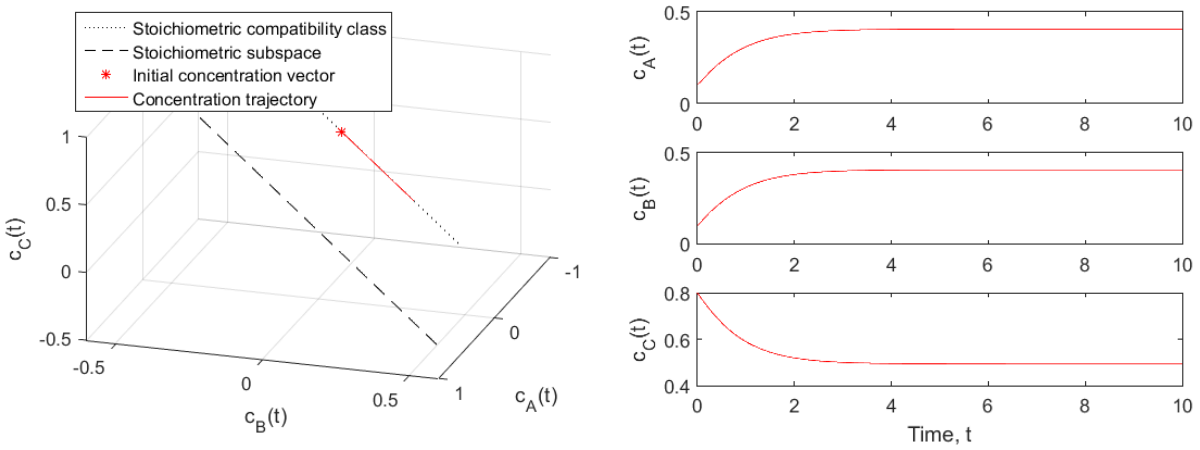
The equality (1.9) shows that a vector concentration c' can belong to the same trajectory as a concentration c only if the difference between them lies in the stoichiometric subspace: we will say that c and c' are **stoichiometrically compatible**. In this case, if we consider that c_0 is the initial concentration vector and that c is the solution of the differential equation, it means that for every time $t \in I$, we must have

$$c(t) \in\; (c_0 + S) \cap \mathbb{R}^m_+,$$

where S denotes the stoichiometric subspace and

$$c_0 + S \;:=\; \{c_0 + s \text{ such that } s \in S\}\,.$$

Stoichiometric compatibility is an equivalence relation that induces a partition of $\mathbb{R}^m$ into equivalence classes called the **stoichiometric compatibility classes** for the network. Geometrically, these classes are obtained by translation from the stoichiometric subspace. The concept is quite important because if we want to study the stability of this kind of networks, we have to study it for each class. Thus several questions can be asked: is there an equilibrium for each class? Is the stability always the same for each class? All these questions will be answered via the following theorems but let us illustrate this concept with an example beforehand.



(a) Phase space

(b) Trajectory evolution

Figure 1.1: Illustration of the stoichiometric subspace and compatibility classes of the system (1.3) for $x_0 = (0.1, 0.1, 0.8)$, $k^+ = 1.2$ and $k^- = 0.4$

Example 1.3. *If we consider the previous example (1.3), we can find the stoichiometric subspace to be*

$$\begin{aligned} S &= span\{A + B - C,\ C - A - B\}, \\ &= span\{A + B - C\}, \\ &= span\left\{(1, 1, -1)^t\right\}. \end{aligned} \tag{1.10}$$

So, the rank of the reaction is one, and this means that the concentration trajectory issued from an initial condition has to stay on a straight line in $\mathbb{R}^3$. As shown in FIGURE *1.1a, there is always a negative concentration if we consider the stoichiometric subspace, so the only feasible point is the origin, i.e. when there is no molecule of species. But if we consider some parallel to this line, we can find stoichiometric compatibility classes in which concentration trajectories have to stay as illustrated in the figure. The evolution of each concentration is shown in* FIGURE *1.1b and we can see that the concentration vector keeps constant after some integration steps meaning that there is a stable equilibrium point in this stoichiometric class.*

This subspace can be found with another method when we assume that the system follows the law of mass action. Let us introduce this method first for linear systems and then, extend it with a differential approach. Let us assume that we have the following diagram

$$\mathrm{A} \underset{\mathrm{k_-}}{\overset{\mathrm{k_+}}{\rightleftharpoons}} \mathrm{B} \tag{1.11}$$

which leads to a linear differential system of equations, given by

$$\begin{pmatrix} \dot{a} \\ \dot{b} \end{pmatrix} = \begin{pmatrix} -k_+ & k_-, \\ k_+ & -k_-. \end{pmatrix} \begin{pmatrix} a \\ b \end{pmatrix}.$$

It is obvious that we have only one restriction $\dot{a} + \dot{b} = 0$, i.e. the sum of the first and the second rows. This can be rewritten with matrices since we have a linear system and a combination of rows can be written as the product between a row vector and the matrix, i.e.

$$\begin{pmatrix} 1 \\ 1 \end{pmatrix}^t \begin{pmatrix} -k_+ & k_-, \\ k_+ & -k_-. \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix}^t.$$

In a more general way, the combination of derivatives that are null can be found by looking for the vector v such that $v^t A = 0$. Then, each vector v_i that we can find can be associated to a constant amount. The stoichiometric subspace is the space of vectors that satisfy all constraints. In other words, this is the set of vectors u such that for all v_i, we have ${v_i}^t u = 0$. For the example (1.11), we have

$$\begin{pmatrix} 1 & 1 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \end{pmatrix} = 0,$$

that implies that $u_1 = -u_2$, and the stoichiometric subspace is then the set spanned by the vector $(1, -1)^t$. Using the definition (1.8) gives us the exact same result. In general, we have that

$$\mathcal{S} = \left\{ u \in \mathbb{R}^m \mid v^t u = 0 \; \forall v : v^t A = 0 \right\}$$

where A is the matrix of the linear system $\dot{x} = Ax$. If we have a nonlinear system of differential equations, we can do exactly the same thing with the Jacobian matrix. In a nutshell, the method consists in first finding the Jacobian matrix J of the system, then computing the vectors v_i such that ${v_i}^t J = 0$ and finally computing the vectors u such that for every vector v_i, we have ${v_i}^t u = 0$. In other words,

$$\begin{aligned} \mathcal{S} &= \left\{ u \in \mathbb{R}^m \mid v^t u = 0 \; \forall v : v^t J = 0 \right\}, \\ &= \left\{ u \in \mathbb{R}^m \mid W^t u = 0 \right\}. \end{aligned} \tag{1.12}$$

where J is the Jacobian matrix of the nonlinear system $\dot{x} = f(x)$, and W is the matrix formed with the vectors v. Let us use this method to find the stoichiometric subspace again for the first example that we have introduced.

Example 1.4. *Let us take the first example of chemical diagram (1.3) and apply the differential method to find the stoichiometric subspace. We know that for the law of mass action, the differential equations induced from this diagram are given by*

$$\begin{aligned} \frac{dc_A}{dt} &= k_- c_C - k_+ c_A c_B, \\ \frac{dc_B}{dt} &= k_- c_C - k_+ c_A c_B, \\ \frac{dc_C}{dt} &= k_+ c_A c_B - k_- c_C. \end{aligned}$$

Therefore, the Jacobian matrix is

$$J = \begin{pmatrix} -k_+ c_B & -k_+ c_A & k_- \\ -k_+ c_B & -k_+ c_A & k_- \\ k_+ c_B & k_+ c_A & -k_- \end{pmatrix}.$$

So we have to find the vectors v such that $v^t J = 0$. After some computation, we find that the vector has to belong to the set spanned by two vectors v_1 and v_2 defined by

$$v_1 = (1,\ 0,\ 1)^t \qquad \textit{and} \qquad v_2 = (0,\ 1,\ 1)^t .$$

Finally, if we look for the vectors u that satisfy ${v_i}^t u = 0$ for $i = 1, 2$, we have

$$\begin{cases} u_A + u_C &= 0, \\ u_B + u_C &= 0. \end{cases}$$

It implies that the vector u has to belong to the space spanned by the vector $(1,\ 1, -1)^t$, like we have previously found (1.10) with the definition (1.8).

We already know that the character s is used to denote the dimension of the stoichiometric subspace, and n to denote the number of complexes present in the reaction diagram. Let us now give a signification for the character l. We could instinctively introduce the following concept since it could be seen as the number of sets of reactions that we find in a reaction diagram, i.e. the number of reactions that we can isolate from each other in a diagram. For example, we can only find one reaction in the previous example, so l should be equal to one. In a more formal way, we can define an equivalence relation and induce a partition of the complexes.

Definition 1.6

Two complexes y and $y' \in \mathcal{C}$ are **directly linked**, denoted by $y \leftrightarrow y'$, if $y \to y'$ or $y' \to y$.

Two complexes are then directly linked if there exists a reaction between both of them, whatever the direction of this reaction. As few complexes are directly linked, we can define another notion that is less demanding.

Definition 1.7

Two complexes y and $y' \in \mathcal{C}$ are **linked** if and only if one of the following conditions are satisfied:

1. $y = y'$,
2. $y \leftrightarrow y'$,
3. $\mathcal{C}$ contains a sequence $\{y_1, y_2, \cdots, y_k\}$ such that

$$y \leftrightarrow y_1 \leftrightarrow y_2 \leftrightarrow \cdots \leftrightarrow y_k \leftrightarrow y'.$$

In this case, we write $y \sim y'$. The equivalence relation $\sim$ induces a partition of $\mathcal{C}$ with a family of equivalence classes denoted by $\{L^\theta\}_{\theta = 1,\ldots,l}$ called the **linkage classes** of the network. We reserve the symbol l for the number of theses classes.

The **deficiency** of a network can now be defined. We will not define it in a formal way here, but this non-negative number is actually the dimension of the positive space that makes the differential equations equal to zero, i.e. the dimension of the equilibrium points (see lectures 3, 4, 5 of [1] for more information). In practice, the deficiency is the non-negative number defined by

$$\delta = n - (l + s), \tag{1.13}$$

and it allows us to classify reaction networks depending on their deficiency index. Moreover, the definition above does not take account of the direction of the arrows between complexes. Nonetheless we can define a similar notion, with respect to the direction.

Definition 1.8

A complex $y \in \mathcal{C}$ **ultimately reacts** to a complex $y' \in \mathcal{C}$ if any of the following conditions is satisfied:

1. $y = y'$,
2. $y \to y'$,
3. the set of complexes $\mathcal{C}$ contains a sequence $\{y_1, y_2, \cdots, y_k\}$ such that

$$y \to y_1 \to y_2 \to \cdots \to y_k \to y'.$$

We will write $y \Rightarrow y'$. We will say that two complexes y and $y' \in \mathcal{C}$ are **strongly linked** if $y \Rightarrow y'$ and $y' \Rightarrow y$, and we will write $y \approx y'$.

It appears that the two notions are really similar but the difference lies in the fact that we take the direction of the arrows (y and y' strongly linked) into account, or we do not (y and y' linked). This notion can thus be used to define reversible and weakly reversible networks.

Definition 1.9

A reaction network is **reversible** if, for that network, the "react to" relation ($\to$) is symmetric, i.e. if $y \to y'$, then $y' \to y$.

This first concept is quite logical because every reaction should be reversible. In practice, if the reverse reaction is much slower than the initial reaction, we can consider that it does not exist. However, as few reaction diagrams admit only reversible reactions, a weaker but similar concept will be defined.

Definition 1.10

A reaction network is **weakly reversible** if, for that network, any of the following (equivalent) conditions is satisfied:

1. the "ultimately react to" relation ($\Rightarrow$) is symmetric, i.e. whenever $y \Rightarrow y'$, we also have $y' \Rightarrow y$,
2. each reaction is contained in a directed cycle, i.e. whenever $y \to y'$, we also have $y' \to y$,
3. each linkage class is a strong linkage class.

Now that we have defined all the necessary tools to study the equilibria and their stability, we can establish the following theorem. It only concerns networks whose deficiency is zero, the existence (or not) of fixed points and their stability.

Theorem 1.1

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network of deficiency zero.

1. If the network is not weakly reversible, then for arbitrary kinetics $\mathcal{K}$, the differential equations of the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K}\}$ can admit neither a positive equilibrium, nor a cycle composition trajectory containing a positive composition.

2. If the network is weakly reversible, then for any mass action kinetics k, the differential equations for the network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ have the following properties:

   - there exists one and only one equilibrium within each positive stoichiometric compatibility class,
   - this equilibrium is asymptotically stable,
   - and it cannot exist a non trivial cyclic composition trajectory.

This theorem is called the **Deficiency Zero Theorem**, and comes from [1, Theorem 3.1]. In fact, there are not lots of deficiency zero reaction networks in real life. Then we would like to find a similar theorem but for other indexes of deficiency. Actually, we can do it if we compute the deficiency of each linkage class L^θ of the diagram, denoted by δ_θ. Let us assume that for each class $\theta = 1, \cdots, l$, we denote by n_θ the number of complexes in this class and by s_θ the dimension of the stoichiometric subspace related to this linkage class. Obviously, we can denote l_θ as the number of linkage classes but we know that this is equal to one. Then, the deficiency of linkage class is

$$\delta_\theta \; = \; n_\theta - (1 + s_\theta).$$

Using this new notion, we can establish another theorem whose name, i.e. **Deficiency One Theorem**, could be unclear and ambiguous because it concerns networks of deficiency bigger than one, but the deficiency of each linkage class is 1 at most.

Theorem 1.2

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with l linkage classes and let δ denote the deficiency of the network and δ_θ the deficiency of each linkage class θ. Let us suppose then that both of the following conditions are satisfied:

1. $\delta_\theta \leq 1 \;\; \forall \theta = 1, \cdots, l$,
2. $\delta = \sum_\theta \delta_\theta$.

If the network is weakly reversible, then for any mass action kinetics k, the differential equations for $\{\mathcal{S}, \mathcal{C}, \mathcal{R}, k\}$ admit precisely one equilibrium in each positive stoichiometric class.

This theorem comes from [1, Theorem 3.2]. Even if both theorems seem really powerful, we usually cannot use them with real reaction networks. We will see in what follows that when the system becomes more complex, it is impossible to use it because the assumptions are not satisfied any more. Let us illustrate both theorems with examples though.

Example 1.5. *Let us consider the example (1.3) that we deal with since the beginning. It is clear to see that there is only one linkage class ($l = 1$) and we have already found that the dimension of the stoichiometric subspace is one ($s = 1$) and there are two complexes ($n = 2$). This allows us to say that this network is of deficiency zero and the previous theorem can be applied because it is also reversible (and then weakly reversible). Whatever the initial condition that we take and consequently, whatever the stoichiometric compatibility class in which we are, there will always be one asymptotically stable equilibrium point. We can even compute the expression of the equilibrium points. Indeed, if we assume that it follows the law of mass action, then the differential equations are equal to zero when $k^+ c_A c_B = k^- c_C$. Given k^+ and k^-, we can find an infinity of equilibria. This is shown in* FIGURE *1.2 where different initial conditions are used and each of them leads to a parallel trajectory to the stoichiometric subspace with a stable equilibrium point. Indeed, if we look at the space of fixed points, we have*

$$\mathcal{P} = \left\{ (c_A, c_B, c_C)^t \in I\!R^3_+ \text{ such that } c_C = \frac{k_+}{k_-} c_A c_B \right\}, \tag{1.14}$$

that is illustrated in FIGURE *1.3. However, we know that each trajectory belongs to a stoichiometric compatability class whose expression is*

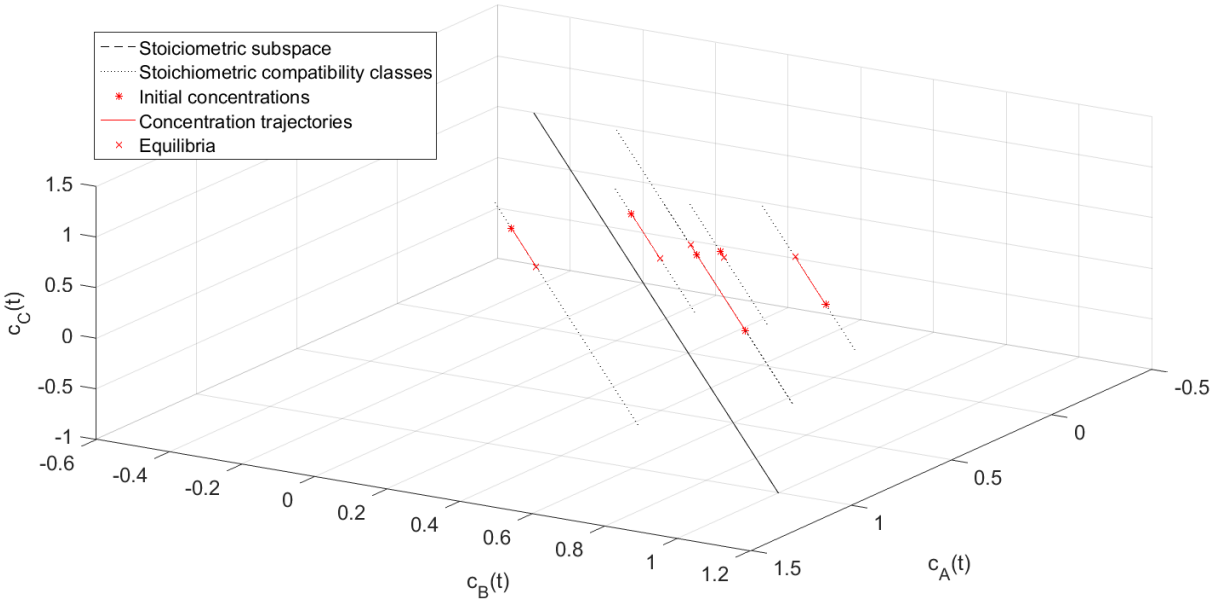


Figure 1.2: Illustration of the Deficiency Zero Theorem

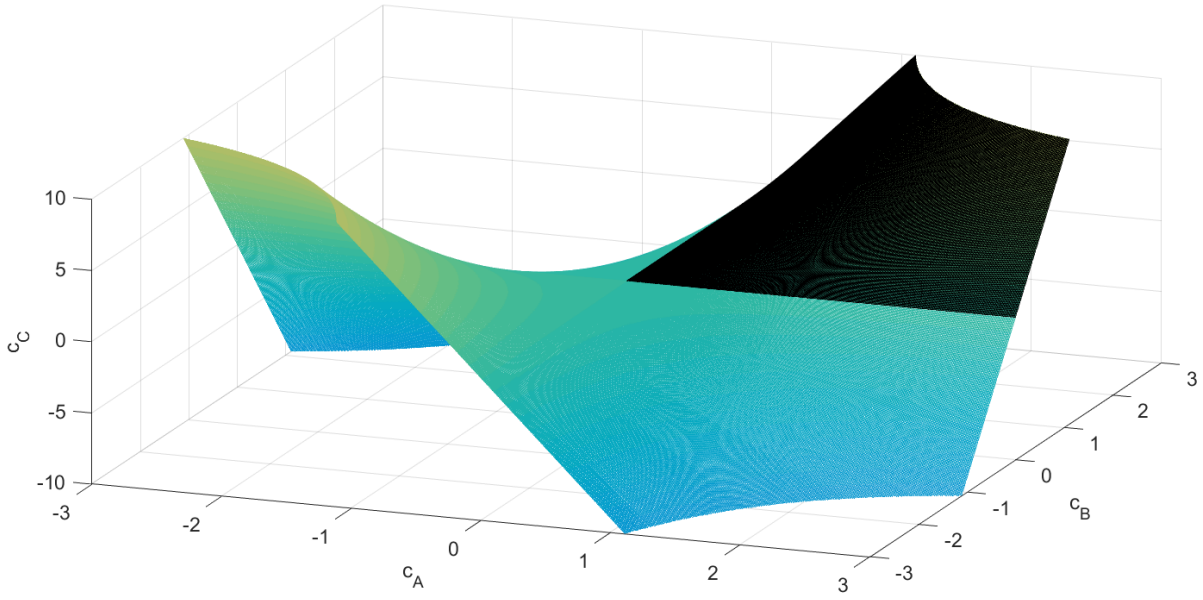
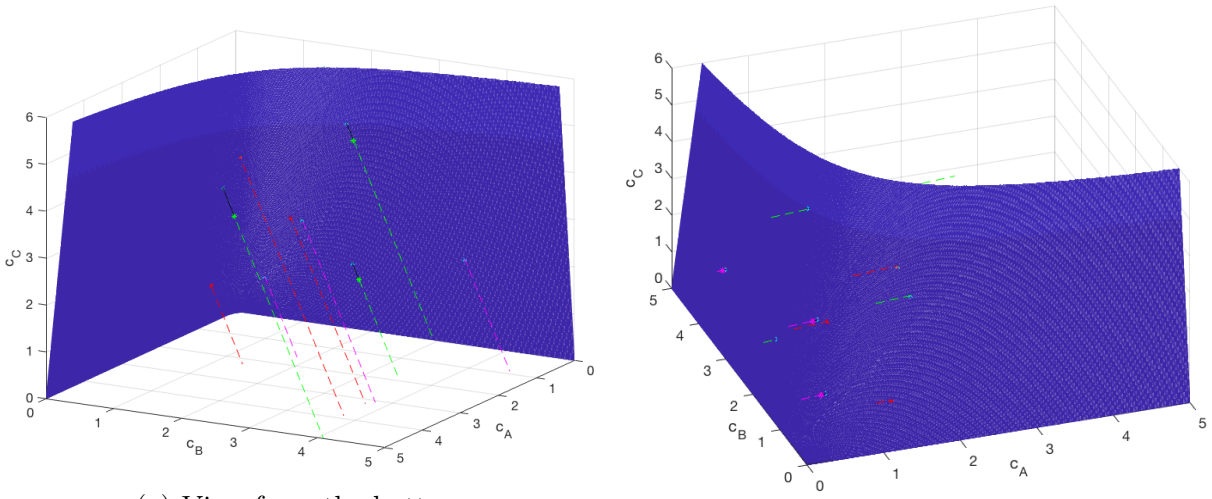


Figure 1.3: Set (1.14) of fixed points in $\mathbb{R}^3$ and the black set is the restriction to $\mathbb{R}^3_+$

$$\begin{aligned} \mathcal{S} &= x_0 + span\{(1,\,1,\,-1)\} \cap I\!R^3_+, \\ &= \{x \;=\; x_0 + \alpha(1,\,1,\,-1) \mid x \geq 0,\; \alpha \in I\!R\}. \end{aligned}$$

Thanks to the Deficiency zero theorem, we expect that the intersection of $\mathcal{S}$ and $\mathcal{P}$ for an initial condition x_0 is 0-dimensional, and then is only one point. This is illustrated in FIGURES *1.4a and 1.4b. We would like to show this result in a formal way. If we want to show that the intersection of these two sets contains one unique point, we have to show that there exists one and only one $\alpha \in I\!R$ such that*



(a) View from the bottom

(b) View from the top

Figure 1.4: Illustration of the unique intersection ($\times$) between the set of fixed points (blue) and some stoichiometric classes (green when $Ka_0b_0 > c_0$, pink when $Ka_0b_0 < c_0$ and red when $Ka_0b_0 = c_0$) for some initial conditions ($*$)

$$\begin{aligned} & c_0 - \alpha &=& K(a_0+\alpha)(b_0+\alpha), \\ \Leftrightarrow\ & c_0 - \alpha &=& K(a_0b_0 + \alpha(a_0+b_0) + \alpha^2), \\ \Leftrightarrow\ & 0 &=& \alpha^2 K + \alpha[K(a_0+b_0)+1] + Ka_0b_0 - c_0, \end{aligned}$$

where K denotes k_+/k_-, and such that $a_0+\alpha$, $b_0+\alpha$ and $c_0-\alpha$ are non-negative. This equation can be solved for α. First of all, we have to be sure that the solutions $\alpha_{1,2}$ will be real, i.e. the discriminant has to be non negative. If we compute it, we have

$$\begin{aligned} \Delta &= [K(a_0+b_0)+1]^2 - 4K(Ka_0b_0 - c_0), \\ &= K^2(a_0+b_0)^2 + 2K(a_0+b_0) + 1 - 4K^2a_0b_0 + 4Kc_0, \\ &= K^2(a_0-b_0)^2 + 2K(a_0+b_0) + 1 + 4Kc_0, \\ &> 0. \end{aligned}$$

So the solutions $\alpha_{1,2}$ are real. Three different cases can be distinguished in function of the sign of the expression $Ka_0b_0 - c_0$.

(i) If the initial condition is already in the space of fixed points (orange case in FIGURE *1.5 and red case in* FIGURE *1.4), this means that $Ka_0b_0 = c_0$. Then, the discriminant becomes*

$$\Delta = [K(a_0+b_0)+1]^2,$$

and the solutions are given by

$$\alpha_{1,2} = \frac{-[K(a_0+b_0)+1] \pm \sqrt{[K(a_0+b_0)+1]^2}}{2K}.$$

In other words, either we have $\alpha_1 = \dfrac{-[K(a_0+b_0)+1]}{K}$, or $\alpha_2 = 0$. This last value of α reminds that the initial condition is in the set of fixed points. Let us show now that α_1 does not work, meaning that there is a unique solution. Indeed, if we compute the first component of the vector x, we have

$$\begin{aligned} x_A &= a_0 + \alpha_1, \\ &= a_0 - \frac{[K(a_0+b_0)+1]}{K}, \\ &= \frac{-(Kb_0+1)}{K}, \\ &< 0. \end{aligned}$$

Since the component is negative, the vector x cannot belong to the stoichiometric compatibility class and then, it does not belong to the intersection with the set of fixed points. We can conclude that if the initial condition already belongs to the set of fixed points, it will be the only point along the trajectory issued from this point. This seems logical since the trajectory will be stable and will not move from the initial condition.

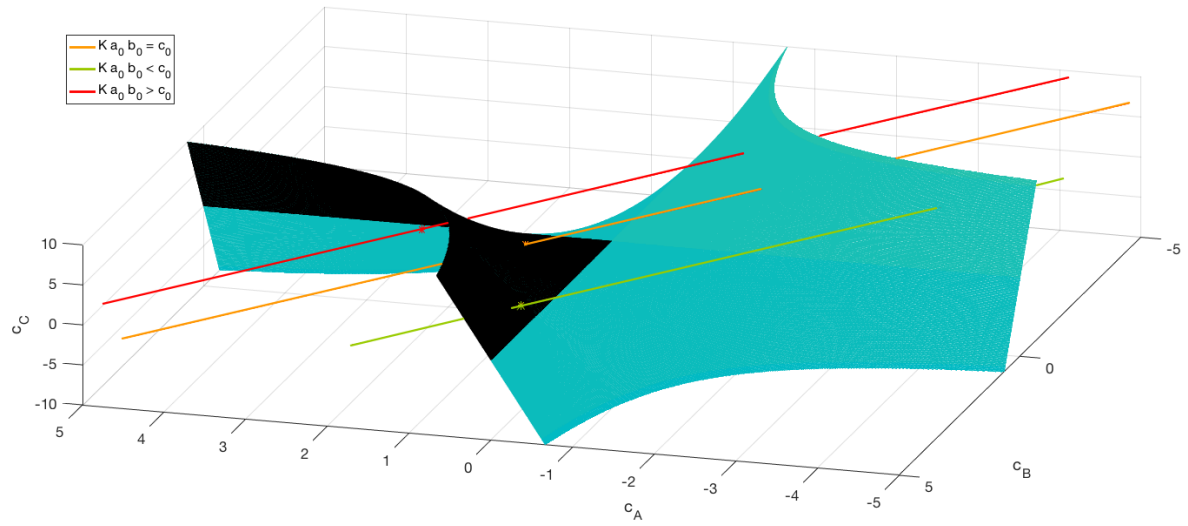


Figure 1.5: Illustration of the intersections between the set of fixed points and the stoichiometric compatibility classes for the three different cases

(ii) If the initial point is over the space of fixed point (green case in FIGURE *1.5 and pink case in* FIGURE *1.4), i.e.* $Ka_0b_0 < c_0$*, then we have that*

$$\begin{aligned} & Ka_0b_0 - c_0 < 0, \\ \Leftrightarrow \quad & -4K(Ka_0b_0 - c_0) > 0, \\ \Leftrightarrow \quad & [K(a_0+b_0)+1]^2 - 4K(Ka_0b_0 - c_0) > [K(a_0+b_0)+1]^2. \end{aligned}$$

By using the monotonicity of the square root function, we can conclude that the square root of the left-hand side is bigger than the square root of the right-hand side. This implies that

$$\begin{aligned} & \alpha_1 < \frac{-[K(a_0+b_0)+1] - \sqrt{[K(a_0+b_0)+1]^2}}{2K}, \\ \Rightarrow \quad & \alpha_1 < -\frac{[K(a_0+b_0)+1]}{K}, \\ \Rightarrow \quad & a_0 + \alpha_1 < a_0 - \frac{[K(a_0+b_0)+1]}{K}, \\ \Leftrightarrow \quad & x_A < -\frac{Kb_0+1}{K}, \\ \Rightarrow \quad & x_A < 0. \end{aligned}$$

This is in contradiction with the stoichiometric compatibility class, since it contains only non-negative components. Then, the first solution α_1 *does not work. What about the second solution* α_2 *? Thanks to the assumption, we know that*

$$\begin{aligned} \alpha_2 &> \frac{-[K(a_0+b_0)+1]+\sqrt{[K(a_0+b_0)+1]^2}}{2K}, \\ \Leftrightarrow \quad \alpha_2 &> 0. \end{aligned}$$

It implies that x_A and x_B are positive, and x_C can only be positive since α_2 has been computed to have the relation

$$\underbrace{c_0-\alpha_2}_{x_C} = K\underbrace{(a_0+\alpha_2)}_{x_A>0}\underbrace{(b_0+\alpha_2)}_{x_B>0}.$$

We have then found one and only one solution for this second case, where $\alpha_2 > 0$. This result seems logical since the initial condition c_0 is bigger than the value Ka_0b_0 obtained at the fixed point. Therefore, α has to be positive in order to reduce the value of x_C.

(iii) Let us finally consider the third and last case, that assumes that $Ka_0b_0 > c_0$ (red case in FIGURE *1.5 and green case in* FIGURE *1.4). In other words, this means that the initial point is under the space of fixed points and that the third component has to increase. This is consistent with the assumption since it implies that both solutions α_1 and α_2 are negative, increasing then the third component of the vector. We know that the solutions α_1 and α_2 are given by*

$$\alpha_{1,2} = -\frac{K(a_0+b_0)+1}{2K} \pm \frac{\sqrt{[K(a_0+b_0)+1]^2-4K(Ka_0b_0-c_0)}}{2K}.$$

Since $K > 0$, we know that α_1 (obtained with the minus) will be smaller than half of the sum of α_1 and α_2. Then, we have

$$\begin{aligned} \alpha_1 &< -\frac{K(a_0+b_0)+1}{2K}, \\ \Rightarrow \quad a_0+\alpha_1 &< a_0-\frac{K(a_0+b_0)+1}{2K}, \\ \Leftrightarrow \quad a &< \frac{K(a_0-b_0)-1}{2K}. \end{aligned}$$

We can do exactly the same thing with b, and we have

$$b < \frac{K(b_0-a_0)-1}{2K}.$$

So one of them will always be negative since either $a_0 < b_0$ or $b_0 < a_0$. This solution is then impossible. However, the solution α_2 will provide a positive solution.

It has been demonstrated that, for each case, there exists one and only one solution. This result is consistent with the Deficiency zero theorem.

As we said before, this theorem cannot be applied to most of the chemical reaction diagrams. Let us take an example to illustrate that statement.

Example 1.6. *Given the following diagram*

$$\begin{array}{ccc} 3\,\mathrm{A} & \xrightarrow{0.1} & \mathrm{A}+2\,\mathrm{B} \\ 1\uparrow & & \downarrow 1 \\ 2\,\mathrm{A}+\mathrm{B} & \xleftarrow{0.1} & 3\,\mathrm{B} \end{array} \tag{1.15}$$

It seems logical that the number of linkage classes is one, i.e. $l = 1$*, and that there are four different complexes:* $3A$*,* $A + 2B$*,* $3B$ *and* $2A + B$*. Finally, the dimension of the stoichiometric subspace is defined by*

$$\begin{aligned} \mathcal{S} &= span\left\{A + 2B - 3A,\ 3B - A - 2B,\ 2A + B - 3B,\ 3A - 2A - B\right\}, \\ &= span\left\{A - B\right\}. \end{aligned}$$

Then, its dimension is one and the deficiency of the system is $4 - 1 - 1 = 2$*. It is then impossible to apply any of both theorems. Instead, let us induce differential equations from it, given by*

$$\begin{aligned} \frac{da}{dt} &= -0.2a^3 - ab^2 + 0.2b^3 + a^2b, \\ &= (a-b)[-0.2a^2 + 0.8ab - 0.2b^2], \\ \frac{db}{dt} &= 0.2a^3 + ab^2 - 0.2b^3 - a^2b, \\ &= (a-b)[0.2a^2 - 0.8ab + 0.2b^2]. \end{aligned}$$

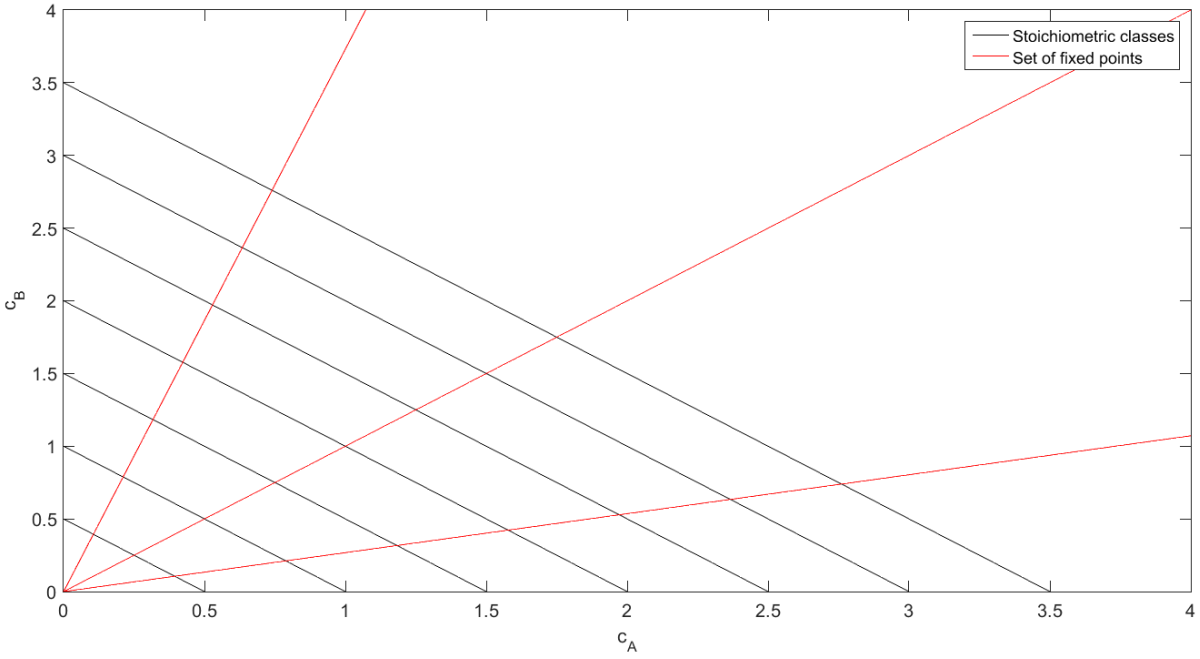


Figure 1.6: Phase space of the diagram (1.15)

We know that trajectories are kept in a 1*-dimensional space, meaning that we cannot have cycles, but only one or several fixed points. After some examples, it seems that in each stoichiometric class, there are several fixed points. If we are looking for the fixed points, we find that*

$$\mathcal{P} \;=\; \{(a,a) \mid a \geq 0\} \cup \{(a, 3.7321a) \mid a \geq 0\} \cup \{(a, 0.2679a) \mid a \geq 0\}.$$

The FIGURE *1.6 displays the set of fixed points. There are definitely three fixed points within a stoichiometric class.*

Chapter 2

Enzymatic reaction

In this section, we will keep on studying the diagram of particular reactions because we will focus on enzymatic reactions, i.e. reactions that are accelerated with a big molecule called an enzyme. Indeed, enzymes lower the free energy of activation of the reaction, but the reaction does not modify the enzyme molecule. The substrate, i.e. the molecule that interacts with the enzyme becomes then the product. This type of reactions have important features. First of all, they are highly specific because an enzyme can usually catalyzes only one reaction thanks to its three-dimensional shape. Then, they are regulated by a complicated set of positive and negative feedback loops. This allows that the activity of enzyme is precisely controlled. Finally, enzymatic reactions are not elementary reactions, i.e. they do not follow the law of mass action in accordance with the real data. In 1913, Michaelis-Menten proposed a two-step process to explain the deviation from the law of mass action. If we denote S for the substrate, E for the enzyme and P for the product, we have

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E}. \tag{2.1}$$

So the enzyme binds the substrate to form a complex denoted by C and then it breaks down into the product P, releasing the enzyme as illustrated in FIGURE 2.1. Let us notice that one reaction is not reversible, but this is explained by the fact that the reverse reaction is very slow. We can use the previous theory to study this reaction network diagram. We can easily see that it contains three complexes ($n = 3$) and only one linkage class ($l = 1$). The stoichiometric subspace, given by

$$\begin{aligned} S &= span\{S + E - C,\ P + E - C\}, \\ &= span\{(1,\ 1,\ -1,\ 0)^t,\ (0,\ 1,\ -1,\ 1)^t\}, \end{aligned}$$

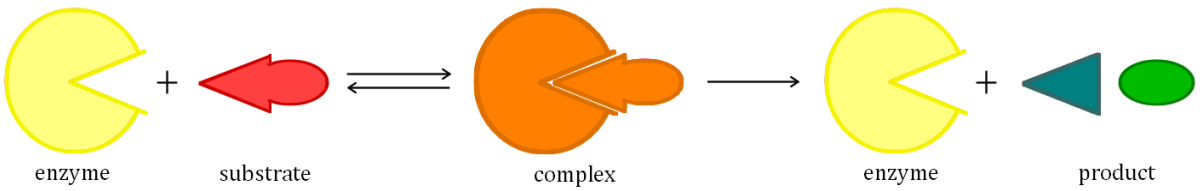


Figure 2.1: Illustration of an enzymatic reaction (2.1)

is two-dimensional. The deficiency is then equal to zero. Unfortunately, the diagram is not weakly reversible, so we can only conclude that the differential equations can admit neither a positive equilibrium (meaning that a species has to disappear) nor a cycle composition trajectory containing a positive composition. Let us then write down the differential equations induced from this enzymatic diagram. We find

$$\frac{ds}{dt} = k_{-1}c - k_1 es, \tag{2.2}$$

$$\frac{de}{dt} = (k_{-1} + k_2)c - k_1 es, \tag{2.3}$$

$$\frac{dc}{dt} = k_1 es - (k_{-1} + k_2)c, \tag{2.4}$$

$$\frac{dp}{dt} = k_2 c. \tag{2.5}$$

With this kind of equations, we will consider that the velocity of the reaction is the rate of production of the product, i.e. the equation (2.5). Let us also notice that a quantity is conserved because

$$\begin{aligned} \frac{d\,(e+c)}{dt} &= \frac{de}{dt} + \frac{dc}{dt}, \\ &= 0. \end{aligned}$$

It implies that $e(t) + c(t)$ is always constant. We will denote this quantity by e_0, the total amount of enzyme. There are two different ways to study these equations: the equilibrium approximation and the quasi-steady-state approximation. Let us describe them in details in the following sections.

2.1 The equilibrium approximation

As the title indicates, this method is an approximation. Hence, it is based on an assumption. According to this assumption, the substrate is instantaneously in equilibrium with the complex, which means that

$$k_1 se \approx k_{-1} c. \tag{2.6}$$

Nevertheless, this relation cannot be a real equality, otherwise any product will not be formed. Actually, this assumption amounts to saying that the product will rather decompose to give back enzyme and substrate, than decompose to form the product, i.e.

$$k_{-1} \gg k_2.$$

Under the initial assumption (2.6), we can isolate and express the concentration of complex c in function of the substrate concentration s and the total amount of enzyme e_0. The velocity of the reaction can then be expressed by

$$V = \frac{V_{max} s}{K_1 + s},$$

where $V_{max} = k_2 e_0$, as this is the maximal reaction velocity reached when all the enzyme is complexed with the substrate. When the substrate concentration is low, then the reaction rate is more or less linear (as a function of total amount of enzyme e_0). On the contrary, when the substrate concentration becomes higher, the reaction velocity saturates to V_{max}. The velocity is then limited by the total amount of enzyme and the rate constant of formation of product. The K_1 value can give an idea of the efficiency of an enzyme molecule, because at this value the velocity is half of its maximum. Then, if K_1 is small, we have an efficient enzyme, otherwise the enzyme is much less efficient while K_1 is high.

According to the initial assumption behind this approximation, k_{-1} is much bigger than k_2. It would be therefore interesting to see the evolution of the accuracy of the approximation while this assumption is wrong. We can see the results in FIGURE 2.2 where k_2 is 0.1 and k_{-1} goes from 0.1 to 100. The result seems quite strange because when the rate constant k_{-1} is smaller than 100, the error is always the same for high substrate concentrations, but as far as small concentrations are concerned, the bigger k_{-1} is, the smaller the error is. Then, this behaviour changes when $k_{-1} = 100$ as the error is smaller and it gets bigger when substrate concentration increases.

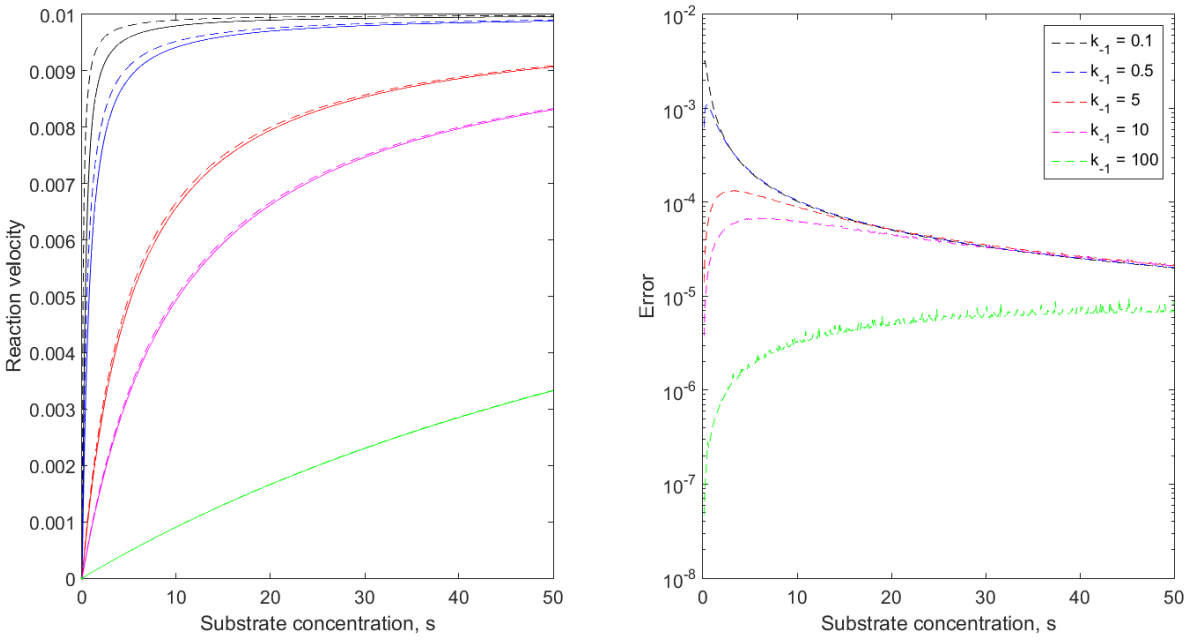


Figure 2.2: Illustration of equilibrium approximation with $k_1 = 1$, $k_2 = 0.2$, $e_0 = 0.1$

2.2 The quasi-steady-state approximation

Even if the initial assumption behind this method differs completely from the previous one, a similar expression for the reaction velocity will be found. Indeed, the purpose of this method is to use dimensionless variables[1] to show that some reactions are faster than the other ones, which allows then to consider that the concentration is constant. In practice, let us consider the following dimensionless variables σ and x defined by

$$\sigma = \frac{s}{s_0} \qquad \text{and} \qquad x = \frac{c}{e_0},$$

and we also define some parameters : $\tau = k_1 e_0 t$, $K = \dfrac{k_{-1}+k_2}{k_1 s_0}$, $\varepsilon = \dfrac{e_0}{s_0}$ and $\alpha = \dfrac{k_{-1}}{k_1 s_0}$. Two differential equations are obtained:

$$\frac{d\sigma}{d\tau} = -\sigma + x(\sigma + \alpha), \tag{2.7}$$

$$\varepsilon\frac{dx}{d\tau} = \sigma - x(\sigma + K). \tag{2.8}$$

As you can see, in the equation (2.8), the derivative of x is multiplied by the parameter ε. However this parameter is assumed to be really small because one of the features of an enzyme, is that the amount of enzyme needed in a reaction is much lower than the amount of substrate. Then, under this assumption, we can suppose that the reaction (2.8) is really fast and equilibrates rapidly. The quasi-steady-state approximation assumes that

$$\varepsilon\frac{dx}{d\tau} \approx 0,$$

and that amounts to saying that $\dfrac{dc}{dt} \approx 0$. Actually, this assumption can be justified by introducing asymptotic expansion of the solution and keeping the lowest order.

Under the quasi-steady-state assumption, the complex concentration can be expressed as a function of the other ones, and finally express the reaction velocity as

$$V = \frac{V_{max} s}{s + K_m}, \tag{2.9}$$

where $K_m = \dfrac{k_{-1}+k_2}{k_1}$ plays the same role as K_1 in the equilibrium approximation, and allows us to describe the efficiency of an enzyme. As we have announced before, we can clearly see the similarity between both expressions of velocity but let us keep in mind that they come from different assumptions. Though, it seems logical that we obtain similar results, but we can notice that it would not have been the case if we had assumed that the reaction was reversible. As we did with the equilibrium approximation, we can study this approximation when the initial assumption is wrong. As illustrated with FIGURE 2.3, it is clear that when the enzyme concentration becomes higher, the approximation is wrong with sometimes an error of the order of 10^1. However it is logical that at low substrate concentration, the error seems bigger since the ratio ε is bigger.

[1] See the appendix of the first chapter of [7] for more information about some methods to find out these dimensionless variables.

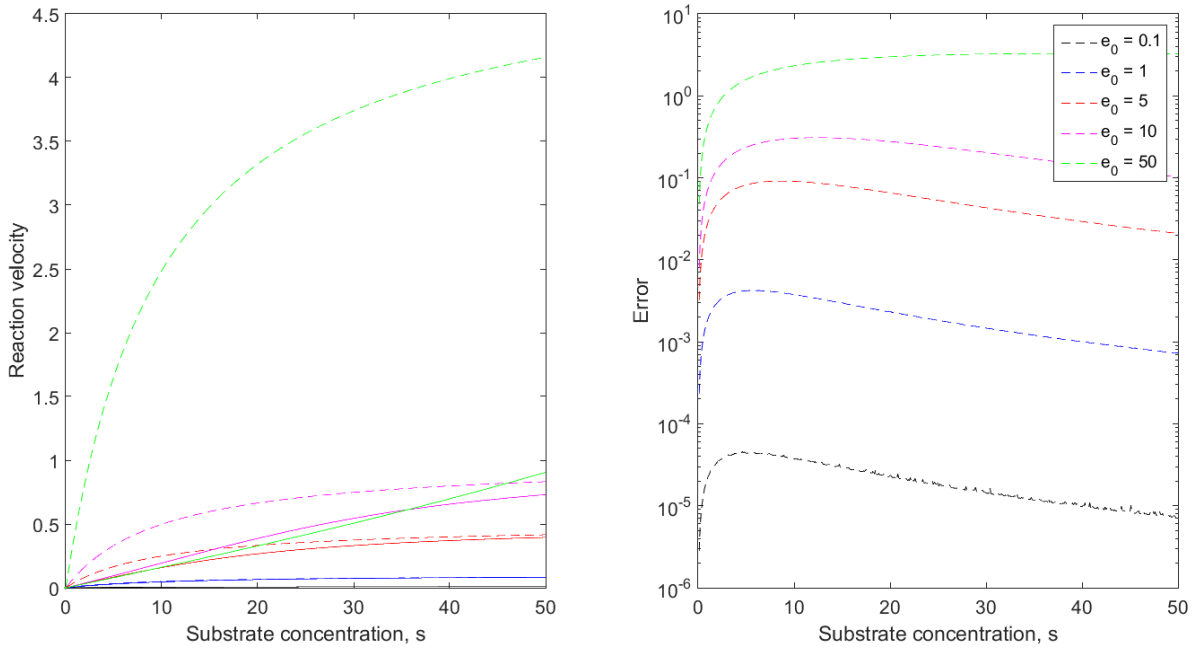


Figure 2.3: Illustration of quasi-steady-state approximation with $k_1 = 1$, $k_{-1} = 10$ and $k_2 = 0.1$

2.3 Enzyme inhibition

Sometimes, the activity of an enzyme can be stopped or reduced with some substances called inhibitors. This inhibition is crucial because it enables to regulate the enzymes.

Definition 2.1

An **enzymatic inhibitor** is a substance that inhibits the catalytic action of the enzyme by binding the enzyme.

There exists a lot of different types of enzymatic inhibitors, but we will only focus on two of them: the competitive inhibitor and the allosteric inhibitor. Before anything else, we have to keep in mind that enzyme molecules are most of the time larger proteins than the substrate molecules and that an enzyme catalyzes a single reaction of substrate with similar structure. Moreover it is noteworthy that an enzyme contains different sites: the active site where the substrate molecule can bind, and other sites called allosteric sites (or regulatory sites) for other bindings.

2.3.1 Competitive inhibitors

Since the enzymatic reaction is a three-dimensional system, if another molecule with a similar shape binds the enzyme molecule, then it prevents the substrate from binding the enzyme. This can be modeled by the following diagram, illustrated in FIGURE 2.4:

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} \mathrm{C_1} \xrightarrow{\mathrm{k_2}} \mathrm{P} + \mathrm{E}.$$

$$\mathrm{E} + \mathrm{I} \underset{\mathrm{k_{-3}}}{\overset{\mathrm{k_3}}{\rightleftharpoons}} \mathrm{C_2}.$$

As we did with the simplest enzymatic reaction, we can study this diagram with using the previous theory. Obviously, the number of linkage classes is two ($l = 2$) and there are five complexes in the diagram ($n = 5$). The dimension of the stoichiometric subspace is three because it corresponds to the linear subspace built on three linear independent vectors:

$$\begin{aligned} S &= span\{S + E - C_1,\ P + E - C_1,\ E + I - C_2\}, \\ &= span\{(1,\ 1,\ -1,\ 0,\ 0,\ 0)^t,\ (0,\ 1,\ -1,\ 0,\ 0,\ 1)^t,\ (1,\ 0,\ 0,\ -1,\ 1,\ 0)^t\}. \end{aligned}$$

Therefore the deficiency of the diagram is zero but it is not weakly reversible. The same conclusion can be made as for the previous diagram. Under the assumption of the law of mass action, differential equations can be written down, given by

$$\frac{ds}{dt} = k_{-1}c_1 - k_1 se, \tag{2.10}$$

$$\frac{de}{dt} = k_{-1}c_1 - k_1 se - k_3 ei + k_{-3}c_2 + k_2 c_1, \tag{2.11}$$

$$\frac{dc_1}{dt} = k_1 se - (k_{-1} + k_2)c_1, \tag{2.12}$$

$$\frac{dc_2}{dt} = k_3 ei - k_{-3}c_2, \tag{2.13}$$

$$\frac{di}{dt} = k_{-3}c_2 - k_3 ei, \tag{2.14}$$

$$\frac{dp}{dt} = k_2 c_1. \tag{2.15}$$

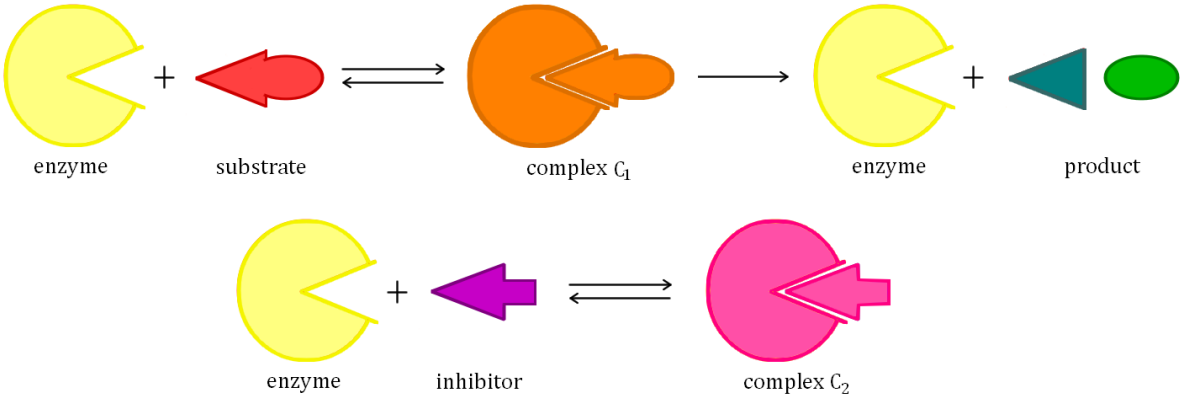


Figure 2.4: Illustration of competitive inhibition

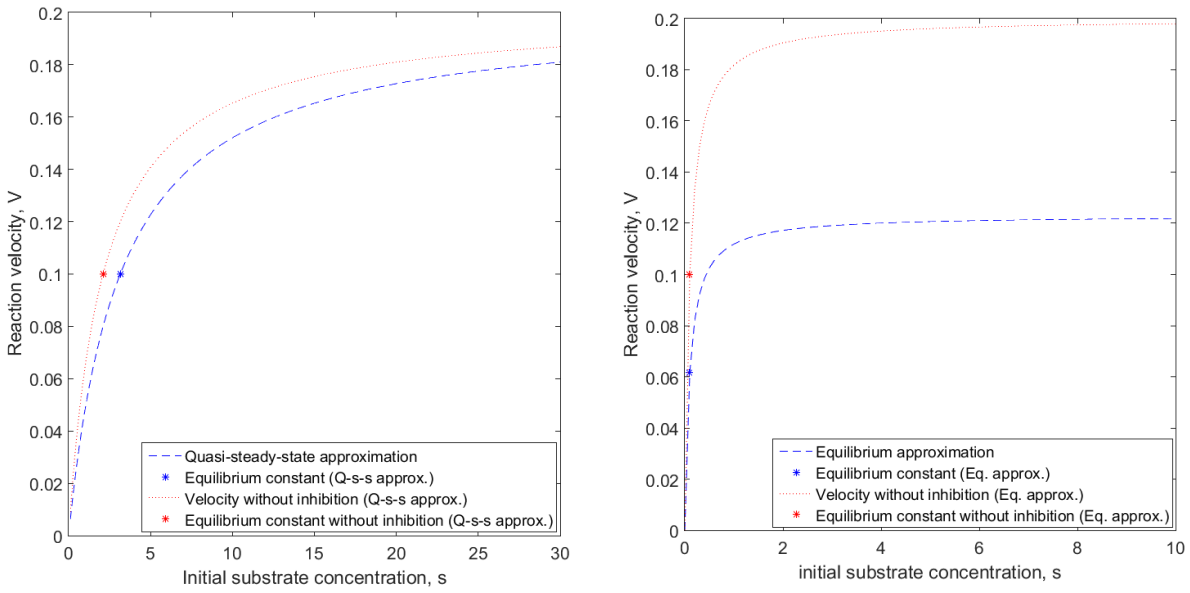
If we add the derivatives of the concentrations of enzyme e and complexes c_1 and c_2, we will have zero. It means that the total amount of enzyme is always constant over time; this quantity will be denoted by e_0. We can use one of the two approximations that we have developed before. Let us take for example the quasi-steady-state approximation. It states that the derivative of complexes can be approximated by zero, so if we solve both equations for c_1 and c_2, we will find

$$\begin{aligned} c_1 &= \frac{K_i e_0 s}{K_m i + K_i s + K_m K_i}, \\ c_2 &= \frac{K_m e_0 i}{K_m i + K_i s + K_m K_i}, \end{aligned}$$

where $K_m = \dfrac{k_{-1} + k_2}{k_1}$ and $K_i = \dfrac{k_{-3}}{k_3}$. Then, the velocity of the reaction is given by

$$V = \frac{V_{max} s}{s + K_m(1 + i/K_i)}, \tag{2.16}$$

with $V_{max} = k_2 e_0$. If we compare this expression to the reaction velocity (2.9) without inhibition, we can see that the introduction of inhibition increases the index of efficiency of the enzyme because the equilibrium constant is now $K_m(1+i/K_i)$ compared to K_m before. The velocity decreases but the maximum velocity remains unchanged, as illustrated in FIGURE 2.5a. It also seems logical that the more the inhibitor works i.e. the bigger k_3 is and therefore the smaller K_i is, the more the velocity decreases since $(1+i/K_i)$ increases.



(a) Competitive inhibitor

(b) Allosteric inhibitor

Figure 2.5: Illustration of reaction velocity with inhibition

2.3.2 Allosteric inhibitors

Beside the active site binding the substrate molecules, it is noteworthy that an enzyme displays several other sites capable of binding different molecules. These bindings can affect the activity of the enzyme (increasing or reducing the enzymatic activity). These binding sites are called allosteric sites or regulatory sites because they allow the regulation of the enzyme.

Definition 2.2

An **effector** (or modifier) is the ligand that binds the allosteric site. If it increases the activity of the enzyme, it is called **allosteric activator**. If it decreases the activity of the enzyme, it is called **allosteric inhibitor**.

The allosteric change is linked to a conformational change of the molecule. This is illustrated in FIGURE 2.6: the allosteric inhibitor will modify the three-dimensional shape of the enzyme molecule, which will prevent it from binding a substrate molecule for example, or will reduce its activity. This behaviour can be modelled by assuming that there exist four possible binding states: the enzyme on its own denoted by E, the enzyme with the inhibitor denoted by Y, the enzyme with a substrate molecule denoted by X and finally the enzyme with both molecules denoted by Z. It seems logical that, to go from one state to another, the enzyme molecule has to bind either the inhibitor or the substrate. The diagram is then

$$\mathrm{E} + \mathrm{S} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{X} \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E}.$$

$$\mathrm{E} + \mathrm{I} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{Y}.$$

$$\mathrm{X} + \mathrm{I} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{Z}.$$

$$\mathrm{Y} + \mathrm{S} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{Z}.$$

If we use the equilibrium approximation, and we assume that each of the four transitions is at equilibrium, we have

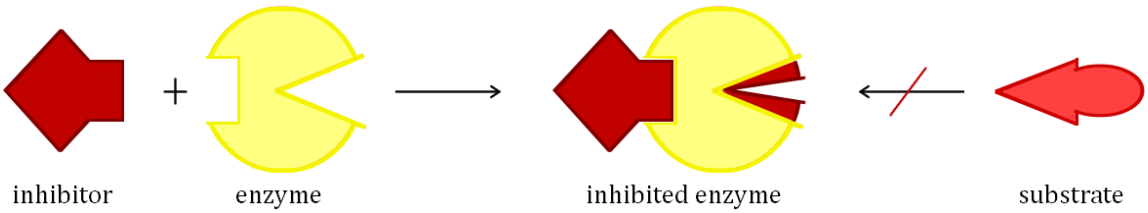


Figure 2.6: Illustration of allosteric inhibition

$$\begin{aligned}(e_0 - x - y - z)s - K_s x &= 0,\\ (e_0 - x - y - z)i - K_i y &= 0,\\ ys - K_s z &= 0,\\ xi - K_i z &= 0,\end{aligned}$$

where $K_s = k_{-1}/k_1$, $K_i = k_{-3}/k_3$ and $e_0 = e + z + y + z$ is the constant total amount of enzyme that we can easily demonstrate using the differential equations, as we did before. These four equations can be rewritten as a linear system of rank three, and we can therefore express x as a function of i and s

$$x = \frac{e_0 K_i}{i + K_i}\frac{s}{K_s + s}.$$

Finally, the reaction velocity is given by the following formula

$$V = \frac{V_{max}}{1 + i/K_i}\frac{s}{K_s + s}, \tag{2.17}$$

where $V_{max} = k_2 e_0$. Thanks to the allosteric inhibition, we can see that the maximal reaction velocity decreases but the equilibrium constant remains unchanged as illustrated in FIGURE 2.5b.

We could have studied the diagram of the allosteric inhibitors with the theory of chemical reaction networks. In this case, the number of linkage classes is four, as it is easily shown, and there are eight complexes in the diagram. Then, we can find the dimension of the stoichiometric subspace, defined by

$$\begin{aligned}S &= span\{E + S - X, , E + P - X, E + I - Y, Y + S - Z, X + I - Z\},\\ &= span\{E + S - X, , E + P - X, Y + S - Z, X + I - Z\},\\ &= span\{(1, 1, 0, -1, 0, 0, 0)^t, (0, 1, 0, -1, 0, 0, 1)^t, (1, 0, 0, 0, 1, -1, 0)^t,\\ &\quad (0, 0, 1, 1, 0, -1, 0)^t\}.\end{aligned}$$

The dimension is then four. The system is of zero deficiency because $\delta = n - (l + s)$, but it is not weakly reversible.

2.4 Cooperativity

The theory that we have developed so far cannot explain some behaviours like the shape of the reaction velocity. Actually, in real experimentations, the curve is not a simple hyperbolic curve but often has a sigmoidal character. This can be explained via cooperative effects though.

Definition 2.3

We talk about **cooperative effects** when an enzyme can bind more than one substrate molecule, and the binding of one substrate affects the binding of the subsequent(s).

We can illustrate this concept with an enzyme with two active sites, i.e. the enzyme can bind two substrate molecules. Then, the diagram looks like

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} \mathrm{C_1} \xrightarrow{\mathrm{k_2}} \mathrm{P} + \mathrm{E}$$

$$\mathrm{S} + \mathrm{C_1} \underset{\mathrm{k_{-3}}}{\overset{\mathrm{k_3}}{\rightleftharpoons}} \mathrm{C_2} \xrightarrow{\mathrm{k_4}} \mathrm{P} + \mathrm{C_1}$$

where E denotes the enzyme without any binding, C_1 denotes the complex of enzyme bound at one substrate molecule and C_2 the complex with two substrate molecules. The value of rate constants can express positive cooperativity or negative cooperativity as well. Before anything else, let us study this diagram. We can clearly identify two linkage classes, so $l = 2$, and six different complexes, hence $n = 6$. Finally, we can compute the dimension of the stoichiometric subspace described by

$$\begin{aligned} S &= span\left\{S + E - C_1,\, P + E - C_1,\, S + C_1 - C_2,\, P + C_1 - C_2\right\}, \\ &= span\left\{S + E - C_1,\, P + E - C_1,\, S + C_1 - C_2\right\}, \\ &= span\left\{(1,\, 1,\, -1,\, 0,\, 0)^t,\, (0,\, 1,\, -1,\, 0,\, 1)^t,\, (1,\, 0,\, 1,\, -1,\, 0)^t\right\}. \end{aligned}$$

The dimension of this subspace is then three, and the deficiency is one but unfortunately, the diagram is not weakly reversible. Thanks to the assumption of the law of mass action, we can write down the differential equations

$$\frac{ds}{dt} = k_{-1}c_1 - k_1 se - k_3 sc_1 + k_{-3}c_2, \tag{2.18}$$

$$\frac{de}{dt} = (k_{-1} + k_2)c_1 - k_1 se, \tag{2.19}$$

$$\frac{dc_1}{dt} = k_1 se - (k_{-1} + k_2)c_1 - k_3 sc_1 + (k_{-3} + k_4)c_2, \tag{2.20}$$

$$\frac{dc_2}{dt} = k_3 sc_1 - (k_{-3} + k_4)c_2, \tag{2.21}$$

$$\frac{dp}{dt} = k_2 c_1 + k_4 c_2. \tag{2.22}$$

As always, the total amount of enzyme is constant, and we denote this quantity by e_0. We can use for example the quasi-steady-state approximation, and then find

$$c_1 = \frac{K_2 e_0 s}{K_1 K_2 + K_2 s + s^2},$$
$$c_2 = \frac{e_0 s^2}{K_1 K_2 + K_2 s + s^2},$$

where $K_1 = \frac{k_{-1} + k_2}{k_1}$ and $K_2 = \frac{k_4 + k_{-3}}{k_3}$. Then, the reaction velocity can be expressed as a function of the substrate concentration s and the total amount of enzyme e_0

$$V = \frac{(k_2 K_2 + k_4 s) e_0 s}{K_1 K_2 + K_2 s + s^2}. \tag{2.23}$$

As announced before, the values of the rate constants can change the cooperative effects. Let us consider three different particular cases. First of all, we can assume that the binding sites act **independently** and **identically**. In terms of rate constants, this be can expressed by the following relations between constants

$$k_1 = 2k_3 \underset{not}{:=} 2k^+ \quad \text{and} \quad k_{-3} = 2k_{-1} \underset{not}{:=} 2k^-,$$

and $2k_2 = k_4$. Then, the reaction velocity can be rewritten as

$$V = 2\left(\frac{V_{max} s}{K + s}\right),$$

where $K = \frac{k^- + k_2}{k^+}$. So we find back the double of reaction velocity (2.3, page 25) without any inhibition, since this behaviour is the behaviour of two binding sites. Secondly, we

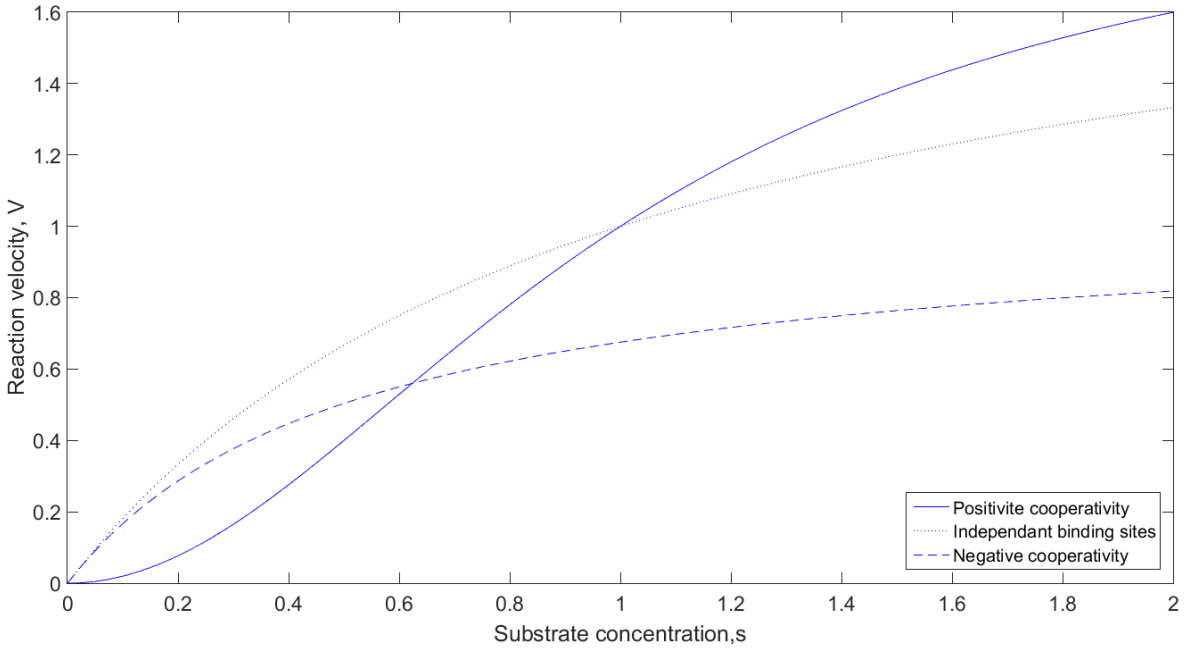


Figure 2.7: Illustration of independence, positive and negative cooperativity

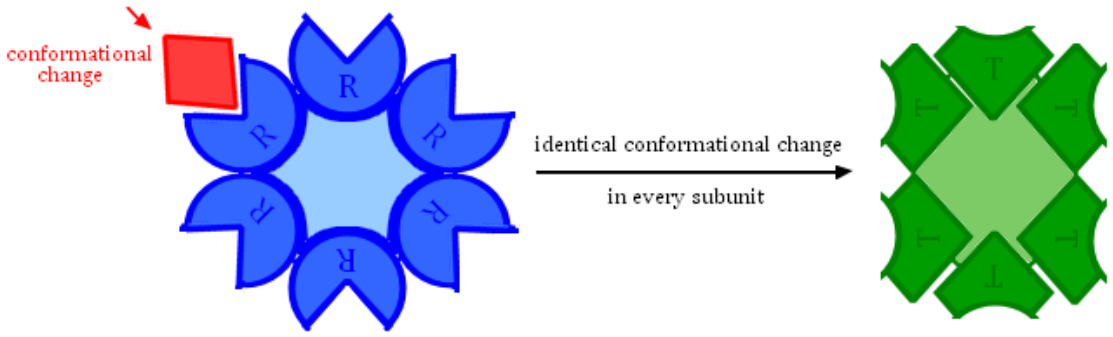


Figure 2.8: Illustration of the conformational changes

can talk about (large) **positive cooperativity**. This means that the binding of the first substrate molecule is slow, but enables the second binding to occur rapidly. In terms of rate constants, this is modelled by the following rules: $k_3 \to \infty$, $k_1 \to 0$ but the product $k_1 k_3$ is constant. This is equivalent to $K_2 \to 0$, $K_1 \to \infty$ and $K_1 K_2$ is constant. Then, the reaction velocity is given by

$$V = \frac{V_{max} s^2}{K_m^2 2 + s^2},$$

where $K_m^2 = K_1 K_2$ and $V_{max} = k_4 e_0$. **Negative cooperativity** can also be expressed by decreasing the value of k_1, and increasing the value of k_3. If we plot the graph of the velocity for each of these three different cases, as we did in FIGURE 2.7, we can see that positive cooperativity can explain the sigmoidal behaviour of this curve.

Some models can explain these cooperative effects. Let us introduce one of them: the **Monod-Wyman-Changeux** model. This model makes some assumptions. The first one concerns the shape of the molecule: it is assumed that cooperative proteins are composed of several identical reacting units called subunits and each of them contains one binding site. Then, the overall protein has two different conformational states denoted by R and T, which differ in their ability to bind ligands. Finally, the individual change impacts the overall change, as illustrated in FIGURE 2.8. This means that if the binding of a ligand to one subunit induces a conformational change in that subunit, then an identical conformational change is induced in every subunit of the protein. In practice, cooperative effects are obtained by the difference between the binding affinity of R and T conformation.

Chapter 3

Glycolysis and glycolic oscillations

We would like to use chemical reaction networks theory to explain and understand some chemical systems and metabolism. This chapter is mainly based on James Sneyd and James Keener's book *Mathematical Physiology 1: Cellular Physiology* [7].

3.1 The glycolysis

First and foremost, let us give a precise definition of the word "metabolism".

Definition 3.1

A **metabolism** is the process of extracting useful energy from chemical bonds.

In other words, the metabolism is the way that human beings stay alive and grow. Actually, it occurs thanks to metabolic pathways.

Definition 3.2

A **metabolic pathway** is the sequence of enzymatic reactions that take place in order to transfer chemical energy from one form to another.

One of the common carriers of energy in the cell is the chemical adenosine triphosphate (ATP) and glycolysis is the source of the production of ATP. Indeed, the hydrolysis[1] of ATP in chemical adenosine diphosphate (ADP) releases a large amount of energy, while the phosphorylation (the process of adding an inorganic phosphate group) of ADP to ATP requires a considerable amount of energy. In practice, the energy is made available to the cell by the oxidation of glucose to carbon dioxide and water, with a net release of energy ($\Delta_\theta = -2878.41$ kJ/mol). The diagram is

$$\mathrm{C_6H_{12}O_6} + 6\,\mathrm{O_2} \longrightarrow 6\,\mathrm{CO_2} + 6\,\mathrm{H_2O} + \text{energy}.$$

Obviously, this reaction is not elementary but it takes place in a series of enzymatic reactions where glycolysis plays a role. In this report, we will only focus on the first three steps of this metabolism, illustrated in FIGURE 3.1. At the beginning, glucose

[1] The hydrolysis is any chemical reaction in which a molecule of water ruptures one or more chemical bonds [12]

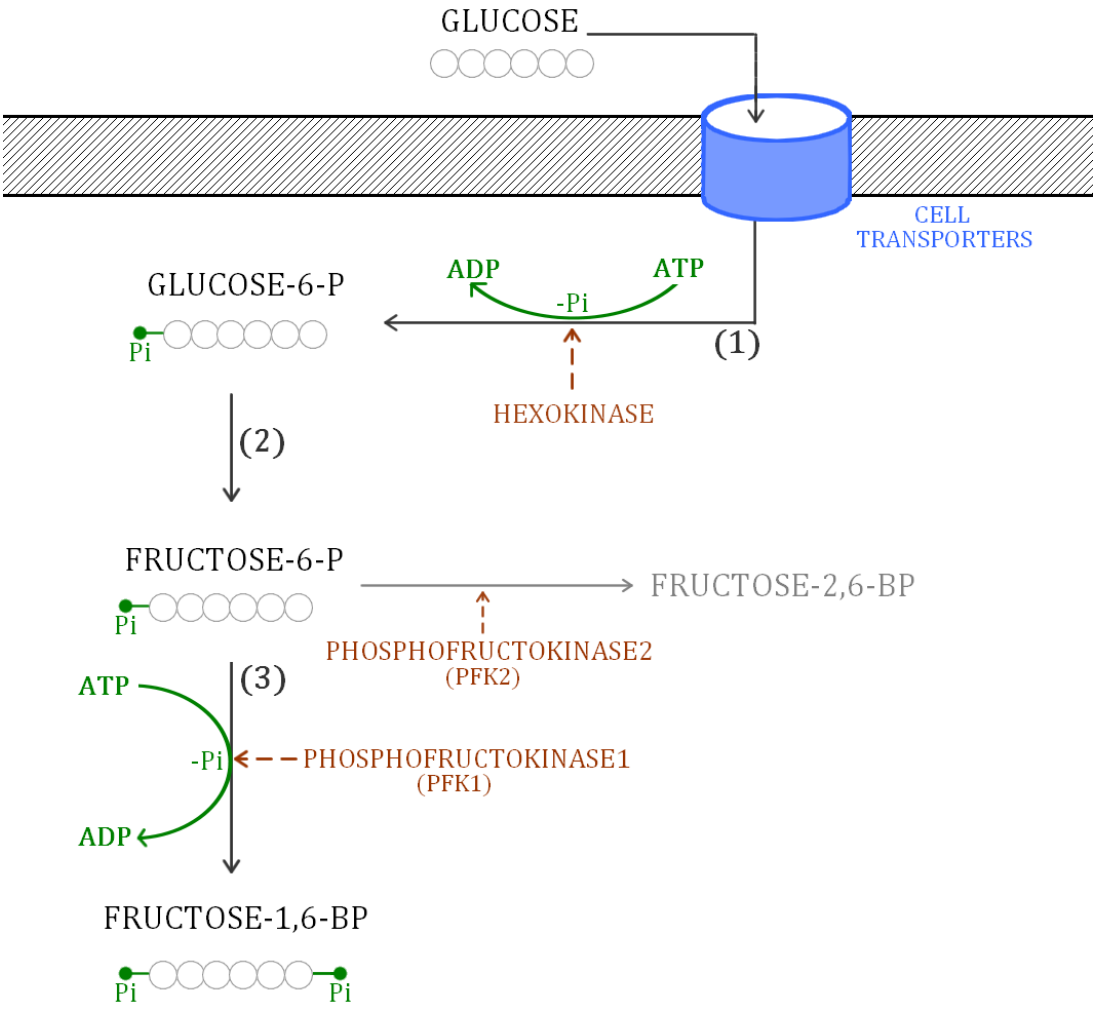


Figure 3.1: Illustration of the first three steps of glycolysis

molecules are outside the cell, and cannot enter by their own: they need transporters. The problem is that transporters can make glucose enter the cell, and can make it go out of the cell as well. It is then necessary to add something on glucose to prevent it from crossing the cell membrane. So, the first step of glycolysis is the **phosphorylation of glucose into glucose-6-phosphate**. This step consists in adding a molecule of phosphate on glucose. This molecule would have come from the release of the hydrolysis of ATP to ADP. This reaction releases a lot of energy which allows the attachment of phosphate onto glucose in order to form the glucose-6-phosphate. Moreover, this reaction is accelerated by a particular enzyme called hexokinase. The second step only consists in an **isomerization of glucose-6-phosphate to fructose-6-phosphate**, i.e. the atoms remain exactly the same, but their arrangement as well as their properties are altered. This new molecule can convert into another molecule called fructose-2,6-bisphosphate and this conversion is accelerated by the enzyme phosphofructokinase 2 (PFK2). The third step of glycolysis is similar to the first one since it consists in the **phosphorylation of fructose-6-phosphate to fructose-1,6-bisphosphate**. A phosphate molecule that results from the hydrolysis of ATP to ADP is added to the fructose-6-phosphate. This reaction is accelerated by the phosphofructokinase 1 (PFK1) enzyme, which is an allosteric enzyme because it is allosterically inhibited by ATP (that is also a substrate) and this

inhibition is removed by AMP (adenosine monophosphate). Then, the activity of PFK1 increases as the ratio of ATP to AMP decreases. In practice, if ATP levels fall, then PFK1 activity increases and thus the production of ATP increases as well. Otherwise, if ATP levels become high, the PFK1 activity decreases and the production of ATP is shut down. There exist other feedback loops. Let us give two examples, a positive one and a negative one. We know that the PFK1 enzyme phosphorylates fructope-6-P while ATP converts to ADP at the same time. Then, ADP converts back to ATP and ADP (adenosine monophosphate) via the reaction

$$2\,\mathrm{ADP} \rightleftharpoons \mathrm{ATP} + \mathrm{AMP}.$$

This reaction increases the activity of the PFK1 enzyme because it decreases the ATP/ADP ratio. We also know that the molecule of fructose-2,6-BP, formed from fructose-6-P thanks to the PFK2 enzyme, increases the activity of PFK1. Then, if the activity of PFK1 falls down, the level of fructose-6-P rises. Obviously, the same happens with fructose-2,6-BP, which increases the activity of PFK1.

Real experimentations and data have shown that under some conditions, the rate of glycolysis is sometimes oscillatory and even chaotic. The purpose is then the understanding of this oscillatory behaviour and the building of a model in accordance with real data. In the following pages, we will focus on two models: the Sel'kov model and its improvement, the Goldbeter-Lefever model.

3.2 Sel'kov scheme

In 1968, Sel'kov established a model, which Goldbeter and Lefever modified/improved in 1972. This model makes some assumptions and only considers the positive feedback that we have described above. However, the conversion of ADP to AMP and ATP is ignored and it is assumed that ADP activates directly the enzyme. Finally, in this model, PFK1 remains inactive as long as it is unbounded, but the binding with some ADP molecules activates it. The related reaction is given by

$$\gamma \mathrm{S}_2 + \mathrm{E} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{ES}_2{}^{\gamma}.$$

where E denotes the PFK1 enzyme, S_2 refers to ADP molecule and γ is the number of ADP molecules needed to activate the enzyme. Then, ATP, that is denoted by S_1, can bind the activated form of PFK1 to product ADP. This is modelled by

$$\mathrm{S}_1 + \mathrm{ES}_2^{\gamma} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\leftrightarrows}} \mathrm{S}_1\mathrm{ES}_2^{\gamma} \xrightarrow{\mathrm{k}_2} \mathrm{ES}_2^{\gamma} + \mathrm{S}_2.$$

Finally, as it is commonly assumed, there is a steady supply rate of ATP and ADP is irreversibly removed from reaction. In terms of diagram, we have

$$\begin{aligned} &\xrightarrow{\nu_1} \mathrm{S}_1, \\ \mathrm{S}_2 &\xrightarrow{\nu_2} \quad . \end{aligned}$$

By applying the law of mass action, we can easily write down the differential equations

$$\frac{ds_1}{dt} = \nu_1 - k_1 s_1 x_1 + k_{-1} x_2, \tag{3.1}$$

$$\frac{ds_2}{dt} = k_2 x_2 - \gamma k_3 {s_2}^{\gamma} e + \gamma k_{-3} x_1 - \nu_2 s_2, \tag{3.2}$$

$$\frac{de}{dt} = k_{-3} x_1 - k_3 {s_2}^{\gamma} e, \tag{3.3}$$

$$\frac{dx_1}{dt} = (k_{-1} + k_2) x_2 + k_3 {s_2}^{\gamma} e - k_1 s_1 x_1 - k_{-3} x_1, \tag{3.4}$$

$$\frac{dx_2}{dt} = k_1 s_1 x_1 - (k_{-1} + k_2) x_2, \tag{3.5}$$

with $x_1 = [ES_2^{\gamma}]$ and $x_2 = [S_1 ES_2^{\gamma}]$. If we add the differential equations (3.3), (3.4) and (3.5) related to the concentration of enzyme, we will obtain zero. Then, the quantity $e + x_1 + x_2$ is constant and denoted by e_0. In order to study this system, we would like to use the quasi-steady-state approximation. Let us then introduce dimensionless variables:

$$\sigma_1 = \frac{k_1 s_1}{k_2 + k_{-1}}, \qquad \sigma_2 = \left(\frac{k_3}{k_{-3}}\right)^{1/\gamma} s_2,$$

$$u_1 = \frac{x_1}{e_0}, \qquad u_2 = \frac{x_2}{e_0}, \qquad t = \frac{k_2 + k_{-1}}{e_0 k_1 k_2}\tau.$$

Then, the equations (3.1), (3.2), (3.4) and (3.5) can be rewritten with these new variables, and we get

$$\frac{d\sigma_1}{d\tau} = \nu - \frac{k_{-1} + k_2}{k_2} u_1 \sigma_1 - \frac{k_{-1}}{k_2} u_2, \tag{3.6}$$

$$\frac{d\sigma_2}{d\tau} = \alpha \left(u_2 - \sigma_1 u_1 - \gamma \frac{k_{-3}}{k_2} {\sigma_2}^{\gamma} (1 - u_1 - u_2) + \gamma \frac{k_{-3}}{k_2} u_1 \right) - \eta \sigma_2, \tag{3.7}$$

$$\varepsilon \frac{du_1}{d\tau} = u_2 - \sigma_1 u_1 + \frac{k_{-3}}{k_2 + k_{-1}} [{\sigma_2}^{\gamma} (1 - u_1 - u_2) - u_1], \tag{3.8}$$

$$\varepsilon \frac{du_2}{d\tau} = \sigma_1 u_1 - u_2, \tag{3.9}$$

where $\varepsilon = \dfrac{e_0 k_1 k_2}{(k_2 + k_{-1})^2}$, $\nu = \dfrac{\nu_1}{k_2 e_0}$, $\eta = \dfrac{\nu_2 (k_2 + k_{-1})}{k_1 k_2 e_0}$ and $\alpha = \dfrac{k_2 + k_{-1}}{k_1} \left(\dfrac{k_3}{k_{-3}}\right)^{1/\gamma}$.
Under the assumption of quasi-steady-state, we have to put the equations (3.8) and (3.9) at zero. Then, we obtain u_1 and u_2 as functions of σ_1 and σ_2 described as

$$u_1 = \frac{{\sigma_2}^{\gamma}}{{\sigma_2}^{\gamma} \sigma_1 + {\sigma_2}^{\gamma} + 1},$$

$$u_2 = \frac{\sigma_1 {\sigma_2}^{\gamma}}{{\sigma_2}^{\gamma} \sigma_1 + {\sigma_2}^{\gamma} + 1} \underset{not}{:=} f(\sigma_1, \sigma_2).$$

Now, we can express the evolution of σ_1 and σ_2 as functions of themselves only, and these equations are

$$\frac{d\sigma_1}{d\tau} = \nu - f(\sigma_1, \sigma_2), \tag{3.10}$$

$$\frac{d\sigma_2}{d\tau} = \alpha f(\sigma_1, \sigma_2) - \eta\sigma_2. \tag{3.11}$$

Since σ_1 is related to the concentration of ATP and σ_2 to the concentration of ADP, we would like to demonstrate that both equations admit oscillatory solutions for some range of the supply rate ν. Let us notice that no solution can be bounded if $\nu > 1$, so we will only consider values of ν between 0 and 1. The nullclines of the system are given by

$$\sigma_1 = \frac{\nu}{1-\nu}\frac{1+{\sigma_2}^\gamma}{{\sigma_2}^\gamma} \quad \left(\frac{d\sigma_1}{d\tau} = 0\right),$$

$$\sigma_1 = \frac{1+{\sigma_2}^\gamma}{{\sigma_2}^{\gamma-1}(p-\sigma_2)} \quad \left(\frac{d\sigma_2}{d\tau} = 0\right),$$

where $p = \alpha/\eta$. Then, the unique steady-state solution can easily be found and satisfies

$$\begin{cases} \sigma_2 = p\nu, \\ \sigma_1 = \dfrac{\nu\left(1+{\sigma_2}^\gamma\right)}{(1-\nu)\,{\sigma_2}^\gamma}. \end{cases}$$

We now have to study the stability of this point. In order to do so, we use the characteristic equation of the linearized system, given by

$$\lambda^2 - \underbrace{(\alpha f_2 - \eta - f_1)}_{\underset{not}{:=}H(\nu)} + f_1\eta = 0$$

where f_i denotes $\dfrac{\partial f}{\partial \sigma_i}$ for $i = 1, 2$. Since $f_1\eta$ is positive, the stability is governed by the sign of the expression $H(\nu)$. Indeed, if H is negative, the system admits two negative eigenvalues and is then stable. Otherwise, if H is non negative, the system is unstable when $H > 0$ and there is an Hopf bifurcation while $H = 0$. If we compute the derivatives of the function f, the function $H(\nu)$ can be rewritten as

$$H(\nu) = \frac{(1-\nu)}{(1+y)}\left[\eta\gamma + (\nu-1)y\right] - \eta,$$

with $y = (p\nu)^\gamma$. Since the value of the function H equals to $-\eta$ when $\nu = 1$ and $\eta(\gamma - 1)$ when $\nu = 0$, by continuity the curve has to change sign if γ is bigger than 1. This is exactly what we can see in FIGURE 3.2.

Example 3.1. *Let us take an example to show the oscillotary solutions that we obtain with this model. We assume that γ is 2, α is 1, η is 0.1 and we take two different values of ν: one when $H(\nu)$ is positive (0.0285), and another one when it is negative (0.0315). If we consider that $\eta = 0.0285$, then the function H is positive, which means that steady-state is unstable and we have a limit cycle. In the example illustrated in* FIGURE *3.3, we*

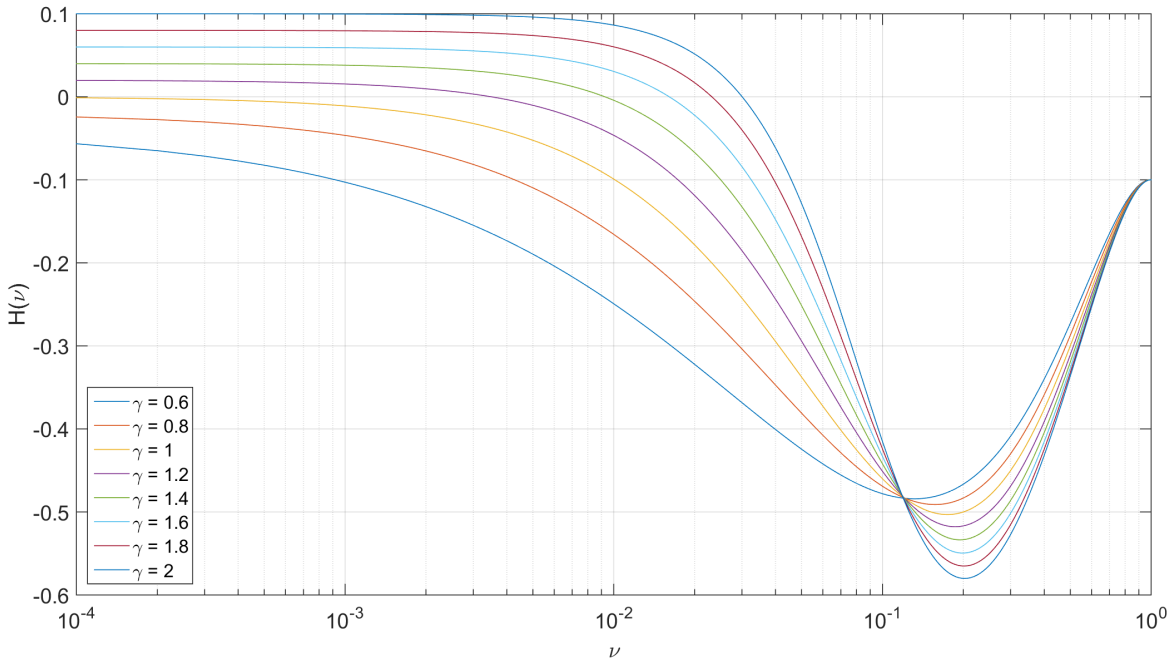
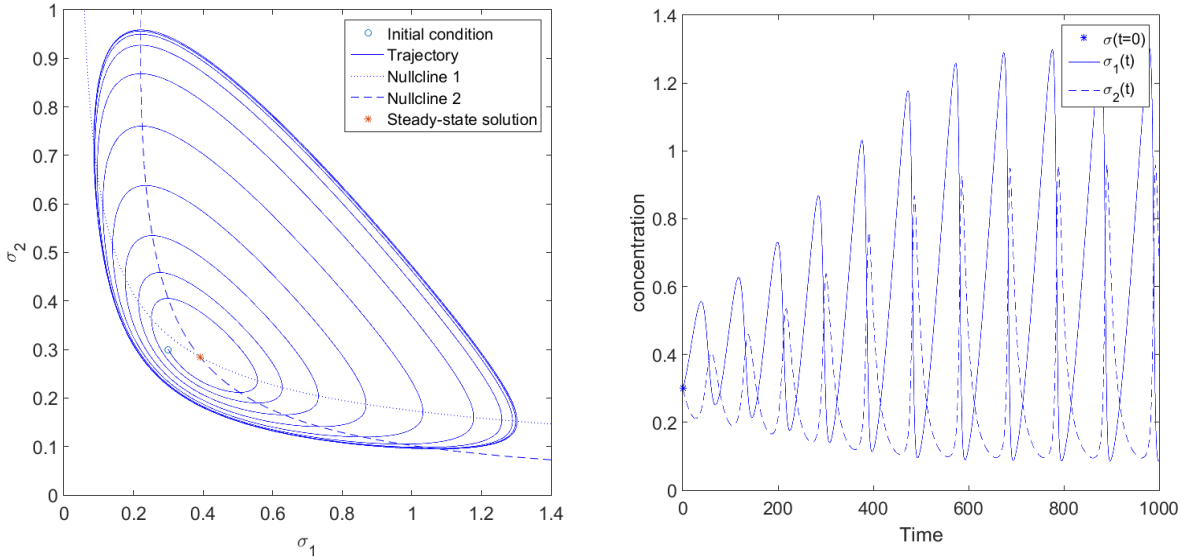


Figure 3.2: Illustration of the function $H(\nu)$ for different values of γ

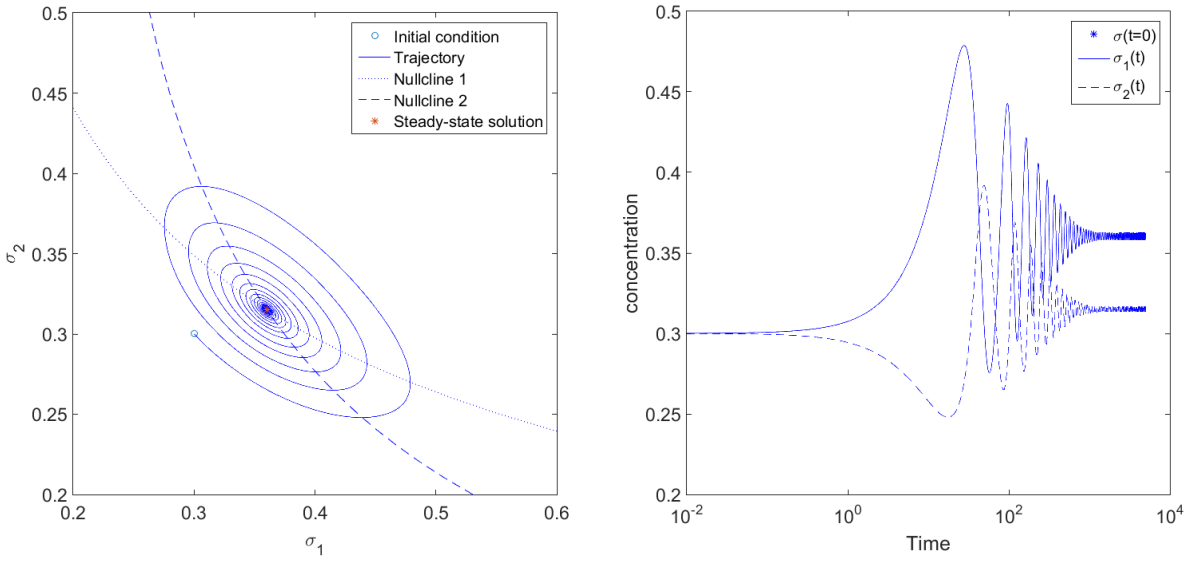
have taken the initial condition $(0.3\,,\,0.3)$ *that leads to oscillatory trajectories as shown in* FIGURE *3.3a.* FIGURE *3.3b reveals the same behaviour. We can do the same thing with* $\nu = 0.0315$*, leading to a negative value of* H*, meaning that the steady-state is stable. As shown in* FIGURE *3.4, we can clearly see that the trajectory goes closer and closer to the steady-state when time increases. The phase space related to this behaviour is shown in* FIGURE *3.4a and the trajectories are illustrated in* FIGURE *3.4b.*



(a) Phase space

(b) Trajectory evolution

Figure 3.3: Illustration of Sel'kov model when $\gamma = 2$ (> 1) when $H(\nu = 0.0285) > 0$



(a) Phase space (b) Trajectory evolution

Figure 3.4: Illustration of Sel'kov model when $\gamma = 2$ (> 1) when $H(\nu = 0.0315) < 0$

Unfortunately, the model of Sel'kov does not fit with the real data since we should have two Hopf bifurcation points. Indeed, in experimental results, there is a stable steady-state solution for high and low substrate injection rates.

3.3 Goldbeter and Lefever scheme

In 1972, Goldbeter and Lefever improved the Sel'kov model using a model of Monod-Wyman-Changeux type. They assume that the PFK1 enzyme is a dimer that can exist in two different states: an active one denoted by R, and an inactive one denoted by T. Other assumptions are made in their model. First, the substrate S_1 can bind both forms of the enzyme, but the product S_2 can only bind the active form. Moreover, the product S_2 can be produced thanks to an irreversible reaction where the R-form decomposes and loses one substrate molecule. Then, as we commonly do, the substrate is assumed to be supplied to the system at a constant rate, and the product to be removed from the system at a rate proportional to its concentration. In what follows, we will denote by T_j the inactive T form of the enzyme bound to j molecules of substrate and the active R form of the enzyme bound to i substrate molecules and j product molecules by R_{ij}. On the one hand, the reaction diagram for the T-form is

$$\mathrm{T}_0 + \mathrm{S}_1 \underset{\mathrm{k}_{-3}}{\overset{2\,\mathrm{k}_3}{\rightleftharpoons}} \mathrm{T}_1.$$

$$\mathrm{T}_1 + \mathrm{S}_1 \underset{2\,\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{T}_2.$$

On the other hand, the reaction diagram for R-form is given by

$$\mathrm{R}_{00} + \mathrm{S}_2 \underset{\mathrm{k}_{-2}}{\overset{2\,\mathrm{k}_2}{\rightleftharpoons}} \mathrm{R}_{01},$$

$$\mathrm{R_{01}} + \mathrm{S_2} \underset{2\,\mathrm{k_{-2}}}{\overset{\mathrm{k_2}}{\rightleftharpoons}} \mathrm{R_{02}},$$

and

$$\mathrm{R_{0}}_i + \mathrm{S_1} \underset{\mathrm{k_{-2}}}{\overset{2\,\mathrm{k_2}}{\rightleftharpoons}} \mathrm{R_{1}}_i,$$

for $i = 0, 1, 2$. Finally, we can go from one state to the other with only one reaction given by

$$\mathrm{T_0} \underset{\mathrm{k_1}}{\overset{\mathrm{k_{-1}}}{\rightleftharpoons}} \mathrm{R_{00}}.$$

In addition, the enzyme complex can dissociate to form the product S_2

$$\mathrm{R_{ij}} \xrightarrow{\mathrm{k}} \mathrm{R}_{i-1,j} + \mathrm{S_2},$$

for $i \geq 1$. Under the assumption of the law of mass action, we can use the quasi-steady-state assumption and then find a linear system of equations to solve. The solution of this system can be substituted into the differential equations for the substrate and the product, and we find

$$\begin{aligned} \frac{ds_1}{dt} &= \nu_1 - F(s_1, s_2), \\ \frac{ds_2}{dt} &= F(s_1, s_2) - \nu_2 s_2, \end{aligned}$$

where

$$F(s_1, s_2) = \left(\frac{2k_2 k_{-1} e_0}{k + k_{-2}}\right) \left[\frac{s_1 \left(1 + \dfrac{k_2}{k + k_{-2}} s_1\right) (s_2 + K_3)^2}{{K_2}^2 k_1 \left(\dfrac{k_3}{k_{-3}} s_1 + 1\right)^2 + k_{-1} \left(1 + \dfrac{k_2}{k + k_{-2}} s_1\right)^2 (K_2 + s_2)^2}\right],$$

with $K_2 = k_{-2}/k_2$. Let us now introduce dimensionless variables

$$\sigma_1 = \frac{s_1}{K_2} \qquad \sigma_2 = \frac{s_2}{K_2} \qquad t = \frac{\tau}{\tau_c}$$

and the parameters

$$\nu = \frac{k_2 \nu_1}{k_{-2} \tau_c} \qquad \eta = \frac{\nu_2}{\tau_c} \qquad \tau_c = \frac{2k_2 k_{-1} k e_0}{k_1 (k + k_{-2})}.$$

The differential equations can then be rewritten in terms of these new variables and parameters, and we find similar equations to the equations (3.10) and (3.11) with $\alpha = 1$ and a different function $f(\sigma_1, \sigma_2)$. We can even find a simple expression for this function thanks to three new assumptions. First, the substrate cannot bind the T-form of the enzyme, which is equivalent to say that the rate constant k_3 is zero. Secondly, the inactive T-form is preferred to the active R-form which, in terms of rate constants, means that $k_1 \gg k_{-1}$. Finally, if the substrate S_1 binds the R-form, then formation of product S_2 is preferred to dissociation, i.e. $k \gg k_{-2}$. Then, under these assumptions, the function is given by

$$f(\sigma_1, \sigma_2) = \sigma_1 (1 + \sigma_2)^2.$$

As we did for the Sel'kov model, we can find the steady-state solutions after having determined the nullclines of the system, described by

$$\begin{aligned} \sigma_1 &= \frac{\nu}{(1+\sigma_2)^2} \quad \left(\frac{d\sigma_1}{d\tau} = 0\right), \\ \sigma_1 &= \frac{\eta\sigma_2}{(1+\sigma_2)^2} \quad \left(\frac{d\sigma_2}{d\tau} = 0\right). \end{aligned}$$

Then, the steady-state solution is given by

$$\begin{aligned} \sigma_2 &= \frac{\nu}{\eta}, \\ \sigma_1 &= \frac{\nu}{(1+\sigma_2)^2}. \end{aligned}$$

The stability of the steady-state points can be determined by the characteristic equation of the linearized system, given by $\lambda^2 - H(\nu)\lambda + f_1\eta = 0$, where the function H is given by

$$\begin{aligned} H(\nu) &= f_2 - f_1 - \eta, \\ &= 2\sigma_1(1+\sigma_2) - (1+\sigma_2)^2 - \eta. \end{aligned}$$

Then, the Hopf bifurcation points will be found by putting the function H to zero. To study the roots of this function, it is easier to define another variable $y = 1 + \frac{\nu}{\eta}$. Then we have

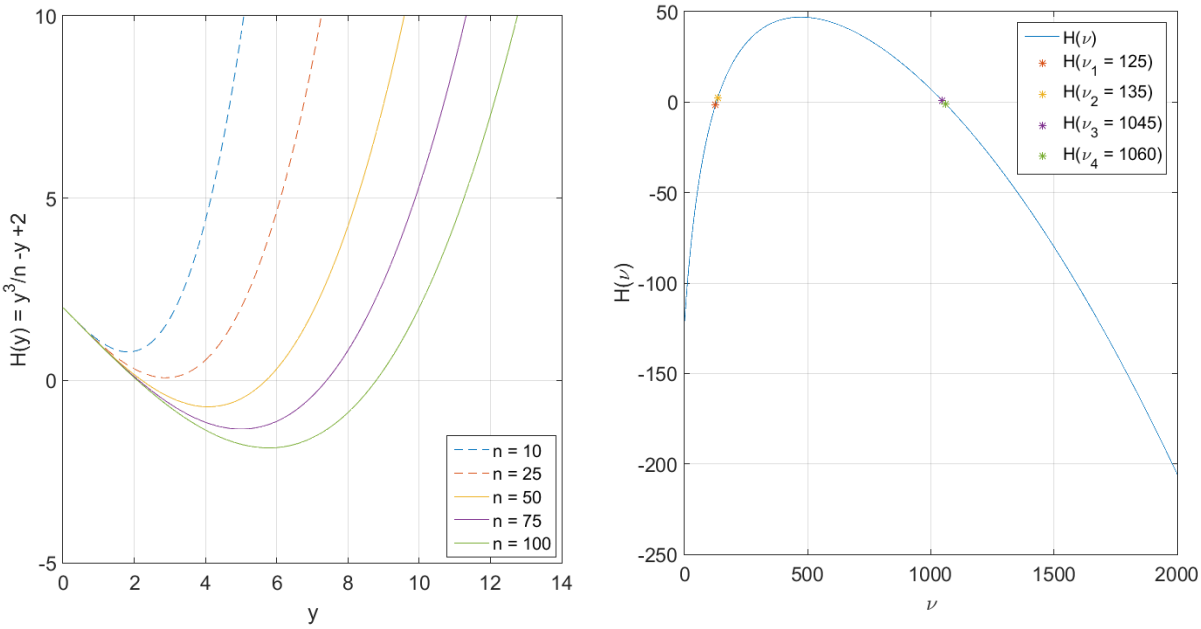
$$\begin{aligned} H(\nu) &= 0, \\ \Leftrightarrow \frac{1}{\eta}y^3 - y + 2 &= 0, \end{aligned} \tag{3.12}$$

We can study the roots of this function for different values of the parameter η. In FIGURE 3.5a, we can see that η has to be high enough to have two roots, as the experimental data require. Actually, Hess and Boiteux (1973) have discovered that there are two stable steady-state solutions: one for high substrate injection rate and another one for the low substrate injection. This is exactly what we can see in FIGURE 3.5a since we know that $(y-1)\eta = v$ with η high enough. Then, small values for y can actually be big values for η. So they also found two Hopf bifurcation points: one at $v = 20$ mM/hr[2] flow rate, and another one at $v = 160$ mM/hr. In order to fit with these data, we assume that

$$\frac{y_2 - 1}{y_1 - 1} = \frac{v_2}{v_1} = \frac{160}{20} = 8. \tag{3.13}$$

Then, if we solve the equation (3.12) under the assumption (3.13), we finally find that $y_1 = 2.08$, $y_2 = 9.61$ and $\eta = 116.7$. This leads to the values $\nu_1 = 126$ and $\nu_2 = 1005$. As we did above, let us illustrate this model with two different values of ν such that H has different sign, and then a different behaviour.

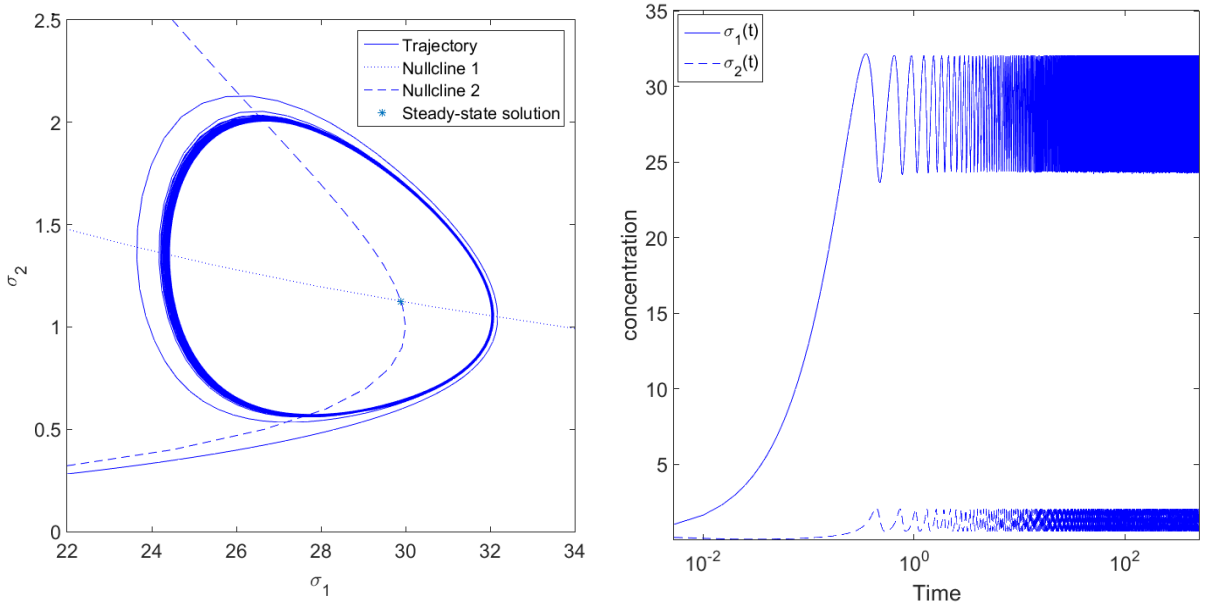
[2] "mM" is a symbol used in chemistry to appoint a concentration unit equals to one mmol per litre, i.e.10^{-3} mol per litre.



(a) $H(y)$ for different values of the parameter η (b) Graph of the function $H(\nu)$ when $\eta = 120$

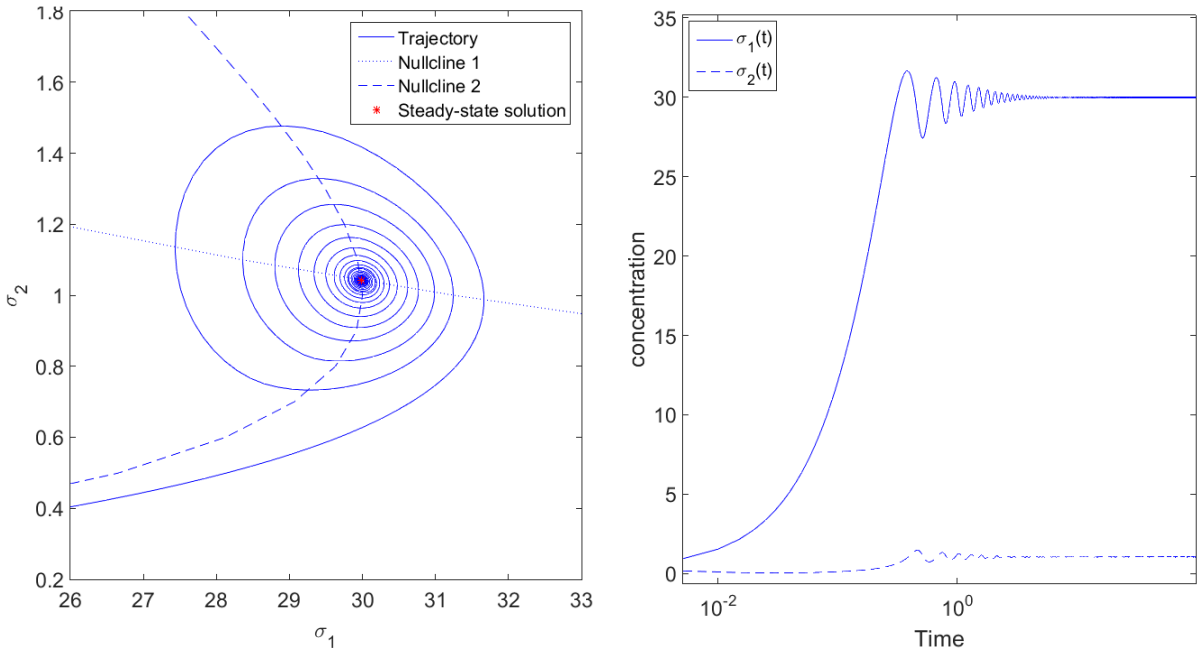
Figure 3.5: Illustration of the function H of the Goldbeter and Lefever scheme

Example 3.2. *Assuming that* $\eta = 120$*, the function* H *admits two roots as* FIGURE *3.5b shows. This means that for small and big values of* ν*, the steady-state is stable. Otherwise, for values of* ν *of* 130 *to* 1050 *(more or less), the steady-state is unstable. If we take* $\nu = 135$*, the function* H *is positive and the steady-state is unstable. Then, the limit cycle should be stable. This is exactly what we can see in* FIGURE *3.6, with the evolution of the trajectories in the phase space in* FIGURE *3.6a and the evolution over*



(a) Phase space (b) Evolution of the trajectories

Figure 3.6: Illustration of the Goldbeter-Lefever model for $\eta = 120$ and $\nu = 135$



(a) Phase space

(b) Evolution of the trajectories

Figure 3.7: Illustration of the Goldbeter-Lefever model for $\eta = 120$ and $\nu = 125$

time in FIGURE *3.6b. The behaviour described in* FIGURE *3.7 concerns the stable case because* $\nu = 125$. *We can clearly see that trajectories become closer and closer to the steady-state. We could have done the same thing near* $\nu = 1050$.

Chapter 4

p-dominance theory

Most of time, high-dimensional linear systems are quite difficult to analyse. We try then to simplify them, and to focus only on a few dominant poles that capture the main properties of the initial system. The analysis is even more complex when the initial system is nonlinear because phase plane analysis can only be done in two dimensions. In this section, we will build a new tool to know the dimension of the dominant behaviour of either a linear or a nonlinear system. An algorithm to test this new concept will also be developed. We base our work on Fulvio Forni and Rodolphe Sepulchre's article [3] of 2017 and its previous version [4].

4.1 Differential approach

Let us begin to formalize the property that a linear system admits a low-dimensional dominant behaviour, whose dimension is denoted by p. For example, if a system has a 0-dimensional dominant behaviour, this will mean that there exists a unique fixed point. No major difference could be spotted between this concept and the contractive systems. Moreover, 1-dominance will signify that there is at least one equilibrium point and it can be associated to differentially positive systems. This notion can be defined for the general case of p-dominance.

Definition 4.1

A linear system $\dot{x} = Ax$ with $A \in \mathbb{R}^{n\times n}$ is **p-dominant** with rate $\lambda \geq 0$ if there exists a symmetric matrix P with inertia $(p, 0, n-p)$ such that

$$A^tP + PA \leq -2\lambda P - \varepsilon I, \tag{4.1}$$

for some $\varepsilon \geq 0$. The property is strict if $\varepsilon > 0$.

Let us remind that a matrix with inertia $(p, 0, n-p)$ means that it admits p negative eigenvalues and $n-p$ positive ones. Moreover, let us notice that for simplicity in what follows, we will denote a matrix with inertia $(p, 0, n-p)$ by a matrix of inertia p. We can reformulate this notion in terms of a quadratic differential storage. Indeed, if we define $V(x) = x^tPx$, then the dissipation inequality (4.1) gives

$$\begin{aligned}\dot{V}(x) &= \dot{x}^t V x + x^t V \dot{x},\\ &= x^t(A^tP + PA)x,\\ &\underset{(4.1)}{\leq} -2\lambda V(x) - \varepsilon\,|x|^2.\end{aligned}$$

It implies that for positive ε, the two cones defined by

$$\mathcal{K}^- = \{x \in \mathbb{R}^n \mid V(x) \leq 0\} \quad \text{and} \quad \mathcal{K}^+ = \{x \in \mathbb{R}^n \mid V(x) \geq 0\}$$

are strictly contracting, i.e.

$$\forall t > 0 : e^{-At}\mathcal{K}^+ \subset \mathcal{K}^+ \quad \text{and} \quad e^{At}\mathcal{K}^- \subset \mathcal{K}^-.$$

Let us notice that the values of p and $\lambda \geq 0$ are closely related to each other. Actually, the parameter λ measures the shift on the spectrum and p is the number of eigenvalues that are non-negative after this shift. This could seem quite easy for a linear system, but we will see thereafter that it becomes more complicated with nonlinear systems since the Jacobian matrix depends on the variables, and then the eigenvalues can differ.

Furthermore, some characterizations of the concept of p-dominance can be found. Some of them are provided in the following proposition (see [3, Proposition 1]) whose proof is not developed in this piece of work but can be found in the previous paper [4] of [3].

Proposition 4.1. *For $\varepsilon > 0$, the linear matrix inequality (4.1) is equivalent to any of the following conditions*

(1) The matrix $A + \lambda I$ has p eigenvalues with strictly positive real part, and $n - p$ eigenvalues with strictly negative real part,

(2) There exists an invariant subspace splitting $\mathbb{R}^n = \mathcal{H} \oplus \mathcal{V}$ such that $A\mathcal{H} \subset \mathcal{H}$ and $A\mathcal{V} \subset \mathcal{V}$, and moreover the dimension of $\mathcal{H}$ is p, and the dimension of $\mathcal{V}$ is $n - p$. Furthermore, there exist constants $0 \leq \underline{c} \leq 1 \leq \overline{c}$ and $\overline{\lambda} > \lambda > \underline{\lambda}$ such that

$$\begin{aligned}\forall x \in \mathcal{H} : \quad \left|e^{At}x\right| &\geq \underline{c}\, e^{-\underline{\lambda}t}\,|x| \quad t \geq 0,\\ \forall x \in \mathcal{V} : \quad \left|e^{At}x\right| &\leq \overline{c}\, e^{-\overline{\lambda}t}\,|x| \quad t \geq 0.\end{aligned}$$

⌟

Then, if a linear system is p-dominant, it ensures that we can consider $n - p$ transient modes and p dominant modes that dictate alone the asymptotic behaviour of the system. Let us notice that for 0-dominant, the quadratic form $V(x)$ is a Lyapunov function since it is positive, the derivative is strictly negative along the trajectories, and $V(0) = 0$. In a more general way, $V(x)$ is a Lyapunov function for the restriction of flow in the transient space $\mathcal{V}$. Finally, the matrix inequality (4.1) is equivalent to the conic constraint

$$\begin{bmatrix} \dot{x} \\ x \end{bmatrix}^t \begin{bmatrix} O & P \\ P & 2\lambda P + \varepsilon I \end{bmatrix} \begin{bmatrix} \dot{x} \\ x \end{bmatrix} \leq 0. \tag{4.2}$$

For your information, we can extend p-dominance to open systems using dissipativity theory, and augment the internal dissipation inequality with an internal supply. This is done is the seventh section of [3].

Now that the concept is defined for linear system, we can study nonlinear systems differentially. Let us consider the nonlinear system

$$\dot{x} \;=\; f(x), \quad x \in \mathcal{X}.$$

Then dominance for nonlinear systems is defined through the linear dissipation inequality

$$\begin{bmatrix} \dot{\delta x} \\ \delta x \end{bmatrix}^t \begin{bmatrix} O & P \\ P & 2\lambda P + \varepsilon I \end{bmatrix} \begin{bmatrix} \dot{\delta x} \\ \delta x \end{bmatrix} \;\leq\; 0, \tag{4.3}$$

for every $\delta x \in T_x\mathcal{X}$, and where P is a matrix with inertia p and $\varepsilon \geq 0$. We would like to have a metric on the space $\mathcal{X}$, then we assume that this subspace is a smooth Riemannian manifold of dimension n, where $|\delta x|$ denotes the Riemannian metric.

Definition 4.2

A nonlinear system $\dot{x} \;=\; f(x)$ is **p-dominant** with rate $\lambda \geq 0$ if there exists a symmetric matrix P with inertia p such that (4.3) is satisfied by the solutions of the prolonged system

$$\begin{cases} \dot{x} &= f(x), \\ \dot{\delta x} &= \partial f(x)\delta x, \end{cases}$$

where $\partial f(x)$ is the differential of f at x, for some $\varepsilon \geq 0$.

We can use the same approach as for the linear systems, which means that we will reformulate the notion in terms of the quadratic function $V(\delta x) \;:=\; \delta x^t P \delta x$. Then, we have

$$\begin{aligned} \dot{V}(\delta x) &= \delta x^t \left[\partial f(x)^t P + P \partial f(x)\right] \delta x, \\ &\leq -2\lambda V(\delta x) - \varepsilon |\delta x|^2. \end{aligned}$$

For positive ε, the two cone fields

$$\mathcal{K}^+(x) \;:=\; \{\delta x \in T_x\mathcal{X} \mid V(\delta x) \geq 0\} \;\text{ and }\; \mathcal{K}^-(x) \;:=\; \{\delta x \in T_x\mathcal{X} \mid V(\delta x) \leq 0\}$$

are strictly contracting either in forward time or in backward time respectively

$$\begin{aligned} \forall\, t \;>\; 0 : \;\; \partial\psi^{-t}(x)\, \mathcal{K}^+(x) \;&\subset\; \mathcal{K}^+(\psi^{-t}(x)), \\ \forall\, t \;>\; 0 : \;\; \partial\psi^{t}(x)\, \mathcal{K}^-(x) \;&\subset\; \mathcal{K}^-(\psi^{t}(x)). \end{aligned}$$

Proposition 4.1 can be reformulated in a differential way and an invariant splitting in the linearized flow can be demonstrated. The following result is given by [3, Theorem 1].

Theorem 4.1

Let $\mathcal{A} \subseteq \mathcal{X}$ be a compact invariant set and let $\dot{x} = f(x)$ be a strictly p-dominant with rate $\lambda \leq 0$. Then, for each $x \in \mathcal{A}$, there exists an invariant splitting $T_x\mathcal{X} = \mathcal{H}_x \oplus \mathcal{V}_x$ such that

$$\forall\, t \in \mathbb{R}, \quad \partial\psi^t(x)\mathcal{H}_x \subseteq \mathcal{H}_{\psi^t(x)},$$

$$\forall\, t \in \mathbb{R}, \quad \partial\psi^t(x)\mathcal{V}_x \subseteq \mathcal{V}_{\psi^t(x)}.$$

$\mathcal{H}_x$ and $\mathcal{V}_x$ are distributions of dimension p and $n-p$ respectively. Furthermore, there exist constants $\underline{c} \leq 1 \leq \bar{c}$ and $\underline{\lambda} < \lambda < \overline{\lambda}$, such that

$$\forall\, x \in \mathcal{A},\, \forall\, \delta x \in \mathcal{H}_x : \quad |\partial\psi^t(x)\delta x| \geq \underline{c}\, e^{-\underline{\lambda} t}\, |\delta x|,$$

$$\forall\, x \in \mathcal{A},\, \forall\, \delta x \in \mathcal{V}_x : \quad |\partial\psi^t(x)\delta x| \leq \bar{c}\, e^{-\overline{\lambda} t}\, |\delta x|.$$

Then, as we did it with the linear systems, we can conclude that there is an invariant splitting between $n-p$ transient modes and p dominant modes. Likewise, these p modes dictate the asymptotic behaviour and the quadratic form $V(\delta x)$ can be seen as a differential Lyapunov function in $\mathcal{V}_x$. For the space $\mathcal{X} = \mathbb{R}^n$, the asymptotic behaviour of the dominant system can be defined in the following theorem (see [3, Theorem 2]).

Theorem 4.2

For $\mathcal{X} = \mathbb{R}^n$, let $\dot{x} = f(x)$ be a strictly p-dominant system with rate $\lambda \geq 0$. Then, the flow on any compact ω-limit set is topologically equivalent to a flow on a compact invariant set of a Lipschitz system in $\mathbb{R}^p$.

All this theory is interesting when p is much smaller than n, otherwise it does not really help. The following corollary treats the best cases, i.e. when p is zero, one or two (see [3, Corollary 1]).

Corollary 4.1.
Under the assumptions of Theorem 4.1, every bounded solution asymptotically converges to

- *a unique fixed point if $p = 0$,*
- *a fixed point if $p = 1$,*
- *a simple attractor if $p = 2$, that is a fixed point, a set of fixed points and connecting arcs, or a limit cycle.* ⌟

Further information about this corollary and the Theorem 4.2 can be found in the references [3], [4] and [5]. In particular, the difference between 0-dominance and contraction is discussed, and between the differential positivity and the 1-dominance as well.

4.2 Algorithmic test for p-dominance

In this section, we try to build an algorithmic process to establish p-dominance for a given nonlinear system. This method, which is introduced in [3, section VI], is a two-step process based on different results. The following theorem provides the first step.

Theorem 4.3

Let the nonlinear system $\dot{x} = f(x)$ with $x \in \mathcal{X}$, be a strictly p-dominant system. Then, there exists a maximal interval $(\lambda_{min}, \lambda_{max})$ such that $\partial f(x)+\lambda I$ has p unstable eigenvalues and $n-p$ stable eigenvalues for each $\lambda \in (\lambda_{min}, \lambda_{max})$, for every $x \in \mathcal{X}$.

This theorem implies that the spectrum of the families of Jacobian matrices $\partial f(x) + \lambda I$ has to admit a uniform splitting. Since this is a necessary condition, it has to be tested in first. Then, the first step of this algorithmic process consists in analysing the spectrum of the Jacobian matrix and, from this analysis, assigning relevant values for the parameters p and λ. Unfortunately, this condition is not sufficient to have dominance. Actually, it is provided by the inequalities

$$\partial f(x)^t P + P\partial f(x) + 2\lambda P + \varepsilon I \ \leq \ 0, \tag{4.4}$$

for every $x \in \mathcal{X}$, and for some $\varepsilon \leq 0$. Let us remind that the matrix P also has to satisfy an inertia constraint. However, it seems in fact that this assumption can be dropped after having checked it was at least satisfied for one λ. In the end, we have to solve an infinite family of LMIs that we can actually reduce to a finite family through convex relaxation. Let $\mathcal{A} = \{A_1, \cdots, A_N\}$ be a family of matrices such that the Jacobian matrix $\partial f(x)$ belongs to the convex hull[1] of $\mathcal{A}$ for all x. We can write

$$\partial f(x) \ = \ \sum_{i=1}^{N} \rho_i(x) A_i,$$

at each x, for a given set $\{\rho_i(x)\}_i$ of parameters whose sum is one. Then, we can rewrite the right-hand side of the relation (4.4) as

$$\begin{aligned} \partial f(x)^T P + P\partial f(x) + 2\lambda P + \varepsilon I \ &= \ \left(\sum_{i=1}^{N} \rho_i(x) {A_i}^t\right) P + P\left(\sum_{i=1}^{N} \rho_i(x) A_i\right) + 2\lambda P + \varepsilon I, \\ &= \ \sum_{i=1}^{N} \rho_i(x) \left({A_i}^t P + P A_i + 2\lambda P + \varepsilon I\right). \end{aligned}$$

Then, any solution P to

$${A_i}^t P + P A_i + 2\lambda P + \varepsilon I \ \leq \ 0 \tag{4.5}$$

is also a solution to (4.4). Let us use this algorithmic test on simple examples.

[1] The convex hull of a finite point set is the set of all convex combinations of its points

Example 4.1. *Let us first consider a one degree of freedom mechanical system with nonlinear spring actuated by a DC motor with a PI feedback control. At the beginning, we consider the mechanical system given by*

$$\left\{ \begin{array}{rcl} \dot{x}_p & = & x_v, \\ \dot{x}_v & = & -\alpha(x_p) - cx_v + u, \end{array} \right. \tag{4.6}$$

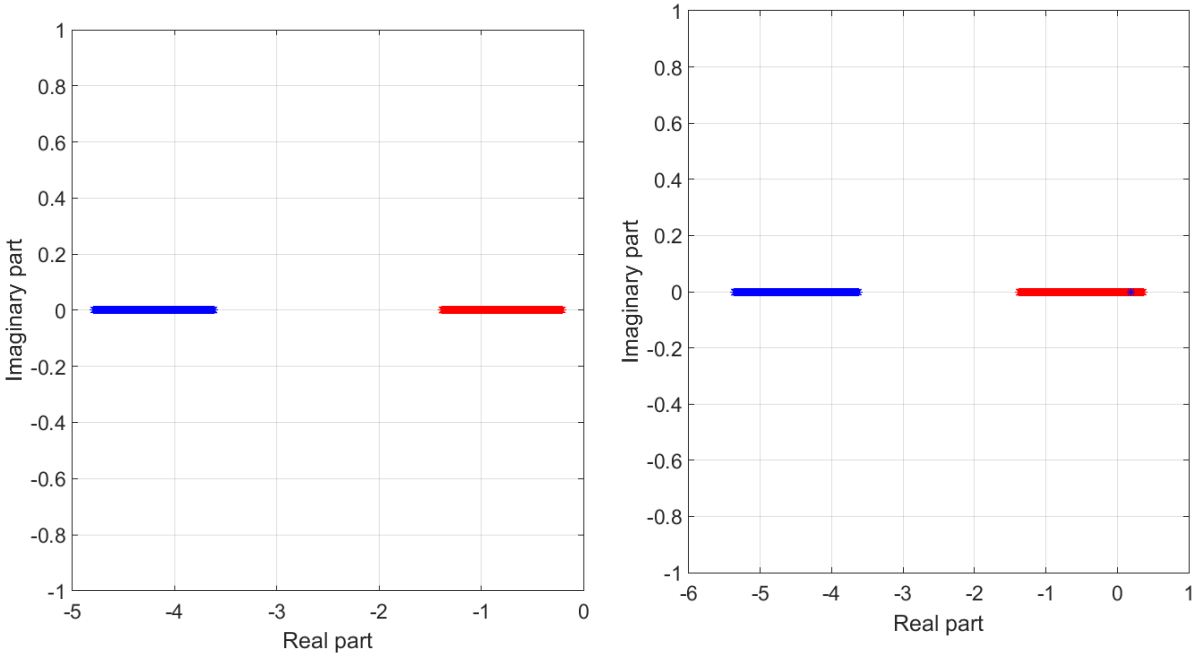
where x_p denotes the position and x_v the velocity, u denotes the force input, c the damping coefficient and $\alpha(x_p)$ derives from a mechanical potential $U : \mathbb{R} \to \mathbb{R}$. If we assume that $c = 5$ and $1 \leq \partial\alpha(x_p) \leq 5$, we can study the spectrum of the Jacobian matrix of this system, shown in FIGURE *4.1a. We can either use $\lambda = 0$ and then find the 0-dominance, or use $\lambda = 2$ for example and then find 1-dominance. Nevertheless, the idea is to find the smallest p such that the system is p-dominant. For example, we can find (via CVX and SeDuMi) the matrix*

$$P = \begin{pmatrix} 0.5074 & 0.2675 \\ 0.2675 & 0.4926 \end{pmatrix},$$

whose inertia is 0 that satisfies the convex relaxation (4.5) for the matrices

$$A_1 = \begin{pmatrix} 0 & 1 \\ -1 & -5 \end{pmatrix} \quad \text{and} \quad A_2 = \begin{pmatrix} 0 & 1 \\ -5 & -5 \end{pmatrix}.$$

Sometimes, the configuration of the Jacobian matrix prevents from using small values of p. Let us take for example the assumption that as before $c = 5$ but $-2 \leq \partial\alpha(x_p) \leq 5$. We can find the spectrum shown in FIGURE *4.1b where we can see that some eigenvalues are sometimes positive, which prevents us from finding a rate $\lambda \geq 0$ such that $p = 0$. If we try to find a matrix P for $\lambda = 2$ and*



(a) under the assumption that $1 \leq \partial\alpha(x_p) \leq 5$

(b) under the assumption that $-2 \leq \partial\alpha(x_p) \leq 5$

Figure 4.1: Spectrum analysis of the first system (4.6)

$$A_1 = \begin{pmatrix} 0 & 1 \\ 2 & -5 \end{pmatrix} \quad \text{and} \quad A_2 = \begin{pmatrix} 0 & 1 \\ -5 & -5 \end{pmatrix},$$

then we will find the matrix

$$P = \begin{pmatrix} -2.0873 & 1.6137 \\ 1.6137 & 3.0873 \end{pmatrix},$$

whose eigenvalues are -2.5492 *and* 3.5492*. Then, we can conclude that for* $\lambda = 2$*, the system is* 1*-dominant, i.e. the dimension of the asymptotic behaviour is one. We can now suppose that the mechanical system is driven by a DC motor modelled by the equation*

$$u = k_f x_i,$$

where k_f *is a static approximation of the current and* x_i *is the current of the circuit whose evolution is given by*

$$L\dot{x}_i = -Rx_i - k_e x_v + V,$$

where L *and* R *are inductance and resistance respectively,* k_e *is the back electromotive force coefficient, and the voltage* V *is an additional input. Let us assume that* $L = 0.1$*,* $R = 1$*,* $k_f = 1$ *and* $k_e = 1$ *and then the complete system is given by*

$$\begin{cases} \dot{x}_p &= x_v, \\ \dot{x}_v &= -\alpha(x_p) - 5x_v + x_i, \\ \dot{x}_i &= -10x_i - 10x_v + 10V. \end{cases} \tag{4.7}$$

The Jacobian matrix related to this system is

$$J = \begin{pmatrix} 0 & 1 & 0 \\ -\partial\alpha(x_p) & -5 & 1 \\ 0 & -10 & -10 \end{pmatrix}.$$

After studying the spectrum of this matrix under the assumption that $-2 \leq \partial\alpha(x_p) \leq 5$*, we can easily conclude that we cannot find a rate* $\lambda \geq 0$ *such that the system is* 0*-dominant, but for* $\lambda = 2$ *we can find* 1*-dominance. Indeed, the matrix*

$$P = \begin{pmatrix} -8.4990 & -0.6691 & -1.0525 \\ -0.6691 & 3.4540 & 0.0442 \\ -1.0525 & 0.0442 & 1.0926 \end{pmatrix}$$

whose inertia is 1*, satisfies the linear matrix inequalities (4.5) for the matrices*

$$A_1 = \begin{pmatrix} 0 & 1 & 0 \\ -5 & -5 & 1 \\ 0 & -10 & -10 \end{pmatrix} \quad \text{and} \quad A_2 = \begin{pmatrix} 0 & 1 & 0 \\ 2 & -5 & 1 \\ 0 & -10 & -10 \end{pmatrix}.$$

Finally, we can express the voltage V *as*

$$V = k_P(r - x_p) + k_I x_c,$$

where k_P and k_I are proportional and integral gains respectively, and x_c is the integrator variable whose evolution is governed by the expression

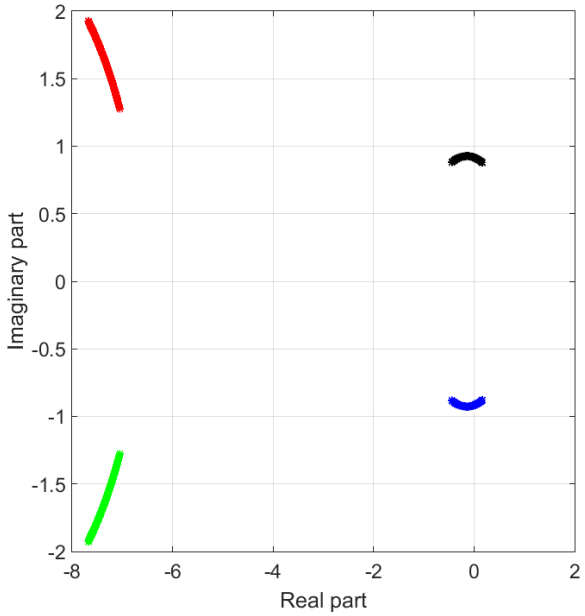
$$\dot{x}_c = r - x_p,$$

with r the reference. The final differential equations are then given by

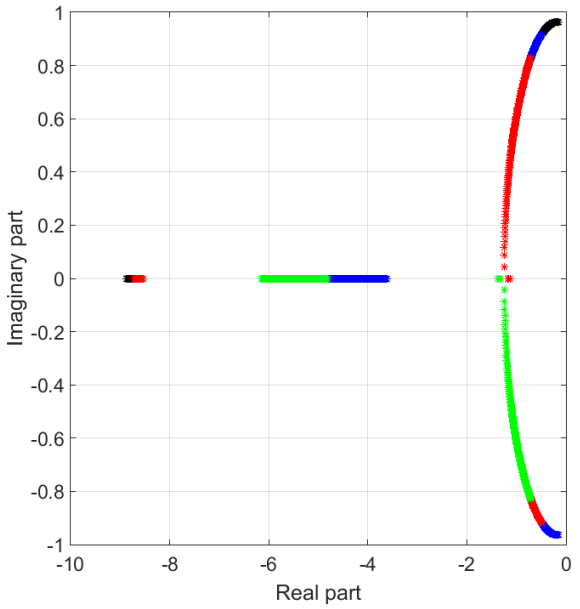
$$\begin{cases} \dot{x}_p &= x_v, \\ \dot{x}_v &= -\alpha(x_p) - 5x_v + x_i, \\ \dot{x}_i &= -10x_i - 10x_v + 10k_P(r - x_p) + 10k_I x_c, \\ \dot{x}_c &= r - x_p. \end{cases} \tag{4.8}$$

The behaviour of the system depends on the values of the parameters k_I and k_P. Let us assume that $k_I = 5$ and that k_P can either be 1 or 5. The spectrum analysis of each case can be seen in FIGURE *4.2, where the first case (*FIGURE *4.2a) suggests 2-dominance with rate $\lambda = 2$ while the second case (*FIGURE *4.2b) suggests 0-dominance with rate $\lambda = 0$. Indeed, for $k_P = 1$ we can find the matrix P defined by*

$$P = \begin{pmatrix} -34.3935 & -1.6337 & -5.3284 & 30.4221 \\ -1.6337 & 8.2615 & 0.9390 & -1.6074 \\ -5.3284 & 0.9390 & 1.1741 & 8.2117 \\ 30.4221 & -1.6074 & 8.2117 & -225.6082 \end{pmatrix},$$



(a) $k_I = 5$ and $k_P = 1$



(b) $k_I = 5$ and $k_P = 5$

Figure 4.2: Spectrum analysis of the system with a DC motor and a PI control (4.8) under the assumption that $-2 \leq \partial\alpha(x_p) \leq 5$

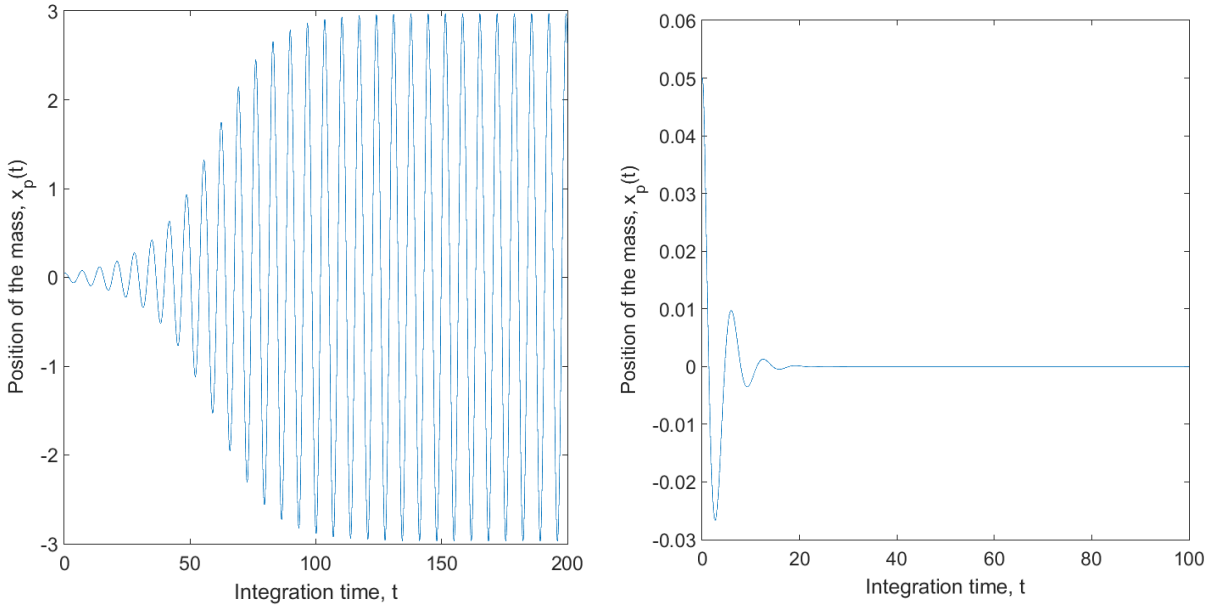
whose inertia is 2, *and that satisfies the linear matrix inequalities (4.5) for the matrices*

$$A_1 = \begin{pmatrix} 0 & 1 & 0 & 0 \\ 2 & -5 & 1 & 0 \\ -10 & -10 & -10 & 50 \\ -1 & 0 & 0 & 0 \end{pmatrix} \quad \textit{and} \quad A_2 = \begin{pmatrix} 0 & 1 & 0 & 0 \\ -5 & -5 & 1 & 0 \\ -10 & -10 & -10 & 50 \\ -1 & 0 & 0 & 0 \end{pmatrix}. \quad (4.9)$$

We can do exactly the same thing for the second case where $k_P = 5$ *and then find a matrix* P *of inertia* 0 *given by*

$$P = \begin{pmatrix} 224.0874 & 37.1648 & 3.7895 & -76.5634 \\ 37.1648 & 21.9257 & 0.2444 & -17.6387 \\ 3.7895 & 0.2444 & 0.4136 & -1.2192 \\ -76.5634 & -17.6387 & -1.2192 & 193.3991 \end{pmatrix}.$$

Obviously, this matrix satisfies the linear matrix inequalities related to the matrices A_1 *and* A_2. *The same definitions as (4.9) are used, but the element (3,1) equals to* -50 *rather than* -10. *This result can be illustrated in* FIGURE *4.3b where we can see that the trajectory tends to a fixed point, in contrast to* FIGURE *4.3a where the trajectory oscillates for* $k_P = 1$. *So, it will be interesting to study how much variation the parameters of the system can undergo without changing the dominance of the system, i.e. the robustsness of the system.*



(a) $k_I = 5$ and $k_P = 1$

(b) $k_I = 5$ and $k_P = 5$

Figure 4.3: Example of trajectory with $x_0 = (0.05, 0, 0, 0)$ of the system with a DC motor and a PI control (4.8) under the assumption that $-2 \leq \partial\alpha(x_p) \leq 5$

The p-dominance theory can be applied to any any differential equations. In particular we can use it for differential equations induced from chemical reaction system we talked about a few chapters ago. However, we already know that we can establish constraints from the chemical diagram. Let us illustrate both notions with the simplest chemical reaction (1.3) that we have previously studied, and try to guess the link that can exist between these two concepts.

Example 4.2. *Let us consider the first chemical reaction diagram (1.3) that we remind here below*

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C}$$

Under the assumption of the law of mass action with k_+ and k_- the forward and backward rate constants respectively, we can write down the differential equations induced from this diagram. Then, we have equations similar to (1.6), i.e.

$$\begin{aligned} \frac{dc_A}{dt} &= k_- c_C - k_+ c_A c_B, \\ \frac{dc_B}{dt} &= k_- c_C - k_+ c_A c_B, \\ \frac{dc_C}{dt} &= k_+ c_A c_B - k_- c_C. \end{aligned}$$

First of all, we can compute the Jacobian matrix of this system. We have

$$J = \begin{pmatrix} -k_+ c_B & -k_+ c_A & k_- \\ -k_+ c_B & -k_+ c_A & k_- \\ k_+ c_B & k_+ c_A & -k_- \end{pmatrix}. \tag{4.10}$$

*We assume for example that $0 \leq c_A \leq 10$ and $0 \leq c_B \leq 10$, and study therefore the spectrum of the Jacobian matrix. It results from this analysis (*FIGURE *4.4) that we expect 2-dominance for the rate $\lambda = 0.2$ and $\varepsilon = 0.001$. Indeed, we find the matrix P*

$$P = \begin{pmatrix} -152.0349 & 84.2339 & -69.9704 \\ 84.2339 & -152.0349 & -69.9704 \\ -69.9704 & -69.9704 & -137.6682 \end{pmatrix},$$

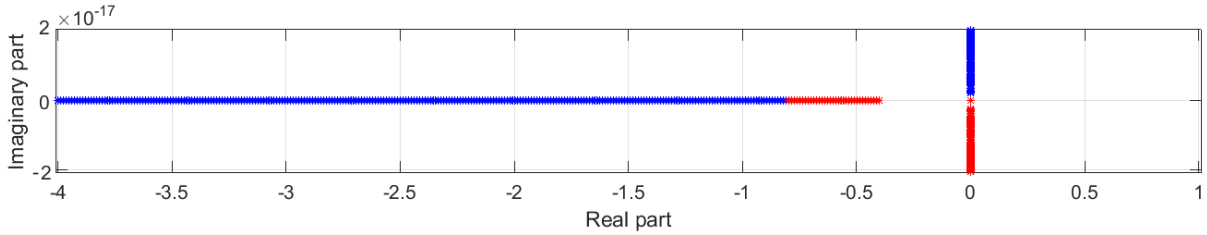


Figure 4.4: Spectrum analysis of the Jacobian matrix (4.10) of the chemical reaction diagram (1.3) under the assumption that $0 \leq c_A, c_B \leq 10$

whose inertia is 2. *Nevertheless, we did not expect this result because we have already shown that this system satisfies the assumption of the Deficiency zero theorem. Then, we know that the trajectory always tends to a unique fixed point. The dominance of the system is however* 2. *It appears that the p-dominance theory is less restrictive than the chemical reaction networks theory. One way to explain this concerns the stoichiometric classes: the p-dominance theory does not take them into account. In this case, this means that the set of all the fixed points forms a* 2*-dimensional set.*

Remark: as we have already said, the first step of the algorithmic test consists in studying the spectrum of the Jacobian matrix. Therefore, it could be interesting to make it simpler without changing the spectrum. For example, if we consider the Jacobian matrix (4.10) and we want to simplify it, we can isolate the parameter k_+ like

$$J = k_+ \underbrace{\begin{pmatrix} -c_B & -c_A & K \\ -c_B & -c_A & K \\ c_B & c_A & -K \end{pmatrix}}_{J^*},$$

with $K = k_-/k_+$. Then, the structure of the spectrum of the Jacobian matrix J is similar to the spectrum of the new matrix J^* since the eigenvalues will only be divided by the positive parameter k_+. This operation does not change the order of the eigenvalues. The interest of this modification also lies in the reduction of the number of parameters. Indeed, there is only one parameter K left. The robust analysis of the following chemical diagrams could be easier.

We can finally apply the p-dominance theory to the chemical reaction diagram (1.15) on which it is impossible to apply deficiency theorems since the deficiency is different from zero.

Example 4.3. *Let us remind the chemical reaction diagram, i.e.*

$$\begin{array}{ccc} 3\,\mathrm{A} & \xrightarrow{0.1} & \mathrm{A} + 2\,\mathrm{B} \\ 1 \uparrow & & \downarrow 1 \\ 2\,\mathrm{A} + \mathrm{B} & \xleftarrow{0.1} & 3\,\mathrm{B} \end{array}$$

and let us induce differential equations from it, given by

$$\begin{aligned} \frac{da}{dt} &= -0.2a^3 - ab^2 + 0.2b^3 + a^2b, \\ &= (a-b)[-0.2a^2 + 0.8ab - 0.2b^2], \\ \frac{db}{dt} &= 0.2a^3 + ab^2 - 0.2b^3 - a^2b, \\ &= (a-b)[0.2a^2 - 0.8ab + 0.2b^2]. \end{aligned}$$

We know that from an initial condition $x_0 = (a_0, b_0)$, the trajectory will stay in the subspace spanned by the vector $(1, -1)^t$. If we want to find the dimension of the dominant subspace,

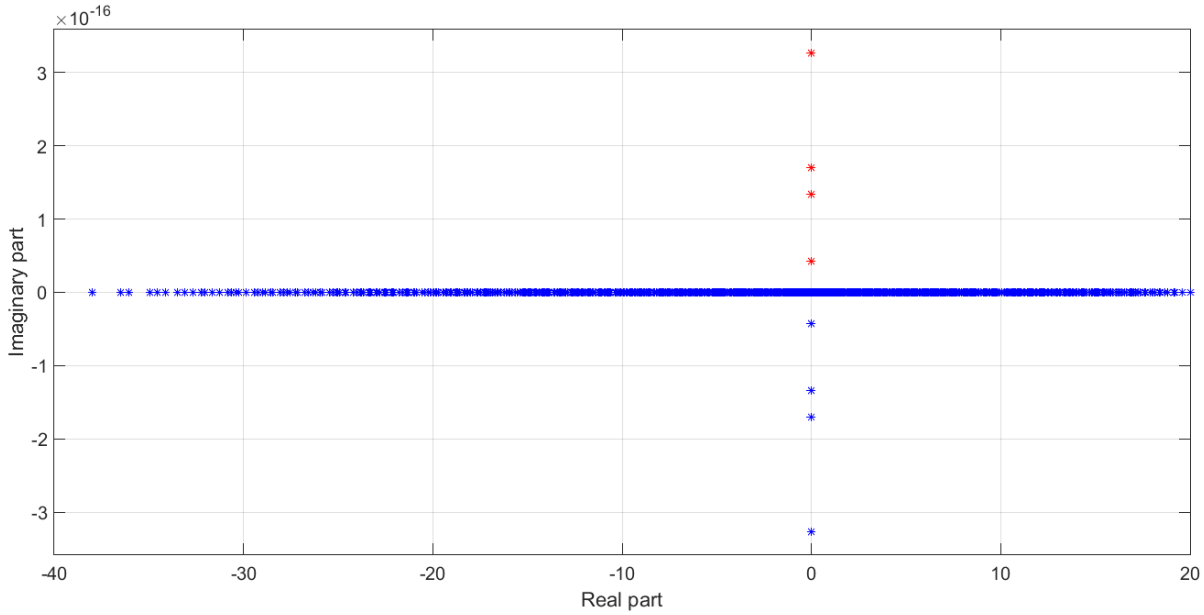


Figure 4.5: Spectrum analysis of the diagram (1.15)

*we have to make the analysis of the spectrum (*FIGURE *4.5) of the Jacobian matrix given by*

$$J = \begin{pmatrix} -0.6a^2 - b^2 + 2ab & -2ab + 0.6b^2 + a^2 \\ 0.6a^2 + b^2 - 2ab & 2ab - 0.6b^2 - a^2 \end{pmatrix}.$$

It does not seem that we can divide the eigenvalues of the spectrum, so if we take $\lambda = 40$*, we will find* 2*-dominance with the matrix* P *defined by*

$$P = \begin{pmatrix} -1.3935 & -0.0094 \\ -0.0094 & -1.3935 \end{pmatrix},$$

whose inertia is 2*, and* $\varepsilon = 0.001$*. This matrix has been computed under this assumption that* $0.1 \leq a, b \leq 5$*. This result does not really help us, and the dimension of the stoichiometric classes is finally more useful than the p-dominance.*

It seems that the p-dominance theory and the chemical reaction networks theory can help to understand a system independently. After using them for the previous examples, it seems that a new index could be interesting if it takes both notions of stoichiometric classes and p-dominance into account. Thus we would have a kind of dominance within each stoichiometric class. This will be discussed in the following chapter.

Chapter 5

Asymptotic behaviour of chemical reaction networks

In the previous chapters, we have introduced different concepts; two of which are the stoichiometric compatibility classes and the dominant behaviour. Let us remind that the first notion has been developed for the chemical reaction networks, and describes the space in which the concentration trajectories will wander over time. The dimension of this space, previously denoted by s, is always the same no matter the initial concentrations but the space itself is different. This value can already give some information about the asymptotic behaviour of the system. Indeed, the dimension of this behaviour will be smaller than s necessarily. For example, if the dimension of the stoichiometric subspace is one, it prevents the system from having limit cycles, and the only asymptotic behaviour will be one unique or more than one fixed points. Since trajectories will always stay in the same stoichiometric class than that one that the initial condition belongs to, i.e.

$$\begin{aligned} & W^t x \;=\; c \;=\; W^t y, \\ \Leftrightarrow \quad & W^t\,(x-y) \;=\; 0. \end{aligned}$$

It means that the difference between those two trajectories will belong to the stoichiometric subspace. However, the difference between two trajectories can help us to know the asymptotic behaviour of a system. This is the reason why we will use the stoichiometric subspace, i.e.

$$\Delta S \;=\; \left\{\delta x \mid W^t \delta x \;=\; 0\right\}. \tag{5.1}$$

The dominance theory on the other hand gives information about the dimension of the asymptotic space. We can find a matrix P such that

$$\partial f(x)^t P + P\partial f(x) + 2\lambda P \;<\; 0,$$

meaning that the function $V(x) \;=\; x^t P x$ is decreasing along the trajectories, either becoming negative at a moment, or it will tend to 0. So we can define the space

$$K^- \;=\; \left\{\delta x \mid \delta x^t\, P\, \delta x \;\leq\; 0\right\}. \tag{5.2}$$

5.1 Theoretical results

It seems that the two notions we talked about are quite different but could be used together to have an idea of the asymptotic behaviour of the trajectory in each stoichiometric class. We could for example find conclusions similar to the deficiency theorems from two parameters s and p, or something similar to the theorem 4.1 about the dimension of the asymptotic behaviour within each stoichiometric class. Actually, we will look at the intersection between ΔS and K^- denoted by Q. Let us first show a simple result about the nature of this intersection.

Lemma 5.1. *If ΔS and K^- denote the stoichiometric subspace and the p-cone as defined in (5.1) and (5.2) respectively, then the intersection $Q := \Delta S \cup K^-$ is still a cone.* ⌟

Proof. We have to show that for any $\alpha, \beta \geq 0$, and any δx, $\delta y \in Q$, either $\alpha\,\delta x + \beta\,\delta y$ or $\alpha\,\delta x - \beta\,\delta y$ belongs to Q. It is obvious that any linear combination always belongs to ΔS, so let us demonstrate that it also belongs to K^-. If we compute $V(\alpha\,\delta x \pm \beta\,\delta y)$ we find

$$\alpha^2\,\delta x^t P\,\delta x \pm \alpha\beta\left(\delta x^t P\,\delta y + \delta y^t P\,\delta x\right) + \beta^2\,\delta y^2 P\,\delta y \tag{5.3}$$

Since δx and $\delta y \in K^-$, we know that $V(\delta x)$ and $V(\delta y)$ are non-positive. So one of the expressions (5.3) will be non-positive since the sum $\delta x^t P\,\delta y + \delta y^t P\,\delta x$ will either be positive or negative. □

Let us notice that $\mathcal{K}^-$ is not a convex pointed cone, as we usually see. This is the reason why we do not prove that the intersection between $\mathcal{K}^-$ and $-\mathcal{K}^-$ is the null vector. We could say that $\mathcal{K}^-$ already contains its opposite. Finally, the next theorem allows us to conclude about the existence and the uniqueness of the fixed points thanks to the dimension of the space Q.

Theorem 5.1

If the system $\dot{x} = f(x)$ is strictly p-dominant with the rate $\lambda \geq 0$ and the matrix P of inertia p, and the intersection between K^- and ΔS is 0-dimensional, then there exists a unique fixed point within each stoichiometric class.

Proof. Let us take two initial conditions x_1 and x_2 in the same stoichiometric compatibility class, i.e.

$$\begin{aligned} W^t x_1 &= c = W^t x_2, \\ \Rightarrow\ W^t(x_1 - x_2) &= 0, \end{aligned}$$

implying that the difference between these two points belongs to the stoichiometric subspace ΔS. Since the trajectories issued from x_1 and x_2 will always stay in the same stoichiometric class, it means that for every positive time t, we have

$$W^t \underbrace{\left(\varphi^t(x_1) - \varphi^t(x_2)\right)}_{:=\,\delta x(t)} = 0,$$

meaning that the vector $\delta x(t)$ belongs to the stoichiometric subspace for every $t \geq 0$. We know that the system is strictly p-dominant so the derivative of $V(\delta x) = \delta x\, P\, \delta x$ is

$$\begin{aligned}\dot{V}(\delta x) &= \delta x^t \left(\partial f(x)^t P + P\partial f(x)\right) \delta x, \\ &< -2\lambda V(\delta x).\end{aligned}$$

This implies that either there exists time $T > 0$ such that $V(\delta x) < 0$, or $V(\delta x) \to 0$ when $t \to +\infty$. So it means that δx belongs to K^- asymptotically, and then

$$\delta x(t) \in \left(K^- \cap \Delta S\right),$$

when time t tends to infinity. However this intersection only contains the null vector, meaning that $\delta x(t)$ converges to 0. It follows that there exists a unique fixed point.

□

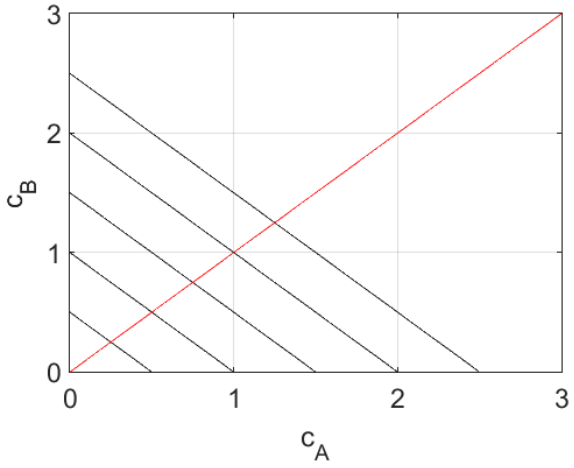
Let us illustrate this theorem with a linear example and the first nonlinear example that we have introduce at the beginning.

Example 5.1. *At the beginning, we have introduced the differential approach of the stoichiometric subspace via a linear example (1.11) given by*

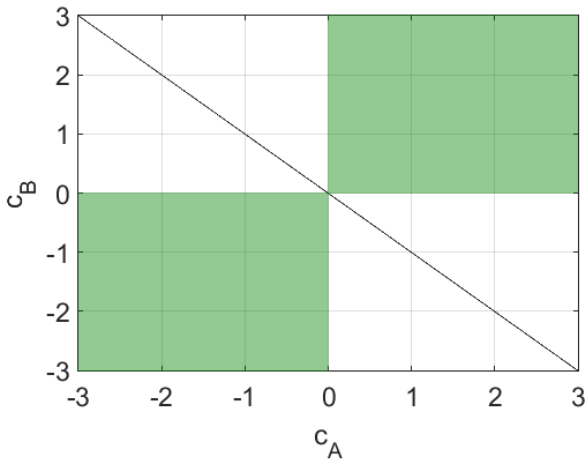
$$\mathrm{A} \underset{\mathrm{k_-}}{\overset{\mathrm{k_+}}{\rightleftharpoons}} \mathrm{B}$$

We have already shown that the stoichiometric subspace is given by the set spanned by the vector $(1, -1)^t$, and then the stoichiometric classes are parallel to this space as we can see in the FIGURE *5.1a. Moreover, the Jacobian matrix admit two eigenvalues: 0 and $-(k_+ + k_-)$, preventing us from having 0-dominance. Let us assume for example that both rate constants are one. We can obviously have 1-dominance with a rate $\lambda = 1$, between 0 and $(k_+ + k_-) = 2$, and the matrix P given by*

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



(a) Some stoichiometric classes in black and the set of fixed points in red



(b) Stoichiometric subspace ΔS in black and K^- in green

Figure 5.1: Illustration of the linear example (1.11)

whose eigenvalues are ± 1*, i.e. the inertia is one. Then, the set* K^- *illustrated in* FIGURE *5.1b is given by*

$$\begin{aligned} K^- &= \left\{\delta x \mid \delta x^t \, P \, \delta x \leq 0\right\}, \\ &= \left\{\delta x \mid -2\delta a \, \delta b \leq 0\right\}, \\ &= \left\{\delta x \mid \delta a \, \delta b \geq 0\right\}. \end{aligned}$$

It is then obvious that the intersection Q *between the two sets is the origin, and then the dimension of this set is* 0*, meaning that each stoichiometric class admits a unique fixed point.*

Let us now see what happens with the first example that we deal with.

Example 5.2. *Let us recall that the first example (1.3) was*

$$\mathrm{A} + \mathrm{B} \rightleftharpoons \mathrm{C},$$

and we already know that we can apply the deficiency zero theorem, and then conclude that there is a unique fixed point in each stoichiometric class themselves defined by

$$\begin{aligned} S &= \left\{ u \in I\!R^3 \text{ such that } \begin{pmatrix} 1 & 0 & 1 \\ 0 & 1 & 1 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \right\}, \\ &= span\left\{(1,\, 1,\, -1)^t\right\}. \end{aligned}$$

We have already shown that there is a unique intersection between the set of fixed points and a stoichiometric class, and we have also demonstrated that the system is 2*-dominant for the rate* $\lambda = 0.2$ *with the matrix* P *defined by*

$$P = \begin{pmatrix} -152.0349 & 84.2339 & -69.9704 \\ 84.2339 & -152.0349 & -69.9704 \\ -69.9704 & -69.9704 & -137.6682 \end{pmatrix}.$$

Let us now consider the two sets of vectors ΔS *and* K^-*, and find the intersection between them. We know that in the stoichiometric class, the components have to satisfy that* $u_1 = u_2$ *and* $u_1 = -u_3$*. We can then see and find what we have when we compute* $u^t P u$ *when the vector* u *satisfies the previous property. We finally find that*

$$\begin{aligned} u^t P u &= (-2 * 152.0349 - 137.6682 + 4 * 69.9704 + 2 * 84.2339)\, {u_1}^2, \\ &= 6.6114\, {u_1}^2, \end{aligned}$$

and this expression is never non-positive expect when $u = 0$*, meaning that the intersection* Q *between* ΔS *and* K^- *is only the null vector, i.e.*

$$\begin{aligned} Q &= \Delta S \cap K^-, \\ &= \{0\}. \end{aligned}$$

Then, the dimension of this space is 0*, and this is consistent with the result that we found with the deficiency zero theorem and the previous theorem.*

We can easily extend this theorem for any dimension of Q since p-dominance guarantees that trajectories will belong to the set K^-, and we know that we always stay in a space of the dimension of the stoichiometric subspace.

Theorem 5.2

If the system $\dot{x} = f(x)$ is strictly p-dominant with rate $\lambda \geq 0$, then the flow on any compact ω-limit set is topologically equivalent to a flow on a compact invariant set of a Lipschitz in $\mathbb{R}^{p_q}$, where p_q is the dimension of the largest subspace that $Q = K^- \cap \Delta S$ can contain.

This theorem can help us to know the asymptotic behaviour of the system, since we can establish the same corollary than the corollary 4.1 with p_q instead of p.

Corollary 5.1.
Under the assumptions of Theorem 5.1, every bounded solution asymptotically converges to

- *a unique fixed point if* $p_q = 0$*,*
- *a fixed point if* $p_q = 1$*,*
- *a simple attractor if* $p_q = 2$*, that is a fixed point, a set of fixed points and connecting arcs, or a limit cycle.* ⌟

5.2 Simplest reaction diagrams

For each previous reaction diagram, we computed the deficiency of the system and we studied whether the deficiency theorems could be applied to these systems. Unfortunately, we have seen that even if most of diagrams admit a zero deficiency, they are all not weakly reversible. It is then impossible to conclude about the existence of fixed points via these theorems. However, we can conclude that there doesn't exist a positive fixed point, meaning that a species at least will always disappear from the reaction if we tend to a fixed point. This result cannot be ignored since we will have to keep it in mind when we will study the spectrum of the Jacobian matrices. However, we have introduced a new theorem that can help us to know the asymptotic behaviour of the system by using both chemical reaction networks theory and p-dominance theory. Let us try to apply it in the few next chemical examples.

5.2.1 Enzymatic reaction

First of all, let us focus on the simplest enzymatic reaction

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{C} \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E}, \tag{5.4}$$

and assume that it follows the law of mass action. We have already found that the dimension of the stoichiometric subspace is two, so the dimension of the stoichiometric classes is two, and they are defined by

$$\mathcal{S} = \begin{pmatrix} s_0 \\ e_0 \\ c_0 \\ p_0 \end{pmatrix} + span\left\{ \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix} \right\}. \tag{5.5}$$

We can also find it via the differential approach. Before, we have to induce some differential equations (2.2-2.5) from this diagram (5.4), and then we will also be able to study the dominance of this differential system using the algorithmic test. The Jacobian matrix is given by

$$J = \begin{pmatrix} -k_1 e & -k_1 s & k_{-1} & 0 \\ -k_1 e & -k_1 s & k_{-1}+k_2 & 0 \\ k_1 e & k_1 s & -(k_{-1}+k_2) & 0 \\ 0 & 0 & k_2 & 0 \end{pmatrix}. \tag{5.6}$$

Let us compute the vectors $v \in \mathbb{R}^4$ such that $v^t J = 0$, or equivalently $J^t v = 0$. We have

$$\begin{pmatrix} -k_1 e & -k_1 e & k_1 e & 0 \\ -k_1 s & -k_1 s & k_1 s & 0 \\ k_{-1} & k_{-1}+k_2 & -(k_{-1}+k_2) & k_2 \\ 0 & 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

This matrix equality leads to a three-equation system defined by

$$\begin{cases} 0 &= k_1 e(-v_1 - v_2 + v_3), \\ 0 &= k_1 s(-v_1 - v_2 + v_3), \\ 0 &= k_{-1}(v_1 + v_2 - v_3) + k_2(v_2 - v_3 + v_4). \end{cases}$$

It is easy to conclude from these equations that the matrix W will be like

$$W^t = \begin{pmatrix} 1 & 0 & 1 & 1 \\ 0 & 1 & 1 & 0 \end{pmatrix}.$$

Then, the stoichiometric subspace can be rewritten like the set of vectors s such that $W^t s = 0$, which is exactly the same space than that we have defined before.

Let us now focus on the p-dominance analysis. The first step consists of studying the spectrum of the Jacobian matrix. As we can see, this matrix depends on the variables of enzyme and substrate concentrations, and it is defined with the rate constants k_1, k_{-1} and k_2. Moreover, we can assume that the study of this system will be done with initial concentration of complex and product equal to zero. This implies that the concentrations of enzyme and substrate cannot increase too much, and be greater than the initial values. Let us take for example some values for the rate constants given by

$$k_1 = 1.2,\ k_{-1} = 0.8 \text{ and } k_2 = 1.5, \tag{5.7}$$

and let us see what the trajectories will be for different initial conditions (with c_0 and p_0 assumed to be equal to zero). The result can be seen in the FIGURE 5.2. It seems clear that at the beginning, the concentration of the complex increases, decreasing then the concentrations of substrate and enzyme. The product is obtained, decreasing the concentration of the complex but increasing back the concentration of enzyme. It is then necessary to consider that the concentration of substrate can be zero. Moreover, we know from the deficiency zero theorem that it is impossible to neither have a positive fixed point nor a cycle trajectory with a positive concentration. Actually, we can try to make the same thing that we did for the example 4.2, i.e. we can find the fixed points within a stoichiometric class. The first step consists of finding the set of fixed points. We find

$$\mathcal{P} = \{(0, e, 0, p) \mid c, p \geq 0\} \cup \{(s, 0, 0, p) \mid e, p \geq 0\}.$$

This means that to be a fixed point, it has to be no complex concentration and at least no enzyme or no substrate concentration (or even both). Let us assume that $x_0 = (e_0,\ s_0,\ c_0,\ p_0)$ is the initial condition, and that $x = (x_0 + S) \cap \mathbb{R}^4_+$ is in the stoichiometric class, i.e.

$$x = \begin{pmatrix} s_0 \\ e_0 \\ c_0 \\ p_0 \end{pmatrix} + \alpha \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \end{pmatrix} + \beta \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix},$$

belongs to the set of fixed points. We have two different cases.

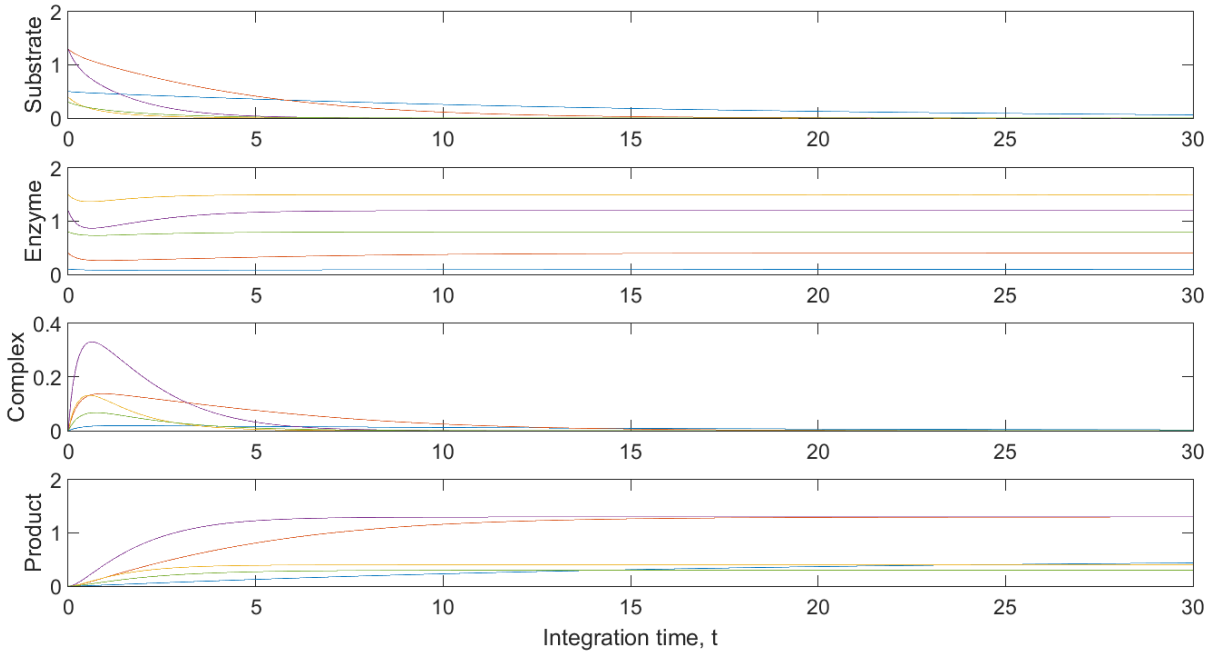


Figure 5.2: Examples of concentration trajectories for the initial conditions: $x_0 = (0.5, 0.1, 0, 0)$ in blue, $x_0 = (1.3, 0.4, 0, 0)$ in red, $x_0 = (0.4, 1.5, 0, 0)$ in yellow, $x_0 = (1.3, 1.2, 0, 0)$ in violet and $x_0 = (0.3, 0.8, 0, 0)$ in green

(i) If $e_0 = c_0 = 0$, i.e. there is neither enzyme nor complex at the beginning of the reaction, it seems logical that we find a fixed point since any of the reaction cannot be done without enzyme and a complex. We have that

$$\begin{cases} s &= 0 \\ c &= 0 \end{cases} \Leftrightarrow \begin{cases} s_0 + \alpha &= 0 \\ -\alpha - \beta &= 0 \end{cases}$$

We finally find that $\alpha = -s_0$ and $\beta = s_0$. The concentration vector becomes then

$$x^* = (0,\, 0,\, 0,\, p_0 + s_0)\,.$$

On other hand, if we assume that $e = 0$ and $c = 0$, we find that $\alpha = -\beta$ and that the point becomes

$$x^* = (s_0 + \alpha,\, 0,\, 0,\, p_0 - \alpha)\,.$$

The solutions that we get can only be possible under the assumption that $e_0 = c_0 = 0$. But, the initial condition x_0 is a fixed point under this condition.

(ii) If e_0 and c_0 are non null, then it is impossible to have $e = 0$ and $c = 0$ at the same time. So, the only solution is when $s = 0$ and $c = 0$. Then, we have that

$$x^* = (0,\, e_0 + c_0,\, 0,\, p_0 + s_0 + c_0)\,,$$

which seems quite logical and is exactly what we got with the examples (FIGURE 5.2).

We can make the assumption that the concentrations of enzyme and substrate will be between two values, i.e.

$$0 \leq s(t) \leq 5 \qquad \text{and} \qquad 0.05 \leq e(t) \leq 5.$$

Under these assumptions, the spectrum of the Jacobian matrix gives the FIGURE 5.3 where we can see that there are actually four groups of eigenvalues. For each Jacobian

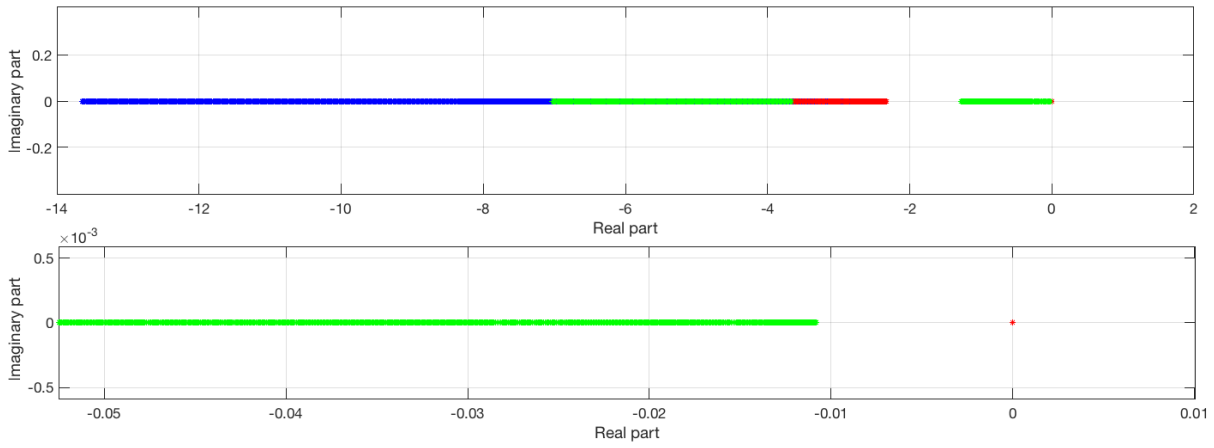


Figure 5.3: Spectrum analysis of the Jacobian matrix (5.6) of (5.4)

matrix, we have two null eigenvalues (0 and a value of order 10^{-14}) that prevent us from having 0 or 1-dominance. The two other eigenvalues are either between -14 and -2.3, or between 0.005 and -1.3. This means that theoretically we can find 2-dominance with rate $\lambda = 0.01$ and 3-dominance with rate $\lambda = 2$. In practice, we can use CVX with SeDuMi to find the matrix P that we are looking for. Let us demonstrate the 3-dominance of the system by finding a symmetric matrix P of inertia $(3, 0, 1)$ that satisfies the linear matrix inequalities (4.4) for $\lambda = 2$ and some ε. Convex relaxation can be used with four matrices defined as the Jacobian matrix evaluated at four different points:

$$\begin{aligned} p_1 &= (0,\, 0.05,\, 0,\, 0)^t, & p_2 &= (5,\, 0.05,\, 0,\, 0)^t, \\ p_3 &= (0,\, 5,\, 0,\, 0)^t, & p_4 &= (5,\, 5,\, 0,\, 0)^t. \end{aligned}$$

The matrix P given by

$$P = \begin{pmatrix} -9.4312 & 1.6198 & -6.9794 & -2.2823 \\ 1.6198 & -6.8292 & -5.5176 & 1.5575 \\ -6.9794 & -5.5176 & -8.1448 & -1.1252 \\ -2.2823 & 1.5575 & -1.1252 & -3.1467 \end{pmatrix}$$

of inertia $(3, 0, 1)$ satisfies then the linear matrix inequalities of the convex relaxation for $\lambda = 2$ and $\varepsilon = 0.001$. The system is then 3-dominant. We would like to know the intersection of the two spaces that we have defined before, i.e.

$$Q = \left\{\delta x \mid \delta x^t\, P\, \delta x < 0\right\} \cap \left\{\delta_x \mid W^t \delta x = 0\right\}.$$

To do this, we can consider some combinations of the two vectors that spanned the stoichiometric subspace, and then check the sign of the expression $\delta x^t\, P\, \delta x$. Let us then take a vector δx that belongs to the set ΔS, i.e. this vector can be written as a linear combination of two vectors

$$\delta x = \alpha \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \end{pmatrix} + \beta \begin{pmatrix} 0 \\ 1 \\ -1 \\ 1 \end{pmatrix} = \begin{pmatrix} \alpha \\ \alpha + \beta \\ -(\alpha + \beta) \\ \beta \end{pmatrix},$$

where α and β are real parameters. We can now compute the expression $\delta x^t\, P\, \delta x$ under this assumption. We find a second degree expression given by

$$\begin{aligned} \delta x^t\, P\, \delta x &= -1.7201\, \beta^2 + 10.1216 \alpha\, \beta + 3.8284 \alpha^2, \\ &= -1.7201\, (\beta + 0.3566\alpha)\, (\beta - 6.2403\alpha), \end{aligned}$$

and that allows us to say that the expression will be negative either when β is bigger than -0.3556α and 6.2409α, or when β is smaller than the same values. These conditions define two zones that are shown FIGURE 5.4, where we have developed the vectors in the basis formed by the vectors that spanned the stoichiometric subspace, described in (5.5). This space actually contains a 1-dimensional subspace, meaning that we can conclude that there exists at least one fixed point within each stoichiometric class.

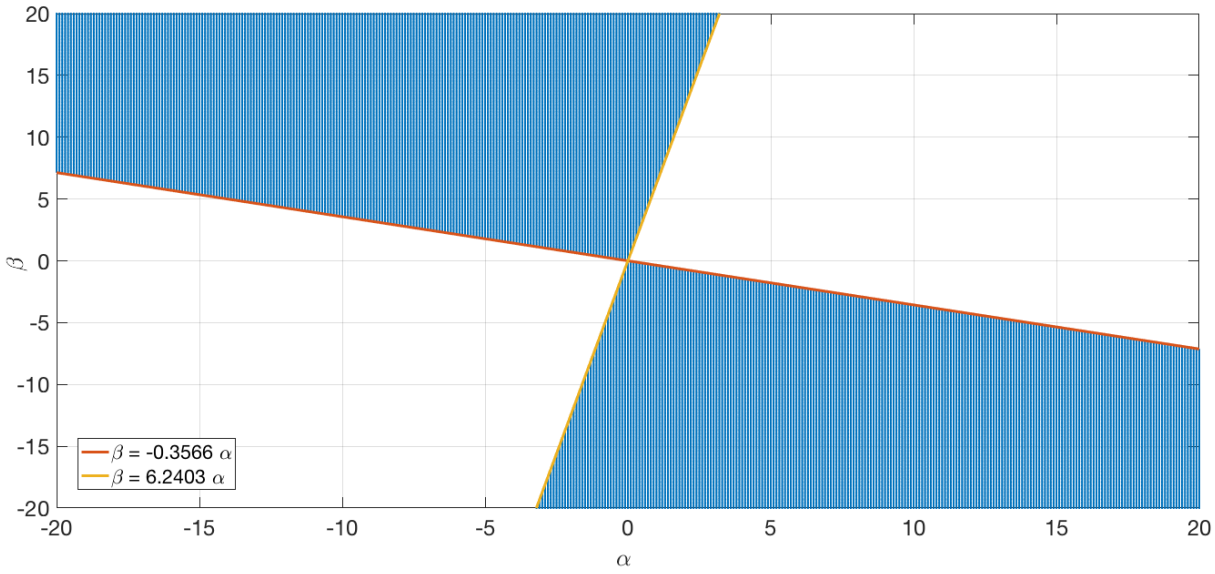


Figure 5.4: Set of vectors q in Q where $q = \alpha(1, 1, -1, 0)^t + \beta(0, 1, -1, 1)^t$

Besides, it is impossible to find a matrix P with the rate $\lambda = 0.001$ because there is always a positive eigenvalue among those of the matrices

$$A_i^t P + P A_i + 2\lambda P.$$

It seems that the method has not enough accuracy to be able to find this matrix, even if it could be actually possible.

Remark: in a previous example, we have suggested that we could slightly modify the Jacobian matrix to make the spectrum analysis easier. For this system (5.6), we can rewrite it like

$$J = k_1 \begin{pmatrix} -e & -s & K_1 & 0 \\ -e & -s & K_1 + K_2 & 0 \\ e & s & -K_1 - K_2 & 0 \\ 0 & 0 & K_2 & 0 \end{pmatrix} \tag{5.8}$$

with $K_1 = k_{-1}/k_1$ and $K_2 = k_2/k_1$. The spectrum analysis of this matrix is done in FIGURE 5.5, where we can see that we have the same disposition but different values. For example, 3-dominance could be found with a rate $\lambda = 1.7$, rather than 2 for the initial matrix. This new matrix will be even more useful for robust analysis since the number of parameters is reduced.

We know that the fixed points look like $x^* = (0, e, 0, p)$, with e and p, two non-negative values. We also know that the Jacobian matrix only depends on the value of the substrate and the enzyme concentrations. So, if we assume that $e = 1$, we can evaluate the Jacobian matrix at this point and look for a matrix P that would satisfy the linear inequality. We find then a matrix P of inertia 2 such that the intersection with the

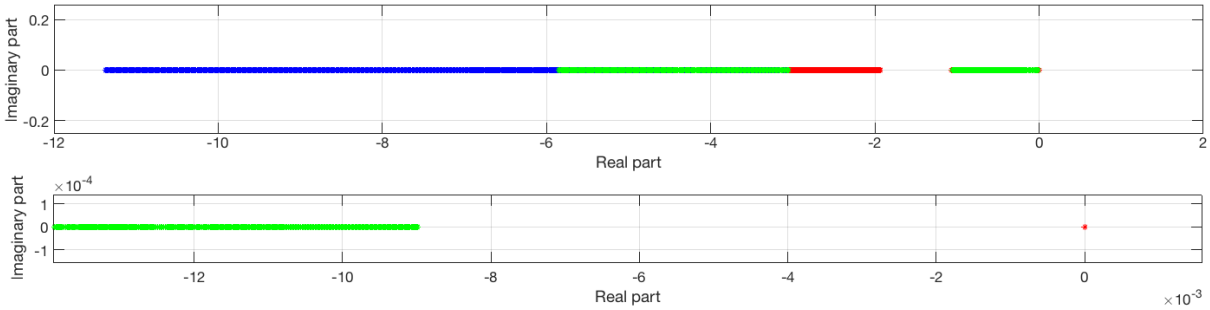


Figure 5.5: Spectrum analysis of the Jacobian matrix (5.8)

stoichiometric subspace is 0-dimensional, meaning that there exists a unique fixed point obviously. What happens if we move away from the fixed point? Let us assume that the substrate concentration is between 0 and 0.6, and the enzyme concentration between 0.4 and 1.6. Then, we can find a matrix P defined by

$$P = \begin{pmatrix} -15.3769 & 19.5308 & -1.6252 & -24.4335 \\ 19.5308 & -42.7626 & -31.4748 & 10.8809 \\ -1.6252 & -31.4748 & -37.1094 & -12.5295 \\ -24.4335 & 10.8809 & -12.5295 & -22.1929 \end{pmatrix}$$

of inertia 2 for the rate 0.2 and $\varepsilon = 10^{-4}$, and if we look at the intersection with ΔS, we only find the vector null. Indeed, if we do exactly the same thing than before, we find that the expression $V(\delta_x)$ becomes

$$\delta x^t \, P \, \delta x \; = \; 10.0128\alpha^2 \; + \; 6.4213\alpha\beta \; + \; 7.7057\beta^2.$$

This expression is always non-negative whatever the values of α and β we take. It is only null when both α and β are 0, meaning that the intersection Q is 0-dimensional.We can then conclude that there exists a unique fixed point thanks to the theorem demonstrated before.

5.2.2 Competitive inhibitors

Let us now focus on the reaction diagram of competitive inhibitor, that is

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{C}_1 \xrightarrow{\mathrm{k}_2} \mathrm{P} + \mathrm{E},$$

$$\mathrm{E} + \mathrm{I} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{C}_2,$$

and we assume that this system follows the law of mass action. We have already shown that the stoichiometric classes are defined by

$$\mathcal{S} = \begin{pmatrix} s_0 \\ e_0 \\ c_{10} \\ c_{20} \\ i_0 \\ p_0 \end{pmatrix} + span \left\{ \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ -1 \\ 0 \\ 0 \\ 1 \end{pmatrix}, \begin{pmatrix} 1 \\ 0 \\ 0 \\ -1 \\ 1 \\ 0 \end{pmatrix} \right\}$$

whose dimension is then $s = 3$. As we did before, we would like to find the stoichiometric subspace thanks to the differential approach and to study the dominance of this system. To do this, we will use the differential equations (2.10-2.15) to find the Jacobian matrix and analyse the spectrum of this matrix. The Jacobian matrix is given by

$$J = \begin{pmatrix} -k_1 e & -k_1 s & k_{-1} & 0 & 0 & 0 \\ -k_1 e & -k_1 s - k_3 i & k_{-1} + k_2 & k_{-3} & -k_3 e & 0 \\ k_1 e & k_1 s & -(k_{-1} + k_2) & 0 & 0 & 0 \\ 0 & k_3 i & 0 & -k_{-3} & k_3 e & 0 \\ 0 & -k_3 i & 0 & k_{-3} & -k_3 e & 0 \\ 0 & 0 & k_2 & 0 & 0 & 0 \end{pmatrix}, \tag{5.9}$$

and depends on the variables e, s and i. First of all, let us find the vectors $v \in \mathbb{R}^6$ such that $v^t J = 0$. This leads to a 6-dimensional system of equations given by

$$\begin{cases} 0 &= k_1 e\,(-v_1 - v_2 + v_3), \\ 0 &= k_1 s\,(-v_1 - v_2 + v_3) + k_3\,(-v_2 + v_4 - v_5), \\ 0 &= k_{-1}\,(v_1 + v_2 - v_3) + k_2\,(v_2 - v_3 + v_6), \\ 0 &= k_{-3}\,(v_2 - v_4 + v_5), \\ 0 &= k_3 e\,(-v_2 + v_4 - v_5), \end{cases}$$

and it could be reduced to three equations. Finally, we can find a matrix W defined by

$$W^t = \begin{pmatrix} 1 & 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & -1 & 0 \\ 0 & 0 & 0 & 1 & 1 & 0 \end{pmatrix}.$$

Then, we can find the stoichiometric subspace as the set of vector s such that $W^t s = 0$. In this way, we can find exactly the same space than by the previous definition.

Now, given some values for the rate constants, we can analyse the spectrum of this matrix but before all, let us observe some trajectories to know which assumptions we have to make for the study of the spectrum of the Jacobian matrix. We can see in FIGURE 5.6 that the substrate and the first complex disappear from the reaction and each concentration tends to a constant value after a few integration time. This allows us to know which type of assumption that we can make. The substrate concentration will be between zero and five for example, the enzyme concentration will be between 0.05 and

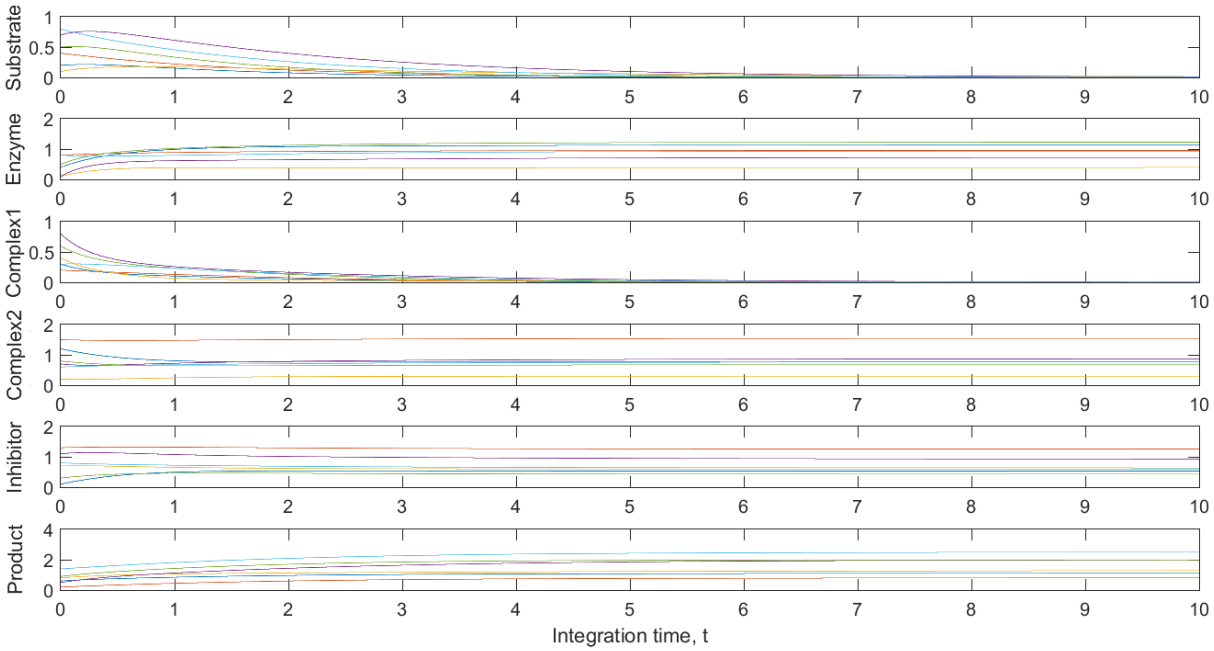


Figure 5.6: Examples of trajectories for some initial conditions for the equations (2.10-2.15)

5 and the inhibitor concentration as well. If we assume that the rate constants have the following values:

$$k_1 = 1.2,\ k_{-1} = 0.8,\ k_2 = 1.5,\ k_3 = 0.9 \text{ and } k_{-3} = 0.7,$$

we can finally study the spectrum of the Jacobian matrix (5.9) under these assumptions. The result is illustrated in FIGURE 5.7, where we can see that, at first glance, there is no value that can divide the eigenvalues. If we look into the details, we can see that there is no eigenvalues between -0.01 and 0. This means that we could find a matrix P with the rate $\lambda = 0.01$ theoretically. Unfortunately, it is more complicated in fact since it is not possible do to it numerically. However, we can do it for the rate $\lambda = 18$ for example, and we find the matrix

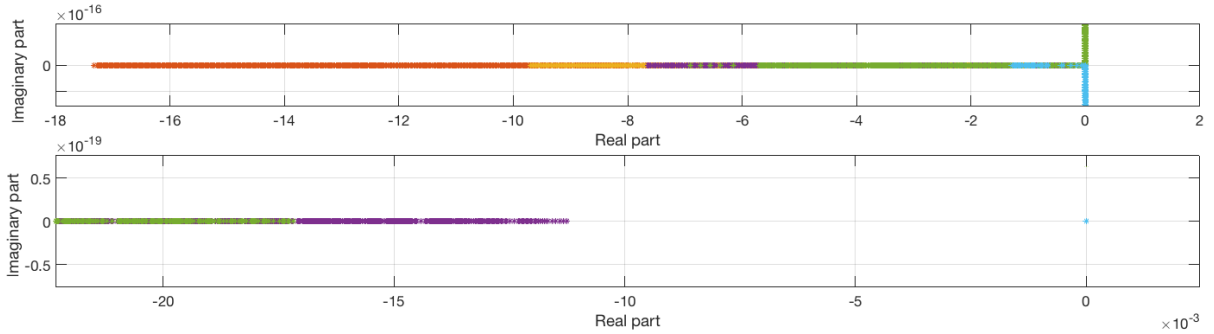


Figure 5.7: Spectrum analysis of the Jacobian matrix (5.9) of the competitive inhibitor diagram under the assumptions that $0 \leq s(t) \leq 5$ and $0.05 \leq e(t), i(t) \leq 5$

$$P = \begin{pmatrix} -2.0154 & -0.3262 & 0.1077 & -0.0413 & -0.0426 & 0.0081 \\ -0.3262 & -2.2948 & 0.1362 & 0.0568 & -0.2571 & 0.0158 \\ 0.1077 & 0.1362 & -1.7268 & 0.0543 & -0.0311 & 0.0575 \\ -0.0413 & 0.0568 & 0.0543 & -1.6415 & 0.1035 & -0.0055 \\ -0.0426 & -0.2571 & -0.0311 & 0.1035 & -1.9047 & 0.0063 \\ 0.0081 & 0.0158 & 0.0575 & -0.0055 & 0.0063 & -1.6260 \end{pmatrix},$$

of inertia 6, which doesn't really help us. So the most interesting information for this system is the dimension of the stoichiometric classes, since it allows us to know that the asymptotic behaviour will be at most in a 3-dimensional space. Let us notice that if we could find a matrix P for the rate $\lambda = 0.01$, it would imply that the system is 3-dominant. So, at first, this result doesn't really help us. Moreover, it seems stupid to compute the intersection between the two spaces defined by W and P since the matrix P will define the whole space of $\mathbb{R}^6$ actually.

Since our last assumptions seem to lead to an unexpected result, let us reduce the space of convex relaxation. Let us assume for example that the species concentrations belong to a smaller space, i.e.

$$0 \leq s(t) \leq 1 \quad \text{and} \quad 0.05 \leq e(t), i(t) \leq 1. \tag{5.10}$$

This allows us to get a similar spectrum than that one illustrated in FIGURE 5.7, but with a separation for $\lambda = 0.7$ as illustrated with the FIGURE 5.8. We can then finally search for a matrix P that will satisfy the linear matrix inequalities for the Jacobian matrix evaluated at 8 different points given by

$$\begin{aligned} p_1 &= (0,\, 0.05,\, 0,\, 0,\, 0.05,\, 0)^t, & p_2 &= (1,\, 0.05,\, 0,\, 0,\, 0.05,\, 0)^t, \\ p_3 &= (0,\, 1,\, 0,\, 0,\, 0.05,\, 0)^t, & p_4 &= (0,\, 0.05,\, 0,\, 0,\, 1,\, 0)^t, \\ p_5 &= (1,\, 1,\, 0,\, 0,\, 0.05,\, 0)^t, & p_6 &= (0,\, 1,\, 0,\, 0,\, 1,\, 0)^t, \\ p_7 &= (1,\, 0.05,\, 0,\, 0,\, 1,\, 0)^t, & p_8 &= (1,\, 1,\, 0,\, 0,\, 1,\, 0)^t, \end{aligned}$$

and find the matrix P given by

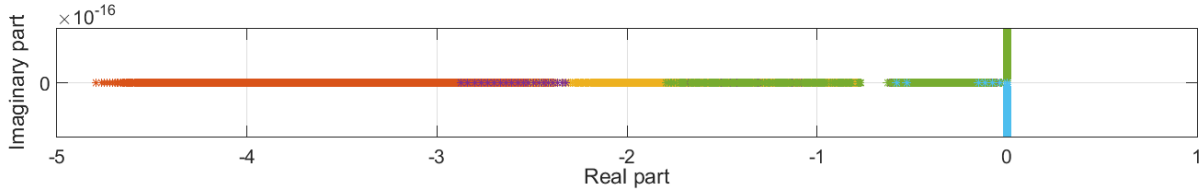


Figure 5.8: Spectrum analysis of the Jacobian matrix (5.9) of the competitive inhibitor diagram under the assumptions (5.10)

$$P = \begin{pmatrix} -14.1891 & 4.9762 & -8.8110 & 4.2838 & 0.5737 & -3.8729 \\ 4.9762 & -9.0783 & -10.9088 & -7.5788 & 3.3762 & 2.2770 \\ -8.8110 & -10.9088 & -18.2386 & -7.3771 & 3.7771 & -4.9351 \\ 4.2838 & -7.5788 & -7.3771 & -1.6662 & -9.4954 & 1.1452 \\ 0.5737 & 3.3762 & 3.7771 & -9.4954 & -11.5518 & -1.3223 \\ -3.8729 & 2.2770 & -4.9351 & 1.1452 & -1.3223 & -6.6078 \end{pmatrix}$$

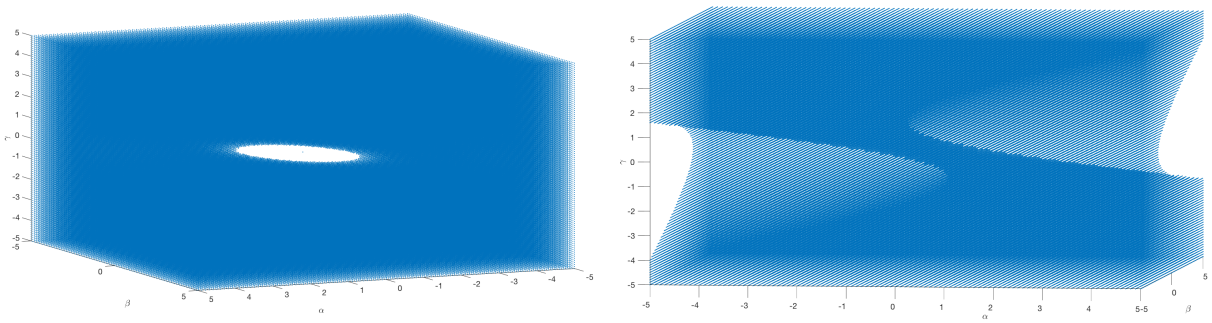
whose inertia is 4, meaning that the system is 4-dominant in the space that we have defined via the convex relaxation. It seems then that neither the dominance of the system nor the dimension of the stoichiometric subspace can help us to know the asymptotic behaviour of the system. Let us then focus on the intersection of these two spaces. Since the stoichiometric subspace is 3-dimensional, it will be more difficult than for the previous system obviously. Let us consider a vector δ_x that belongs to ΔS, it means that it can be expressed like

$$\delta x = \alpha \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix} + \beta \begin{pmatrix} 0 \\ 1 \\ -1 \\ 0 \\ 0 \\ 1 \end{pmatrix} + \gamma \begin{pmatrix} 1 \\ 0 \\ 0 \\ -1 \\ 1 \\ 0 \end{pmatrix},$$

and let us compute the expression $\delta x\, P\, \delta x$ to check the sign of this expression. We find

$$\delta x^t\, P\, \delta x = 7.8859\alpha^2 + 2.3169\beta^2 - 15.8366\gamma^2 + 23.2538\alpha\beta - 8.6225\alpha\gamma + 14.4949\beta\gamma.$$

It is not as easy as before to know the sign of this expression, but it seems that the sign can change. First of all, if we take each basis vector and we check the sign, we find that they are all positive, but this doesn't mean that any linear combination of these three vector will lead to a positive value since $V(\delta x)$ is not a linear function. For example, the vector $v_1 - v_2$ leads to a negative value, and then belongs to the intersection Q. In a more general way, we can see in the FIGURES 5.9a and 5.9b the intersection Q expressed in the basis of the three vectors of ΔS.



(a) (b)

Figure 5.9: Set of vectors q in Q expressed in the basis of the stoichiometric subspace, i.e. $q = \alpha(1, 1, -1, 0, 0, 0) + \beta(0, 1, -1, 0, 0, 1) + \gamma(0, 1, 0, -1, 1, 0)$

5.2.3 Allosteric inhibitors

After the diagram of the competitive inhibitor, we can naturally care about the reaction diagram of allosteric inhibitors given by

$$\begin{gathered}
\mathrm{E}+\mathrm{S} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{X} \xrightarrow{\mathrm{k}_2} \mathrm{P}+\mathrm{E}, \\
\mathrm{E}+\mathrm{I} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{Y}, \\
\mathrm{X}+\mathrm{I} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{Z}, \\
\mathrm{Y}+\mathrm{S} \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{Z}.
\end{gathered}$$

We have already studied the stoichiometric subspace of this diagram in the section 2.3.2. From this analysis, we can easily say that the stoichiometric compatibility classes are defined by

$$\mathcal{S} = \begin{pmatrix} s_0 \\ e_0 \\ i_0 \\ x_0 \\ y_0 \\ z_0 \\ p_0 \end{pmatrix} + span \left\{ \begin{pmatrix} 1 \\ 1 \\ 0 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ 0 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 1 \\ -1 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 0 \\ -1 \\ 0 \end{pmatrix} \right\},$$

and that their dimension is four. As always, we can find this subspace with the Jacobian matrix. First, we can induce differential equations from this diagram by using the law of mass action that are given by

$$\frac{ds}{dt} = k_{-1}(x+z) - k_1 s(e+y), \tag{5.11}$$

$$\frac{de}{dt} = (k_{-1}+k_2)x - (k_1 s + k_3 i)e + k_{-3}y, \tag{5.12}$$

$$\frac{di}{dt} = k_{-3}(y+z) - k_3 i(e+x), \tag{5.13}$$

$$\frac{dx}{dt} = -(k_{-1}+k_2)x + k_1 es - k_3 xi + k_{-3}z, \tag{5.14}$$

$$\frac{dy}{dt} = -(k_{-3}+k_1 s)y + k_3 ei + k_{-1}z, \tag{5.15}$$

$$\frac{dz}{dt} = -(k_{-1}+k_{-3})z + k_1 ys + k_3 xi, \tag{5.16}$$

$$\frac{dp}{dt} = k_2 x, \tag{5.17}$$

Obviously, since the reaction diagram becomes more difficult, the differential equations induced become also more difficult and more complicated to study. This difficulty can

be notably seen in the Jacobian matrix since it will depend on more and more variables, implying that the analysis spectrum is more and more difficult. By the way, the Jacobian matrix of the system is given by

$$J = \begin{pmatrix} -k_1(e+y) & -k_1 s & 0 & k_{-1} & -k_1 s & k_{-1} & 0 \\ -k_1 e & -(k_1 s + k_3 i) & -k_3 e & k_{-1} + k_2 & k_{-3} & 0 & 0 \\ 0 & -k_3 i & -k_3(e+x) & -k_3 i & k_{-3} & k_{-3} & 0 \\ k_1 e & k_1 s & -k_3 x & -(k_{-1} + k_2) - k_3 i & 0 & k_{-3} & 0 \\ -k_1 y & k_3 i & k_3 e & 0 & -(k_{-3} + k_1 s) & k_{-1} & 0 \\ k_1 y & 0 & k_3 x & k_3 i & k_1 s & -(k_{-1} + k_{-3}) & 0 \\ 0 & 0 & 0 & k_2 & 0 & 0 & 0 \end{pmatrix},$$

The search for vector $v \in \mathbb{R}^7$ such that $J^t v = 0$ is more difficult as well. Without going into the details, we can finally find the matrix W defined by

$$W^t = \begin{pmatrix} 1 & 0 & 0 & 1 & 0 & 1 & 1 \\ 0 & 1 & 0 & 1 & 1 & 1 & 0 \\ 0 & 0 & 1 & 0 & 1 & 1 & 0 \end{pmatrix}.$$

This matrix can allow us to find the set of vectors s such that $W^t s = 0$, which is exactly the same space than the stoichiometric subspace. As we did since the first system, we will have to assume that the concentrations are bounded by some values and we are going to define them thanks to some examples of trajectories illustrated in FIGURE 5.10. We can clearly see that the substrate and two of the complexes concentrations tend to zero after a few integration time. Then, let us assume that

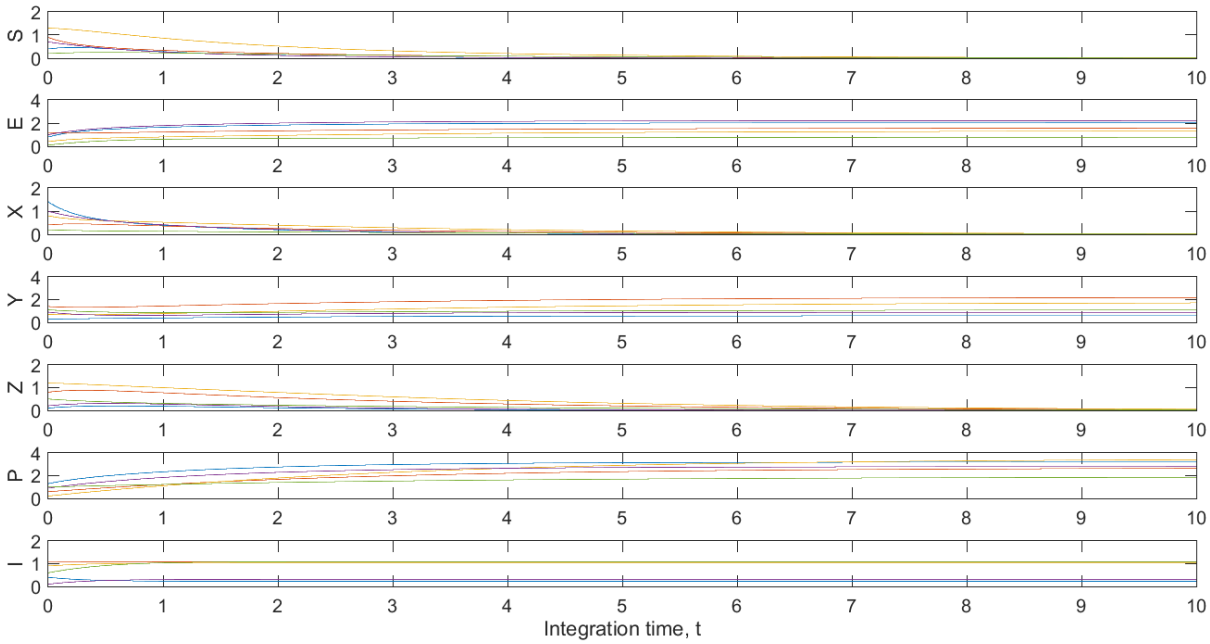


Figure 5.10: Examples of trajectories for some initial conditions for the equations (5.11-5.17)

$$0 \leq s(t), x(t), z(t) \leq 1 \quad \text{and} \quad 0.05 \leq e(t), i(t), y(t), p(t) \leq 1.$$

We can then study the spectrum of this matrix under the assumptions that we have described above, and let assume for example that the rate constants are given by

$$k_1 = 1.2, \quad k_{-1} = 0.8, \quad k_2 = 1.5, \quad k_3 = 0.9 \quad \text{and} \quad k_{-3} = 0.7.$$

Finally we can find a matrix P defined by

$$P = \begin{pmatrix} -13.8297 & 3.1660 & 2.5724 & -10.8362 & 6.4841 & -12.3751 & -3.3247 \\ 3.1660 & -12.3800 & 6.1796 & -12.6305 & -8.3768 & -4.5150 & 3.8360 \\ 2.5724 & 6.1796 & -14.6764 & 9.7243 & -12.7364 & -9.4237 & -1.9176 \\ -10.8362 & -12.6305 & 9.7243 & -18.8445 & -2.6980 & -12.4721 & -4.0430 \\ 6.4841 & -8.3768 & -12.7364 & -2.6980 & -3.9768 & -1.7910 & 3.1947 \\ -12.3751 & -4.5150 & -9.4237 & -12.4721 & -1.7910 & -8.0958 & -0.1065 \\ -3.3247 & 3.8360 & -1.9176 & -4.0430 & 3.1947 & -0.1065 & -10.2015 \end{pmatrix},$$

whose inertia is 4 since the eigenvalues are -42.3150, -27.3926, -25.0047, -9.3426, 3.5301, 5.1748 and 13.3454. This means that the system is 4-dominant in the space defined by the convex relaxation. We could now look at the intersection between K^- and ΔS, but the problem is that in this case, it is impossible de see what the intersection looks like since ΔS is 4-dimensional. This example raises a question about the way that we can find the dimension p_q.

5.2.4 Cooperativity

Finally, we can study the last theoretical reaction diagram that we have introduced, which is the cooperativity reaction diagram given by

$$\mathrm{S} + \mathrm{E} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} \mathrm{C_1} \xrightarrow{\mathrm{k_2}} \mathrm{P} + \mathrm{E},$$

$$\mathrm{S} + \mathrm{C_1} \underset{\mathrm{k_{-3}}}{\overset{\mathrm{k_3}}{\rightleftharpoons}} \mathrm{C_2} \xrightarrow{\mathrm{k_4}} \mathrm{P} + \mathrm{C_1}.$$

Hopefully it seems that this system is easier than the last ones. The analysis of the stoichiometric subspace has already been done, and that allows us to define the stoichiometric compatibility classes by

$$\mathcal{S} = \begin{pmatrix} s_0 \\ e_0 \\ c_{10} \\ c_{20} \\ p_0 \end{pmatrix} + span \left\{ \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ -1 \\ 0 \\ 1 \end{pmatrix}, \begin{pmatrix} 1 \\ 0 \\ 1 \\ -1 \\ 0 \end{pmatrix} \right\},$$

whose dimension is three. This will allow us to illustrate the intersection Q in what follows, in contrast to the previous example. This subspace can also be found via the

differential approach. First, some differential equations (2.18-2.22) can be induced from this diagram, and the Jacobian matrix is

$$J = \begin{pmatrix} -k_3c_1 - k_1e & -k_1s & k_{-1} - k_3s & k_{-3} & 0 \\ -k_1e & -k_1s & k_{-1} + k_2 & 0 & 0 \\ -k_3c_1 + k_1e & k_1s & -(k_{-1} + k_2 + k_3s) & k_{-3} + k_4 & 0 \\ k_3c_1 & 0 & k_3s & -(k_{-3} + k_4) & 0 \\ 0 & 0 & k_2 & k_4 & 0 \end{pmatrix}, \tag{5.18}$$

which depends on the concentrations of substrate, enzyme and the first complex denoted by s, e and c_1 respectively. We can look for the vector $v \in \mathbb{R}^4$ such that $J^t v = 0$, and we find the 4-dimensional system of equations given by

$$\begin{cases} 0 &= k_3c_1\,(-v_1 - v_3 + v_4) + k_1e\,(-v_1 - v_2 + v_3), \\ 0 &= k_1s\,(-v_1 - v_2 + v_3), \\ 0 &= k_{-1}\,(v_1 + v_2 - v_3) + k_3s\,(-v_1 - v_3 + v_4) + k_2\,(v_2 - v_3 + v_5), \\ 0 &= k_{-3}\,(v_1 + v_3 - v_4) + k_4\,(v_3 - v_4 + v_5). \end{cases}$$

These equations can lead to a set of solutions, and to the matrix W defined by

$$W^t = \begin{pmatrix} 1 & 0 & 1 & 2 & 1 \\ 0 & 1 & 1 & 1 & 0 \end{pmatrix}.$$

Finally, the stoichiometric subspace can be defined as the set of vector s such that $W^t s = 0$, and this leads to the same set than with the previous definition.

Let us now focus on the study of dominance of this system. We know that the Jacobian matrix depends on three variables, i.e. the substrate, enzyme and complex concentrations. We would like to know which bound we have to define to study the spectrum of the Jacobian matrix. Let us take some initial conditions and see what happens with time in FIGURE 5.11. We can clearly see that the substrate concentrations and the complex concentrations tend to be zero after a few integration time, while the enzyme and product concentrations are never zero. This allows us to define the following bounds:

$$0 \leq s(t), c1(t), c2(t) \leq 5 \qquad \text{and} \qquad 0.05 \leq e(t), p(t) \leq 5.$$

It is now possible to study the spectrum of the Jacobian matrix under these assumptions if we assume that the rate constants have some fixed values. For example, we take

$$k_1 = 1.2, \;\; k_{-1} = 0.8, \;\; k_2 = 1.5, \;\; k_3 = 0.9, \;\; k_{-3} = 0.7 \;\; \text{and} \;\; k_4 = 1.$$

We can guess via the FIGURE 5.12 that we could divide the eigenvalues with a rate of $\lambda = 1.4$. It seems that three of the eigenvalues are bigger than $-\lambda = -1.4$, and two other ones are smaller meaning that we should expect 3-dominance. Indeed, the first eigenvalue is between -13 and -2, the second one belongs to the interval $]-13, -1.5]$, the third one sits between -1.3 (not included) and -0.01 more or less, the fourth and fifth ones are

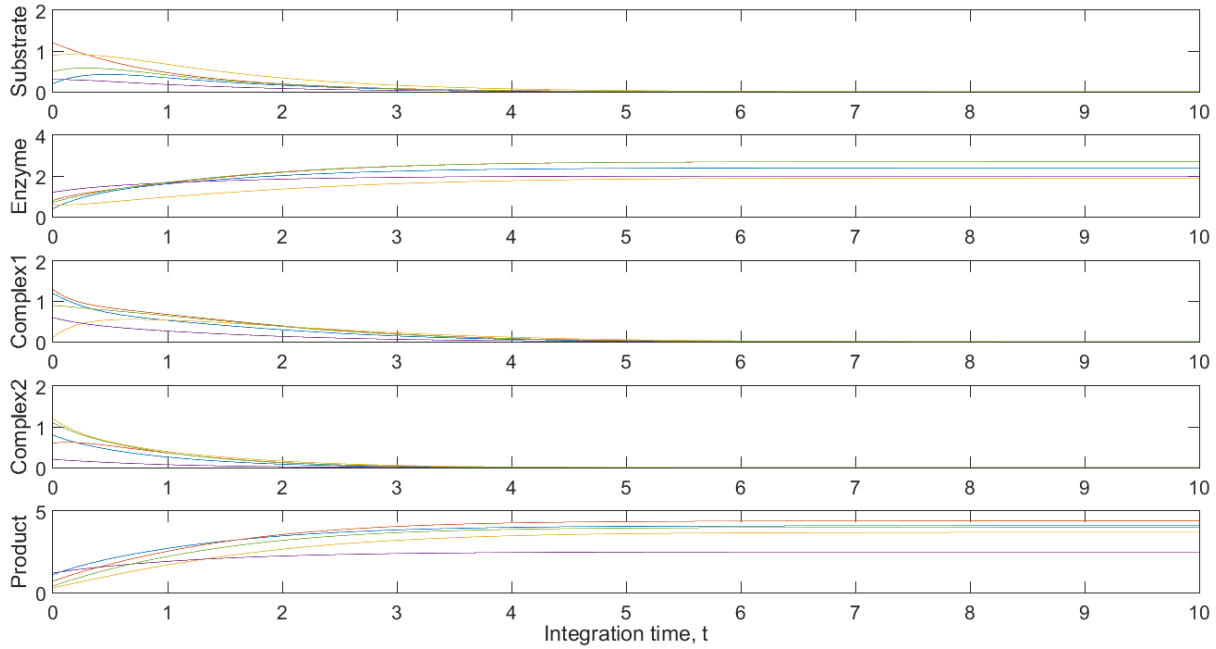


Figure 5.11: Examples of trajectories for some initial condition for the equations (2.18-2.22)

between 0 (included) and 0.4. Unfortunately, it is numerically impossible to find such a matrix P. We decide then to reduce the space that we consider, and we assume that

$$0 \leq s(t), c1(t), c2(t) \leq 2.2 \qquad \text{and} \qquad 0.05 \leq e(t), p(t) \leq 2.2.$$

Under these assumptions, we can study the spectrum analysis which is just a small part

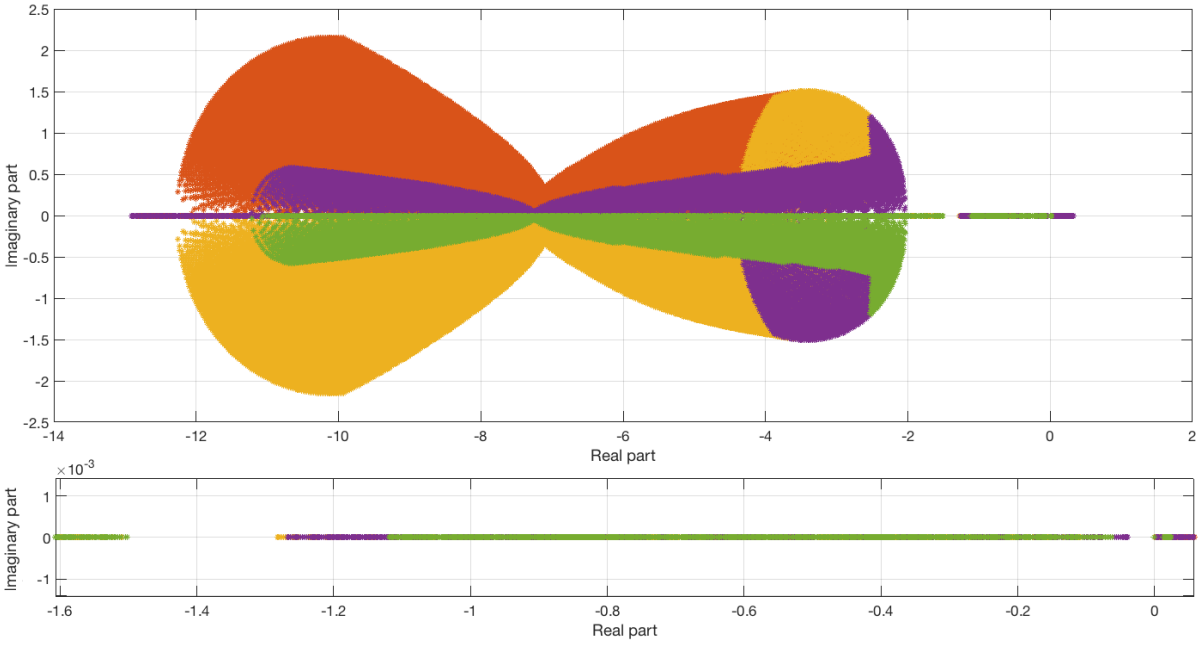


Figure 5.12: Spectrum analysis of the Jacobian matrix (5.18)

of the big one, illustrated in FIGURE 5.12. Then if we consider $\lambda = 1.1$, we can find a matrix P given by

$$P = \begin{pmatrix} -7.2832 & 3.8387 & -3.8839 & -13.4568 & -2.4906 \\ 3.8387 & -9.7814 & -5.8967 & -5.4280 & 3.3850 \\ -3.8839 & -5.8967 & -6.2872 & -13.9224 & 0.2015 \\ -13.4568 & -5.4280 & -13.9224 & -15.2119 & -1.4400 \\ -2.4906 & 3.3850 & 0.2015 & -1.4400 & -3.8533 \end{pmatrix},$$

whose inertia is 3, meaning that the system is 3-dominant. Let us now look at the intersection between the set K^- and the stoichiometric subspace ΔS. In practice, let us consider a vector δx that belongs to ΔS, i.e.

$$\delta x = \alpha \begin{pmatrix} 1 \\ 1 \\ -1 \\ 0 \\ 0 \end{pmatrix} + \beta \begin{pmatrix} 0 \\ 1 \\ -1 \\ 0 \\ 1 \end{pmatrix} + \gamma \begin{pmatrix} 1 \\ 0 \\ 1 \\ -1 \\ 0 \end{pmatrix} = \begin{pmatrix} \alpha + \gamma \\ \alpha + \beta \\ -\alpha - \beta + \gamma \\ -\gamma \\ \beta \end{pmatrix},$$

and let us now compute the expression $\delta x \, P \, \delta x$. We find

$$\delta x^t \, P \, \delta x = 3.8868\alpha^2 - 1.7615\beta^2 + 18.2084\gamma^2 + 8.2806\alpha\beta + 3.8166\alpha\gamma - 2.4610\beta\gamma.$$

As we could expect, this expression is quite complicated to study. It seems easier to look at the FIGURE 5.13 where we can see the vectors that belong to Q, expressed in the vector basis of ΔS. Unfortunately, we have the same problem as before since we can not find the dimension p_q of the biggest subspace that Q can contain. This question could be answered with a following work.

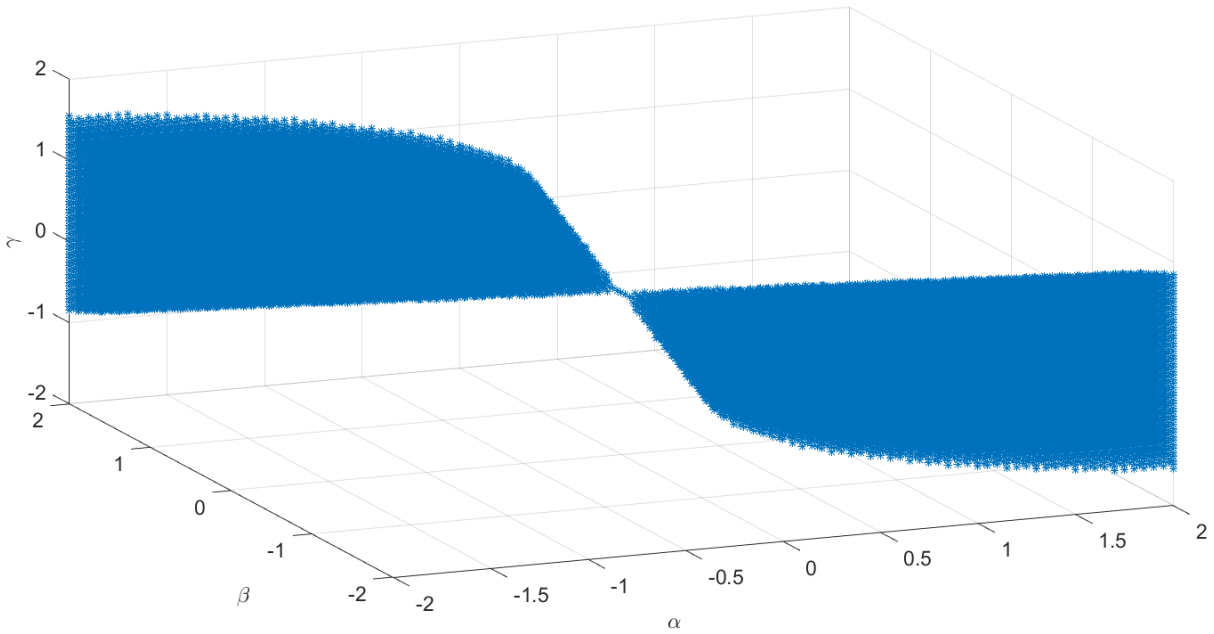


Figure 5.13: Set of vectors q in Q expressed in the basis of the stoichiometric subspace, i.e. $q = \alpha(1, 1, -1, 0, 0) + \beta(0, 1, -1, 0, 1) + \gamma(1, 0, 1, -1, 0)$

5.3 Preliminary analysis of glycolic oscillations

In this section, we would like to explain the oscillatory behaviour of glycolysis with the p-dominance theory and the space $K^- = \{\delta_x \mid \delta_x^t P \delta_x < 0\}$, and the stoichiometric subspace ΔS. Let us remind that the Sel'kov diagram is given by

$$\gamma \mathrm{S}_2 + \mathrm{E} \underset{\mathrm{k}_{-3}}{\overset{\mathrm{k}_3}{\rightleftharpoons}} \mathrm{X}_1,$$

$$\mathrm{S}_1 + \mathrm{X}_1 \underset{\mathrm{k}_{-1}}{\overset{\mathrm{k}_1}{\rightleftharpoons}} \mathrm{X}_2 \xrightarrow{\mathrm{k}_2} \mathrm{X}_1 + \mathrm{S}_2,$$

$$0 \xrightarrow{\nu_1} \mathrm{S}_1,$$

$$\mathrm{S}_2 \xrightarrow{\nu_2} 0,$$

where X_1 denotes the complex ES_2^γ formed with the enzyme and γ molecules of S_2, and X_2 denotes the complex $S_1 E S_2^\gamma$ formed with X_1 and S_1. There are eight different complexes, so $n = 8$. Finally, the stoichiometric subspace is given by

$$\begin{aligned}
\mathcal{S} &= span\{\gamma S_2 + E - X_1,\ S_1 + X_1 - X_2,\ S_2 + X_1 - X_2,\ S_1, -S_2\}, \\
&= span\{\gamma S_2 + E - X_1,\ S_2 + X_1 - X_2,\ S_1, -S_2\}, \\
&= span\left\{ \begin{pmatrix} 0 \\ \gamma \\ 1 \\ -1 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ 1 \\ 0 \\ 1 \\ -1 \end{pmatrix}, \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} 0 \\ -1 \\ 0 \\ 0 \\ 0 \end{pmatrix} \right\}.
\end{aligned}$$

This means that $s = 4$. We can even check this result using the differential approach related to the differential equations (3.1-3.5) induced from the chemical diagram. The Jacobian matrix is given by

$$J = \begin{pmatrix}
-k_1 x & 0 & 0 & -k_1 s_1 & k_{-1} \\
0 & -\gamma^2 k_3 e s_2^{\gamma-1} - \nu_2 & -\gamma k_3 s_2^\gamma & \gamma k_{-3} & k_2 \\
0 & -\gamma k_3 e s_2^{\gamma-1} & -k_3 s_2^\gamma & k_{-3} & 0 \\
-k_1 x & \gamma k_3 e s_2^{\gamma-1} & k_3 s_2^\gamma & -k_1 s_1 - k_{-3} & k_{-1} + k_2 \\
k_1 x & 0 & 0 & k_1 s_1 & -(k_{-1} + k_2)
\end{pmatrix}. \tag{5.19}$$

We can then compute the set of vectors v such that $v^t J = 0$, or equivalently $J^t v = 0$. We have

$$\begin{cases}
0 &= k_1 x\,(-v_1 - v_4 + v_5), \\
0 &= \gamma k_3 e s_2^{\gamma-1}\,(-\gamma v_2 - v_3 + v_4) - \nu_2 v_2, \\
0 &= k_3 s_2^\gamma\,(-\gamma v_2 - v_3 + v_4), \\
0 &= k_1 s_1\,(-v_1 - v_4 + v_5) + k_{-3}\,(\gamma v_2 + v_3 - v_4), \\
0 &= k_{-1}\,(v_1 + v_4 - v_5) + k_2\,(v_2 + v_4 - v_5).
\end{cases}$$

These equations imply that $v_1 = v_2 = 0$, and the three other components have to be the same. This means that the vector v has to belong to the set spanned by the vector $(0, 0, 1, 1, 1)^t$. Then, if we are looking for the vectors u such that $v^t u = 0$, we find that

$$u \in span\left\{\begin{pmatrix}1\\0\\0\\0\\0\end{pmatrix}, \begin{pmatrix}0\\1\\0\\0\\0\end{pmatrix}, \begin{pmatrix}0\\0\\-1\\0\\1\end{pmatrix}, \begin{pmatrix}0\\0\\0\\-1\\1\end{pmatrix}\right\},$$

and this space is the same than the stoichiometric subspace.

As we did before, we can assume for example that the rate constants are given by

$$k_1 = 1.2, \qquad k_{-1} = 0.8, \qquad k_2 = 1.5, \qquad k_3 = 0.9,$$
$$k_{-3} = 0.7, \qquad \nu_1 = 0.5 \qquad \text{and} \qquad \nu_2 = 2.$$

We have learned in the third chapter that under some assumptions, we could have oscillations or fixed points. One of them tells us that γ has to be greater than 1, so we can assume for example that $\gamma = 2$. Furthermore, the analysis of the system is done thanks to the quasi-steady-state approximation, meaning that some dimensionless variables are defined. Then, we can use the value of the parameter to know exactly the values of these new variables and parameters. We have

$$\begin{aligned}\varepsilon &= \frac{e_0 k_1 k_2}{(k_2 + k_{-1})^2}, & \eta &= \frac{\nu_2(k_2 + k_{-1})}{k_1 k_2 e_0}, & p &= \frac{\alpha}{\eta},\\ &= \frac{1.8}{(2.3)^2} e_0. & &= \frac{2.3}{0.9 e_0}. & &= \frac{3 * 0.9}{1.2 * \sqrt{7}} e_0.\end{aligned}$$

$$\begin{aligned}\nu &= \frac{\nu_1}{k_2 e_0}, & \alpha &= \frac{k_2 + k_{-1}}{k_1}\left(\frac{k_3}{k_{-3}}\right)^{1/\gamma}, & y &= (p\nu)^\gamma,\\ &= \frac{1}{3 e_0}. & &= \frac{3 * 2.3}{1.2 * \sqrt{7}}. & &= \frac{(0.75)^2}{7}.\end{aligned}$$

We can then study the function H with these parameters, and express it as a function of e_0, the initial amount of enzyme. For example, the assumption that ν as to be between 0 and 1 is equivalent to say that e_0 has to be strictly greater than 1/3. The analysis of the function $H(e_0)$ tells us that when e_0 is bigger than 0.7303 than we have an unstable fixed point and then a limit cycle, and otherwise we have a fixed point. Since the dimension of ΔS is 4, we know that it will be impossible to represent the intersection Q with K^-. So, let us try to study the dominance around a fixed point. Actually, if we try to find the fixed points of the equations (3.1-3.5), we will easily find that $y = \nu_1/k_2$ and $s_2 = \nu_1/\nu_2$. Then, we have to use that $e_0 = e + x + y$ to find that

$$s_1 = \frac{(\nu_1 + k_{-1} y)}{k_1 x} \qquad \text{and} \qquad x = \frac{k_3(e_0 - y){s_2}^\gamma}{k_{-3} + k_3 {s_2}^\gamma}.$$

Let us assume for example that the initial amount of enzyme e_0 is 0.72. Then, the fixed point is given by

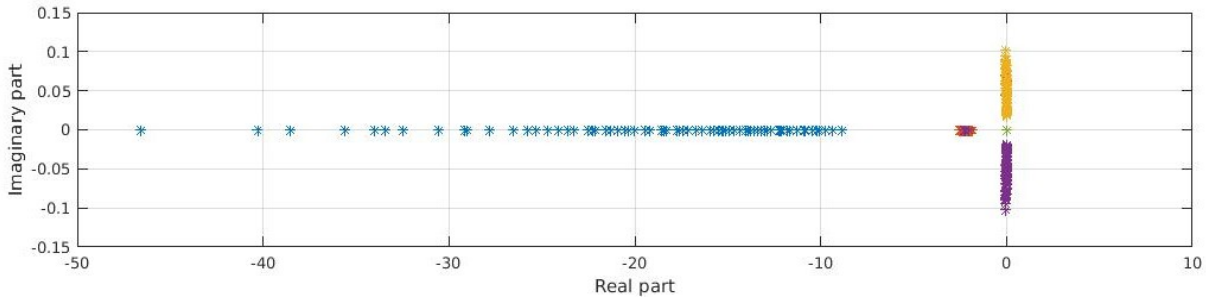


Figure 5.14: Spectrum analysis of the Jacobian matrix of the Sel'kov diagram when $0.7304 \leq e_0 \leq 0.8304,\ 0.15 \leq s_2 \leq 0.35$ and $0.2333 \leq y \leq 0.4333$

$$x^\star = (\,22.2142,\ 0.2500,\ 0.3579,\ 0.0288,\ 0,3333\,).$$

If we look at the eigenvalues of the Jacobian matrix evaluated at this point , denoted by J, we find four eigenvalues with a negative real part and one null eigenvalue. This suggests that at this point, the system can be 1-dominant. Indeed, we can find a matrix P of inertia 1 such that the matrix $A'P + PA - 2\lambda P$ admits five negative real part eigenvalues. This result is consistent with the previous result since we have a fixed point. We can also look at the result when the initial amount of enzyme is bigger than 0.7303. We know that the variables x, s_1 and e depend on the values of e_0, s_2 and y. So, let us see what happens when we slightly modify their values. Let us assume for example that e_0 is between 0.7304 and 0.8304, s_2 is between 0.15 and 0.35 and finally, y is between 0.2333 and 0.4333. In this case, the spectrum of the Jacobian matrix is given by the FIGURE 5.14, where we can see that we can expect 3-dominance. This is still consistent with the system since the initial amount of enzyme is bigger than 0.7303, meaning that the fixed point is unstable and there is a limit cycle.

Conclusion and prospects

All along this work, we have tried to build a new tool that we could use to explain the oscillatory trajectories of glycolysis. To that end, we have first looked at some notions and results that already exist in mathematics and in science, to finally establish a new theorem.

We have begun by looking for interesting results in the chemical reaction networks theory in the first chapter. We have pointed out two notions. The first one is the stoichiometric subspace and the stoichiometric compatibility classes in which the trajectories always have to stay. Then the dimension of this space is already a good way to reduce the dimension we have to deal with, and to learn some information about the asymptotic behaviour of the system. We have particularly worked with examples with a 1-dimensional stoichiometric subspace, meaning that only fixed points can be reached. The second one is the deficiency. Two theorems are besides based on its value, and allow us to conclude about the existence and the uniqueness of a fixed point. Unfortunately, we cannot apply these theorems to any systems. The second chapter is used as an introduction for the third chapter since we explain a lot of chemical reactions. Along this chapter, we have applied the theory developed in the previous chapter to each chemical diagram we have encountered. Then, we have finally been able to talk about the glycolysis and the feedback loops that interest us. The three first sections have been realised on basis of the book [7] of J. Keener and J. Sneyd, and the lectures [1] delivered in 1980 by M. Feinberg.

However, the dimension of the stoichiometric subspace usually becomes bigger when the dimension of the system increases, meaning that it is impossible to draw conclusions about trajectories. We have then looked into another tool that could help us: the p-dominance. Developed by F. Forni and R. Sepulchre in the article [3] of 2017, this notion tells us the dimension of the space the asymptotic trajectories belong to. It has been first illustrated with an ordinary example where we have pointed out some properties of this concept. And then, it has been applied to some easy chemical diagram that we have used all along the work to illustrate every concept. Nevertheless, sometimes the p-dominance that we find doesn't seem to fit with the reality. For example, we could find 2-dominance for a system even if a previous theorem has concluded that there exists a unique fixed point. Actually, this concept doesn't take into account the stoichiometric compatibility classes.

It seems that these two notions cannot always help us, used alone. This observation has led us to combine these two concept to finally have a more accurate information about the asymptotic behaviour, and to be able to apply this new tool to any kind of chemical diagram. Then some new theorems have been established in the fifth chapter of this work, and we have applied them to the chemical reactions that we had introduced before, in the second ans third chapters. Furthermore, these examples have raised some questions

and problems, including the way to find the dimension of the largest subspace that the intersection Q can contain. The space on which we compute the dominance is also a question to ask.

This work could be easily carried on actually. First of all, we have already talked about the problem of finding the right p_q involved in the new theorems. So it would be important to know how to find it. Then, we have also seen that a lot of computations cannot be done due to a lack of machine accuracy. Rather than trying to improve this accuracy, we could find another method. Until now, the matrice P of p-dominance is constant. But it could be really interesting to find a matrix field $P(x)$ that satisfy the linear matrix inequalities, and then a cone field. All this work could finally lead to a publication with Fulvio Forni.

Bibliography

[1] M. FEINBERG, *Lectures on Chemical Reaction Networks*, University of Wisconsin-Madison, 1980

[2] M. FEINBERG, *Foundations of Chemical Reaction Network Theory*, Springer, 2019

[3] F. FORNI & R. SEPULCHRE, *Differential dissipativity theory for dominance analysis*, IEEE Transaction of Automatic control, pp. 99, 2017

[4] F. FORNI & R. SEPULCHRE, *A dissipativity theorem for p-dominant systems*, 56th IEEE Conference on Decision and Control, 2017

[5] F. FORNI & R. SEPULCHRE, *Differentially positive systems*, IEEE Transactions on Automatic Control, 61(2), pp. 346-359, 2014

[6] E. JASPARD, *Régulation de la glycolyse*, http://biochimej.univ-angers.fr/, Université d'Angers, 2014

[7] J. KEENER, J. SNEYD, *Mathematical Physiology I: Cellular Physiology*, Interdisciplinary Applied Mathematics. 8/1 (2 ed.), New York, Springer, 1998

[8] A. L. LEHNINGER, D. L. NELSON & M. M. COX, *Principles of Biochemistry*, W.H. Freeman and Company, New York, 2005

[9] R.D. LEVINE, *Free Energy of Activation. Definition, Properties, and Dependent Variables with Special Reference to "Linear" Free Energy Relations*, The Journal of Physical Chemistry, Vol. 83, No. 1, 1979

[10] NINJA NERD SCIENCE, *Metabolism | Glycolysis*, Youtube, mai 2017

[11] NINJA NERD SCIENCE, *Metabolism | Regulation of Glycolysis*, Youtube, juin 2017

[12] WIKIPEDIA, *Hydrolysis*, https://en.wikipedia.org/wiki/Hydrolysis, 15/08/19