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A graph-based approach for the approximate solution of the chemical master equation

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Declaration

I declare that this thesis was composed by myself and that the work contained therein is my own, except where explicitly stated otherwise in the text.

(*Raffaele Basile*)

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Lay Summary

Chemical reactions were known since antiquity: fire, fermentation and reduction of ores to metal had been the basis of the first civilizations. Later on, philosophers and alchemists have tried to understand their origin, but it was not until the sixteenth century that scientists started developing theories based on experimentally observed chemical transformations. Soon those theories lead to the creation of chemical equations: graphical illustration of what happens in a chemical reaction. Converting the chemical equations into mathematical equations has been the effort of researchers since then.

The main difficulty is to convey the behaviour of many molecules, too many to study their individual motions, to the understanding of a whole system. Two different, but very related, approaches have achieved that.

The first one is a so called "deterministic" method: a process that always return a unique forecast for a given initial condition. The law of mass action is a model based on the assumption that the rate of a reaction, a quantification of how much the reaction produces, is proportional to the concentrations of the reactants. This model is based on both theoretical and empirical results and it has proved to be very effective in most of the situations. The idea behind it, is that the number of molecules that collide in a small gap of time causing a reaction for a given concentration of molecules is always, more or less the same. However, this does not approximate well the reality when not so many molecules are present in the system. To model this situation a "non-deterministic" method is more appropriate. These methods give up the uniqueness of their forecast providing instead the probability that the system will evolve in any of the possible ways. In the case of chemical reactions, this is achieved assuming that the probability of having a collision is proportional to the number of molecules of the reactants.

The main problem with non-deterministic methods is that the number of possible way a system can develop can be very big, making exact calculations difficult, if not impossible. That is why approximating techniques becomes necessary. In this thesis one of these techniques is presented.

The case when some reactions occur much less often than others is dealt with. It is shown how these "slow" reactions affect the system: how different the system would behave if only the "fast" reactions were present.

Abstract

The chemical master equation (CME) represents the accepted stochastic description of chemical reaction kinetics in mesoscopic systems. As its exact solution – which gives the corresponding probability density function – is possible only in very simple cases, there is a clear need for approximation techniques. Here, we propose a novel perturbative three-step approach which draws heavily on graph theory: (i) we expand the eigenvalues of the transition state matrix in the CME as a series in a non-dimensional parameter that depends on the reaction rates and the reaction volume; (ii) we derive an analogous series for the corresponding eigenvectors via a graph-based algorithm; (iii) we combine the resulting expansions into an approximate solution to the CME. We illustrate our approach by applying it to a reversible dimerization reaction; then, we formulate a set of conditions, which ensure its applicability to more general reaction networks. We follow attempting to apply the results to a more complicated system, namely push-pull, but the problem reveals too complex for a complete solution. Finally, we discuss the limitations of the methodology.

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Chapter 1

Introduction

In this thesis a new approach to chemical master equations has been developed.

Chemical reaction kinetics have traditionally been modelled by means of rate equations. These are (sets of) deterministic ordinary differential equations that describe the time-evolution of the concentrations of chemical species; see, *e.g.*, [24] and the references therein. However, it is well known that chemical reaction kinetics are inherently stochastic [12]: while the dynamics average out and appear deterministic if the spatial scale is sufficiently large, on mesoscopic scales the probabilistic nature of reaction networks cannot be ignored [19]. Hence, rate equations are useful in the description of reaction kinetics in macroscopic volumes such as test tubes and large-size chemical reactors, but cannot accurately describe the kinetics in smaller volumes; a prominent example are biochemical reactions occurring inside biological cells [19].

The chemical master equation (CME) constitutes the accepted mesoscopic description of chemical reaction processes; it can be derived from combinatorial arguments [33] or from microscopic physics [11]. The derivation typically assumes well-mixed and dilute conditions, as in [11]; however, a modified version also exists for non-dilute regimes [20]. The CME contains information about the mean concentrations of reactants and the fluctuations about them at all points in time; mathematically, it is a set of linear differential equations for the probabilities of the states in the system.

1.1 The Chemical Master Equation

Consider a volume containing a mixture of molecules of different molecular species $(X_j)_{j=1,..,n}$. These molecules would move in an erratic way hitting each other. Some of the molecules would react when they hit each other forming a new molecule of a different species.

In this model the state of the system is described by an n-dimensional vector $\mathbf{n}$ that contains the number of molecules for each molecular species. Initially the system is set to a state $\overline{\mathbf{n}}$.

A reaction R is determined by a set of so called stoichiometric coefficients s_j, $r_j \geq 0$ that give the number of reagents and products in a single reaction. It is represented in the form

$$R : s_1X_1 + s_2X_2 + \cdots + s_nX_n \xrightarrow{k} r_1X_1 + r_2X_2 + \cdots + r_nX_n, \tag{1.1}$$

where k represents the rate coefficient of the reaction and it is explained below in the section. Since the probability of a three body collision is considered to be negligible, $\sum_j s_j = 1$ or $\sum_j s_j = 2$.

When a reaction R occurs the system is taken from a state $\mathbf{n}$ to a state $\mathbf{n}+\mathbf{v}_R$ with $\mathbf{v}_R[j] = r_j - s_j$.

We will make two assumptions:

- the probability of having a reaction will depend only on the state in which the system is, and not on the past reactions;
- the probability to have more than one reaction in a time period δt is $o(\delta t)$.

Remark 1. *These two assumptions correspond to the infinitesimal definition of continuous in time Markov chains (for more particulars on Markov processes see [31] or [3]).*

From these premises we can construct a differential equation for the probability of each state $\mathbf{n}$. In fact,

$$\frac{d}{dt}P(\mathbf{n}, t) = \lim_{\delta t \to 0} \frac{P(\mathbf{n}, t + \delta t) - P(\mathbf{n}, t)}{\delta t}. \tag{1.2}$$

Using conditional probability,

$$P(\mathbf{n}, t + \delta t) = \left(\sum_{\mathbf{n}' \neq \mathbf{n}} P(\mathbf{n}', t)P(\mathbf{n}, t + \delta t|\mathbf{n}', t) \right) + P(\mathbf{n}, t + \delta t|\mathbf{n}, t)P(\mathbf{n}, t) + o(\delta t), \tag{1.3}$$

$$\begin{aligned} &P(\mathbf{n}, t + \delta t) - P(\mathbf{n}, t) = \\ &= \sum_{\mathbf{n}' \neq \mathbf{n}} \Big(P(\mathbf{n}', t)P(\mathbf{n}, t + \delta t|\mathbf{n}', t) \Big) - \Big(1 - P(\mathbf{n}, t + \delta t|\mathbf{n}, t) \Big) P(\mathbf{n}, t) + o(\delta t) \\ &= \sum_{\mathbf{n}' \neq \mathbf{n}} \Big(P(\mathbf{n}', t)P(\mathbf{n}, t + \delta t|\mathbf{n}', t) - P(\mathbf{n}', t + \delta t|\mathbf{n}, t)P(\mathbf{n}, t) \Big) + o(\delta t). \end{aligned} \tag{1.4}$$

The limits

$$W_{\mathbf{n}'\mathbf{n}} := \lim_{\delta t \to 0} \frac{P(\mathbf{n}, t + \delta t|\mathbf{n}', t)}{\delta t}, \tag{1.5}$$

and

$$W_{\mathbf{n}\mathbf{n}'} := \lim_{\delta t \to 0} \frac{P(\mathbf{n}', t + \delta t|\mathbf{n}, t)}{\delta t}, \tag{1.6}$$

are the transition probability from $\mathbf{n}'$ to $\mathbf{n}$ and from $\mathbf{n}$ to $\mathbf{n}'$.

Combinatorial arguments [33] and microscopic physics [11] have shown that the transition probabilities are proportional to the number of molecules of each species involved in the reaction. When a species A is involved s times in the same reaction, then the transition probability is proportional to $\prod_{i=0}^{s-1}(n_A - i)$, where

n_A is the number of molecules of A (this quantity is proportional to the number of ways the molecules of A can be combined).

Equation (1.2) can be written as

$$\frac{d}{dt}P(\mathbf{n},t) = \sum_{\mathbf{n}'} \left\{ W_{\mathbf{n}'\mathbf{n}} P(\mathbf{n}',t) - W_{\mathbf{n}\mathbf{n}'} P(\mathbf{n},t) \right\}. \tag{1.7}$$

This is called the master equation of the system. This equation can be written in matrix form as

$$\frac{d}{dt}\mathbf{P}(t) = \mathbf{W}\mathbf{P}(t), \tag{1.8}$$

where $\mathbf{P}(t)$ is the vector of probabilities $P(\mathbf{n},t)$, and $\mathbf{W}$ is the matrix

$$\mathbf{W}[\mathbf{n},\mathbf{n}'] := \begin{cases} \lim_{\delta t \to 0} \frac{P(\mathbf{n}', t+\delta t | \mathbf{n}, t)}{\delta t} & \text{if } \mathbf{n} \neq \mathbf{n}' \\ -\sum\limits_{\mathbf{n}'' \neq \mathbf{n}} W_{\mathbf{n}\mathbf{n}''} & \text{otherwise} \end{cases} \tag{1.9}$$

Equation (1.8) is the matrix form of the Chapman-Kolmogorov equation for the Markov chain. A proof of the equivalence between Chapman-Kolmogorov equations and the master equation in the most general case of Markov chains with continuous space and time can be found in [33].

Remark 2. *Matrix element* $\mathbf{W}[\mathbf{n},\mathbf{n}']$ *represents the transition probability from state* $\mathbf{n}'$ *to state* $\mathbf{n}$*. This notation is consistent with the present CME literature (e.g. [33, 26]). On the other side, it might be cause of confusion since an edge running from a node* v *to a node* w *in the associated graph actually represents the possibility to move from* w *to* v*.*

The solution of (1.8) can be found exactly

$$\mathbf{P}(t) = \mathrm{e}^{\mathbf{W}t}\mathbf{P}(0), \tag{1.10}$$

where $\mathbf{P}(0)$ is the probability distribution at time 0. (When the initial number of molecules is known $\mathbf{P}(0)$ equals 1 in correspondence to the initial condition state and 0 elsewhere.) However, the dimension of the matrix $\mathbf{W}$ is closely connected with the number of molecules initially present in the system. This means that Equation (1.10) changes of dimension when the initial condition varies, forcing a recalculation of a matrix exponential, notoriously very hard to achieve [27].

Example 1. *Consider a system with thee molecular species* A*,* B C *and* D*. Let assume the possible reactions between these species are given by:*

$$R_1 : 2A \xrightarrow{k_1} B; \tag{1.11}$$

$$R_2 : C + B \xrightarrow{k_2} D; \tag{1.12}$$

$$R_3 : D \xrightarrow{k_3} C + B. \tag{1.13}$$

The stoichiometric coefficients for these reactions and the vectors $\mathbf{v}_{R_i}$ *are*

$$R_1: \begin{array}{llll} s_1 = 2, & s_2 = 0, & s_3 = 0, & s_4 = 0; \\ r_1 = 0, & r_2 = 1, & r_3 = 0, & r_4 = 0; \\ & \mathbf{v}_{R_1} = (-2, 1, 0, 0)^T; & & \end{array} \tag{1.14}$$

$$R_2: \begin{array}{llll} s_1 = 0, & s_2 = 1, & s_3 = 1, & s_4 = 0; \\ r_1 = 0, & r_2 = 0, & r_3 = 0, & r_4 = 1; \\ & \mathbf{v}_{R_2} = (0, -1, -1, 1)^T; & & \end{array} \tag{1.15}$$

$$R_3: \begin{array}{llll} s_1 = 0, & s_2 = 0, & s_3 = 0, & s_4 = 1; \\ r_1 = 0, & r_2 = 1, & r_3 = 1, & r_4 = 0; \\ & \mathbf{v}_{R_3} = (0, 1, 1, -1)^T. & & \end{array} \tag{1.16}$$

Hence, from state $(\overline{n}_A, \overline{n}_B, \overline{n}_C, \overline{n}_D) = (2, 0, 1, 0)$ *the only non-zero transition probability is given by* R_1 *and it is equal to* $2 \cdot 1k_1 = 2 \cdot k_1$*. The matrix associated with the system with initial condition* $(2, 0, 1, 0)$ *is*

$$\begin{pmatrix} -2k_1 & 0 & 0 \\ 2k_1 & -k_2 & k_3 \\ 0 & k_2 & -k_3 \end{pmatrix}. \tag{1.17}$$

However, the initial condition $(2, 1, 1, 0)$ *leads to a different matrix*

$$\begin{pmatrix} -2k_1 - k_2 & 0 & 0 & k_3 \\ 2k_1 & -2k_2 & k_3, & 0 \\ 0 & 2k_2 & -k_3 & 2k_1 \\ k_2 & 0 & 0 & -2k_1 - k_3 \end{pmatrix}, \tag{1.18}$$

and the solution of Equation (1.10) *would need to be computed again.*

Since Equation (1.10) does not provide enough insight of the behaviour of a system, a range of approximation techniques have been developed to investigate systems composed of both first-order and second-order (bimolecular) processes. Their aim is to provide an estimate that takes into account the system architecture (its possible reactions) and in which the number of initial molecules is only a variable that does not influence the shape (dimension, degree) of the analytical solution. Amongst these the most popular are the linear-noise (Gaussian) approximation (LNA) [33, 7] and moment-closure approximations [13, 8]. However, only the former technique provides a systematic approximation algorithm, whereas the latter is based on an ad-hoc truncation of the moment equations [18]. (An alternative approach, the so-called Poisson representation [9], transforms the CME into an equivalent Fokker-Planck equation (FPE); however, the corresponding solution typically cannot be found in closed form, but also has to be approximated.) On the other hand, the principal disadvantage of LNA is that it gives results in the limit of large reaction volumes and, hence, that it is not well-suited to the investigation of reaction processes in small volumes [21, 15, 16].

Another prominent algorithm is the finite state projection method (FSP) [30]. The main idea of such method is to restrict the state space to a bulk of important states while projecting the others to a single "absorbing" state. The solution is then found using a matrix exponential on such reduced space, which however suffers of runtime and conditioning problems [27] and hence it is only used to find a solution for a set “final” time. The concept of reducing the state space is very useful when introduction of molecules is present, making such space infinite in cardinality.

Finally, it is worth mentioning the Kramers-Moyal expansion which is a Taylor expansion of the master equation [25, 28]. The second order truncation of such expansion is called the Fokker-Planck approximation. To make this expansion possible an assumption over slow change between close states of the probability distribution is made. However, a systematic expansion of the master equation in powers of a small parameter reveals that successive orders do not correspond to successive terms of the Kramers-Moyal expansion [33].

We use a perturbative approach. Before us, others have used perturbation techniques, among those [32, 14]. In these and other articles there is a tendency to try to project the same methods used for the deterministic model of rate equations, namely reduction to invariant or central manifold, to the CME. However, rate equations are usually set of non-linear-differential equation, hence, we believe, a different approach trying to exploit the linearity of the CME should be attempted.

We do this developing a new graph theoretical method to find an eigenvalue and eigenvector expansion. This will allow to find the diagonal form of matrix **W** (we will only consider diagonalizable matrices since eigenvalues of algebraic multiplicity greater than one will be source of complications) and, consequently, the matrix exponential in Equation (1.10). However, this last passage requires the calculation of the following

$$\mathbf{E}^{-1} \mathrm{e}^{\mathbf{\Lambda} t} \mathbf{E}\, \mathbf{P}(0), \tag{1.19}$$

where **E** is the eigenvector matrix and **Λ** is the eigenvalues matrix.

It is easy to overcome the eigenvector matrix inversion problem calculating left eigenvectors. However, the matrix product involved in Equation (1.19), although much more computationally feasible, still suffers of the same dimensionality issue of Equation (1.10) we mentioned before: it can only allow the computation of a closed formula for each initial condition rather than a unique closed formula that embodies the behaviour of the system as the initial condition changes. This led us to improve the basic idea using a Laplace transform to directly compute the exponential in Equation (1.10) in a similar fashion we compute the eigenvectors but avoiding their explicit calculation and therefore the product in Equation (1.19).

We shall prove that there is a correspondence between eigenvalues and states of the Markov chain. Furthermore, the leading term of the eigenvalue expansion depends only on the corresponding state, while the first order correction depends on the cycles passing through the state itself or, under some conditions, only on its neighbourhood. We will also show that, when eigenvalues with algebraic multiplicity greater than one are present, a “link” between possibly far states is created.

The eigenvectors, on the other end, are proved to be dependent on the paths between couples of states. Although many of these paths will not need to be included in order to get the first terms of the expansion, this will prove to be the main obstacle of the methodology.

We apply the method to a simple reaction system (i.e. Dimerization) showing very accurate results that outperform LNA for small times and approaching the steady state. We try then to apply the same idea to a much more complicated system (i.e. Push-Pull), but the complexity of finding the relevant paths revealed too difficult.

The thesis is structured as follow. In Chapter 2, we introduce the CME for a dimerization reaction, we reduce it to non-dimensional matrix form, and we approximate the eigenvalues of the transition state matrix in the CME by a series expansion in powers of a non-dimensional combination of the reaction rate constants and the reaction volume. We then proceed developing the graph-based methodology for determining the adjoint matrix of any given square matrix and showing how this relates to the eigenvectors of a matrix. We combine the results to construct an approximate solution to the CME. We also compare our theoretical results with "exact" solutions of the CME – *i.e.*, with solutions obtained by numerical integration – and with the LNA.

In Chapter 3, we explore the applicability of our graph-based approach to general sets of chemical reactions. We try to apply these techniques to the push-pull system in Chapter 4, showing what are the main difficulties and ideas of the approach. We then summarise and discuss our findings in Chapter 5.

We conclude with two of appendices: in Appendix A, we cite general eigenvector formulae to supplement those in Section 2.3; in Appendix B, we present a brief derivation of LNA in the context of dimerization.

Chapter 2

Dimerization

In this chapter we consider the simplest reversible bimolecular reaction, namely dimerization, whereby a pair of monomer molecules (species A) react to form a single dimer molecule (species B); the latter can dissociate back into free monomers: $A + A \rightleftharpoons B$. Despite its simplicity, dimerization is a ubiquitous component in various intracellular reaction networks [23].

The Markov chain underlying this system is a birth and death process. As such, the exact representation of the steady state solution can be exactly computed [33]. However, up to our knowledge, a solution valid as the time varies has not been given before.

The chapter is structured as follows: in Section 2.1, we introduce the CME for a dimerization reaction, we reduce it to non-dimensional matrix form, and we approximate the eigenvalues of the transition state matrix in the CME by a series expansion in powers of a non-dimensional combination of the reaction rate constants and the reaction volume.

In Section 2.2, we develop the main theoretical result of the chapter in its general form, a graph-based methodology for determining the adjoint matrix of any given square matrix.

In Section 2.3, we revisit the dimerization reaction to find an expansion for the matrix of eigenvectors of the transition matrix, as well as for the associated inverse matrix, on the basis of the theory developed in Section 2.2.

Finally, in Section 2.4, we combine the results of the preceding three sections to construct an approximate solution to the corresponding CME. We also compare our theoretical results with "exact" solutions of the CME – *i.e.*, with solutions obtained by numerical integration – and with the LNA.

2.1 Dimerization CME

In the following, we will assume the dimerization reaction, $A + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$, to occur in a compartment of volume Ω, with no influx or efflux of particles. We will also enforce well-mixed conditions such that the state of the system at any point in time can simply be described by the number of molecules of species A and B.

The CME for this system given by Equation (1.7) is

$$\begin{aligned}\frac{d}{dt}P(n_A,n_B,t) = &\frac{k_1}{\Omega}(n_A+2)(n_A+1)\,P(n_A+2,n_B-1,t)\\ &+k_2(n_B+1)\,P(n_A-2,n_B+1,t)\\ &-\frac{k_1}{\Omega}n_A(n_A-1)\,P(n_A,n_B,t)-k_2n_B\,P(n_A,n_B,t). \qquad (2.1)\end{aligned}$$

As discussed in Section 1.1

- the transition probability from a state (n_A, n_B) to a state (n_A+2, n_B-1) is proportional to the number of molecules for the species involved in reaction $B \longrightarrow A + A$, i.e. n_B. The coefficient of proportionality is given by k_2;
- the transition probability from a state (n_A, n_B) to a state $(n_A + 2, n_B - 1)$ is proportional to the number of molecules for the species involved in reaction $A + A \longrightarrow B$. Since A is involved twice in the reaction, it will contribute with a term proportional to $n_A(n_A-1)$ (a molecule cannot collide itself). Also, because the reaction in question is bimolecular, the coefficient of proportionality is inversely proportional to the volume (larger volumes make collisions less likely). Hence, such coefficient is k_1/Ω.

For more details on how Equation (2.1) is obtained and why bimolecular proportionality coefficients are inversely proportional to the volume refer to [33].

2.1.1 Non-dimensionalization and reduction

The dimerization reaction introduced above possesses a simple conservation law, namely, the total number of monomers (in free and bound form) is constant for all times: $n_{\text{tot}} := n_A + 2n_B$. In particular, the number of molecules of B can be expressed in terms of those of A, as $n_B = (n_{\text{tot}} - n_A)/2$. Thus, the possible states which can be accessed by the system are

$$n_A = \begin{cases} 1, 3, \ldots, n_{\text{tot}} - 2, n_{\text{tot}} & \text{if } n_{\text{tot}} \text{ is odd,} \\ 0, 2, \ldots, n_{\text{tot}} - 2, n_{\text{tot}} & \text{if } n_{\text{tot}} \text{ is even.} \end{cases}$$

For the following analysis, we may restrict ourselves to the case where n_{tot} is even, as the odd case can be treated in an analogous fashion. Moreover, we introduce the new constant $n_{\text{tot}} = 2\Omega\alpha$, where α represents half the maximum concentration of monomers in the reaction volume Ω. It follows that $n_B = \Omega\alpha - n_A/2$ and, hence, that the CME, Equation (2.1), can be reduced to univariate form:

$$\begin{aligned}\frac{d}{dt}P(n_A,t) = &\frac{k_1}{\Omega}(n_A+2)(n_A+1)\,P(n_A+2,t)\\ &+k_2\Big(\Omega\alpha-\frac{n_A}{2}+1\Big)\,P(n_A-2,t)\\ &-\frac{k_1}{\Omega}n_A(n_A-1)\,P(n_A,t)-k_2\left(\Omega\alpha-\frac{n_A}{2}\right)P(n_A,t). \qquad (2.2)\end{aligned}$$

Next, we non-dimensionalize Equation (2.2) by dividing the equation by k_2 and by rescaling the time variable via $t \longrightarrow k_2 t$ to obtain

$$\begin{aligned}\frac{d}{dt}P(n_A,t) = {}& K(n_A+2)(n_A+1)\,P(n_A+2,t) \\ & + \left(\Omega\alpha - \frac{n_A}{2} + 1\right) P(n_A-2,t) \\ & - K n_A(n_A-1)\,P(n_A,t) - \left(\Omega\alpha - \frac{n_A}{2}\right) P(n_A,t). \qquad (2.3)\end{aligned}$$

Here, $K := k_1/(k_2\Omega)$, and we again denote the new non-dimensional time by t (with an abuse of notation).

Remark 3. *An alternative non-dimensionalization is obtained by dividing out k_1/Ω from Equation (2.2) and by rescaling time accordingly; since the resulting equation is similar to (2.3), it is omitted here.*

Equation (2.3) can conveniently be written in matrix form as

$$\frac{d}{dt}\mathbf{P}(t) = \mathbf{M}\mathbf{P}(t), \qquad (2.4)$$

where

$$\mathbf{P}(t) := \begin{pmatrix} P(0,t) \\ P(2,t) \\ \vdots \\ P(2\Omega\alpha - 2, t) \\ P(2\Omega\alpha, t) \end{pmatrix}$$

and $\mathbf{M}$ is the matrix given in Equation (2.5). The graph associated to matrix $\mathbf{M}$ is shown in Fig. 2.3.

By Equation (2.4), the $(n+1)$-th row in the matrix $\mathbf{M}$ corresponds to the equation for the probability $P(2n,t)$ of the system being in a state with $2n$ molecules of A at time t. For that reason, in what follows, we will conveniently relabel each state with $n_A = 2n$ as n.

As we mentioned in Chapter 1, the approximation developed in this thesis is perturbative in nature. The strategy we follow consists in expanding the exact solution of (2.4) in an asymptotic series in powers of K, for K sufficiently small. We shall perform this expansion in three steps: we first construct an approximation for the eigenvalue matrix $\mathbf{\Lambda}$ (Section 2.1.2); then, in Sections 2.3.1 and 2.3.2, we approximate the eigenvector matrix $\mathbf{E}$ and its inverse, respectively; finally, in Section 2.4, we combine the resulting formulae to obtain the desired approximation for $\mathbf{P}(t)$.

2.1.2 Eigenvalue expansion

In this subsection, we approximate the set of eigenvalues of the transition matrix $\mathbf{M}$ defined in Equation (2.5) by a series expansion in terms of the non-dimensional

$$\begin{pmatrix} -g(0) & f(1)K & 0 & \cdots & \cdots & \cdots & 0 \\ g(0) & -f(1)K-g(1) & f(2)K & 0 & \cdots & \cdots & 0 \\ 0 & g(1) & -f(2)K-g(2) & f(3)K & \ddots & \cdots & 0 \\ \vdots & \ddots & \ddots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & \ddots & g(n-2) & -f(n-1)K-g(n-1) & f(n)K & 0 \\ \vdots & \cdots & \cdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & \cdots & \cdots & 0 & g(\Omega\alpha-1) & -f(\Omega\alpha)K \end{pmatrix}, \tag{2.5}$$

$$f(n) := 2n(2n-1) \qquad g(n) := \Omega\alpha - n. \tag{2.6}$$

parameter K. As is well known, eigenvalues of $\mathbf{M}$ are obtained by solving the eigenvalue equation

$$\det(\lambda\mathbf{I} - \mathbf{M}) = 0 \tag{2.7}$$

for λ. Expanding $\lambda = \lambda_0 + \lambda_1 K + o(K)$ and omitting the $o(K)$ terms result in the matrix $\mathbf{M}_\lambda := \lambda\mathbf{I} - \mathbf{M}$ given in Equation (2.10).

We can now apply the determinant property

$$\det(\mathbf{M}_\lambda) = \sum_{\sigma\in\mathcal{S}} \operatorname{sgn}(\sigma) \prod_{n=0}^{\Omega\alpha} \mathbf{M}_\lambda[n, \sigma(n)], \tag{2.8}$$

where $\mathcal{S}$ is the set of all permutations of $\{0, 1, \ldots, \Omega\alpha\}$ and $\mathbf{M}_\lambda[i, j]$ denotes the (i, j)-th entry in $\mathbf{M}_\lambda$.

The advantage of employing the expression in (2.8) when evaluating the determinant of $\mathbf{M}_\lambda$ lies in the fact that most of the terms in the above sum are either zero or $o(K)$ and, hence, negligible to the order considered here. In fact, the only non-zero permutations in (2.8) will be the ones that exchange pairs of neighbouring numbers $(n, n+1)$. Each time a pair of such numbers is exchanged, the factor $\mathbf{M}_\lambda[n, n+1] \cdot \mathbf{M}_\lambda[n+1, n] = Kf(n+1)g(n)$ appears in the product in Equation (2.8). Hence, the only permutation that contributes to the constant term in (2.8) is the identity. Similarly, the only permutations contributing to the $O(K)$ term in Equation (2.8) are the ones that exchange pairs of neighbouring numbers, *i.e.*, all cyclic permutations of the form $\sigma_n := (n\ n+1)$, with $n = 0, 1, \ldots, \Omega\alpha - 1$.

$$\begin{pmatrix} g(0)+\lambda_0+\lambda_1 K & -f(1)K & 0 & \cdots & 0 \\ -g(0) & f(1)K+g(1)+\lambda_0+\lambda_1 K & -f(2)K & \ddots & \vdots \\ 0 & \ddots & \ddots & \ddots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \cdots & 0 & -g(\Omega\alpha-1) & f(\Omega\alpha)K+\lambda_0+\lambda_1 K \end{pmatrix}. \qquad (2.10)$$

Thus, it follows that Equation (2.8) can be written as

$$\begin{aligned}\det(\mathbf{M}_\lambda) &= \prod_{i=0}^{\Omega\alpha} \mathbf{M}_\lambda[i,i] + \sum_{j=0}^{\Omega\alpha-1} \operatorname{sgn}(\sigma_j) \prod_{i=0}^{\Omega\alpha} \mathbf{M}_\lambda[i,\sigma_j(i)] + o(K) \\ &= \prod_{i=0}^{\Omega\alpha} [g(i) + \lambda_0 + f(i)K + \lambda_1 K] - K \sum_{j=0}^{\Omega\alpha-1} f(j+1)\, g(j) \prod_{\substack{i=0 \\ i\neq j, i\neq j+1}}^{\Omega\alpha} [g(i) + \lambda_0] \\ &\quad + o(K), \end{aligned} \tag{2.9}$$

where the functions f and g are defined in Equation (2.6). (Here and in the following, conventional "big-O" notation indicates exact knowledge of the order in K of a given expression, whereas "small o" is used otherwise, as in the case of the error resulting from the truncation at $O(K)$ above.)

For Equation (2.7) to be satisfied, the terms in the expansion in (2.9) must equal zero separately, *i.e.*, order-by-order in K. Setting the $O(1)$ term to zero, we find the $\Omega\alpha + 1$ solutions

$$\lambda_0^n := -g(n) = n - \Omega\alpha, \quad \text{with } n = 0, 1, \ldots, \Omega\alpha.$$

Next, we observe that

$$\prod_{i=0}^{\Omega\alpha} [g(i) + \lambda_0^n + f(i)K + \lambda_1^n K] = [f(n)K + \lambda_1^n K] \prod_{\substack{i=0 \\ i\neq n}}^{\Omega\alpha} [g(i) - g(n)] + o(K)$$

and

$$K\sum_{j=0}^{\Omega\alpha} f(j+1)\,g(j)\prod_{\substack{i=0\\ i\neq j, i\neq j+1}}^{\Omega\alpha}[g(i)-g(n)] = K\sum_{\substack{j=n-1\\ j=n}} f(j+1)\,g(j)\prod_{\substack{i=0\\ i\neq j, i\neq j+1}}^{\Omega\alpha}[g(i)-g(n)]+o(K).$$

Hence, evaluating the $O(K)$ terms in Equation (2.9) to zero

$$\begin{aligned}[f(n)K+\lambda_1^n K]\prod_{\substack{i=0\\ i\neq n}}^{\Omega\alpha}[g(i)-g(n)] =&K\ f(n)\,g(n-1)\prod_{\substack{i=0\\ i\neq n-1, i\neq n}}^{\Omega\alpha}[g(i)-g(n)]\\ &+f(n+1)\,g(n)\prod_{\substack{i=0\\ i\neq n, i\neq n+1}}^{\Omega\alpha}[g(i)-g(n)]. \end{aligned} \tag{2.11}$$

Dividing by $K\prod_{\substack{i=0\\ i\neq n}}^{\Omega\alpha}[g(i)-g(n)]$

$$\lambda_1^n = -f(n)+\frac{f(n)\,g(n-1)}{g(n-1)-g(n)}+\frac{f(n+1)\,g(n)}{g(n+1)-g(n)}; \tag{2.12}$$

the corresponding eigenvalue of $\mathbf{M}$ will be denoted by $\lambda_n = \lambda_0^n + \lambda_1^n K + o(K)$. (Here, we remark that $f(0)g(-1) = 0 = f(\Omega\alpha+1)g(\Omega\alpha)$, which is due to $f(0) = 0 = g(\Omega\alpha)$; cf. again Equation (2.6).)

Remark 4. *We note that λ_1^n consists of three terms which correspond to the identity, the "left" permutation $(n-1\ n)$, and the "right" permutation $(n\ n+1)$, respectively; all other permutations annihilate the last product in the second line of Equation (2.9), as $\lambda_0^n = -g(n)$. Interpreting the above observation in a graph-theoretic context [2], we may conclude that the expansion for λ_n only depends on neighbouring vertices in the graph associated to $\mathbf{M}$, at least to the order considered here; cf. also Section 2.3, where we will determine a graph-based approximation for the corresponding eigenvectors, as well as in the next chapter, where the extension of the approach developed in this chapter to more general reaction networks is discussed.*

Substituting the definition of the functions f and g from Section 2.1.1 into Equation (2.12), we obtain

$$\lambda_1^n = -2(\Omega\alpha - n)(4n+1), \quad \text{with } n = 0, 1, \dots, \Omega\alpha,$$

for the first-order term in the expansion of λ_n.

In sum, a compact expression for the n-th eigenvalue of the transition matrix $\mathbf{M}$ is then given by

$$\lambda^n = (n-\Omega\alpha) + 2(n-\Omega\alpha)(4n+1)K + o(K), \quad \text{for } n = 0, 1, \dots, \Omega\alpha. \tag{2.13}$$

Remark 5. *It follows from standard linear algebra [1] that* λ^n *is* C^∞ *smooth in* K*; hence, the expansion in* (2.13) *can in principle be taken to any order. However, we note that this expansion may only be an asymptotic series in* K*; in other words, it may not be convergent.*

2.2 Eigenvector expansion

In this section, we develop the main theoretical result of this chapter, a graph-based algorithm for calculating the adjoint matrix of a given square matrix that is inspired by "method (B)" of [29]. Our proof of Proposition 1 below relies on an application of the Laplace expansion for the determinant of a matrix which also underlies the analysis in [29] and which is, to the best of our knowledge, novel in the context of the CME, as considered here. We begin by recalling that any non-zero column of the adjoint of $\lambda\mathbf{I} - \mathbf{M}$ is an eigenvector of the matrix $\mathbf{M}$, corresponding to the eigenvalue λ. In the subsequent section, we will apply our approach to the dimerization reaction to obtain a series expansion (in K) for the matrix of eigenvectors of the transition state matrix defined in Equation (2.5).

2.2.1 Preliminaries

The next (well-known) result on the relationship between a given (square) matrix and its adjoint matrix follows directly from Laplace's expansion of the determinant of a matrix; see, *e.g.*, [1] for a proof.

Lemma 1. *For any matrix* $\mathbf{H}$*,*

$$\mathbf{H} \cdot \mathrm{Adj}(\mathbf{H}) = \det(\mathbf{H})\mathbf{I},$$

where $\mathrm{Adj}(\mathbf{H})$ *is the adjoint matrix of* $\mathbf{H}$.

This Lemma has special interest for our purposes when $\mathbf{H} = \lambda\mathbf{I} - \mathbf{M}$, since it follows that

Corollary 1. *For a matrix* $\mathbf{M}$ *and one of its eigenvalues* λ*, every non-zero column of* $\mathrm{Adj}(\lambda\mathbf{I} - \mathbf{M})$ *is an eigenvector.*

Proof. Since λ is an eigenvalue of $\mathbf{M}$, then $\det(\lambda\mathbf{I} - \mathbf{M}) = 0$. Hence, by Lemma 1 , $(\lambda\mathbf{I} - \mathbf{M}) \cdot \mathrm{Adj}(\lambda\mathbf{I} - \mathbf{M}) = \mathbf{0}$ or $\mathbf{M} \cdot \mathrm{Adj}(\lambda\mathbf{I} - \mathbf{M}) = \lambda\, \mathrm{Adj}(\lambda\mathbf{I} - \mathbf{M})$. □

Remark 6. *A non-zero column always exists when* λ *has geometric multiplicity one; cf. [4].*

2.2.2 Calculation of adjoint

We now extend "method (B)", as developed in [29], with the aim of obtaining an algorithmic procedure for the calculation of the adjoint of a given matrix. In [29], the Laplace expansion is applied to adjacency matrices of "chemical" graphs, *i.e.*, to graphs in which vertices correspond to the atoms in the compound under consideration, while edges represent chemical bonds between those atoms. Hence, their results is naturally fitted for unweighed and non-directed graphs; moreover, they obtain no explicit formula for the sign associated with a given path. By contrast, our extension is valid for weighed directed graphs, and we do find a simple expression for the corresponding sign, as specified in detail below.

Proposition 1. *Let G be the graph with adjacency matrix $\mathbf{M}$, and let $\mathbf{A}$ be the adjoint matrix of $\lambda\mathbf{I} - \mathbf{M}$, with λ an eigenvalue of $\mathbf{M}$. Then,*

$$\mathbf{A}[i,j] = \begin{cases} Q(G \setminus \{i\}, \lambda) & \text{if } i = j, \\ \displaystyle\sum_{\mathcal{P}_{ij}} \omega(\mathcal{P}_{ij}) Q(G \setminus \mathcal{P}_{ij}, \lambda) & \text{otherwise,} \end{cases} \tag{2.14}$$

where the sum is calculated over all paths $\mathcal{P}_{ij}$ between the vertices $i, j \in V(G)$. Here, $V(G)$ is the set of vertices in G, $\omega(\mathcal{P}_{ij})$ is the product of the weights of the edges in $\mathcal{P}_{ij}$, and $Q(G, \lambda)$ is the characteristic polynomial of the graph G, expressed in terms of λ, with the additional requirement that $Q(\emptyset, x) = 1$.

Proof. The proof consists in applying Laplace's expansion alternatively to the rows and the columns of $\lambda\mathbf{I} - \mathbf{M}$ until the problem is reduced to finding the characteristic polynomial $Q(G \setminus \mathcal{P}_{ij}, \lambda)$ of the graph $G \setminus \mathcal{P}_{ij}$, *i.e.*, the determinant of the adjacency matrix corresponding to $G \setminus \mathcal{P}_{ij}$ minus $\lambda\mathbf{I}$.

When $i = j$, the adjacency matrix $\mathbf{M}_{i,i}$ of $G \setminus \{i\}$ is simply obtained by $\mathbf{M}$ removing the i-th row and column. Hence, $Q(G \setminus \{i\}, \lambda)$ is the determinant of $\lambda\mathbf{I} - \mathbf{M}_{i,i}$, which is, in fact, $A[i,i]$.

Consider now the case $i \neq j$. Let $\mathbf{H} := \lambda\mathbf{I} - \mathbf{M}$; then, we denote by $\boldsymbol{\mathcal{H}}^{c_1,c_2,c_3,\dots}_{r_1,r_2,r_3,\dots}$ the matrix that is obtained from $\mathbf{H}$ by elimination of rows $r_1, r_2, r_3, \dots$ and of columns $c_1, c_2, c_3, \dots$. Moreover, we will refer to a particular row or column in the sub-matrix $\boldsymbol{\mathcal{H}}^{c_1,c_2,c_3,\dots}_{r_1,r_2,r_3,\dots}$ not by its index in $\boldsymbol{\mathcal{H}}^{c_1,c_2,c_3,\dots}_{r_1,r_2,r_3,\dots}$, but by its original index in the matrix $\mathbf{H}$. (Thus, for instance, when referring to column 2 in matrix $\boldsymbol{\mathcal{H}}^1_1$, we actually mean the first column of that matrix, as $\boldsymbol{\mathcal{H}}^1_1$ is obtained from $\mathbf{H}$ by elimination of the first row and the first column. In the same way, we cannot consider the first column of $\boldsymbol{\mathcal{H}}^1_1$, since such matrix contains columns ranging from the second to the last.)

Now, the (i,j)-th entry $\mathbf{A}[i,j]$ of the adjoint matrix $\mathbf{A}$ of $\mathbf{H}$ equals the cofactor $\mathbf{C}[j,i]$ of $\mathbf{H}$, which is defined as the determinant of the matrix $\boldsymbol{\mathcal{H}}^i_j$ times $(-1)^{i+j}$ [1]. We apply the Laplace expansion over row i of $\boldsymbol{\mathcal{H}}^i_j$, *i.e.*, over the i-th row of $\mathbf{H}$. Since the i-th column is missing, the only non-zero terms in that row are the neighbours of vertex i in G. We have

$$\det\left(\boldsymbol{\mathcal{H}}^i_j\right) = \sum_{x_1 : i \to x_1} (-1)^{s_{x_1}} \mathbf{H}[i, x_1] \det\left(\boldsymbol{\mathcal{H}}^{i,x_1}_{j,i}\right), \tag{2.15}$$

where $i \to x_1$ means there is an edge from i to x_1 and s_{x_1} is the sum of the actual position of row i and column x_1 in matrix $\boldsymbol{\mathcal{H}}^i_j$. Moreover, we recall that $\mathbf{H}[i, x_1]$ is minus the weight of the edge (i, x_1) connecting i and x_1.

Let us now fix $x_1 : i \to x_1$. We again apply Laplace's expansion over row x_1

of $\boldsymbol{\mathcal{H}}_{j,i}^{i,x_1}$, obtaining

$$\det\left(\boldsymbol{\mathcal{H}}_{j,i}^{i,x_1}\right) = \sum_{\substack{x_2 : x_1 \to x_2 \\ x_2 \neq i}} (-1)^{s_{x_2}} \mathbf{H}[x_1, x_2] \det\left(\boldsymbol{\mathcal{H}}_{j,i,x_1}^{i,x_1,x_2}\right);$$

here, s_{x_2} is the sum of the actual position of row x_1 and column x_2 in matrix $\boldsymbol{\mathcal{H}}_{j,i}^{i,x_1}$.

Iterating this procedure p times gives

$$\det\left(\boldsymbol{\mathcal{H}}_{j,i,x_1,x_2,\ldots,x_{p-2}}^{i,x_1,x_2,\ldots,x_{p-1}}\right) = \sum_{\substack{x_p : x_{p-1} \to x_p \\ x_p \neq i, x_1, \ldots, x_{p-2}}} (-1)^{s_{x_p}} \mathbf{H}[x_{p-1}, x_p] \det\left(\boldsymbol{\mathcal{H}}_{j,i,x_1,x_2,\ldots,x_{p-2},x_{p-1}}^{i,x_1,x_2,\ldots,x_{p-1},x_p}\right), \tag{2.16}$$

where s_{x_p} is the sum of the actual position of row x_{p-1} and column x_p in matrix $\boldsymbol{\mathcal{H}}_{j,i,x_1,x_2,\ldots,x_{p-2}}^{i,x_1,x_2,\ldots,x_{p-1}}$. We note that $i, x_1, x_2, \ldots, x_{p-1}$ is a path in G starting from i.

We can represent this strategy as a tree $\mathcal{T}$:

1. the root of $\mathcal{T}$ is the cofactor $\mathbf{C}[j,i] = \det(\boldsymbol{\mathcal{H}}_j^i)$;
2. each node situated on the h-th level is the determinant of matrix $\boldsymbol{\mathcal{H}}_{j,i,x_1,\ldots,x_{h-1}}^{i,x_1,x_2,\ldots,x_h}$ for some path $\{x_0 = i, x_1, x_2, \ldots, x_h\}$ in G;
3. the children of each internal node $y = \det(\boldsymbol{\mathcal{H}}_{j,i,x_1,x_2,\ldots,x_{h-1}}^{i,x_1,x_2,\ldots,x_h})$ are the cofactors computed in the Laplace expansion of y on row x_h;
4. a node $y = \det(\boldsymbol{\mathcal{H}}_{j,i,x_1,x_2,\ldots,x_{h-1}}^{i,x_1,x_2,\ldots,x_h})$ is a leaf if either all the entries in row x_h are null; or $x_h = j$.

In $\mathcal{T}$, each node is linear combination of its children since Equation (2.16) holds. In particular, the root is linear combination of the leaves.

Imagine to traverse $\mathcal{T}$ in depth first: each time we reach a leaf we have followed a path $\{i, x_1, x_2, \ldots, x_p\}$. By construction rule 4:

- either all the entries in the x_p row are null, which means that the contribution of that leaf is null and the path $\{i, x_1, x_2, \ldots, x_p\}$ is at a dead end (there are no other neighbours of x_p);
- or $x_p = j$ and we have managed to eliminate the same rows and columns $i, j, x_1, \ldots, x_{p-1}$, *i.e.*, we have reduced the problem to finding the determinant of the matrix $\boldsymbol{\mathcal{H}}_{i,j,x_1,\ldots,x_{p-1}}^{i,j,x_1,\ldots,x_{p-1}}$ that corresponds to the characteristic polynomial $Q(G \setminus \mathcal{P}, \lambda)$, with $\mathcal{P}$ being the path $\{i, x_1, \ldots, x_{p-1}, j\}$. (In other words, we have found one path in the sum in (2.14).)

An illustration of the above procedure can be found in Example 2 below.

Finally, the sign in front of a path $\mathcal{P} = \{x_0, x_1, \ldots, x_d\}$ with $x_0 := i$ and $x_d := j$ is given by the product $(-1)^d(-1)^{i+j}\prod_{p=1}^{d}(-1)^{s_{x_p}}$, where the factor $(-1)^d$ comes form the fact $\mathbf{H}[x_l, x_{l+1}] = -\mathbf{M}[x_l, x_{l+1}] = -\omega(x_l, x_{l+1})$.

We need to find $d + i + j + \sum_{p=1}^{d} s_{x_p}$ mod 2. Let us define

$$m_{\beta,\gamma}^{\mathcal{P}} := \begin{cases} 1 & \text{when } x_\gamma < x_\beta, \\ 0 & \text{when } x_\beta < x_\gamma \end{cases}$$

for $\beta, \gamma \in \{0, 1, \ldots, d\}$, and let

$$\mathbf{H}_p^{\mathcal{P}} := \begin{cases} \boldsymbol{\mathcal{H}}_j^i & \text{for } p = 1, \\ \boldsymbol{\mathcal{H}}_{j,i,x_1,x_2,\ldots,x_{p-2}}^{i,x_1,x_2,\ldots,x_{p-1}} & \text{for } p > 1. \end{cases}$$

We have already shown that $s_{x_p} = r_p^{\mathcal{P}}(x_{p-1}) + c_p^{\mathcal{P}}(x_p)$, where $r_p^{\mathcal{P}}(x)$ and $c_p^{\mathcal{P}}(x)$ denote the actual row index and column index of x, respectively, in $\mathbf{H}_p^{\mathcal{P}}$. It is easy to see that

$$r_p^{\mathcal{P}}(x_{p-1}) = x_{p-1} - m_{p-1,d}^{\mathcal{P}} - \sum_{r=0}^{p-2} m_{p-1,r}^{\mathcal{P}} \quad \text{and} \quad c_p^{\mathcal{P}}(x_p) = x_p - \sum_{r=0}^{p-1} m_{p,r}^{\mathcal{P}}.$$

Summing over all p, we obtain

$$\sum_{p=1}^{d} s_{x_p} = i + j + \sum_{p=1}^{d-1} x_p + \sum_{p=2}^{d} x_{p-1} - \sum_{p=0}^{d-1} m_{p,d}^{\mathcal{P}} - \sum_{p=1}^{d-1} \sum_{r=0}^{p-1} m_{p,r}^{\mathcal{P}} - \sum_{p=1}^{d} \sum_{r=0}^{p-1} m_{p,r}^{\mathcal{P}}.$$

Taking the result modulo 2, one finds

$$\sum_{p=1}^{d} s_{x_p} \bmod 2 \equiv i + j - \sum_{p=0}^{d-1} m_{p,d}^{\mathcal{P}} - \sum_{r=0}^{d-1} m_{d,r}^{\mathcal{P}} \bmod 2 \equiv i + j + d.$$

Hence, we have

$$d + i + j + \sum_{p=1}^{d} s_{x_p} \bmod 2 \equiv 0,$$

therefore, simply a positive sign is needed independently of the path. ☐

Remark 7. *Proposition 1 implies, in particular, that the eigenvectors of a matrix* $\mathbf{M}$ *which depends smoothly on a parameter* K *and whose eigenvalues are all distinct are* C^∞ *smooth in* K*: by Section 2.2.1, any non-zero column of* $\operatorname{Adj}(\lambda\mathbf{I} - \mathbf{M})$ *yields an eigenvector corresponding to a given eigenvalue* λ*; the proposition affirms that every entry of this adjoint is proportional to a characteristic polynomial which is* C^∞ *smooth in* K*.*

We now illustrate the proof of Proposition 1 by studying a simple example.

Example 2. *Consider the matrix*

$$\mathbf{M} = \begin{pmatrix} * & 1 & 1 & 0 & 0 \\ 1 & * & 0 & 1 & 0 \\ 1 & 0 & * & 1 & 1 \\ 0 & 1 & 1 & * & 1 \\ 0 & 0 & 1 & 1 & * \end{pmatrix}$$

and its associated undirected graph G*, as shown in Fig. 2.1. (Here, we ignore the values on the diagonal of* $\mathbf{M}$*, as those would correspond to "loops" in the graph.)*

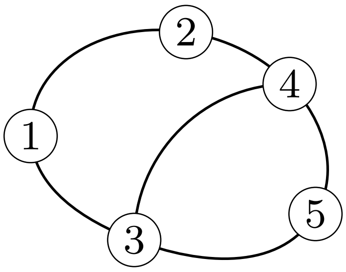


Figure 2.1: Graph G corresponding to the matrix $\mathbf{M}$ defined in Fig. 2.2. The paths connecting 4 and 1 are given by $\{4, 2, 1\}$, $\{4, 3, 1\}$, and $\{4, 5, 3, 1\}$, corresponding to the terms in (a), (b), and (d), respectively, in Fig. 2.2. The term in (c) corresponds to the path $\{4, 3, 5\}$ and equals zero, since that path does not end in 1.

We intend to calculate the term $\mathbf{A}[4, 1]$*, where* $\mathbf{A} := \mathrm{Adj}(\mathbf{M})$*; in particular, retracing the procedure developed in the proof of Proposition 1, we will show that* $\mathbf{A}[4, 1]$ *depends on the determinants of the sub-matrices associated to the graphs* $G \setminus \mathcal{P}$ *for all paths* $\mathcal{P}$ *connecting vertices* 1 *and* 4*.*

Hence, we need to find the cofactor C_{14} *of* $\mathbf{M}$ *which, by definition, equals the determinant of the topmost matrix in Fig. 2.2 (ignoring again any greyed-out entries). Applying the Laplace expansion of the determinant over row* 4 *(the crossed-out row in that same matrix), we decompose the original determinant into the sum of determinants of the three sub-matrices (left, center, and right) shown in the second row in Fig. 2.2; the sign of each term in the sum depends on the position at which we are applying the cofactor. In the context of the graph* G *given in Fig. 2.1, each of these sub-matrices corresponds to a neighbour of vertex* 4*, as indicated by a non-zero term in row* 4 *of* $\mathbf{M}$*. (Following the convention in the above proof, we also include greyed-out rows when counting.) Specifically, the circled numbers represent, respectively, the second, third and fifth entries in row* 4*, or, equivalently, vertices* 2*,* 3 *and* 5 *in* G*. (We remark that, when considering weighted graphs, each of the determinants involved must additionally be multiplied by the weight of the corresponding edge.)*

Next, we need to apply another Laplace expansion to each of the three sub-matrices in the second row in Fig. 2.2 (which, incidentally, do not themselves have any graph-theoretical meaning).

1. *Left matrix: we expand the determinant over row* 2 *and find the one non-zero entry corresponding to vertex* 1*, the only remaining neighbour of* 2*. That is the vertex we intended to reach; in fact, the resulting sub-matrix (a) in Fig. 2.2 corresponds to the adjacency matrix of the graph* $G \setminus (4, 2, 1)$*. (We note that all diagonal entries have fallen into place, since we eliminated rows and columns with the same indices* 1*,* 2*, and* 4*.)*

2. *Center matrix: expanding over row* 3*, we find two non-zero values, corresponding to vertices* 1 *and* 5*, which are the remaining neighbours of* 3*. The cofactor over* $(3, 1)$ *results in sub-matrix (b) in Fig. 2.2, which is the adjacency matrix of* $G \setminus (4, 3, 1)$*; again, all diagonal entries are correctly placed.*

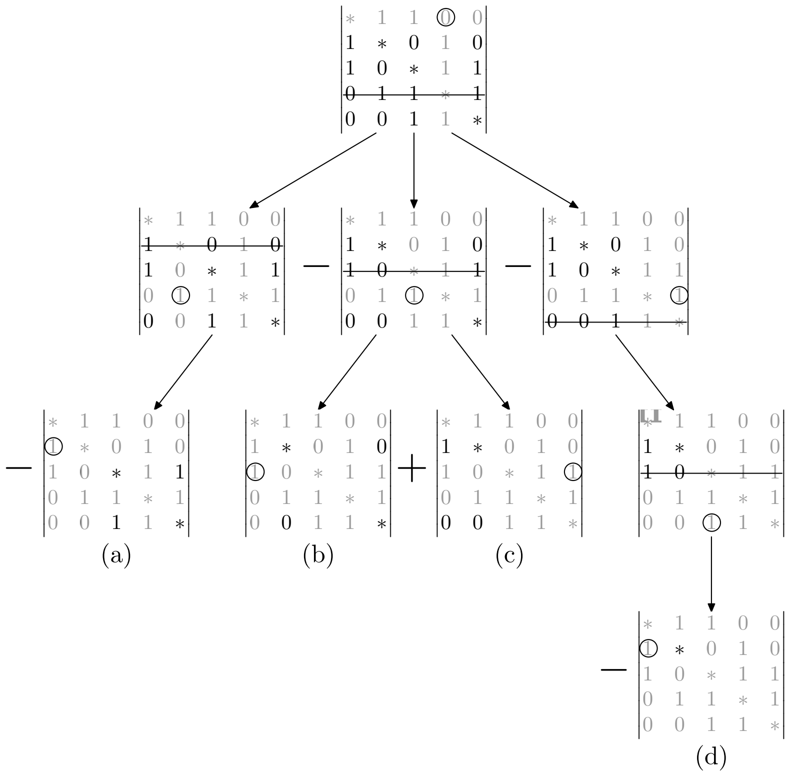


Figure 2.2: Example of tree $\mathcal{T}$ in the proof of Proposition 1. Our aim is to calculate $\mathbf{A}[4,1]$: greyed-out entries have been removed from the matrix, crossed-out rows are the ones we are applying the Laplace expansion to, and circled entries indicate the calculation of a cofactor. The corresponding graph G is shown in Fig. 2.1.

> *The cofactor over* $(3,5)$*, on the other hand, yields sub-matrix (c), whose determinant is* 0*, since vertex* 5 *has no neighbours other than the already considered vertices* 4 *and* 3*; thus, its corresponding row only contains zero entries.*

3. *Right matrix: expanding over row* 5*, we find that only the third entry is non-zero, which gives the rightmost matrix in the third row of matrices in Fig. 2.2. Expanding one more time over row* 3*, we obtain sub-matrix (d), which corresponds to the graph* $G \setminus (4,5,3,1)$*, i.e., to the vertex* 2 *itself.*

In sum, it is instructive to verify how, in following the above procedure, we have covered all paths between vertices 4 *and* 1 *in the graph* G *shown in Fig. 2.1.*

While we intend to approximate the "full" eigenvector matrix that is associated with a given matrix $\mathbf{M}$, the required computational effort is reduced by the observation that it suffices to determine one column of $\mathrm{Adj}(\lambda\mathbf{I} - \mathbf{M})$ for each eigenvalue λ of $\mathbf{M}$. Moreover, we note that no assumption is made in Proposition 1 on the order (in K) of the expressions involved in the evaluation of that adjoint; in fact, as we will show below, many of the paths $\mathcal{P}_{ij}$ occurring in Equation (2.14) are of higher order and, hence, can be neglected when applying the very general result of the proposition to the dimerization reaction.

2.3 Dimerization revisited

In this section, we apply the results of the previous section to the reaction $A + A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B$, *i.e.*, to the corresponding transition state matrix $\mathbf{M}$ that is defined in (2.5). The graph of that reaction, which we shall denote by G_d, is illustrated in Fig. 2.3.

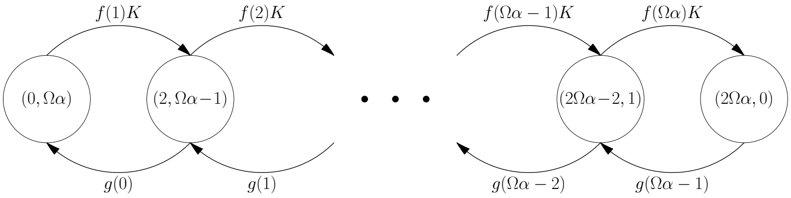


Figure 2.3: Graph associated to the transition state matrix $\mathbf{M}$ defined in (2.5). The vertices correspond to all possible states in the system, while the edges are weighted with the transition probabilities; specifically, the edge connecting states i and j is weighted with the probability of going from j to i. (No edge is drawn when that probability is zero.) Although this notation may seem counter-intuitive, it is consistent with much of the relevant literature; see, *e.g.*, [33, 10]. Loops, corresponding to the principal diagonal of matrix $\mathbf{M}$, are omitted to enhance the drawing appearance.

We remark that there is a natural correspondence between the eigenvalues of the matrix $\mathbf{M}$ and the vertices of the associated graph G_d. In fact, for $K = 0$, $\mathbf{M}$ reduces to a triangular matrix; hence, the n-th eigenvalue λ_n equals the element $\mathbf{M}[n,n]$ on the diagonal of $\mathbf{M}$ which, in turn, corresponds to the n-th vertex in the graph G_d. Similarly, for $K > 0$, we assign to $n \in V(G_d)$ the eigenvalue whose leading-order term is given by $\mathbf{M}[n,n]$; we recall the corresponding series expansion (in K) for λ_n, Equation (2.13), from Section 2.1.2.

2.3.1 Eigenvector matrix

We now discuss how the methodology developed in Section 2.2 can be applied to approximate (to first order in K) the matrix of eigenvectors $\mathbf{E}$ of the transition matrix $\mathbf{M}$. As the eigenvalues λ_n of $\mathbf{M}$ are distinct, with $n = 0, 1, \ldots, \Omega\alpha$, we have $\Omega\alpha + 1$ corresponding eigenvectors; see again Section 2.1.2.

Next, we note that, for each pair of vertices $i, j \in V(G_d)$, there exists only one path $\mathcal{P}_{ij}$ connecting i and j; cf. Fig. 2.3. Hence, the weight $\omega(\mathcal{P}_{ij})$ of that path is given by

$$\omega(\mathcal{P}_{ij}) = \prod_{r=i}^{j-1} \omega((r, r+1)) = \prod_{r=i}^{j-1} \mathbf{M}[r, r+1] = K^{j-i} \prod_{r=i}^{j-1} f(r+1) \quad \text{for } i < j \tag{2.17}$$

and by

$$\omega(\mathcal{P}_{ij}) = \prod_{r=j}^{i-1} \omega((r+1,r)) = \prod_{r=j}^{i-1} \mathbf{M}[r+1,r] = \prod_{r=j}^{i-1} g(r) \quad \text{for } i > j. \tag{2.18}$$

Remark 8. *For $i = j$, we do not have a proper path in G_d, in the sense that we only have a vertex and no edges, which corresponds to the first case in Equation (2.14).*

Since we are interested in the asymptotics of $\omega(\mathcal{P}_{ij})$ up to and including first-order terms in K, it is evident from Eqs. (2.17) and (2.18) that we only need to consider the three cases where $i = j - 1$, $i = j$, and $i > j$ here. We require the following definition.

Definition 1. *Given the eigenvalue λ_n of $\mathbf{M}$ that corresponds to vertex $n \in V(G_d)$, we define*

$$\lambda_n^+ := \lambda_n - \frac{f(n+1)g(n)}{g(n+1) - g(n)} K$$

and

$$\lambda_n^- := \lambda_n + \frac{f(n)g(n-1)}{g(n) - g(n-1)} K.$$

The definition of $\lambda_n^\pm$ agrees with the expression for λ_n given in Equation (2.12), up to one of the permutations considered there; specifically, we omit the “right” permutation in λ_n^+ and the “left” one in λ_n^-.

Proposition 2. *Let $i, j \in \{1, \dots, \Omega\alpha - 1\}$, and let $\mathcal{S}_{ij}$ be the set of vertices $\mathcal{S}_{ij} = \{\mu - 1, \mu, \mu + 1, \dots, \nu, \nu + 1\} \subseteq V(G_d)$, where $\mu = \min(i,j)$ and $\nu = \max(i,j)$. Then,*

$$Q(G_d \setminus \mathcal{P}_{ij}, \lambda_n) = (\lambda_n - \lambda_{\mu-1}^+)(\lambda_n - \lambda_{\nu+1}^-) \prod_{\substack{r=0 \\ r \notin \mathcal{S}_{ij}}}^{\Omega\alpha} (\lambda_n - \lambda_r) + o(K). \tag{2.19}$$

Proof. The statement follows by adapting the results of Section 2.1.2 to the graph $G_d \setminus \mathcal{P}_{ij}$ or, equivalently, to the characteristic polynomial of that graph. In particular, it follows that any eigenvalue associated with a vertex outside $\mathcal{S}_{ij}$ agrees with the corresponding eigenvalue in G_d, up to and including terms of order K. Similarly, the eigenvalues λ_μ and λ_ν have the same $O(1)$ term in G_d and in $G_d \setminus \mathcal{P}_{ij}$; however, when determining the first-order term in K, one permutation drops out, as one of the neighbouring vertices $\mu + 1$ and $\nu - 1$, respectively, does not enter the calculation any more, leading to the introduction of $\lambda_{\mu-1}^+$ and $\lambda_{\nu+1}^-$, respectively, and to a discrepancy at $O(K)$. □

When $\mu = 0$ or $\nu = \Omega\alpha$, Equation (2.19) is still valid provided that the terms $(\lambda_n - \lambda_{\mu-1}^+)$ and $\lambda_n - (\lambda_{\nu+1}^-)$, respectively, are ignored. Hence, defining $\mathbf{A}_n := \mathrm{Adj}(\lambda_n \mathbf{I} - \mathbf{M})$ to be the adjoint matrix of $\lambda_n \mathbf{I} - \mathbf{M}$ and combining the results of Propositions 1 and 2, we can obtain the eigenvector of $\mathbf{M}$ corresponding to λ_n from the n-th column of $\mathbf{A}_n$. Normalising the resulting expression by dividing out a common (non-zero) factor of $\prod_{r=0}^{n-3}(\lambda_n - \lambda_r)$ from $\mathbf{A}_n[i,n]$, denoting the normalised column by $\widetilde{\mathbf{A}}_n[i,n]$, and assuming that $n \neq 0, 1, \Omega\alpha$, for simplicity, we find

$$\widetilde{\mathbf{A}}_n[i,n] = \begin{cases} Kf(n)(\lambda_n - \lambda^+_{n-2})(\lambda_n - \lambda^-_{n+1}) \displaystyle\prod_{r=n+2}^{\Omega\alpha} (\lambda_n - \lambda_r) & \text{if } i = n-1; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n-2}) \displaystyle\prod_{r=n+2}^{\Omega\alpha} (\lambda_n - \lambda_r) & \text{if } i = n; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{i+1})(\lambda_n - \lambda_{n-2}) \displaystyle\prod_{r=i+2}^{\Omega\alpha} (\lambda_n - \lambda_r) \prod_{r=n}^{i-1} g(r) & \text{if } n < i < \Omega\alpha; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda_{n-2}) \displaystyle\prod_{r=n}^{\Omega\alpha-1} g(r) & \text{if } i = \Omega\alpha; \\ o(K) & \text{otherwise.} \end{cases} \tag{2.20}$$

While Equation (2.20) gives $\widetilde{\mathbf{A}}_n[i,n]$ in its most compact form, the above expressions still contain terms that are insignificant to the order considered here, *i.e.*, terms of order K^2 and higher. In Appendix A, we quote alternative formulae that are truncated to $O(K)$ and that are hence more convenient for our purposes; moreover, we treat the cases when $n = 0, 1, \Omega\alpha$.

2.3.2 Inverse eigenvector matrix

In this subsection, we discuss how the inverse $\mathbf{E}^{-1}$ of the matrix of eigenvectors $\mathbf{E}$, as defined in Equation (1.10), can be approximated; to that end, we slightly adapt the methodology developed in the previous subsection.

We begin by observing that the left eigenvector $\mathbf{y}_n$ of the transition matrix $\mathbf{M}$, corresponding to the eigenvalue λ_n, solves the equation

$$(\lambda_n \mathbf{I} - \mathbf{M}^T)\mathbf{y}_n = \mathbf{0}, \quad \text{with } n = 0, 1, \ldots, \Omega\alpha.$$

By standard linear algebra [1], $\mathbf{E}^{-1}$ can be determined from the set of the left eigenvectors of $\mathbf{M}$; specifically, $\mathbf{E}^{-1}$ is the matrix whose rows are suitably normalized versions of these eigenvectors.

Remark 9. *For future reference, we note that the vector* $\mathbb{1}$ *(as well as any non-zero multiple thereof) is always a left eigenvector of* $\mathbf{M}$.

Given the result of Proposition 1, we need to determine (one column of) the matrix $\mathbf{B}_n := \mathrm{Adj}(\lambda_n \mathbf{I} - \mathbf{M}^T)$, as noted in Section 2.3.1. The only difference between the graph corresponding to $\mathbf{M}^T$ and the one corresponding to $\mathbf{M}$ lies in the orientation of the edges, which are inverted now. Hence, Equation (2.19) remains valid, while the weights of the paths are again given by Eqs. (2.17) and

(2.18), albeit with reversed conditions on the index i; correspondingly, we have

$$\omega(\mathcal{P}_{ij}) = \prod_{r=j}^{i-1} \omega((r+1,r)) = \prod_{r=j}^{i-1} \mathbf{M}^T[r+1,r] = K^{i-j} \prod_{r=j}^{i-1} f(r+1) \quad \text{for } i > j$$

and

$$\omega(\mathcal{P}_{ij}) = \prod_{r=i}^{j-1} \omega((r,r+1)) = \prod_{r=i}^{j-1} \mathbf{M}^T[r,r+1] = \prod_{r=i}^{j-1} g(r) \quad \text{for } i < j.$$

The only cases of interest are $i = j+1$, $i = j$, and $i < j$. For $n \neq 0, \Omega\alpha - 1, \Omega\alpha$, we find

$$\widetilde{\mathbf{B}}_n[n,i] = \begin{cases} Kf(n+1)(\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{n+2}) \prod_{r=0}^{n-2} (\lambda_n - \lambda_r) & \text{if } i = n+1; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n+2}) \prod_{r=0}^{n-2} (\lambda_n - \lambda_r) & \text{if } i = n; \\ (\lambda_n - \lambda^+_{i-1})(\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n+2}) \prod_{r=0}^{i-2} (\lambda_n - \lambda_r) \prod_{r=i}^{n-1} g(r) & \text{if } 0 < i < n; \\ (\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n+2}) \prod_{r=i}^{n-1} g(r) & \text{if } i = 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{2.21}$$

Here, $\widetilde{\mathbf{B}}_n[n,i]$ is obtained from $\mathbf{B}_n[n,i]$ by dividing the latter by the non-zero product $\prod_{r=n+3}^{\Omega\alpha} (\lambda_n - \lambda_r)$, in analogy to the definition of $\widetilde{\mathbf{A}}_n[i,n]$. As was the case in Section 2.3.1, the above Equation (2.21) represents the most compact expression for $\widetilde{\mathbf{B}}_n[n,i]$ which may, however, still contain insignificant (higher-order) terms. We refer the reader to Appendix A for the solution to order K, as well as for a discussion of the cases where $n = 0, \Omega\alpha - 1, \Omega\alpha$.

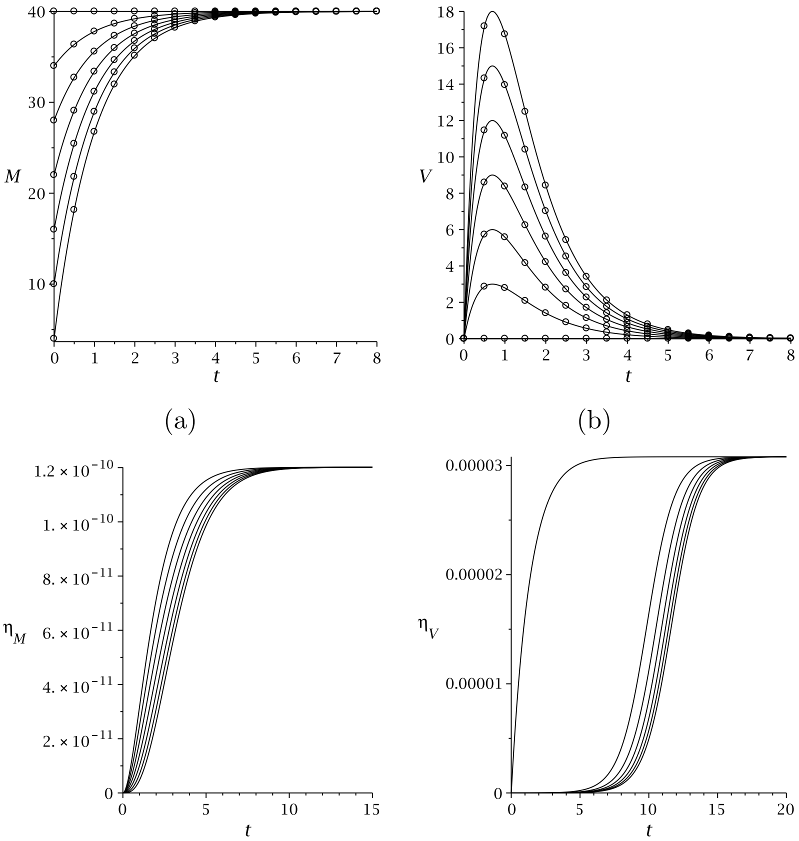
Finally, the inverse matrix $\mathbf{E}^{-1}$ of $\mathbf{E}$ is found from Equation (2.21) by normalization. The normalizing values can be found by multiplication of the matrix that is defined by (2.20) with the matrix given by (2.21). The result is a diagonal matrix, up to terms of order K. Dividing each left eigenvector of $\mathbf{M}$ by the corresponding value in that matrix, we obtain $\mathbf{E}^{-1}$. This normalization procedure can easily be performed numerically for any fixed value of the non-dimensional parameter $\Omega\alpha$. However, a better approach that completely avoids the use of eigenvectors, therefore allowing a purely analytical solution, will be shown in Section 3.3.

2.4 Numerical validation

We are now ready to construct our approximation to the solution $\mathbf{P}(t)$ of the CME, Equation (2.4), as defined in (1.10). To that end, we combine the results of Sections 2.1.2, 2.3.1, and 2.3.2: expanding the eigenvalues of $\mathbf{M}$ as in Equation

(2.13), we construct the diagonal eigenvalue matrix $\mathbf{\Lambda}$; applying the expansions from Eqs. (2.20) and (2.21), we approximate the corresponding matrix of eigenvectors $\mathbf{E}$ and its inverse $\mathbf{E}^{-1}$, respectively. Substituting into Equation (1.10) and retaining terms of at most order K, we obtain the desired approximate solution.

Remark 10. *Remark 7 and the derivation of Eqs. (2.20) and (2.21) above imply that both* $\mathbf{E}$ *and its inverse* $\mathbf{E}^{-1}$ *are* C^∞ *smooth in* K*, in all of their entries.*



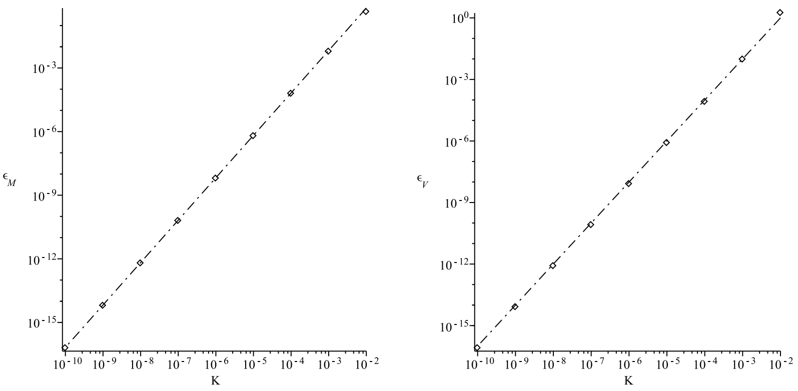
(a) (b)

(c) (d)

Figure 2.4: Comparison of the graph-based approximation and the exact (numerical) solution. In panels (a) and (c), we plot the mean number M of monomer molecules and the relative error in the mean η_M as a function of time for different initial conditions; panels (b) and (d) show the variance V in the number of monomer molecules and the corresponding relative error η_V, respectively. The non-dimensional parameter $\Omega\alpha$ is fixed to 20, allowing for a maximum of 40 monomer molecules in the system, while $K = 10^{-7}$ throughout.

In panels (a) and (b) of Fig. 2.4, we compare the mean M and the variance V, respectively, of the number of monomer molecules, as calculated from our approximate solution (open circles) and the numerical solution of the CME, Equation (2.4) (solid lines), for a total of 40 monomers and $K = 10^{-7}$. The numerical solution has been computed using standard routines from Maple 15 LinearAlgebra package (however, in this particular example, the MatixExponential routine experienced runtime problems) and we will refer to it as the “exact” solution of

(2.4) for fixed values of $\Omega\alpha$ and K. The two solutions are in excellent agreement – and are, in fact, indistinguishable on the scale of panels (a) and (b) in Fig. 2.4 – which strongly supports the validity of our perturbation approach. In panels (c) and (d) of Fig. 2.4, we show the corresponding relative error in the mean and the variance, respectively. (Here, the relative error is equal to the modulus of the absolute error, divided by the exact solution.) We remark that, in both cases, the relative error grows from zero to some maximum that is achieved at steady state, independently of initial conditions.



(a) (b)

Figure 2.5: Maximum absolute error in the mean (ϵ_M) and the variance (ϵ_V) of the number of monomer molecules as a function of K, as shown in panels (a) and (b), respectively. Here, $\Omega\alpha$ is alternatively set to 5 (circles), 10 (crosses), and 20 (diamonds). The maximum error is attained when steady-state conditions ensue; in practice, we evaluated our approximate probability density at $t = 15$. The solid, dashed, and dotted lines represent $\frac{2}{3} \cdot 10^4 K^2$, $6 \cdot 10^4 K^2$, and $5 \cdot 10^5 K^2$ in panel (a) and $10^4 K^2$, $\frac{1}{3} \cdot 10^6 K^2$, and $10^7 K^2$ in panel (b), respectively. The initial condition is $P(n_A = 0, t = 0) = 1$ in all cases.

In Fig. 2.5, we plot the maximum absolute error in the mean and the variance of the number of monomer molecules – which are denoted by ϵ_M and ϵ_V, respectively – as a function of K for $\Omega\alpha$ equal to 5, 10, and 20. In all cases, the maximum absolute error scales like $O(K^2)$, which is consistent with our first-order truncation of the series expansion in K for the solution $\mathbf{P}(t)$ of the CME.

2.4.1 Comparison with LNA

As discussed already, LNA [33, 7] is based on an expansion procedure that is different from the perturbative approach developed in this thesis. Nevertheless, it is still possible to compare the two approaches for fixed values of the volume Ω, the total semi-concentration α, and the non-dimensional parameter K. A concise derivation of LNA for the dimerization reaction considered here can be found in Appendix B.

In Figs. 2.6 and 2.7, we compare the relative error in the mean and the variance that is predicted by the two approaches for several different values of K; throughout, we set $\Omega\alpha = 20$, *i.e.*, we allow for a maximum of 40 monomer molecules in the system. We note that the mean concentrations according to LNA are the same as those obtained from the conventional rate equations. For very small $K = O(10^{-5})$, the perturbative approach outperforms LNA for practically all times; see panels (c) and (d) in Figs.2.6 and 2.7. For larger values of $K = O(10^{-3})$, our methodology performs better for short times only. Hence, it can be stated that our approach is always superior to LNA for K sufficiently small; moreover, this statement is independent of the number of molecules in the system.

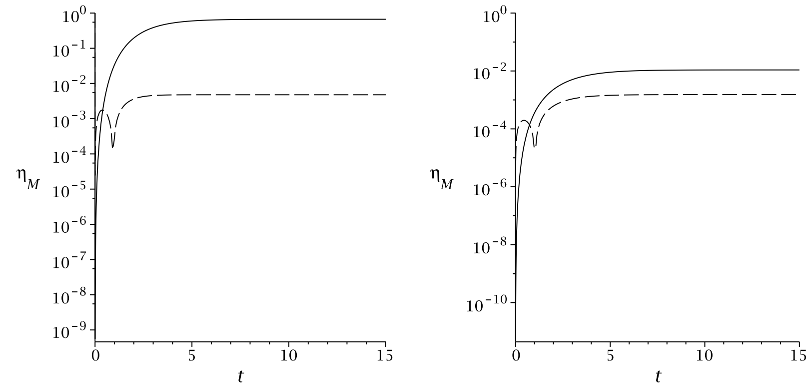
Next, we compare our perturbative expansion for the probability distribution $P(n_A, t)$ of the number of monomer molecules with the approximation given by LNA, cf. Eqn. (B.5), as well as with the distribution obtained from the standard stochastic simulation algorithm (SSA) [12]. (We note that, in all three cases, the height of the histogram for fixed n_A is calculated by integrating the corresponding density over the range $n_A - 1$ to $n_A + 1$; as indicated also in Appendix B, the continuous probability distribution resulting from LNA is discretized by this procedure and, hence, becomes directly comparable to the other two (discrete) distributions.) The result is shown in Fig. 2.8 for K fixed to 10^{-4} and three different values of t, the choice of which is motivated by the very fast convergence to steady state that is observed in the context of the probability distribution, as opposed to the moments considered earlier. We find that LNA is inaccurate both at short times and at long times, as seen in panels (a) and (c), while it performs reasonably well at intermediate times, as shown in panel (b); by contrast, our graph-based approximation achieves a uniformly high accuracy throughout. The poor performance of LNA in this scenario is due to the fact that it predicts a Gaussian monomer distribution for all times, whereas the true distribution is highly skewed and non-Gaussian whenever the mean number of monomer molecules is close to the two natural boundaries, *i.e.*, to zero and to the total number of monomers in the system.

Our findings are validated by Fig. 2.9, where we show the Kullback-Leibler (K-L) divergence [5] of our approach (dashed line) and of LNA (solid line) with respect to the distribution obtained from SSA as a function of time. (For consistency with Fig. 2.8, we have again taken $K = 10^{-4}$ and assumed that no monomer molecules are present initially.) One observes that, for all times, the K-L divergence is significantly lower for our graph-based methodology than it is for LNA; thus, for small values of K, the difference between the probability distribution predicted by our approach and the true solution of the CME, Equation (2.1), is much smaller than the difference between the probability distribution predicted by LNA and the true solution.

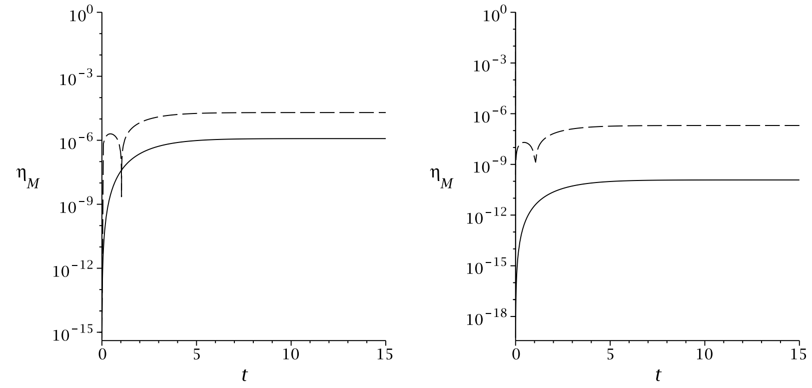
Since, on the other hand, our methodology is perturbative, its accuracy deteriorates with increasing K, as illustrated in panel (a) of Fig. 2.10: when K is not sufficiently small, our series expansion for the distribution $P(n_A, t)$ may become inconsistent; in other words, it may predict negative probabilities. Such inconsistencies are well-known in the literature, see, *e.g.*, [17] and the references therein for details: in general, the asymptotic expansion of a probability distribution is not a distribution itself and, hence, does not satisfy the non-negativity conditions required of the latter. Nevertheless, our approach can still yield a decent approximation for "intermediate" values of K when t is small, as seen in panel (b) of

Fig. 2.10.

Remark 11. *We note that the derivation of LNA in Appendix B is based on the original (dimensional) CME, Equation (2.1), as is conventional, rather than on its non-dimensionalized equivalent in (2.3). In order to avoid a rescaling of time when comparing LNA with our approach, we have chosen $k_2 = 1$ throughout this section. (Clearly, the value of k_2 is irrelevant for the remainder of our analysis, as only the non-dimensional parameter K is considered.)*

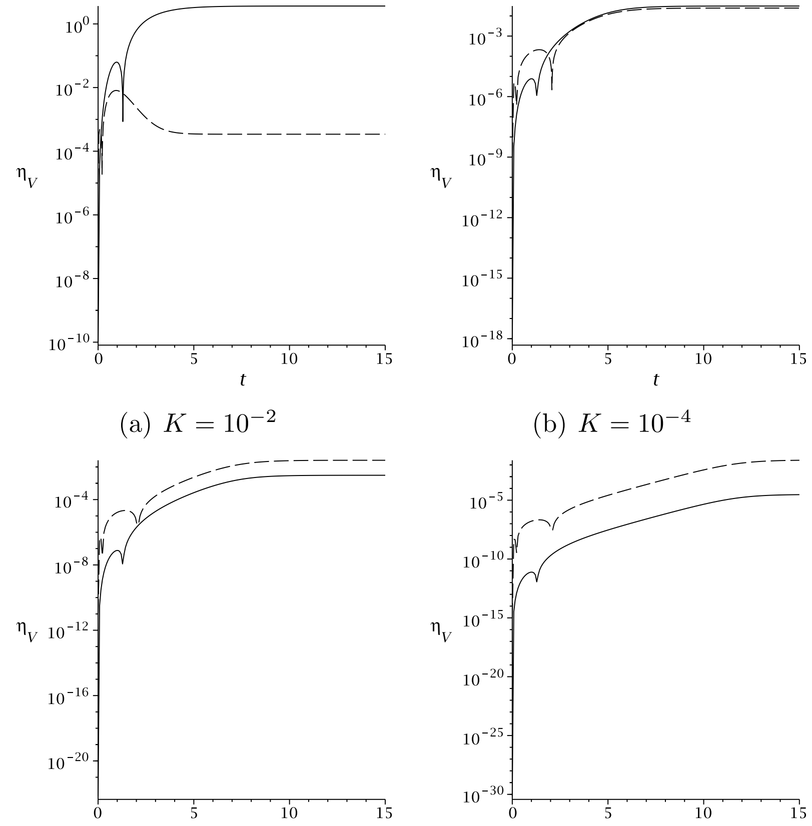


(a) $K = 10^{-2}$ (b) $K = 10^{-3}$



(c) $K = 10^{-5}$ (d) $K = 10^{-7}$

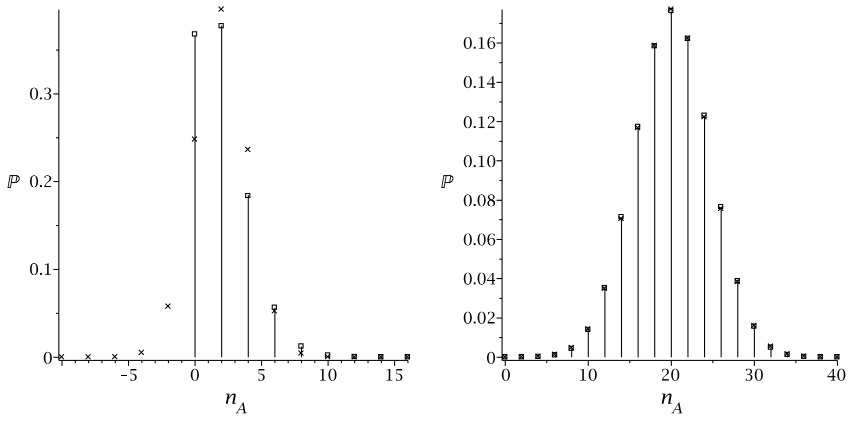
Figure 2.6: Relative error η_M in the mean of the number of monomer molecules as a function of time and for different values of K, as given by our perturbation approach (solid lines) versus LNA (dashed lines). The parameter $\Omega\alpha$ is fixed to 20 throughout. Although LNA performs better most of the time in panels (a) and (b), there is a short time interval during which our approach is superior. For sufficiently small K, the perturbative approach is more accurate than LNA for practically all times; see panels (c) and (d). (The sharp dips in the dashed graphs actually go down to zero, but are truncated here for aesthetic reasons. These dips correspond to times at which the difference between the exact and the approximate solution changes sign; see also [18].)



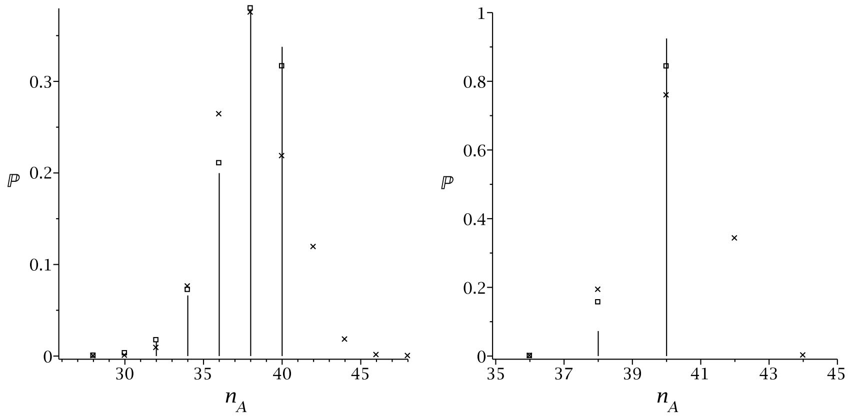
(a) $K = 10^{-2}$ (b) $K = 10^{-4}$

(c) $K = 10^{-5}$ (d) $K = 10^{-7}$

Figure 2.7: Relative error η_V in the variance of the number of monomer molecules as a function of time and for different values of K, as given by our perturbation approach (solid lines) versus LNA (dashed lines). The parameter $\Omega\alpha$ is fixed to 20 throughout. Although LNA performs better most of the time in panels (a) and (b), there is a short time interval during which our approach is superior. For sufficiently small K, the perturbative approach is more accurate than LNA for practically all times; see panels (c) and (d).



(a) $t = 0.05$ (b) $t = 0.7$



(c) $t = 3$ (d) $t = 10$

Figure 2.8: Comparison between the probability distribution obtained from SSA (histogram), our perturbative approach (squares), and LNA (crosses) for $\Omega\alpha = 20$ and $K = 10^{-4}$ fixed and three points in time. (The initial condition is set to $n_A = 0$ in all cases.) Our methodology agrees with SSA on the scale of the figure for small times, as seen in panel (a); as the distribution approaches steady state, the quality of the approximation decreases, yet still exceeds the accuracy achieved by LNA, as shown in panels (c) and (d).

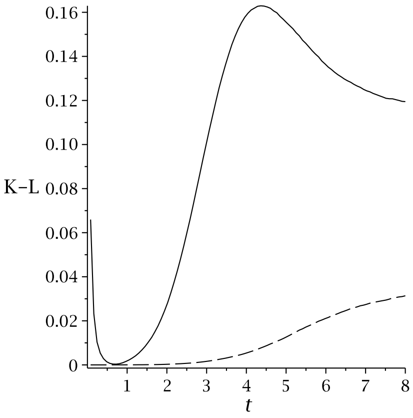
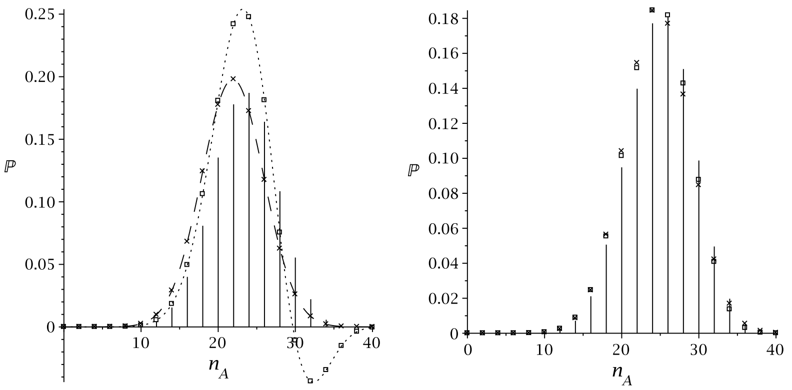


Figure 2.9: Kullback-Leibler (K-L) divergence of our approach (dashed line) and LNA (solid line) with respect to the distribution obtained from SSA, with $2 \cdot 10^5$ trajectories; here, we have fixed $\Omega\alpha = 20$ and $K = 10^{-4}$, and chosen $n_A = 0$ initially throughout. We observe that the K-L divergence of our approach is lower for all times.



(a) $K = 10^{-2}$

(b) $K = \frac{1}{6} \cdot 10^{-2}$

Figure 2.10: Comparison between the distribution obtained from SSA (histogram), our perturbative approach (squares), and LNA (crosses) for $\Omega\alpha = 20$ and $t = 1$ fixed and two different values of K. (As before, we assume that, initially, $n_A = 0$.) In panel (a), we have joined individual points with lines – dotted for our approach and dashed for LNA – to guide the reader's eye.

Chapter 3

Generalizations

In this chapter we explain how the ideas and techniques develop in Chapter 2 can be used for a more general set of reactions. Throughout the chapter, we formalise the assumptions that were implicitly adopted in the previous chapter.

The chapter is structured as follows: in Section 3.1 we show how to non-dimensionalize the CME in order to have a suitable parameter for asymptotic expansion. We set the first assumptions to guarantee the existence of a "small" parameter and to avoid the presence of "big" terms that would compensate on the parameter.

In Section 3.2 we generalize the eigenvalues approach previously developed in Section 2.1.2 highlighting the relation, until now only mentioned in Remark 4, between permutations and cycles in the graph associated to the system. The fundamental assumption of an acyclic "fast" graph is given and another optional assumption to reduce the cycles to be considered only to cycles of length two, corresponding to neighbours, is presented. The problem is studied in the most favourable case of eigenvalues with different leading order in Subsection 3.2.1, as well as when eigenvalues with same leading order in Subsection 3.2.2.

Finally, in Section 3.3 we show how to avoid the product in Equation (1.19), as well as the normalization of the left eigenvector matrix to become the inverse of the eigenvector matrix, using the Laplace transform.

3.1 Non-dimensionalization

Consider the chemical master equation for a system with finite number of possible states labelled from 1 to n

$$\frac{d}{dt}\mathbf{P}[m](t) = \sum_{l} \mathbf{M}[m,l]\mathbf{P}[l] - \mathbf{M}[l,m]\mathbf{P}[m]. \tag{3.1}$$

This equation has the physical dimension of the inverse of time T^{-1}. The transition probability from l to m $\mathbf{M}_{ml}$ can assume one of the three forms

1. $k_R l_A$ when the reaction R that transforms l into m is uni-molecular with reactant A;

2. $(k_R/\Omega)l_A l_B$ when the reaction R that transforms l into m is bi-molecular with reactants A and B.

3. $(k_R/\Omega)l_A(l_A-1)$ when the reaction R that transforms l into m is a homo-dimer reaction with reactant A.

In the first case k_R has dimension of the inverse of time T^{-1}, in the second and third of volume times the inverse of time $\mathrm{V}\,\mathrm{T}^{-1}$. Hence, for any reaction R it is possible to non-dimensionalize Equation (3.1) dividing by k_R and, in case R is bi-molecular or homo-dimer, multiplying by Ω.

We consider the case when the reactions can occur at two different speeds.

Assumption 1. *There are a reaction R and a small parameter K so that the set of reactions $R_i \neq R$ that satisfy*

$$\begin{aligned} \frac{k_{R_i}}{k_R} &= c_i K \quad \textit{when } R \textit{ and } R_i \textit{ are both uni or bi-molecular;} \\ \frac{k_{R_i}}{k_R \Omega} &= c_i K \quad \textit{when } R \textit{ is uni-molecular and } R_i \textit{ bi-molecular;} \\ \frac{k_{R_i}\Omega}{k_R} &= c_i K \quad \textit{when } R \textit{ is bi-molecular and } R_i \textit{ uni-molecular,} \end{aligned} \tag{3.2}$$

where c_i is a constant, is non-empty.

We will study the case $K \to 0$. Unless this limit is obtained letting Ω going to infinitive while keeping constant all k_i, we are in fact enforcing a direction in the parameter space. This is quite common in literature (e.g. the catalytic mechanism in [6]).

Definition 2.

1. *The reactions that satisfy Equation (3.2) are called slow reactions. All the others are called fast reactions and we will denote their set $\mathcal{F}$.*

Also, we will call

2. *fast system: the system constituted only by the reactions in $\mathcal{F}$;*

3. *fast graph: the graph corresponding to the system without all the edges generated by slow reactions (note that such graph might be disconnected and in genral contains the graph associated to the fast system);*

4. *fast molecules: all the molecular species involved as reactant in at least one reaction in $\mathcal{F}$ denoting their set $\mathcal{M}_F$.*

Example 3. *Consider the Michaelis Menten kinetics*

$$E + S \underset{k_r}{\overset{k_f}{\rightleftharpoons}} ES \xrightarrow{k_{cat}} E + P. \tag{3.3}$$

A possible non-dimensionalization is achieved dividing everything by k_r

$$E + S \underset{1}{\overset{c_1}{\rightleftharpoons}} ES \xrightarrow{K} E + P, \tag{3.4}$$

here c_1 is the inverse of the dissociation constant k_r/k_f. When $K = k_{cat}/k_r \to 0$, the substrate reaches equilibrium on a much faster time-scale than the product is formed and we obtain the equilibrium approximation used in the original analysis by Michaelis and Menten themselves [22]. Recalling that c_1 must be constant in our analysis, we can obtain such limit when $k_{cat} \to 0$.

The corresponding fast system is

$$E + S \underset{1}{\overset{c_1}{\rightleftharpoons}} ES, \tag{3.5}$$

and the fast molecules are $\mathcal{M}_F = \{E, S, ES\}$, since P is the product of the catalysis but it is not involved in any other reaction as reactant. Finally, the graph and the fast graph associated to the system with initial condition $(n_E, n_S, n_{ES}, n_P) = (1, 2, 0, 0)$ are reported in Fig. 3.1.

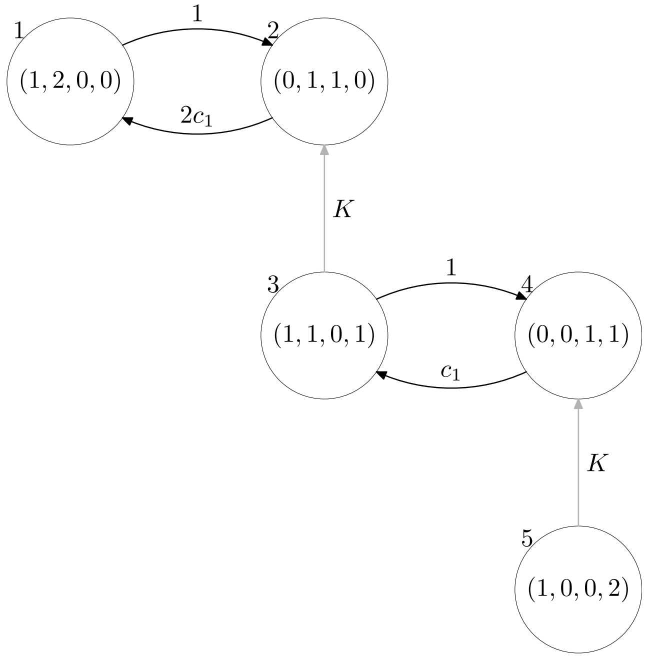


Figure 3.1: The graph corresponding to the system (3.4) with initial conditions $(n_E, n_S, n_{ES}, n_P) = (1, 2, 0, 0)$. The fast graph is obtained by removing all the grey edges. Note that such graph is disconnected and differs from the graph associated to the fast system which is only formed by the nodes 1 and 2; and the edges between them.

Because we want the transition probability through a slow reactions to behave similarly (to be "slow") from any state, we need to ensure the following

Assumption 2. *There is no introduction of molecules in the volume Ω.*

This guarantees that, given an initial condition, the number of molecules in the volume remains bounded. In other words, the transition probability through a slow reaction is a $O(K)$ for each state.

Example 4. *A simple example of system that does not satisfy Assumption 2 is*

$$\begin{aligned} R_1 &: \emptyset \longrightarrow A; \\ R_2 &: A \longrightarrow B + C; \end{aligned}$$

and let us assume that R_2 is slow. For any (small) $K > 0$ and any (big) const $\in \mathbb{R}$ there is a state $\mathbf{n}$ such that the transition probability from such state through R_2 satisfies

$$c_2 K n_A > const. \tag{3.6}$$

Remark 12. *Most chemical systems have a degradation mechanism which overpowers the introduction of molecules, when present. This means that, out of the infinite number of states, only a finite fraction will have a significant chance to happen. The other states may be disregarded or the finite state projection described in [30] may be used.*

Under these assumptions the matrix of (non-dimensionalized) transition probabilities can be written as

$$\mathbf{M} = \mathbf{M}_0 + K\mathbf{M}_1, \tag{3.7}$$

where all the elements in the matrices $\mathbf{M}_0$ and $\mathbf{M}_1$ remain constant when K tends to 0.

3.2 General Eigenvalues

The eigenvalues of $\mathbf{M}$ solve the eigenvalue equation

$$\det(\lambda \mathbf{I} - \mathbf{M}) = 0. \tag{3.8}$$

Let us define

$$\mathbf{M}_\lambda := (\lambda \mathbf{I} - \mathbf{M}). \tag{3.9}$$

The Leibniz formula for the determinant of $\mathbf{M}_\lambda$ is

$$\det(\mathbf{M}_\lambda) = \sum_{\sigma \in S_n} \operatorname{sgn}(\sigma) \prod_{i=1}^{n} \mathbf{M}_\lambda[i, \sigma(i)], \tag{3.10}$$

where S_n is symmetric group of degree $n := |\mathcal{S}|$.

Since $\mathbf{M}_\lambda[i, j]$ is non-zero if $i \to j$ in $\mathbf{G}$ or $j = i$, a permutation σ written as compositions of disjoint cycles as $\sigma_1 \sigma_2 \dots \sigma_l$ contributes to the sum in Equation (3.10) if and only if the σ_is correspond to cycles in $\mathbf{G}$.

In order to be able to easily solve Equation (3.8)'s leading order in K, we need the following

Assumption 3. *Cycles in $\mathbf{G}$ have weight $o(1)$ or, equivalently, $\mathbf{G}$ is an acyclic directed graph for $K = 0$.*

Thanks to this assumption, the only relevant term in Equation (3.10) for the leading order is given by the identity, which is an even permutation. Hence the leading term of Equation (3.8) is

$$\prod_i (\lambda_0 - \mathbf{M}_0[i,i]) = \prod_i \mathbf{M}_\lambda[i,i]\bigg|_{K=0} = 0, \tag{3.11}$$

where λ_0 is the leading term in the asymptotic expansion $\lambda = \lambda_0 + \lambda_1 K + o(K)$. This equation results immediately in the $|\mathcal{S}|$ solutions for the leading term

$$\lambda_0^i := \mathbf{M}_0[i,i], \quad i = 1,\dots,|\mathcal{S}|. \tag{3.12}$$

Remark 13. *Every state i is naturally associated to the eigenvalue λ^i whose leading term is $\lambda_0^i = \mathbf{M}_0[i,i]$.*

Assumption 3 not only significantly simplifies the equation for the leading order of the eigenvalues, but it also makes possible to consider only the identity and cycles that contain i for the computation of the next term approximation of the i-th eigenvalue. In fact, the permutations in Equation (3.10) that contain two or more cycles are immediately excluded since they are of order $o(K)$, while a permutation σ that contains a cycle but that does not change i contains the factor $\mathbf{M}_\lambda[i,i]$, which is already of order K for $\lambda = \lambda^i$, making the weight of σ of order $o(K)$.

Substituting Equation (3.12) into Equation (3.8) gives

$$K(\lambda_1^i - \mathbf{M}_1[i,i]) \prod_{j\neq i} (\lambda_0^i - \mathbf{M}_0[j,j]) - \sum_C (-1)^{l(C)} \omega(C) \prod_{j\notin C} (\lambda_0^i - \mathbf{M}_0[j,j]) = 0, \tag{3.13}$$

where the sum is taken over the cycles C of order K containing i, and $l(C)$ is the length of C.

We will consider the two cases:

1. all the eigenvalues have different leading order;
2. some eigenvalues have same leading order.

3.2.1 Different eigenvalues

Let us first consider the easiest case.

Assumption 4. *All the eigenvalues of $\mathbf{M}_0$ are different.*

Then Equation (3.13) becomes

$$\lambda_1^i = \mathbf{M}_1[i,i] - \sum_C (-1)^{l(C)} \frac{\omega(C)}{K} \prod_{\substack{j\in C\\ j\neq i}} \frac{1}{\mathbf{M}_0[j,j] - \mathbf{M}_0[i,i]}, \tag{3.14}$$

where again the sum is taken over the cycles C of order K containing i.

Remark 14. *It may not be feasible to try to find the next order approximation of λ^i since, in addition to the cycles of order K^2 containing i, all the cycles of order K, independently on whether they pass through i or not, contribute to it.*

With the following optional assumption, only the identity and permutations that exchange exclusively i and j with $i \sim j$ ($i \leftarrow j$ and $i \rightarrow j$) are needed.

Assumption 5. *The weights of cycles of length three or more are of order $o(K)$.*

Remark 15. *Assumption 5 combined together with Assumption 3 affirms that the cycles of length two are all the cycles with weight $\theta(K)$. These correspond to all the reversible reactions.*

Equation (3.14) is then simplified into

$$\lambda_1^i = \mathbf{M}_1[i,i] - \sum_{j:i\sim j} \frac{\mathbf{M}_1[i,j]\mathbf{M}_0[j,i] + \mathbf{M}_0[i,j]\mathbf{M}_1[j,i]}{\mathbf{M}_0[j,j] - \mathbf{M}_0[i,i]}. \tag{3.15}$$

Remark 16. *Because of Assumption 3, one term between $\mathbf{M}_1[i,j]\mathbf{M}_0[j,i]$ and $\mathbf{M}_0[i,j]\mathbf{M}_1[j,i]$ is zero.*

Combining Equation (3.12) and Equation (3.15) we get the formula

$$\begin{aligned}\lambda^i =& \mathbf{M}_0[i,i] + \mathbf{M}_1[i,i]K \\ &- K\sum_{j:i\sim j} \frac{\mathbf{M}_1[i,j]\mathbf{M}_0[j,i] + \mathbf{M}_0[i,j]\mathbf{M}_1[j,i]}{\mathbf{M}_0[j,j] - \mathbf{M}_0[i,i]} + o(K),\end{aligned} \tag{3.16}$$

that can be compacted into

$$\lambda^i = \mathbf{M}[i,i] - \sum_{j:i\sim j} \frac{\mathbf{M}[i,j]\mathbf{M}[j,i]}{\mathbf{M}_0[j,j] - \mathbf{M}_0[i,i]} + o(K), \tag{3.17}$$

Characteristic polynomial

In order to apply Proposition 1 we need the characteristic polynomial $Q(\mathbf{G}\backslash\mathcal{P}, \lambda)$. We will essentially re-derive Proposition 2 in a more general setting. To that end, we first need to generalize Definition 1. Recalling that, by Remark (13), each state n corresponds uniquely to an eigenvalue λ^n of $\mathbf{M}$, we have

Definition 3. *Let $\mathcal{P}$ be a path in $\mathbf{G}$, let $n \in V(\mathbf{G})$ such that $n \sim n'$ for some $n' \in \mathcal{P}$, and let λ^n be the eigenvalue corresponding to vertex n. Then, we define*

$$\lambda_{\mathcal{P}}^n := \lambda^n + \sum_{\substack{n'\in\mathcal{P} \\ n'\sim n}} \frac{\mathbf{M}[n,n']\mathbf{M}[n',n]}{\mathbf{M}_0[n',n'] - \mathbf{M}_0[n,n]}. \tag{3.18}$$

In other words, $\lambda_{\mathcal{P}}^n$ is equal to λ^n (up to first-order terms in K) minus all terms corresponding to permutations that exchange m with an index in $\mathcal{P}$. (Here, we note that these terms are negative, which implies the change in sign in (3.18), as compared to Equation (3.17).)

In analogy to Proposition 2, we thus obtain

Proposition 3. *Let the conditions of Proposition 1 be satisfied, let $\mathcal{P}$ be a path in $\mathbf{G}$, and let $\mathcal{S}_\mathcal{P} := \{m' \in V(\mathbf{G}) : m' \sim m, m \in \mathcal{P}\}$. (Here, we note that $\mathcal{P} \subseteq \mathcal{S}_\mathcal{P}$.) Then,*

$$Q(\mathbf{G} \setminus \mathcal{P}, \lambda^n) = \prod_{m' \in \mathcal{S}_\mathcal{P} \setminus \mathcal{P}} (\lambda_\mathcal{P}^{m'} - \lambda^n) \prod_{m' \notin \mathcal{S}_\mathcal{P}} (\lambda^{m'} - \lambda^n) + o(K). \tag{3.19}$$

Remark 17. *As was the case for the dimerization reaction discussed in Section 2.3, the eigenvalues of $\mathbf{G} \setminus \mathcal{P}$ differ from the corresponding eigenvalues in $\mathbf{G}$ only due to permutations dropping out following the elimination of vertices associated with $\mathcal{P}$. Hence, for some values of n, the eigenvalue λ^n will have to be replaced with $\lambda_\mathcal{P}^n$ in the resulting characteristic polynomial. When $n \notin \mathcal{S}_\mathcal{P}$, the term $(\lambda^n - \lambda^n)$ is a factor in Equation (3.19), hence $Q(\mathbf{G} \setminus \mathcal{P}, \lambda^n) = o(K)$. When $n \in \mathcal{S}_\mathcal{P} \setminus \mathcal{P}$, then the factor $(\lambda_\mathcal{P}^n - \lambda^n)$, which is $O(K)$ by Definition 3, is a factor in Equation (3.19), hence $Q(\mathbf{G} \setminus \mathcal{P}, \lambda^n) = O(K)$.*

3.2.2 Eigenvalues with same leading order

It is still possible, despite being more difficult, to find an expansion in this case. However, this will prove less effective since we will only be able to do it for a fixed initial condition, falling in the same problem Equation (1.10) was presenting.

First, let us understand when two eigenvalues have the same leading order, and when this is a problem. Let two states x and y have the corresponding eigenvalues of $\mathbf{M}_0$ equal, which implies $\mathbf{M}_0[x,x] = \mathbf{M}_0[y,y]$. Then, recalling the terminology in Definition 2,we have

$$\sum_{R_i \in \mathcal{F}} c_i g_i(x) = \sum_{R_i \in \mathcal{F}} c_i g_i(y). \tag{3.20}$$

There are two possible cases

1. $g_i(x) = g_i(y)$ for all $i : R_i \in \mathcal{F}$: then the two eigenvalues remain equal regardless the value of $\mathbf{c}$;
2. $g_i(x) = g_i(y)$, $\exists i : R_i \in \mathcal{F}$: then varying slightly some of the parameters c_i will result in different eigenvalues.

The second case can be easily ruled out for example assuming that the ratios of the c_i are not in $\mathbb{Q}$. Hence, we will put ourselves in the first situation. A simple example when the first case occurs is when two or more states are wells for the fast system, meaning that no fast reaction can occur when the system is in such states. In the fast graph these nodes are actually sources rather than wells, since an edge from i to j represent the transition probability from j to i, Fig. 3.2.

Let i be a state such that the set $I := \{j : \lambda_0^i = \lambda_0^j\}$ has cardinality strictly greater than one (note that $i \in I$). Then the first term in Eq. (3.13), corresponding to the identity permutation in Eq. (3.10), becomes

$$K^{|I|} \prod_{j \in I} (\lambda_1^i - \mathbf{M}_1[j,j]) \prod_{s \notin I} (\lambda_0^i - \mathbf{M}_0[s,s]). \tag{3.21}$$

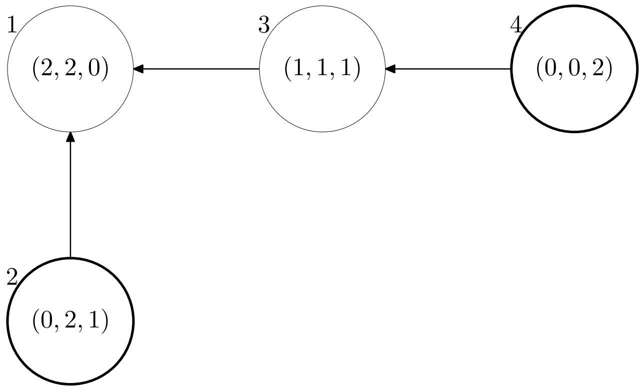


Figure 3.2: The (fast) graph corresponding to the system with only fast reactions $A + B \longrightarrow C$, $2A \longrightarrow C$ and initial conditions $n_A = 2$, $n_B = 2$, $n_C = 0$. The states $(0, 2, 1)$ and $(0, 0, 2)$ are two wells, hence the corresponding nodes 2 and 4 are actually sources and $\lambda_0^2 = \lambda_0^4 = 0$ contradicting Assumption 4.

We want to ask ourselves if other permutations contribute with terms of lower order in K.

Consider a permutation $\mathcal{P}$, let $\mathcal{C}_\mathcal{P}$ be the correspondent cycle (note that it could be a union of disjoint cycles), and let $C^c_\mathcal{P}$ be the subset of all states s such that $\mathcal{P}(s) = s$. Then $\mathcal{P}$ contributes to Eq. (3.10) with

$$\operatorname{sgn}(\mathcal{P}) K^{|\mathcal{C}^c_\mathcal{P} \cap I|} \omega(\mathcal{C}_\mathcal{P}) \prod_{j \in C^c_\mathcal{P} \cap I} (\lambda_1^i - \mathbf{M}_1[j, j]) \prod_{s \in C^c_\mathcal{P} \cap I^c} (\lambda_0^i - \mathbf{M}_0[s, s]). \tag{3.22}$$

Since we want to find the permutations that result in the lowest order terms, we can assume that each disjoint cycle of $\mathcal{C}_\mathcal{P}$ contains at least one element of I. In fact, if $\mathcal{C}_1$ is a disjoint cycle of $\mathcal{C}_{\mathcal{P}_1}$, then we can construct a permutation $\mathcal{P}_2$ that leaves all the nodes in $\mathcal{C}_1$ fixed, and that equals $\mathcal{P}_1$ elsewhere. Because of Assumption 3, $\omega(\mathcal{C}_1) = o(1)$, thus $\omega(\mathcal{C}_{\mathcal{P}_1}) = \omega(\mathcal{C}_1)\omega(\mathcal{C}_{\mathcal{P}_2}) = o(\omega(\mathcal{C}_{\mathcal{P}_2}))$ and $|\mathcal{C}^c_{\mathcal{P}_2} \cap I| = |\mathcal{C}^c_{\mathcal{P}_1} \cap I|$. Therefore, Equation (3.22) leads to a smaller order term when calculated in $\mathcal{P}_2$.

When all the disjoint cycles $\mathcal{C}_1, \mathcal{C}_2, \ldots, \mathcal{C}_r$ of $\mathcal{C}_\mathcal{P}$ contain exactly one element of I, the number of the cycles r equals $|\mathcal{C}_\mathcal{P} \cap I|$ and $\omega(\mathcal{C}_\mathcal{P}) = \prod_j \omega(\mathcal{C}_j) = O(K^{|\mathcal{C}_\mathcal{P} \cap I|})$ for $\omega(\mathcal{C}_j) = O(K)$ by Assumption 3. Consequently, The term given by Equation (3.22) is $O(|I|)$.

However, when a single cycle contains two or more elements, smaller order terms might appear unless the following is ensured

Assumption 6. *The weight of cycles containing $r > 1$ elements of I is $o(K^r)$.*

With this condition, if $\mathcal{C}_\mathcal{P}$ contains a cycle with two or more elements of I, the term in Equation (3.22) corresponding to $\mathcal{P}$ would be $o(K^{|I|})$ and thus irrelevant.

Remark 18. *It is unclear of what happens in case Assumption 6 is not verified. In this case an equation of smaller degree results, which appears to be a positive fact. However, most systems satisfy Assumption 6, so we preferred to concentrate on this case.*

Summing over all the permutations such that $w(\mathcal{C}_{\mathcal{P}}) = \Theta(K^{|C_{\mathcal{P}} \cap I|})$, dividing everything by $\prod_{s \notin I} (\lambda_0^i - \mathbf{M}_0[s,s])$ and setting everything equal to 0, we obtain an equation in λ_1^i

$$K^{|I|} \prod_{j \in I} (\lambda_1^i - \mathbf{M}_1[j,j]) - K^{|I|} \sum_{\mathcal{P}} (-1)^{l(\mathcal{C}_{\mathcal{P}})} \frac{w(\mathcal{C}_{\mathcal{P}})}{K^{|C_{\mathcal{P}} \cap I|}} \frac{\prod_{j \in C_{\mathcal{P}}^c \cap I} (\lambda_1^i - \mathbf{M}_1[j,j])}{\prod_{s \in C_{\mathcal{P}} \cap I^c} (\lambda_0^i - \mathbf{M}_0[s,s])} = 0, \tag{3.23}$$

where $l(\mathcal{C}_{\mathcal{P}})$ is the sum of the lengths of the disjoint cycles that form $\mathcal{C}_{\mathcal{P}}$.

Remark 19. *Equation (3.23) is the same for all λ_1^s with $s \in I$. We lost the bijection between states and eigenvalues, now we rather have a group of l eigenvalues corresponding to a group of l states.*

In most practical cases, finding all the terms of the form of Eq. (3.23) is still a reasonable task (especially if $|I| = 2$ or 3), since most of the cycles will be of high order. Unfortunately, the result will be an equation in λ_1^i of degree $|I|$, which, in turn, depends on the initial condition.

An important special case is obtained when also Assumption 5 is verified. The relevant terms in Equation (3.23), then, are given by permutations that fix some of the elements in I and exchange all the others with one of their neighbours. The following example illustrates this event.

Example 5. *Consider the system*

$$\begin{aligned} &A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C, \\ &2A \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C, \end{aligned} \tag{3.24}$$

in the case $k_2 \to 0$. Dividing for k_1/Ω and defining $K := k_2/k_1$ leads to the following non-dimensional system

$$\begin{aligned} &A + B \underset{K}{\overset{1}{\rightleftharpoons}} C, \\ &2A \underset{K}{\overset{1}{\rightleftharpoons}} C. \end{aligned} \tag{3.25}$$

If the initial conditions are $(n_A, n_B, n_C) = (2, 2, 0)$, we have that nodes 3 and 8 are two sources in the fast graph, Fig. 3.3, hence their corresponding eigenvalues have both null leading order.

Remark 20. *The eigenvalues corresponding to nodes 1 and 7 have also same leading order, but this happened because we used the same rate constants for both the reversible reactions in (3.24). In other words, we put ourselves into case 2, and varying slightly one of the rate coefficient would make the two eigenvalues different.*

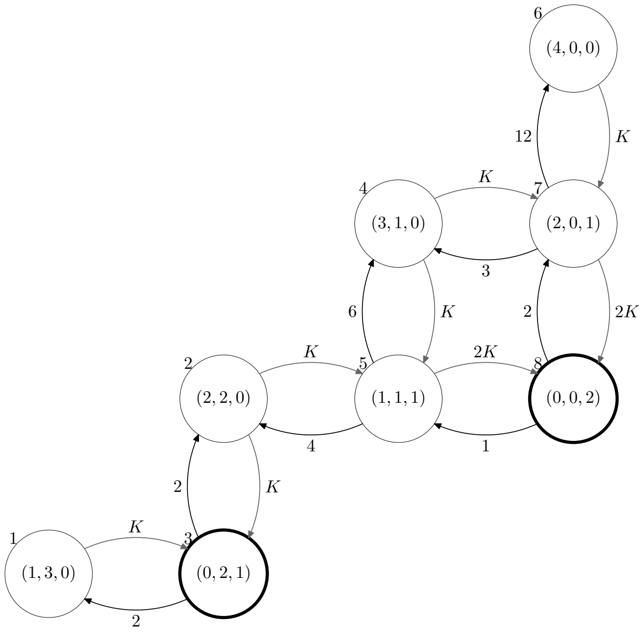


Figure 3.3: The graph corresponding to the system (3.25) with initial conditions $n_A = 2$, $n_B = 2$, $n_C = 0$. The grey edges correspond to slow reactions, hence the fast graph is the one obtained considering only black edges. Nodes 3 and 8 are sources in the fast graph. Recalling that an edge from i to j represent the transition probability from j to i, it follows that the states $(0, 2, 1)$ and $(0, 0, 2)$ are wells for the system (they are sources in the graph), hence $\lambda_0^3 = \lambda_0^8 = 0$ contradicting Assumption 4.

We want to find an equation for $x := \lambda_1^3$ *(which will be the same for* λ_1^8*). The permutations of lowest order that contain the term* λ_1^3 *are:*

Identity
$K^2(x+2)(x+4)$,

(1 3)
$-K^2(x+4)$,

(1 3)(5 8)
$2K^2$,

(1 3)(7 8)
$2K^2$,

(2 3)
$-\frac{1}{3}K^2(x+4)$,

(2 3)(5 8)
$\frac{2}{3}K^2$,

(1 3)(7 8)
$\frac{2}{3}K^2$,

(5 8)
$-2K^2(x+2)$,

(7 8)
$-2K^2(x+2)$.

Summing all the terms, we obtain the following equation

$$x^2 + \frac{2}{3}x = 0, \tag{3.26}$$

which has solutions $x = 0, -2/3$. *The two eigenvalues are*

$$\begin{aligned} \lambda^3 &= 0 + o(K); \\ \lambda^8 &= -\frac{2}{3}K + o(K). \end{aligned} \tag{3.27}$$

Consider now the same system 3.25 with initial conditions $(n_A, n_B, n_C) = (3, 2, 0)$. *Now three nodes are sources in the fast graph, Fig. 3.4.*

All the relevant permutations and their contribution are listed below

Identity
$K^3(x+1)(x+4)^2$,

(1 2)
$-\frac{1}{4}K^3(x+4)^2$,

(4 7)
$-2K^3(x+1)(x+4)$,

(6 7)
$-K^3(x+1)(x+4)$,

(6 10)
$-K^3(x+1)(x+4)$,

(9 10)
$-2K^3(x+1)(x+4)$,

(1 2)(4 7)
$\frac{1}{2}K^3(x+4)$,

(1 2)(6 7)
$\frac{1}{4}K^3(x+4)$,

(1 2)(6 10)
$\frac{1}{4}K^3(x+4)$,

(1 2)(9 10)
$\frac{1}{2}K^3(x+4)$,

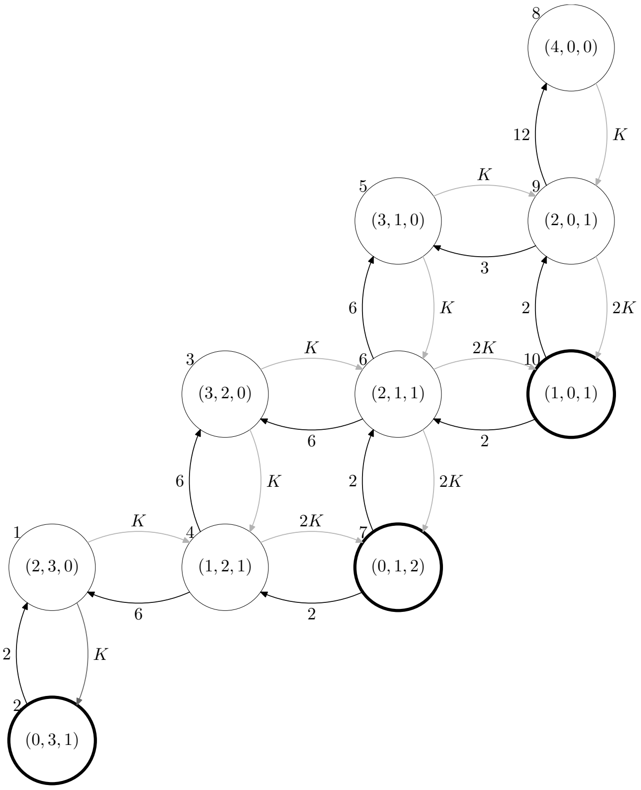


Figure 3.4: The graph corresponding to the system (3.25) with initial conditions $n_A = 3$, $n_B = 2$, $n_C = 0$. The grey edges correspond to slow reactions, hence the fast graph is the one obtained considering only black edges. Nodes 2, 7 and 10 are sources in the fast graph. Recalling that an edge from i to j represent the transition probability from j to i, it follows that the states $(0,3,1)$, $(0,1,2)$ and $(1,0,1)$ are wells for the system (they are sources in the graph), hence $\lambda_0^2 = \lambda_0^4 = \lambda_0^{10} = 0$ contradicting Assumption 4.

$$\begin{array}{ll} (4\,7)(6\,10) & (4\,7)(9\,10) \\ 2K^3(x+1), & 4K^3(x+1), \end{array}$$

$$\begin{array}{l} (6\,7)(9\,10) \\ 2K^3(x+1), \end{array}$$

$$\begin{array}{lll} (1\,2)(4\,7)(6\,10) & (1\,2)(4\,7)(9\,10) & (1\,2)(6\,7)(9\,10) \\ -\dfrac{1}{2}K^3 & -K^3, & -\dfrac{1}{2}K^3, \end{array}$$

leading to equation

$$x^3 + \frac{11}{4}x^2 + \frac{3}{2}x = 0, \tag{3.28}$$

which has solutions $x = 0, -3/4, -2$.

As expected, the eigenvalue equation has increased its degree to three. It is unclear whether Equations (3.26) *and* (3.28) *can be obtained by a general formula (perhaps making use of the regularity of the graph).*

Characteristic polynomial

When two or more eigenvalues have the same leading order, finding the characteristic polynomial $Q(\mathbf{G}\backslash\mathcal{P})$ following the ideas of the previous sections is extremely challenging. There are mainly two complications:

1. when the path $\mathcal{P}$ contains a neighbour j of a vertex $i \in I$, it is not as easy as in Equation (3.18) to define a new eigenvalue. In fact, all the terms corresponding to the permutations containing $(i\ j)$ have to be removed, rather than just one single term as in Equation (3.18);

2. when the path $\mathcal{P}$ contains a vertex $i \in I$, all the eigenvalues corresponding to $I \setminus \{i\}$ are drastically changed. In fact, Equation (3.23) becomes one degree smaller.

   Remark 21. *Despite the fact the method seems ineffective for system with eigenvalues with same leading order, we were able to show an interesting, although vague, concept:*

   - *when the eigenvalues have all different leading orders, up to the first order correction, neighbouring nodes seem to have the most relevant connection;*
   - *by contrast, when some eigenvalues leading orders are equal, nodes that are far in the graph could affect each other.*

3.3 Avoiding matrix products

In Section 2.2 we showed how to compute the eigenvectors using the adjoint matrix of $\lambda\mathbf{I} - \mathbf{M}$. Moreover, we computed the left eigenvector matrix $\mathbf{L}$ using the same idea in order to find an expression for $\mathbf{E}^{-1}$. However, this expression did not come free since

$$\mathbf{LE} = \mathbf{D} \tag{3.29}$$

for some diagonal matrix $\mathbf{D}$, hence we had to find $\mathbf{D}$ and "normalize" $\mathbf{L}$

$$\mathbf{E}^{-1} = \mathbf{D}^{-1}\mathbf{L}. \tag{3.30}$$

In order to find $\mathbf{D}$ we had to actually compute the product in Equation (3.29). Also, we had to compute the matrix products in Equation (1.19). Since it is not possible in general to analytically make these calculation, the solution could only be found once the initial condition was fixed. However, it is possible to overcome this obstacle using the Laplace transform.

3.3.1 Laplace transform

Let $\mathbf{V}(s)$ be the Laplace transform of $\mathbf{P}(t)$

$$\mathbf{V}(s) = \int_0^\infty e^{-ts}\mathbf{P}(t)dt, \quad s \in \mathbb{C}. \tag{3.31}$$

Note that we are considering the Laplace transform in time.

Integrating Equation (3.31) by part we get

$$\mathbf{V}(s) = \left(-\frac{e^{-ts}}{ts}\mathbf{P}(t)\right)\Big|_0^\infty + \frac{1}{s}\int_0^\infty e^{-ts}\frac{d}{dt}\mathbf{P}(t)dt = \frac{1}{s}\big(\mathbf{P}(0) + \mathbf{M}\,\mathbf{V}(s)\big). \tag{3.32}$$

Consequently

$$\mathbf{V}(s) = \big(s\mathbf{I} - \mathbf{M}\big)^{-1}\mathbf{P}(0), \tag{3.33}$$

for all s different from the eigenvalues of $\mathbf{M}$.

By Cramer's rule, we obtain

$$\big(s\mathbf{I} - \mathbf{M}\big)^{-1} = \frac{\operatorname{Adj}\big(s\mathbf{I} - \mathbf{M}\big)}{\det\big(s\mathbf{I} - \mathbf{M}\big)}. \tag{3.34}$$

The inverse Laplace transform of a function f with Laplace transform F is given by

$$f(t) = \frac{1}{2\pi i}\lim_{T\to\infty}\int_{\gamma-iT}^{\gamma+iT} e^{st}F(s)\,ds, \tag{3.35}$$

for a $\gamma \in \mathbb{R}$ that is greater than the real part of each pole of F.

This integral can be evaluated considering first the contour integral on the curve $\mathcal{C}_1$ composed by the segment $[\gamma - iT, \gamma + iT]$ and the left semi circumference joining its extremes, Figure 3.5. From the residue theorem

$$\oint_{\mathcal{C}_1} e^{st}F(s)\,ds = 2\pi i \sum_{\substack{z \\ \text{pole of } F \\ \text{in } \mathcal{C}_1}} \operatorname{Res}(e^{st}F(s), z). \tag{3.36}$$

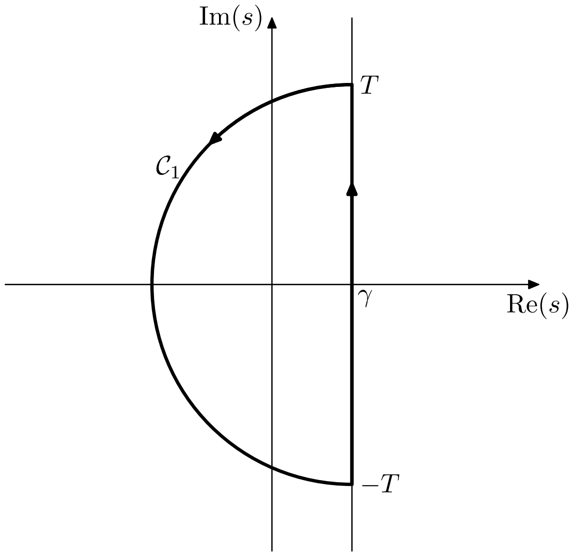


Figure 3.5: The curve $\mathcal{C}_1$.

When T tends to infinity, all the poles of F fall in $\mathcal{C}_1$. Also, the integral along the semi circumference goes to zero so that

$$f(t) = \sum_{\substack{z \\ \text{pole of } F}} \operatorname{Res}(e^{st}F(s), z). \tag{3.37}$$

In our case, we have all simple poles: the eigenvalues of $\mathbf{M}$. Hence,

$$\mathbf{P}(t) = \sum_m e^{\lambda^m t} \frac{\operatorname{Adj}(\lambda^m I - \mathbf{M})}{\prod_{r \neq m}(\lambda^m - \lambda^r)} \mathbf{P}(0). \tag{3.38}$$

The term $\frac{\operatorname{Adj}(\lambda^m I - \mathbf{M})}{\prod_{r \neq m}(\lambda^m - \lambda^r)}[i,j]$, when there is at least one path $\mathcal{P}_{ij}$ with $m \in \mathcal{P}_{ij} \cup \mathcal{N}_{\mathcal{P}_{ij}}$, can be further simplified into

$$\frac{\operatorname{Adj}(\lambda^m I - \mathbf{M})}{\prod_{r \neq m}(\lambda^m - \lambda^r)}[i,j] = \begin{cases} \dfrac{\displaystyle\prod_{r \sim i} \lambda^m - \lambda^r_{\{i\}}}{\displaystyle\prod_{\substack{r \neq m: \\ r \sim i}} \lambda^m - \lambda^r} + o(K) & \text{if } i = j, \\[4em] \displaystyle\sum_{\mathcal{P}_{ij}} \omega(\mathcal{P}_{ij}) \frac{\displaystyle\prod_{r \in \mathcal{N}_{\mathcal{P}_{ij}}} \lambda^m - \lambda^r_{\mathcal{P}_{ij}}}{\displaystyle\prod_{\substack{r \in \mathcal{P}_{ij} \cup \mathcal{N}_{\mathcal{P}_{ij}} \\ r \neq m}} \lambda^m - \lambda^r} + o(K) & \text{if } i \neq j. \end{cases} \tag{3.39}$$

Where the paths $\mathcal{P}_{ij}$ in the sum are such that $m \in \mathcal{P}_{ij} \cup \mathcal{N}_{\mathcal{P}_{ij}}$.

Remark 22. *By Remark 17, each path $\mathcal{P}_{ij}$ between i and j so that $m \notin \mathcal{P}_{ij} \cup \mathcal{N}_{\mathcal{P}_{ij}}$, only contributes with an $o(K)$ term. Also, each path $\mathcal{P}_{ij}$ with $m \in \mathcal{N}_{\mathcal{P}_{ij}}$ contributes* *with an* $O(K)$ *term.*

Chapter 4

Push-Pull

In this chapter we study the push-pull mechanism.

We will not be able to find a complete solution, but we will show the typical problems in which the methodology incurs and also introduce some ideas to try to approach them.

In Section 4.1 the system and its reduction laws are introduced. The CME is then non-dimensionalized in Section 4.2. In Section 4.3 the eigenvalues leading terms are found and simple condition to guarantee them to be all different are given. After that, their next order correction is found. Finally, in Section 4.4 an attempt to use Equation (3.39) is tried.

4.1 Reactions and Reduction

The push-pull mechanism can be seen as a composition of two Michaelis-Menten systems where activating and deactivating enzymes are transforming molecules of two species into one another. Formally, the reactions are described by

$$W + E_a \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_a \xrightarrow{k_3} E_a + X,$$

$$X + E_d \underset{k_5}{\overset{k_4}{\rightleftharpoons}} C_d \xrightarrow{k_6} E_d + W.$$

We start noticing that Assumption 2 is satisfied since there is no exchange of particles between Ω and the outside.

The system is coerced by a number of conservation laws

$$n_{E_a} + n_{C_a} = A \Longrightarrow n_{C_a} = A - n_{E_a}, \tag{4.1}$$

$$n_{E_d} + n_{C_d} = D \Longrightarrow n_{C_d} = D - n_{E_d}, \tag{4.2}$$

$$n_W + n_X + n_{C_a} + n_{C_d} = S \Longrightarrow n_X = S - A - D + n_{E_a} + n_{E_d} - n_W, \tag{4.3}$$

for the three constants A (total activating enzyme), D (total deactivating enzyme) and S (total substrate). Hence, a state $(n_W, n_{E_a}, n_{E_d}, n_{C_a}, n_{C_d}, n_X)$ can be represented by the triplet (n_W, n_{E_a}, n_{E_d}). We will still use the extended notation most of the time for clarity of notation, but we shall use the compact representation occasionally.

An example of space of states is shown in Fig. 4.1. From such figure we will infer general conclusions about the graph for any initial condition, because of the regularity of the problem.

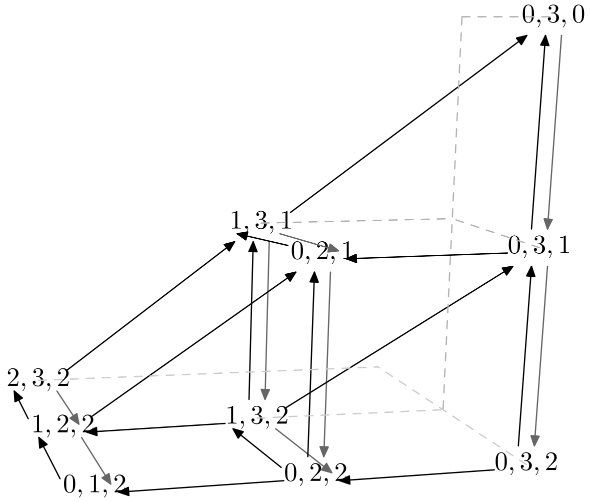


Figure 4.1: The states graph for a Push-Pull mechanism with initial condition $(n_W, n_{E_a}, n_{E_d}) = (2, 3, 2)$, total activating enzyme $A = 3$, total deactivating enzyme $D = 2$ and total substrate $S = 2$. The black arrows represent "fast" reactions, while the grey arrows are the "slow" reactions. As usual, an edge from a node i to a node j represent a reaction from j to i. The dashed light grey lines are only intended to guide the reader's eye in the three dimensional visualisation.

4.2 Non-dimensionalization

Consider the case $k_2, k_4 \longrightarrow 0$ so that $c := k_4/(\Omega k_2)$ is constant. Dividing the master equation by k_1/Ω, defining $K := \Omega k_2/k_1$, and rescaling the time, we get

$$\begin{aligned}\frac{d}{dt}P(\mathbf{n},t) =&\big(E_W E_{E_a} E_{C_a}^{-1} - 1\big) n_W\, n_{E_a}\; P(\mathbf{n},t) + K\big(E_W^{-1} E_{E_a}^{-1} E_{C_a} - 1\big) n_{C_a}\; P(\mathbf{n},t)\\ &+ \frac{\Omega k_3}{k_1}\big(E_{E_a}^{-1} E_{C_a} E_X^{-1} - 1\big) n_{C_a} P(\mathbf{n},t) + cK\big(E_X E_{E_d} E_{C_d}^{-1} - 1\big) n_X n_{E_d} P(\mathbf{n},t)\\ &+ \frac{\Omega k_5}{k_1}\big(E_X^{-1} E_{E_a}^{-1} E_{C_d} - 1\big) n_{C_d} P(\mathbf{n},t) + \frac{\Omega k_6}{k_1}\big(E_W E_{E_a} E_{C_a}^{-1} - 1\big) n_{C_d} P(\mathbf{n},t),\end{aligned} \tag{4.4}$$

where we have written $\mathbf{n} = (n_W, n_{E_a}, n_{E_d}, n_{C_a}, n_{C_d}, n_X)$, for brevity.

Hence, Assumption 1 is satisfied. It is evident from Fig. 4.1 that for $K = 0$ the states graph is acyclic, thus Assumption 3 is fulfilled.

Remark 23. *When non-dimentionalizing Push-Pull , one should consider that:*

- *obviously one between k_1 and k_2; and one between k_4 and k_5 must go to zero in order for Assumption 3 to be satisfied;*

- *one between k_1 and k_4 must go to zero to avoid cycles as*

$$(0,3,0),(0,3,1),(0,2,1),(1,3,1),(0,3,0); \tag{4.5}$$

- *while letting more coefficients go to zero increases the chances of satisfying Assumption 3, it makes less likely that Assumption 4 will be satisfied. For example, when k_2, k_3 and k_4 go to zero such assumption will not be met (two states with different quantity of n_{C_a} might correspond to two eigenvalues with same leading order). However, k_2, k_3 and k_5 or k_2, k_3 and k_6 may go to zero at the same time (it will not change the structure of Equation (4.6)).*

4.3 Eigenvalues

The leading order of the eigenvalues is given by

$$\lambda_0^{\mathbf{n}} = -n_W n_{E_a} - \frac{\Omega k_3}{k_1} n_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} n_{C_d}. \tag{4.6}$$

We want to show that all the eigenvalues leading terms are different.

The eigenvalues corresponding to the two states $\mathbf{m}$ and $\mathbf{n}$ have the same leading order if

$$m_W m_{E_a} - n_W n_{E_a} + \frac{\Omega k_3}{k_1}(m_{C_a} - n_{C_a}) + \frac{\Omega(k_5+k_6)}{k_1}(m_{C_d} - n_{C_d}) = 0. \tag{4.7}$$

Assuming that $\frac{\Omega k_3}{k_1}$ and $\frac{\Omega(k_5+k_6)}{k_1}$ are not in $\mathbb{N}$ and their ratio $\frac{k_3}{k_5+k_6}$ is not in $\mathbb{Q}$, implies that

$$m_W m_{E_a} - n_W n_{E_a} = 0, \tag{4.8}$$
$$m_{C_a} - n_{C_a} = 0, \tag{4.9}$$
$$m_{C_d} - n_{C_d} = 0, \tag{4.10}$$

since the terms cannot mix to zero. Combining Equation (4.9) with the conservation law (4.1) and Equation (4.10) with conservation law (4.2), we get that also

$$m_{E_a} - n_{E_a} = 0, \tag{4.11}$$
$$m_{E_d} - n_{E_d} = 0. \tag{4.12}$$

Substituting Equation (4.11) into Equation (4.8) leads to

$$m_W - n_W = 0. \tag{4.13}$$

Finally, conservation law (4.3) leads to

$$m_X - n_X = 0, \tag{4.14}$$

which means $\mathbf{m} = \mathbf{n}$.

Since all the leading order of the eigenvalues are different, we can use formula (3.17).

The transition probability to exit a state $\mathbf{n} = (n_W, n_{E_a}, n_{E_d}, n_{C_a}, n_{C_d}, n_X)$ through a "fast" reaction is

$$-\mathbf{M}_0[\mathbf{n},\mathbf{n}] = -\lambda_0^{\mathbf{n}} = n_W n_{E_a} + \frac{\Omega k_3}{k_1} n_{C_a} + \frac{\Omega(k_5+k_6)}{k_1} n_{C_d}. \tag{4.15}$$

The transition probability to go through a "slow" reaction is

$$-K\mathbf{M}_1[\mathbf{n},\mathbf{n}] = K n_{C_a} + K c n_X n_{E_d}. \tag{4.16}$$

There are only four cycles of length 2 passing through a general vertex $\mathbf{v}$, two for each of the reversible reactions

1. $W + E_a \rightleftharpoons C_a$: which results in the two neighbours $\mathbf{n}' = (n_W+1, n_{E_a}+1, n_{E_d}, n_{C_a}-1, n_{C_d}, n_X)$ and $\mathbf{n}'' = (n_W-1, n_{E_a}-1, n_{E_d}, n_{C_a}+1, n_{C_d}, n_X)$ and the corresponding terms

$$\frac{\mathbf{M}[\mathbf{n},\mathbf{n}']\mathbf{M}[\mathbf{n}',\mathbf{n}]}{\mathbf{M}_0[\mathbf{n}',\mathbf{n}'] - \mathbf{M}_0[\mathbf{n},\mathbf{n}]} = -K\frac{n_{C_a}(n_W+1)(n_{E_a}+1)}{n_W + n_{E_a} + 1 - c}, \tag{4.17}$$

$$\frac{\mathbf{M}[\mathbf{n},\mathbf{n}'']\mathbf{M}[\mathbf{n}'',\mathbf{n}]}{\mathbf{M}_0[\mathbf{n}'',\mathbf{n}''] - \mathbf{M}_0[\mathbf{n},\mathbf{n}]} = K\frac{(n_{C_a}+1)n_W n_{E_a}}{n_W + n_{E_a} - 1 - c}. \tag{4.18}$$

2. $X + E_d \rightleftharpoons C_d$: which results in the two neighbours $\mathbf{n}' = (n_W, n_{E_a}, n_{E_d}+1, n_{C_a}, n_{C_d}-1, n_X+1)$ and $\mathbf{n}'' = (n_W, n_{E_a}, n_{E_d}-1, n_{C_a}, n_{C_d}+1, n_X+1)$ and the corresponding terms

$$\frac{\mathbf{M}[\mathbf{n},\mathbf{n}']\mathbf{M}[\mathbf{n}',\mathbf{n}]}{\mathbf{M}_0[\mathbf{n}',\mathbf{n}'] - \mathbf{M}_0[\mathbf{n},\mathbf{n}]} = K\frac{k_1}{\Omega(k_5+k_6)} n_{C_d}(n_X+1)(n_{E_d}+1), \tag{4.19}$$

$$\frac{\mathbf{M}[\mathbf{n},\mathbf{n}'']\mathbf{M}[\mathbf{n}'',\mathbf{n}]}{\mathbf{M}_0[\mathbf{n}'',\mathbf{n}''] - \mathbf{M}_0[\mathbf{n},\mathbf{n}]} = -K\frac{k_1}{\Omega(k_5+k_6)}(n_{C_d}+1)n_X n_{E_d}. \tag{4.20}$$

Using Equation (3.17) we find

$$\begin{aligned}\lambda_{\mathbf{n}} = &- n_W n_{E_a} - \frac{\Omega k_3}{k_1} n_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} n_{C_d} - K n_{C_a} - K c n_X n_{E_d} \\ &+ K\frac{n_{C_a}(n_W+1)(n_{E_a}+1)}{n_W + n_{E_a} + 1 - c} - K\frac{(n_{C_a}+1)n_W n_{E_a}}{n_W + n_{E_a} - 1 - c} \\ &+ K\frac{k_1}{\Omega(k_5+k_6)}(n_X n_{E_d} - (n_X + n_{E_d} + 1)n_{C_d})\end{aligned} \tag{4.21}$$

4.4 Paths

In this section we try to find all the possible paths and their corresponding weights that are needed in Equation (3.39). We will categorize them in constant paths and first order paths.

4.4.1 Constant paths

Because the leading term of $\lambda^s_{\mathcal{P}_{ij}}$ is equal to that of λ^s, the leading term of (3.39) is just given by

$$\frac{\operatorname{Adj}(\lambda^m I - \mathbf{M})}{\prod_{s\neq m}(\lambda^m - \lambda^s)}[i,j] = \begin{cases} 1 + O(K) & \text{if } i = j, \\ \displaystyle\sum_{\mathcal{P}_{ij}} \frac{\omega(\mathcal{P}_{ij})}{\displaystyle\prod_{\substack{s\in\mathcal{P}_{ij}\\ s\neq m}} \lambda^m - \lambda^s} + O(K) & \text{if } i \neq j, \end{cases} \tag{4.22}$$

where the sum is over the paths between i and j that pass through m. At the moment, the paths $\mathcal{P}$ so that $m \in \mathcal{N}_{\mathcal{P}}$ are not needed because only contribute to higher order, as we noticed in Remark 22.

We have that

$$\sum_{\mathcal{P}_{ij}} \frac{\omega(\mathcal{P}_{ij})}{\displaystyle\prod_{\substack{s\in\mathcal{P}_{ij}\\ s\neq m}} \lambda^m - \lambda^s} = \sum_{\mathcal{P}_{im}} \frac{\omega(\mathcal{P}_{im})}{\displaystyle\prod_{\substack{s\in\mathcal{P}_{im}\\ s\neq m}} \lambda^m - \lambda^s} \times \sum_{\mathcal{P}_{mj}} \frac{\omega(\mathcal{P}_{mj})}{\displaystyle\prod_{\substack{s\in\mathcal{P}_{mj}\\ s\neq m}} \lambda^m - \lambda^s} \tag{4.23}$$

The two sums in the right hand side have the same form, so it sufficent to study only one of them

$$\sum_{\mathcal{P}_{im}} \frac{\omega(\mathcal{P}_{im})}{\displaystyle\prod_{\substack{s\in\mathcal{P}_{im}\\ s\neq m}} \lambda^m - \lambda^s}. \tag{4.24}$$

We need to understand what the paths $\mathcal{P}_{im}$ look like. The four constant reactions R_1, R_3, R_5 and R_6 correspond to the vectors

$$\mathbf{v_1} = \begin{pmatrix} -1 \\ -1 \\ 0 \\ 1 \\ 0 \\ 0 \end{pmatrix}, \quad \mathbf{v_3} = \begin{pmatrix} 0 \\ 1 \\ 0 \\ -1 \\ 0 \\ 1 \end{pmatrix}, \quad \mathbf{v_5} = \begin{pmatrix} 0 \\ 0 \\ -1 \\ 0 \\ 1 \\ 1 \end{pmatrix}, \quad \mathbf{v_6} = \begin{pmatrix} 1 \\ 0 \\ 1 \\ 0 \\ -1 \\ 0 \end{pmatrix}. \tag{4.25}$$

Let $\mathbf{d} := m - i$ and $\mathbf{r} := (r_1, r_3, r_5, r_6)^T$, with r_x the number of times a reaction R_x occurred in $\mathcal{P}_{im}$. (We recall that a path from i to m correspond to a sequence of reactions consecutively applied starting from m to reach i.) Since the only fast reactions that affect W are R_1 and R_6, $i_W = m_W - r_1 + r_6$. Similar considerations can be done for the other molecular species, obtaining the following

$$\begin{aligned} d_1 =& r_1 - r_6, \\ d_2 =& r_1 - r_3, \\ d_3 =& -r_5 - r_6, \\ d_4 =& r_3 - r_1, \\ d_5 =& r_5 + r_6, \\ d_6 =& -r_3 - r_5, \end{aligned}$$

or in matrix notation

$$\begin{pmatrix} \mathbf{v_1} & \mathbf{v_3} & \mathbf{v_5} & \mathbf{v_6} \end{pmatrix} \begin{pmatrix} r_1 \\ r_3 \\ r_5 \\ r_6 \end{pmatrix} = \mathbf{d}. \tag{4.26}$$

The fact that $d_2 = -d_4$, $d_3 = -d_5$ and $d_1 + d_4 + d_5 + d_6 = 0$ is consistent with the conservation laws (4.1), (4.2) and (4.3) respectively. So, both Equation (4.26) and the correspondent homogeneous equation have rank 3, which implies, for the Rouché-Capelli theorem, that there are infinite solutions with one degree of freedom. Of course, these "solutions" include also negative values.

For reasons that will be clear later on, it is best to pick $r := r_1$ as free variable. We obtain the following solutions

$$r_1 = r, \tag{4.27}$$

$$r_3 = r + d_4, \tag{4.28}$$

$$r_5 = -d_6 - d_4 - r, \tag{4.29}$$

$$r_6 = r - d_1. \tag{4.30}$$

To keep all the values positive, r must also satisfy

$$r \geq 0; \quad r \geq d_1; \quad r \geq -d_4; \quad r \leq d_4 + d_6. \tag{4.31}$$

In summary, once we picked how many R_1 reactions occur, the number (but not the order) of all the other reactions is forced. This is easily verifiable in the next example.

Example 6. *Consider Figure 4.1. We recall again that, when an edge between nodes i and j is present, the correspondent reaction goes from j to i.*

With this in mind, reaction R_1 corresponds to all the black edges parallel to the edge from $(1, 2, 2)$ to $(2, 3, 2)$; similarly, reaction R_3 corresponds to all the black edges parallel to the edge from $(0, 2, 2)$ to $(0, 1, 2)$; reaction R_5 to all the black edges parallel to the edge from $(0, 3, 1)$ to $(0, 3, 0)$ and reaction R_6 to all the edges parallel to the edge from $(1, 3, 1)$ to $(0, 3, 0)$.

A sequence of reactions that transforms state $(0, 3, 0)$ (on top) to state $(0, 3, 2)$ (bottom right) must contain either:

1. *no R_1 forcing the presence of two R_5, corresponding to path*

$$(0,3,2),(0,3,1),(0,3,0);$$

2. *one R_1 forcing the presence of one R_3, one R_5 and one R_6 (in some order), corresponding to paths*

$$\begin{gathered}(0,3,2),(0,2,2),(1,3,2),(1,3,1),(0,3,0),\\(0,3,2),(0,2,2),(0,2,1),(1,3,1),(0,3,0),\\(0,3,2),(0,2,2),(1,3,2),(0,3,1),(0,3,0),\\(0,3,2),(0,3,1),(0,2,1),(1,3,1),(0,3,0);\end{gathered}$$

3. *two R_1 forcing the presence of two R_3 and two R_6 (in some order), corresponding to paths*

$$\begin{gathered}(0,3,2),(0,2,2),(0,1,2),(1,2,2),(0,2,1),(1,3,1),(0,3,0),\\(0,3,2),(0,2,2),(1,3,2),(1,2,2),(0,2,1),(1,3,1),(0,3,0),\\(0,3,2),(0,2,2),(0,1,2),(1,2,2),(2,3,2),(1,3,1),(0,3,0),\\(0,3,2),(0,2,2),(1,3,2),(1,2,2),(0,2,1),(1,3,1),(0,3,0).\end{gathered}$$

We can rewrite Equation (4.24) as

$$\sum_{r}\sum_{\substack{\mathcal{P}_{im}:\\ r_1=r}}\frac{\omega(\mathcal{P}_{im})}{\prod\limits_{\substack{s\in\mathcal{P}_{im}\\ s\neq m}}\lambda^m-\lambda^s}. \tag{4.32}$$

The next proposition shows why we picked r_1 as free variable

Proposition 4. *The weight of path corresponding to a sequence of fast reactions R_3, R_5 and R_6 (hence not containing R_1) does not depend on the order in which the reactions occur.*

Proof. Let $\mathbf{n}=(n_W,n_{E_a},n_{E_d},n_{C_a},n_{C_d},n_X)$ be a possible state, and let $\mathbf{n_3}:=\mathbf{n}+\mathbf{v_3}$, $\mathbf{n_5}:=\mathbf{n}+\mathbf{v_5}$ and $\mathbf{n_6}:=\mathbf{n}+\mathbf{v_6}$. Since every permutation can be written as composition of adjacent transpositions, we need to prove that

$$\omega(\mathbf{n_i}+\mathbf{v_j},\mathbf{n_i},\mathbf{n})=\omega(\mathbf{n_j}+\mathbf{v_i},\mathbf{n_j},\mathbf{n}), \tag{4.33}$$

for $i,j=3,5,6$. The claim will follow from the arbitrariness of $\mathbf{n}$.

Equivalently, Equation (4.33) can be written as

$$\omega(\mathbf{n_i}+\mathbf{v_j},\mathbf{n_i})\omega(\mathbf{n_i},\mathbf{n})=\omega(\mathbf{n_j}+\mathbf{v_i},\mathbf{n_j})\omega(\mathbf{n_j},\mathbf{n}), \tag{4.34}$$

for $i,j=3,5,6$.

We will use a proof by exhaustion

$i=3, j=5$ We have

$$\omega(\mathbf{n_3}+\mathbf{v_5},\mathbf{n_3}) = \mathbf{n}_{C_d}, \tag{4.35}$$
$$\omega(\mathbf{n_3},\mathbf{n}) = \mathbf{n}_{C_a}, \tag{4.36}$$
$$\omega(\mathbf{n_5}+\mathbf{v_3},\mathbf{n_5}) = \mathbf{n}_{C_a}, \tag{4.37}$$
$$\omega(\mathbf{n_5},\mathbf{n}) = \mathbf{n}_{C_d}; \tag{4.38}$$

$i=3, j=6$ We have

$$\omega(\mathbf{n_3}+\mathbf{v_6},\mathbf{n_3}) = \mathbf{n}_{C_d}, \tag{4.39}$$
$$\omega(\mathbf{n_3},\mathbf{n}) = \mathbf{n}_{C_a}, \tag{4.40}$$
$$\omega(\mathbf{n_6}+\mathbf{v_3},\mathbf{n_6}) = \mathbf{n}_{C_a}, \tag{4.41}$$
$$\omega(\mathbf{n_6},\mathbf{n}) = \mathbf{n}_{C_d}; \tag{4.42}$$

$i=5, j=6$ We have

$$\omega(\mathbf{n_5}+\mathbf{v_6},\mathbf{n_5}) = \mathbf{n}_{C_d}+1, \tag{4.43}$$
$$\omega(\mathbf{n_5},\mathbf{n}) = \mathbf{n}_{C_d}, \tag{4.44}$$
$$\omega(\mathbf{n_6}+\mathbf{v_5},\mathbf{n_6}) = \mathbf{n}_{C_d}+1, \tag{4.45}$$
$$\omega(\mathbf{n_6},\mathbf{n}) = \mathbf{n}_{C_d}. \tag{4.46}$$

□

Example 7. *In Figure 4.1, the path* $(0,3,2),(0,3,1),(0,2,1)$ *and the similar path* $(0,3,2),(0,2,2),(0,2,1)$ *correspond respectively to the sequences of reactions* R_3, R_5 *and* R_5, R_3 *that transform* $(0,2,1)$ *into* $(0,3,2)$. *They both have weight* $\frac{k_3k_5}{k_1^2}\Omega^2$.

The following corollary follows directly from Proposition 4.

Corollary 2. *Let* $\mathcal{Z}_1$ *and* $\mathcal{Z}_2$ *be two finite sequences of reactions* R_3, R_5 *and* R_6 *(not including* R_1*). Consider a state* x *and the state* y *(if exists) obtained consecutively applying the reactions in* $\mathcal{Z}_1$, R_1 *and the reactions in* $\mathcal{Z}_2$. *Let* $\mathcal{P}_{\mathcal{Z}_1,\mathcal{Z}_2}$ *be the corresponding path starting from* y *(set* $\omega(\mathcal{P}_{\mathcal{Z}_1,\mathcal{Z}_2}) = 0$ *if any reaction is not possible). Then, any path* $\mathcal{P}_{\hat{\mathcal{Z}}_1,\hat{\mathcal{Z}}_2}$ *built in the same way, where* $\hat{\mathcal{Z}}_1$ *and* $\hat{\mathcal{Z}}_2$ *are permutations of* $\mathcal{Z}_1$ *and* $\mathcal{Z}_2$ *respectively, is such that*

$$\omega(\mathcal{P}_{\hat{\mathcal{Z}}_1,\hat{\mathcal{Z}}_2}) = \omega(\mathcal{P}_{\mathcal{Z}_1,\mathcal{Z}_2}) \tag{4.47}$$

Remark 24. *A generalization to a concatenation of* l *sequences of the form* $[\mathcal{Z}_1, R_1, \mathcal{Z}_2, R_1, \ldots, \mathcal{Z}_l]$ *is immediate.*

Once we decide the number of each reaction between all the couples of R_1 reactions, the weight of the path is fixed. Let χ be the set of all such possibilities. An element of $X \in \chi$ is a concatenation $[\mathcal{Z}_1, R_1, \mathcal{Z}_2, R_1, \ldots, \mathcal{Z}_l]$ quotient all the permutations of the $\mathcal{Z}_i$. We get

$$\sum_r \sum_{X \in \chi} \omega(X) \sum_{\substack{\mathcal{P}_{im} \in X: \\ r_1 = r}} \frac{1}{\prod_{\substack{s \in \mathcal{P}_{im} \\ s \neq m}} \lambda^m - \lambda^s}. \tag{4.48}$$

We managed to collect the paths with the same weight. Now we need to find the product in the last denominator. We start noticing the following

Proposition 5. *For any state s*

$$\begin{aligned} \lambda^m - \lambda^{s+a\mathbf{v}_3+b\mathbf{v}_5+c\mathbf{v}_6} &= a(\lambda^m - \lambda^{s+\mathbf{v}_3}) + b(\lambda^m - \lambda^{s+\mathbf{v}_5}) && (4.49)\\ &+ c(\lambda^m - \lambda^{s+\mathbf{v}_6}) + (1-a-b-c)(\lambda^m - \lambda^s) + ac. && (4.50) \end{aligned}$$

Proof. We have

$$\begin{aligned} \lambda^m - \lambda^{s+a\mathbf{v}_3+b\mathbf{v}_5+c\mathbf{v}_6} = &- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\ &+ (s_W + c)(s_{E_a} + a) + \frac{\Omega k_3}{k_1}(s_{C_a} - a) \\ &+ \frac{\Omega(k_5+k_6)}{k_1}(s_{C_d} - b - c). \end{aligned} \tag{4.51}$$

Expanding the products

$$\begin{aligned} &- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\ &+ s_W s_{E_a} + \frac{\Omega k_3}{k_1} s_{C_a} + \frac{\Omega(k_5+k_6)}{k_1} s_{C_d} \\ &+ a \cdot s_W - a\frac{\Omega k_3}{k_1} - b\frac{\Omega(k_5+k_6)}{k_1} + c \cdot s_{E_a} - c\frac{\Omega(k_5+k_6)}{k_1} + ac. \end{aligned} \tag{4.52}$$

The first two lines of Equation (4.52) are $\lambda^m - \lambda^s$. The result follows adding and subtracting the term $(a+b+c)(\lambda^m - \lambda^s)$, since

$$\begin{aligned} a(\lambda^m - \lambda^{s+\mathbf{v}_3}) = &\, a\bigg(- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\ &+ s_W(s_{E_a} + a) + \frac{\Omega k_3}{k_1}(s_{C_a} - 1) + \frac{\Omega(k_5+k_6)}{k_1} s_{C_d} \bigg) \\ = &\, a\bigg(- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\ &+ s_W s_{E_a} + \frac{\Omega k_3}{k_1} s_{C_a} + \frac{\Omega(k_5+k_6)}{k_1} s_{C_d} + s_W - \frac{\Omega k_3}{k_1} \bigg) \\ = &\, a(\lambda^m - \lambda^s) + a \cdot s_W - a\frac{\Omega k_3}{k_1} \\ b(\lambda^m - \lambda^{s+\mathbf{v}_5}) = &\, b\bigg(- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \end{aligned}$$

$$
\begin{aligned}
&+ s_W s_{E_a} + \frac{\Omega k_3}{k_1} s_{C_a} + \frac{\Omega(k_5+k_6)}{k_1}(s_{C_d} - b)\Big) \\
&= b\Big(- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\
&\quad + s_W s_{E_a} + \frac{\Omega k_3}{k_1} s_{C_a} + \frac{\Omega(k_5+k_6)}{k_1} s_{C_d} - \frac{\Omega k_5 + k_6}{k_1}\Big) \\
&= b(\lambda^m - \lambda^s) - b\frac{\Omega(k_5+k_6)}{k_1} + \\
c(\lambda^m - \lambda^{s+\mathbf{v}_6}) &= c\Big(- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\
&\quad + (s_W + c) s_{E_a} + \frac{\Omega k_3}{k_1} s_{C_a} + \frac{\Omega(k_5+k_6)}{k_1}(s_{C_d} - c)\Big) \\
&= c\Big(- m_W m_{E_a} - \frac{\Omega k_3}{k_1} m_{C_a} - \frac{\Omega(k_5+k_6)}{k_1} m_{C_d} \\
&\quad + s_W s_{E_a} + \frac{\Omega k_3}{k_1} s_{C_a} + \frac{\Omega(k_5+k_6)}{k_1} s_{C_d} + s_{E_a} - \frac{\Omega k_5 + k_6}{k_1}\Big) \\
&= c(\lambda^m - \lambda^s) + c \cdot s_{E_a} - c\frac{\Omega(k_5+k_6)}{k_1} \qquad (4.53)
\end{aligned}
$$

□

We will only consider the product up to the first R_1 reaction, putting us in the case $s = m$. Let

$$
\begin{aligned}
\nu_3 &:= (\lambda^m - \lambda^{m+\mathbf{v}_3}); \\
\nu_5 &:= (\lambda^m - \lambda^{m+\mathbf{v}_5}); \qquad (4.54) \\
\nu_6 &:= (\lambda^m - \lambda^{m+\mathbf{v}_6});
\end{aligned}
$$

Then Equation (4.49) becomes

$$\lambda^m - \lambda^{m+a\mathbf{v}_3+b\mathbf{v}_5+c\mathbf{v}_6} = a\nu_3 + b\nu_5 + c\nu_6 + ac. \qquad (4.55)$$

Proposition 6. *Let*

$$f(a,b,c) := \sum_{\mathcal{P}_{im}} \frac{1}{\prod_{s\in\mathcal{P}_{im}} \lambda^m - \lambda^s}, \qquad (4.56)$$

for $i = m + a\mathbf{v}_3 + b\mathbf{v}_5 + c\mathbf{v}_6$. The following recursion holds

$$(a\nu_3 + b\nu_5 + c\nu_6 + ac) f(a,b,c) = f(a-1,b,c) + f(a,b-1,c) + f(a,b,c-1). \qquad (4.57)$$

Proof. Let

$$
\begin{aligned}
i_3 &:= i - \mathbf{v}_3 = m + (a-1)\mathbf{v}_3 + b\mathbf{v}_5 + c\mathbf{v}_6; \\
i_5 &:= i - \mathbf{v}_5 = m + a\mathbf{v}_3 + (b-1)\mathbf{v}_5 + c\mathbf{v}_6; \qquad (4.58) \\
i_6 &:= i - \mathbf{v}_6 = m + a\mathbf{v}_3 + b\mathbf{v}_5 + (c-1)\mathbf{v}_6.
\end{aligned}
$$

We have that

$$\sum_{\mathcal{P}_{im}} \frac{1}{\prod\limits_{s\in\mathcal{P}_{im}} \lambda^m - \lambda^s} = \frac{1}{\lambda^m - \lambda^i}\left[\sum_{\mathcal{P}_{i_3m}} \frac{1}{\prod\limits_{s\in\mathcal{P}_{i_3m}} \lambda^m - \lambda^s} + \sum_{\mathcal{P}_{i_5m}} \frac{1}{\prod\limits_{s\in\mathcal{P}_{i_5m}} \lambda^m - \lambda^s}\right.$$

$$\left. + \sum_{\mathcal{P}_{i_6m}} \frac{1}{\prod\limits_{s\in\mathcal{P}_{i_6m}} \lambda^m - \lambda^s}\right]. \tag{4.59}$$

The claim follows from Equation (4.49), since

$$\lambda^m - \lambda^i = a\nu_3 + b\nu_5 + c\nu_6 + ac. \tag{4.60}$$

□

It is easy to find a solution to recursion (4.57), when the term ac is removed. To illustrate that, consider the case $c = 0$. The resulting recursion is

$$(a\nu_3 + b\nu_5)f(a,b,0) = f(a-1,b,0) + f(a,b-1,0). \tag{4.61}$$

Assuming the solution is of the form

$$f(a,b,0) = \frac{h(a,b)}{\nu_3^a\nu_5^b}, \tag{4.62}$$

for a function h(a,b) independent on ν_3 and ν_5, we obtain

$$(a\nu_3 + b\nu_5)\frac{h(a,b)}{\nu_3^a\nu_5^b} = \frac{h(a-1,b)}{\nu_3^{a-1}\nu_5^b} + \frac{h(a,b-1)}{\nu_3^a\nu_5^{b-1}}, \tag{4.63}$$

or

$$(a\nu_3 + b\nu_5)h(a,b) = \nu_3 h(a-1,b) + \nu_5 h(a,b-1). \tag{4.64}$$

Since this last equation must be valid independently of the values of ν_3 and ν_5, the two following equations must be simultaneously verified

$$a\nu_3 h(a,b) = \nu_3 h(a-1,b); \tag{4.65}$$

$$b\nu_5 h(a,b) = \nu_5 h(a,b-1). \tag{4.66}$$

The variable a and b are separated, therefore a solution is found as the product of the results of the two following recurrences

$$ah_1(a) = h_1(a-1); \tag{4.67}$$

$$bh_2(b) = h_2(b-1). \tag{4.68}$$

We have

$$h_1(a) = \frac{1}{a!}; \tag{4.69}$$

$$h_2(b) = \frac{1}{b!}, \tag{4.70}$$

and

$$f(a, b, 0) = \frac{1}{a!b!}\frac{1}{\nu_3^a \nu_5^b}. \tag{4.71}$$

However, with the presence of the term ac in Equation (4.57), a solution of the form of Equation (4.62), where the coefficients a b and c are separated from ν_3, nu_5 and ν_6, is more unlikely to exist. In fact, in an equation similar to Equation (4.64), the left side term ac would not have a correspondent on the right side hand.

At the moment we are unable to solve Equation (4.57).

Chapter 5

Conclusion

5.1 Summary

A new approach to the chemical master equation (CME) has been developed throughout the thesis.

In Chapter 2 we gradually introduce the method using as base a simple bimolecular reaction, namely Dimerization.

We first introduce the CME for a dimerization reaction, we reduce it using its conservation law and we convert it to non-dimensional matrix form. We show that an exact solution for the equation can be obtained using basic ordinary differential equations. However, such a solution fails to describe the behaviour of the system, because it is tied to the starting number of molecules to such an extent that only changing the initial conditions would result in a different equation (the dimension of the matrix differential equation grows with the number of possible states). A method whose complexity would depend on the number of reactions is sought.

Secondly, we use the Leibniz formula for the computation of a determinant to approximate the eigenvalues of the transition state matrix in the CME by a series expansion in powers of a non-dimensional combination of the reaction rate constants and the reaction volume. Direct evaluation of the Leibniz formula is impractically difficult because of the factorial growth of the number of permutations. However, a very restricted number of permutations contribute with significant terms when asymptotically expanding the eigenvalues. Not only we demonstrate that this number is linear, compared to the factorial number of all permutations, but also we show that those permutations can be categorised into two classes: "left" and "right". We give some insight on how those classes correspond to the "left" and "right" neighbours in the graph associated to the system.

Thirdly, we develop a graph-based methodology for determining the adjoint matrix of any given square matrix. The technique has already been seen in [29] in the context of chemical graphs (the graph representing the structural formula of a chemical compound) and it makes use of the paths of the graph in order to repeatedly apply a Laplace expansion to a determinant. We expand its validity for graphs associated to CMEs (which are directed and weighted) and also find a simple formulation for the sign, which was not computed in the aforementioned article. The adjoint matrix then can be used to compute the eigenvectors of the transition state matrix.

Finally, we use the theoretical instruments developed to compute the left and right eigenvectors associated with the Dimerization. Those eigenvectors are shown in detail in Appendix A. We use the result to numerically compute the final distribution and we compare it against numerical matrix exponentiation. We verify that our solution is indeed very close to the numerical one. Also we compare our method against its closest competitor: linear noise approximation. We show improvement as soon the parameter of our expansion is small enough. In particular, the proposed method outperforms linear noise approximation for small times and near the steady state.

In Chapter 3 we give a more general treatise of the approach, distancing ourselves from the Dimerization system.

We start generalising the non-dimensionalization process, setting out the first main assumption: the system must contain a set reactions that occur "faster" than others; and there should not be introduction of molecules in the system. The non-dimensionalization process is always easy and possible in the CME and could be performed in several different ways.

Then, we study a general way to expand the eigenvalues in a similar fashion we did for the Dimerization system. Here, we fully make use of the graph associated to the system, showing how the relevant permutations correspond to cycles in such a graph. We give the necessary hypotheses to move forward, most notably that the graph only containing "slow" edges must be acyclic. We prove that, when the leading terms of the eigenvalues are all different, the eigenvalues behave as in the case of Dimerization, depending on the neighbourhood of each node, which is very regular due to the nature of the model. We proceed to find the characteristic polynomial in this case. However, when two or more eigenvalues leading orders are equal, more complicated relations between possibly distant nodes emerge. Nevertheless, it is possible, though impractical to find a formula. The result still retains a moderate theoretical interest, since it exposes the presence of "bridges" between distant nodes when eigenvalues with same leading orders are present.

We follow showing a way to bypass the calculation of the eigenvectors, avoiding the numerical computations involved in the products between left and right eigenvector matrices, and delivering a fully analytical solution. The idea is to use the Laplace transform to solve the linear differential equation rather than use the matrix exponential. The Laplace transform is a vastly known method and it has been used in literature to solve linear differential equations in many occasions. The example most relevant to this work is given by [26]. There the author exactly solved the CME associated to the binding reaction $A+B\underset{k_2}{\overset{k_1}{\rightleftharpoons}}C$ firstly applying the Laplace transform and then finding the cofactors needed for the final solution solving a recurrence relation. In Chapter 2 we developed a way to compute the adjoint matrix, *i.e.*, the matrix of the cofactors. Therefore, we use the result to obtain an approximate solution.

In Chapter 4 we study a more complex system, namely Push-Pull mechanism. This system will highlight the main difficulty of the method: the combinatorial complexity of finding paths in a graph. We reduce the system through its conservation laws and non-dimensionalize it. The leading order of the eigenvalues is computed and conditions sufficient to guarantee that all the leading terms are different are found. The expansion formula for the eigenvalues is found. The adjoint matrix presents much more difficulties and, in fact, we are not able to find a solution. The attempt made through the chapter is intended to propose some ideas to collect terms corresponding to paths in the graph with same weight. This eventually led to a recurrence formula that we were not able to solve.

5.2 Discussion

Despite being a simple looking linear differential equation, the CME represents a difficult problem to solve. As for all the linear differential equations associated with continuous in time Markov chains, the difficulty arises because of the dependence of the dimension of the problem with the number of possible states that can occur. This, in turn, often depends on the initial conditions of the system, in the case of molecular reactions: the initial number of molecules. However, chemical systems result in very regular networks of states.

We attempted to use the regularity of the network to develop a method to approximate the CME solution pertubatively. We made use of cycles and paths on this network. We developed a system of assumption for our method to work and found out that, under those assumptions, the eigenvalues of the transition state matrix are associated with the possible states of the chain. Also, their value depend on the neighbourhood of the corresponding state unless two or more eigenvalues have the same leading order. In this last case, a link between possibly far nodes is created.

Finding the eigenvectors of the transition state matrix is found equivalent to find its cofactors. The cofactors, in turn, are found to depend on the paths of the network.

The number of paths needed to find a series expansion of the cofactors grows exponentially with the initial number of molecules. For this reason, our aim is not to list them all one at the time, but rather to collect them in groups. This resulted easy in a simple reaction system as for Dimerization where only one path between each couple of states is present, however it becomes more and more challenging when the number of possible reactions increases.

An attempt to use the regularity of the network to categorise the relevant paths has been made for the Push-Pull mechanism. We managed to collect by weight the paths needed for the computation of the leading order of the cofactors, but only to obtain a recurrence equation that we were not able to solve. It might be possible to collect the paths by some topological property, but we could not find a suitable one.

Although it was not possible to find a solution for the Push-Pull mechanism, we believe that the regular structure of the networks corresponding to chemical reactions should be enough to determine a solution, or at least an approximation to it, of the CME.

This thesis sets some of the ideas that can be used. Further research on the paths structure and topological properties of networks associated to CMEs is needed in order to make progress in his direction.

Appendix A

Eigenvector Formulae for Dimerization

In this appendix, we give complete formulae for the eigenvectors of the transition matrix $\mathbf{M}$ of the Dimerization system, for any value of $n = 0, 1, \ldots, \Omega\alpha$, with $\Omega\alpha > 1$; in particular, we include the special cases where $n = 0, 1, \Omega\alpha$, which were omitted in Section 2.3.1. Then, we quote the corresponding (less compact) expressions that are obtained by retaining only asymptotically relevant terms, *i.e.*, terms up to and including $O(K)$, in these formulae. (We recall that, given an eigenvalue λ_n of $\mathbf{M}$, the n-th column $\mathbf{A}_n[i, n]$ of the adjoint matrix $\mathbf{A}_n$ yields an associated eigenvector, which is then normalized to $\widetilde{\mathbf{A}}_n[i, n]$; cf. again Section 2.3.1.)

$$\boxed{1 < n < \Omega\alpha:}$$

$$\widetilde{\mathbf{A}}_n[i,n] = \begin{cases} Kf(n)(\lambda_n - \lambda^+_{n-2})(\lambda_n - \lambda^-_{n+1}) \displaystyle\prod_{r=n+2}^{\Omega\alpha} (\lambda_n - \lambda_r) & \text{if } i = n-1; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n-2}) \displaystyle\prod_{r=n+2}^{\Omega\alpha} (\lambda_n - \lambda_r) & \text{if } i = n; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{i+1})(\lambda_n - \lambda_{n-2}) \displaystyle\prod_{r=i+2}^{\Omega\alpha} (\lambda_n - \lambda_r) \prod_{r=n}^{i-1} g(r) & \text{if } n < i < \Omega\alpha; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.1}$$

$$\boxed{n = 0:}$$

$$\widetilde{\mathbf{A}}_n[i,0] = \begin{cases} (\lambda_0 - \lambda^-_1) \displaystyle\prod_{r=2}^{\Omega\alpha} (\lambda_0 - \lambda_r) & \text{if } i = 0; \\ (\lambda_0 - \lambda^-_{i+1}) \displaystyle\prod_{r=i+2}^{\Omega\alpha} (\lambda_0 - \lambda_r) \prod_{r=0}^{i-1} g(r) & \text{if } 0 < i < \Omega\alpha; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.2}$$

$$\boxed{n = 1:}$$

$$\widetilde{\mathbf{A}}_n[i,1] = \begin{cases} 2K(\lambda_1 - \lambda_2^-)\displaystyle\prod_{r=3}^{\Omega\alpha}(\lambda_1 - \lambda_r) & \text{if } i = 0; \\ (\lambda_1 - \lambda_0^+)(\lambda_1 - \lambda_2^-)\displaystyle\prod_{r=3}^{\Omega\alpha}(\lambda_1 - \lambda_r) & \text{if } i = 1; \\ (\lambda_1 - \lambda_0^+)(\lambda_1 - \lambda_{i+1}^-)\displaystyle\prod_{r=i+2}^{\Omega\alpha}(\lambda_1 - \lambda_r) & \text{if } 1 < i < \Omega\alpha; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.3}$$

$$\boxed{n = \Omega\alpha:}$$

$$\widetilde{\mathbf{A}}_n[i,\Omega\alpha] = \begin{cases} Kf(\Omega\alpha)(\lambda_{\Omega\alpha} - \lambda_{\Omega\alpha-2}^+) & \text{if } i = \Omega\alpha - 1; \\ (\lambda_{\Omega\alpha} - \lambda_{\Omega\alpha-1}^+)(\lambda_{\Omega\alpha} - \lambda_{\Omega\alpha-2}) & \text{if } i = \Omega\alpha; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.4}$$

Considering only the relevant terms in the above formulae and defining the n-th eigenvector $\mathbf{E}[i,n] := (\text{-}1)^{\Omega\alpha-n}\widetilde{\mathbf{A}}_n[i,n]$, we find

$$\boxed{1 < n \leq \Omega\alpha:}$$

$$\mathbf{E}[i,n]=\begin{cases} 2Kf(n)(\Omega\alpha - n)! & \text{if } i{=}n{-}1; \\ 2(\Omega\alpha{-}n)!\Big\{1{-}2K\big[2(\Omega\alpha)^2{+}(4n^2{-}6n + 6)\Omega\alpha{-}4n^3{+}6n^2{-}15n + 10\big]\Big\} & \text{if } i{=}n; \\ (\text{-}1)^{i-n}\dbinom{\Omega\alpha - n}{\Omega\alpha - i}(\Omega\alpha - n)! \times & \\ \Bigg\{2 - K\Bigg[8(\Omega\alpha)^2 + 4\Omega\alpha\left(2n^2 - 3n - 2i + 6 + \dfrac{n(2n-1)}{i-n+1}\right) & \\ -4\left(2n^3 - n^2 - 2(i-8)n - 2i - 10 + \dfrac{n(2n-1)(n-1)}{i-n+1}\right)\Bigg]\Bigg\} & \text{if } i > n; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.5}$$

$$\boxed{n = 0:}$$

$$\mathbf{E}[i,0] = \begin{cases} (\Omega\alpha)! - 4K\Omega\alpha(\Omega\alpha - 1)(\Omega\alpha)! & \text{if } i = 0; \\ (\text{-}1)^i\dbinom{\Omega\alpha}{\Omega\alpha - i}(\Omega\alpha)!\big[1 - 4K(\Omega\alpha - 1)(\Omega\alpha - i)\big] & \text{if } i > 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.6}$$

$$\boxed{n = 1:}$$

$$\mathbf{E}[i,1]=\begin{cases} -2K(\Omega\alpha - 1)! & \text{if } i = 0; \\ -(\Omega\alpha - 1)! + 4K(\Omega\alpha - 1)(\Omega\alpha + 1)(\Omega\alpha - 1)! & \text{if } i = 1; \\ (\text{-}1)^i\dbinom{\Omega\alpha{-}1}{\Omega\alpha{-}i}(\Omega\alpha{-}1)!\Big\{1{-}K\Big[4(\Omega\alpha)^2{-}4i\Omega\alpha + 2\dfrac{i+1}{i}\Omega\alpha + 8i{-}12\Big]\Big\} & \text{if } i{>}1; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.7}$$

Remark 25. *We note that the particular case where $n = \Omega\alpha$, as given in Eq. (A.4), is contained in the more general Eq. (A.5), after simplification of the latter.*

Similarly, we obtain the following formulae for the n-th row of the adjoint $\mathbf{B}_n$

of $\mathbf{M}^T - \lambda_n \mathbf{I}$ introduced in Section 2.3.2 or, rather, for the normalized version $\widetilde{\mathbf{B}}_n[n,i]$; here, we again assume $n = 0, 1, \dots, \Omega\alpha$, with $\Omega\alpha > 1$.

$$\boxed{1 \leq n < \Omega\alpha - 1:}$$

$$\widetilde{\mathbf{B}}_n[n,i] = \begin{cases} Kf(n+1)(\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{n+2}) \prod_{r=0}^{n-2} (\lambda_n - \lambda_r) & \text{if } i = n+1; \\ (\lambda_n - \lambda^+_{n-1})(\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n+2}) \prod_{r=0}^{n-2} (\lambda_n - \lambda_r) & \text{if } i = n; \\ (\lambda_n - \lambda^+_{i-1})(\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n+2}) \times & \\ \prod_{r=0}^{i-2} (\lambda_n - \lambda_n) \prod_{r=i}^{n-1} g(r) & \text{if } 0 < i < n; \\ (\lambda_n - \lambda^-_{n+1})(\lambda_n - \lambda_{n+2}) \prod_{r=i}^{n-1} g(r) & \text{if } i = 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.8}$$

$$\boxed{n = 0:}$$

$$\widetilde{\mathbf{B}}_n[n,i] = \begin{cases} 2K(\lambda_0 - \lambda^-_2) & \text{if } i = 1; \\ (\lambda_0 - \lambda^-_1)(\lambda_0 - \lambda_2) & \text{if } i = 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.9}$$

$$\boxed{n = \Omega\alpha - 1:}$$

$$\widetilde{\mathbf{B}}_n[\Omega\alpha - 1, i] = \begin{cases} Kf(\Omega\alpha)(\lambda_{\Omega\alpha-1}\lambda^+_{\Omega\alpha-2}) \prod_{r=0}^{\Omega\alpha-3} (\lambda_{\Omega\alpha-1} - \lambda_r) & \text{if } i = \Omega\alpha; \\ (\lambda_{\Omega\alpha-1} - \lambda^+_{\Omega\alpha-2})(\lambda_{\Omega\alpha-1} - \lambda^-_{\Omega\alpha}) \prod_{r=0}^{\Omega\alpha-3} (\lambda_{\Omega\alpha-1} - \lambda_r) & \text{if } i = \Omega\alpha - 1; \\ (\lambda_{\Omega\alpha-1} - \lambda^+_{i-1})(\lambda_{\Omega\alpha-1} - \lambda^-_{\Omega\alpha}) \times & \\ \prod_{r=0}^{i-2} (\lambda_{\Omega\alpha-1} - \lambda_r) \prod_{r=i}^{\Omega\alpha-2} g(r) & \text{if } 0 < i < \Omega\alpha - 1; \\ (\lambda_{\Omega\alpha-1} - \lambda^-_{\Omega\alpha}) \prod_{r=i}^{\Omega\alpha-2} g(r) & \text{if } i = 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.10}$$

$$\boxed{n = \Omega\alpha:}$$

$$\widetilde{\mathbf{B}}_n[\Omega\alpha, i] = 1. \tag{A.11}$$

In particular, the expression for $n = \Omega\alpha$ is obtained by observing that none of the remaining expressions for $\widetilde{\mathbf{B}}_n[n,i]$ equals the vector $\mathbb{1}$ (or a multiple thereof). Hence, by Remark 9, we may take the last row to equal $\mathbb{1}$, after normalization.

In sum, considering only asymptotically relevant terms for $\Omega\alpha > 2$ and defining n-th left eigenvector $\mathbf{E}^{-1}[n,i] := -\widetilde{\mathbf{B}}_n[n,i]$, we have

$$\boxed{0 \leq n < \Omega\alpha - 1 :}$$

$$\mathbf{E}^{-1}[n,i] = \begin{cases} 4K(2n+1)(n+1)! & \text{if } i = n+1; \\ -n!\Big\{2 - 4K\big[(4n^2+6n+9)\Omega\alpha \\ -(4n^3+6n^2+17n+14)\big]\Big\} & \text{if } i = n; \\ \dfrac{n!}{(n-i+1)!}\dfrac{(\Omega\alpha-i)!}{(\Omega\alpha-n)!}\Big\{2(i-n-1) \\ +4K\Big[\big(2n^3-(2i-5)n^2+(i+12)n-2i^2-6i+9\big)\Omega\alpha - 2n^4 \\ +(2i-5)n^3-(i+20)n^2+(2i^2+14i-31)n+14(i-1)\Big]\Big\} & \text{if } 1 \leq i < n; \\ -2\dfrac{(\Omega\alpha)!}{(\Omega\alpha-n)!}\Big\{1-2K\big[(2n^2+3n+9)\Omega\alpha \\ -(2n^3+3n^2+17n+14)\big]\Big\} & \text{if } i = 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.12}$$

$$\boxed{n = \Omega\alpha - 1 :}$$

$$\mathbf{E}^{-1}[\Omega\alpha - 1, i] = \begin{cases} 2K(2\Omega\alpha-1)(\Omega\alpha)! & \text{if } i = \Omega\alpha; \\ -(\Omega\alpha-1)!\big[1-4K(2\Omega\alpha-1)(\Omega\alpha-1)\big] & \text{if } i = \Omega\alpha - 1; \\ (-(\Omega\alpha-1)!\Big\{\Omega\alpha - i - 2K\Big[2(\Omega\alpha)^3 \\ -(2i+5)(\Omega\alpha)^2+3(3i+1)\Omega\alpha-2i(i+2)\Big]\Big\} & \text{if } 0 < i < \Omega\alpha - 1; \\ -(\lambda^-_{\Omega\alpha} - \lambda_{\Omega\alpha-1}) \displaystyle\prod_{r=i}^{\Omega\alpha-2} g(r) & \text{if } i = 0; \\ o(K) & \text{otherwise.} \end{cases} \tag{A.13}$$

$$\boxed{n = \Omega\alpha :}$$

$$\mathbf{E}^{-1}[\Omega\alpha, i] = 1. \tag{A.14}$$

Remark 26. *The particular case of* $n = 0$ *in Eq.* (A.9) *is contained in the more general Eq.* (A.12)*; cf. also Remark* 25 *above.*

Finally, we note that the restriction to $\Omega\alpha > 2$ is necessary to ensure that the products in Eq. (A.10) remain well-defined. When $\Omega\alpha = 2$, particular care has to be taken when evaluating the latter; still, one can show that, while $\widetilde{\mathbf{B}}_1[1,1] = -1+12K$ in that case, the above formulae for the remaining rows $\widetilde{\mathbf{B}}_n[n,i]$ continue to be valid.

Appendix B

Derivation of LNA

In Section 2.4.1, we compared the error incurred by LNA with the accuracy that is achieved by our perturbative approach. In this appendix, we present a concise derivation of LNA for the dimerization reaction on which our comparison was based.

Let $\phi(t)$ and $\psi(t)$ represent the concentrations of molecules of A and B, respectively, at time t. Then, the conventional rate equations [24] for the reaction scheme $A+A\underset{k_2}{\overset{k_1}{\rightleftharpoons}}B$ are given by

$$\begin{aligned}\frac{d}{dt}\phi(t) &= -2k_1\phi(t)^2+2k_2\psi(t),\\ \frac{d}{dt}\psi(t) &= k_1\phi(t)^2-k_2\psi(t).\end{aligned}$$

Assuming that $\phi(0)=0$, *i.e.*, that the initial concentration of A is zero, we find

$$\phi(t)=\frac{4\alpha[\mathrm{e}^{(c-1)t}-1]}{c[\mathrm{e}^{(c-1)t}+1]-2}, \tag{B.1}$$

$$\psi(t)=2\alpha-\phi(t) \tag{B.2}$$

for the time-dependent solution of this pair of coupled differential equations, where

$$c:=1+\sqrt{1+16\frac{k_1}{k_2}\alpha};$$

in particular, the conservation law in (B.2) implies $\psi(0)=2\alpha$.

Now, the CME for the dimerization reaction, Eq. (2.1), can be rewritten as

$$\begin{aligned}\frac{d}{dt}P(n_A,n_B,t) = {}&\frac{k_1}{\Omega}\left[E_A^2E_B^{-1}-1\right]n_A(n_A-1)\,P(n_A,n_B,t)\\ &+k_2\left[E_A^{-2}E_B-1\right]n_B\,P(n_A,n_B,t),\end{aligned} \tag{B.3}$$

where $E^i_{n_j}$ is the step operator defined by

$$E^i_{n_j} f(n_1, n_2, \ldots, n_j, \ldots, n_d) = f(n_1, n_2, \ldots, n_j + i, \ldots, n_d).$$

The principal idea underlying LNA is to make the following change of variables [16] in (B.3):

$$n_A = \Omega\phi(t) + \Omega^{1/2}\xi(t) \quad \text{and} \quad n_B = \Omega\psi(t) + \Omega^{1/2}\eta(t).$$

(Typically, one assumes deterministic initial conditions, *i.e.*, one sets $\xi(0) = 0$ and $\eta(0) = 0$.) The above ansatz has the effect of transforming all functions of n_A and n_B into functions of the continuous random variables ξ and η, leading to a series expansion of Eq. (B.3) in powers of $\Omega^{1/2}$. The derivation is carried out for general chemical reaction networks in [16]; we simply quote the result here, as applied to dimerization:

$$\begin{aligned}\frac{\partial}{\partial t}\Pi = [4k_1\phi(t) + k_2]\frac{\partial}{\partial \xi}(\xi\Pi) + \frac{1}{2}[4k_1\phi(t) + 4k_2\alpha - 2k_2\phi(t)]\frac{\partial^2}{\partial \xi^2}\Pi \\ + O(\Omega^{-1/2}),\end{aligned} \tag{B.4}$$

where $\Pi := \Pi(\xi, t) := P(n_A, t)$ denotes the reduced distribution, rewritten in terms of n_A only. (We note that we have also applied the conservation law from Eq. (B.2) in (B.4) to eliminate η, as $\xi + 2\eta = 0$, as well as that the above initial conditions correspond to assuming $P(n_A = 0, t = 0) = 1$; recall Section 2.4.) The above equation is the Fokker-Planck approximation to the CME; as its drift and diffusion coefficients are linear in ξ, it admits a Gaussian solution at all times.

Multiplying Eq. (B.4) by ξ and integrating, we find a differential equation for the mean $\langle\xi\rangle$,

$$\frac{d}{dt}\langle\xi\rangle = -[4k_1\phi(t) + k_2]\langle\xi\rangle,$$

which, due to the deterministic initial condition $\xi(0) = 0$, implies $\langle\xi\rangle = 0$ for all times. Equivalently, we have

$$\langle n_A\rangle = \Omega\phi(t) + O(\Omega^{-1/2}) \quad \text{and} \quad \langle n_B\rangle = \Omega\psi(t) + O(\Omega^{-1/2}).$$

Hence, the mean concentrations obtained from LNA are identical to those obtained from the conventional rate equations.

The advantage of LNA lies in the resulting simple expression for the second moment $\langle\xi^2\rangle$ of the distribution: multiplying Eq. (B.4) by ξ^2 and integrating with respect to ξ, we find the ordinary differential equation

$$\frac{d}{dt}\langle\xi^2\rangle = -2[4k_1\phi(t) + k_2]\langle\xi^2\rangle + 4k_1\phi(t)^2 + 2k_2\psi(t),$$

which is known as the Lyapunov equation. In particular, the variance in the number of monomer molecules is then given by $\langle n_A^2\rangle - \langle n_A\rangle^2 = \Omega(\langle\xi^2\rangle - \langle\xi\rangle^2) =$

$\Omega\langle\xi^2\rangle$, which implies

$$p(x,t) = \frac{1}{\sqrt{2\pi\Omega\langle\xi^2\rangle}} \exp\Big[-\frac{1}{2}\Big(\frac{x-\Omega\phi(t)}{\sqrt{\Omega\langle\xi^2\rangle}}\Big)^2\Big]$$

for the (continuous) probability density function that is obtained from LNA. Finally, to determine a corresponding discrete probability distribution for a given state n_A, we need to integrate p over a neighbourhood of width 1 around that state:

$$P(n_A,t) = \int_{n_A-1}^{n_A+1} p(x,t)\,dx. \tag{B.5}$$

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