Dimensional Reduction of Chemical Reaction Systems I

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0.1 Introduction and Notation

Invariably in chemical reaction systems do the dynamics of different species vary on different time-scales. It is simple to deal with slow moving variables since they can be assumed to be constant and hence equal to their initial value. Dealing with fast variables is a little trickier. Usually a quasi-steady state assumption is used in which the fast variables are assumed to have settled down to a constant value after an initial transient period. However this needs to be justified. Essentially what is being dealt with here is a singular perturbation of a system of ODEs by a small parameter ϵ. Tichonov's theorems (the first of which is presented here) states the conditions under which the singular perturbation tends to the unperturbed system as $\epsilon \to 0$ and so the dimension of the system of ODEs can be reduced.

Throughout this article $S_1, \ldots, S_n$ will represent species involved in a certain chemical reaction network. The concentrations of these will be denoted $x_1, \ldots, x_n$. It will be assumed that the reactions governing the dynamics of these species can be summarised in a system of ODEs, namely

$$\begin{aligned}\frac{dx_1}{dt} &= f_1(x_1, \ldots, x_n) \\ &\vdots \\ \frac{dx_n}{dt} &= f_1(x_1, \ldots, x_n)\end{aligned}$$

which may be abbreviated to $\frac{dx}{dt} = f(x)$ where $x = (x_1, \ldots, x_n)$ and $f : \mathbf{R}^n \to \mathbf{R}^n$ is a vector valued function.

The aim of this article is to show how to non-dimensionalise a system of ODEs in order to be able to distinguish between variables changing at different speeds and to present the first of Tichonov's theorems. Finally, an example is included at the end which demonstrates how Tichonov can be applied to a simple chemical reaction network and should hopefully convey the idea that when mass-action kinetics are assumed that some of the assumptions of Tichonov are satisfied trivially.

0.2 Non-Dimensionalization

One way to distinguish between variables which are changing on different time-scales is to non-dimensionalize in the following manner

Step 1 For each variable $x_1, \ldots, x_n$ choose constants $X_1, \ldots, X_n$ such that $\forall k \in \{1, \ldots, n\}$, $0 \leq \frac{x_k}{X_k} \leq 1$ for all $t \geq 0$. Then substitute $y_k = \frac{x_k}{X_k}$ into the system of ODEs $\forall k \in \{1, \ldots, n\}$.

Step 2 For each variable y_k in the ODE find the largest coefficient of $f_k(y_1, \ldots, y_n)$. Then for each $k \in \{1, \ldots, n\}$ define the relative time scale for this equation T_{y_k} as the reciprocal of this coefficient. Then multiply the equation for $\frac{y_k}{dt}$ by its relative time-scale.

Step 3 Decide on a time-scale of interest T. Rescale time $\tau = \frac{t}{T}$.

Step 4 The system of equations now has the form

$$
\begin{aligned}
m_1 \frac{dy_1}{d\tau} &= f_1(y_1, \ldots, y_n) \\
&\vdots \\
m_k \frac{dy_k}{d\tau} &= f_1(y_1, \ldots, y_n) \qquad (1) \\
&\vdots \\
m_n \frac{dy_n}{d\tau} &= f_1(y_1, \ldots, y_n)
\end{aligned}
$$

where $m_k = \frac{T_{y_k}}{T}$ for $k \in \{1, \ldots, n\}$. Variable y_k is classed as fast if $m_k \ll 1$, slow if $m_k \gg 1$ and varying on the time-scale of interest if $m_k \approx 1$.

With a bit of thought it is clear what this form of non-dimensionalization is trying to achieve. In the first instance the variables are all scaled so that they vary between 0 and 1 which means that in the second step the terms which have the most influence on the dynamics of the system are identified and scaled to 1. So roughly speaking the terms on the right hand side of the ODEs are approximately of the same order of magnitude and so are comparable. The scaling of time in Step 3 allows one to determine the variables that are varying on a time-scale in which we are interested in.

0.3 Tichonov's Theorem

Tichonov's First Theorem is concerned with equations of the form:

$$\begin{aligned} \frac{dx}{dt} &= f(x,y) \text{ for } x \in \mathbf{R}^n \\ \epsilon\frac{dy}{dt} &= g(x,y) \text{ for } y \in \mathbf{R}^m \end{aligned} \tag{2}$$

with initial conditions $x(0) = x^0$ and $y(0) = y^0$. This is called the full problem. It is clear from the previous section that many systems can be written in this form upon being non-dimensionalized by collecting variables which vary on the time-scale of interest in x and those which are fast in y. Those which are considered to be varying slowly are considered constant and hence equal to their initial value. It is necessary to define the adjoint of system (2) as

$$\frac{dy}{d\tau} = g(x,y) \tag{3}$$

where x is considered as a parameter. Tichonov's theorem provides the conditions under which the solution to the full problem (2) converge to the solution of the problem when $\epsilon = 0$ as $\epsilon \to 0$. If this should hold then the dimension of the problem can be reduced by m for small ϵ. In order to do this we make the following assumptions:

1. For some open $\Omega \subset \mathbf{R}^n \times \mathbf{R}^m$, $f : \Omega \longrightarrow \mathbf{R}^n$ and $g : \Omega \longrightarrow \mathbf{R}^m$ are continuous.

2. $\exists$ a continuous function $\Phi : K \longrightarrow \mathbf{R}^m$ on a compact set $K \subset \mathbf{R}^n$ such that $(x, \Phi(x)) \in \Omega$ and $g(x, \Phi(x)) = 0$ for all $x \in K$.

3. $\exists \eta > 0$ such that $\forall x \in K$ and $y \in \mathbf{R}^m$, $y \neq \Phi(x)$ with $\|y - \Phi(x)\| < \eta$, then $g(x,y) \neq 0$ i.e the root is isolated.

4. $y = \Phi(x)$, the equilibrium of the adjoined system is asymptotically stable $\forall x \in K$.

5. The full and reduced problem have unique solutions in $0 \leq t \leq T$ for some $T \geq 0$. (The reduced problem is defined as

$$\begin{aligned} y &= \Phi(x) \\ \frac{dx}{dt} &= f(x, \Phi(x)) \end{aligned} \tag{4}$$

with initial condition $x(0) = x^0$).

6. $(x^0, y^0) \in \Omega$ and $x^0 \in K$ and (x^0, y^0) lies in the domain of influence of the stable root $y = \Phi(x)$. (i.e the solution of the adjoined system (3) with parameter $x = x^0$ and initial condition $y(0) = y^0$ exists, remains in $\Omega \forall t > 0$ and tends to $\Phi(x^0)$ for $\tau \longrightarrow \infty$.

Tichonov's First theorem states

Theorem 1. *If assumptions 1 to 6 above hold for system (2) then the solution to the full problem $(x(t,\epsilon), y(t,\epsilon))$ is related to the solution of the reduced problem (4), $x_0(t)$, $y_0(t) = \Phi(x_0(t))$ by*

$$\lim_{\epsilon \to 0} x(t,\epsilon) = x_0(t) \quad \forall 0 \leq t < T_0$$

$$\lim_{\epsilon \to 0} y(t,\epsilon) = y_0(t) \quad \forall 0 \leq t < T_0$$

where T_0 is chosen such that $y = \Phi(x_0(t))$ is an isolated stable root of $g(x_0(t), y) = 0 \quad \forall 0 \leq t \leq T_0$. Furthermore, the convergence is uniform on $[0, T_0]$ for $x(t,\epsilon)$ and on $[t_1, T_0] \quad \forall t_1 \in (0, T_0]$ for $y(t,\epsilon)$.

The proof to this theorem will not be stated here. A fairly simple proof for the case when $x, y \in \mathbf{R}$ can be found in [1] which is suitable to give an incite into the intuition behind the theorem. For a complete proof in the more general case see [2].

0.4 Example: Intracellular Calcium

Calcium is an important second messenger utilised by many cells including cardiac, endothelial, fibroblasts, pancreatic, pituitary cells and neurons. It is involved in a number of enzymatic processes in the cell such as smooth muscle contraction, exocytosis and glycogen metabolism [5],[6]. The levels of Ca^{2+} are carefully regulated in the cell in a number of ways. One such mechanism involves the pumping of Ca^{2+} into intracellular stores (or pools) such as the Endoplasmic Reticulum and the Mitochondria which is subsequently released by a process known as Calcium Induced Calcium Release (CICR). There have been many mathematical studies on intracellular calcium concentrations especially since the discovery of oscillations in Ca^{2+} in the cytosol in the mid 1980's. Here a model proposed in a Master's thesis by Sensse [4] as a minimal model in which oscillations are observed is reduced using Tichonov's First Theorem.

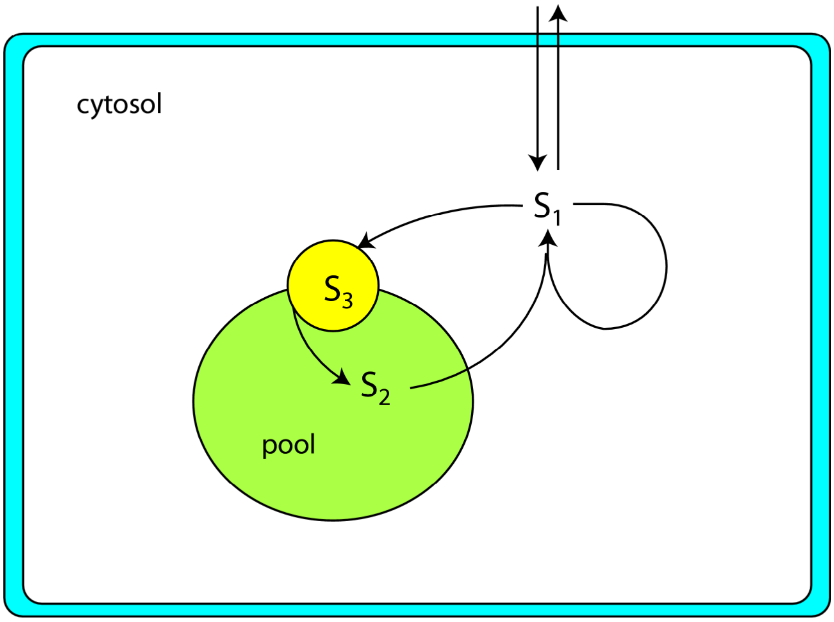

Figure 1: Schematic of the cell. S_1 is the cytosolic Ca^{2+}, S_2 is the Ca^{2+} in the pool and S_3 an enzyme which pumps it from the cytosol to the store.

0.4.1 Assumptions Underlying the Model

Figure 1 summarises the processes which govern the network which will later be analysed. Calcium in the cytosol S_1 and in only one intracellular store S_2 are considered. Calcium is pumped from the cytosol to the pool by an enzyme S_3. We denote by S_4 the complex formed between the enzyme and the calcium and assume that it obeys Michaelis-Menton type kinetics. Calcium is released from the store by CICR, namely calcium in the cytosol influences the release of calcium. The final assumption is that there is an in and outflux of the calcium from the cytosol. The above assumptions give rise to the reaction network:

$$O \rightleftharpoons^{k_{21}}_{k_{12}} S_1$$

$$S_1 + S_2 \rightarrow^{k_{43}} 2S_1 \tag{5}$$

$$S_1 + S_3 \rightleftharpoons^{k_{65}}_{k_{56}} S_4 \rightarrow^{k_{76}} S_2 + S_3$$

Assuming mass-action kinetics and letting $[S_j] = x_j$ for $j = 1, \ldots, 4$ the reaction scheme (5) can be converted into a set of coupled ordinary differential equations:

$$\begin{aligned} \frac{dx_1}{dt} &= k_{21} - k_{12}x_1 + k_{43}x_1x_2 - k_{65}x_1x_3 + k_{56}x_4 \\ \frac{dx_2}{dt} &= -k_{43}x_1x_2 + k_76x_4 \\ \frac{dx_3}{dt} &= -k_{65}x_1x_3 + k_{56}x_4 + k_{76}x_4 \\ \frac{dx_4}{dt} &= -k_{56}x_4 + k_{65}x_1x_3 - k_{76}x_4 \end{aligned} \tag{6}$$

Using conservation laws the system can be reduced by noting that $x_3(t)+x_4(t)$ is a constant. Then if the initial conditions are $x_1(0) = X_1$, $x_2(0) = X_2$, $x_3(0) = E$ and $x_4(0) = 0$, the equation for $\frac{dx_3}{dt}$ can be omitted and $x_3 = E - x_4$ substituted in to obtain

$$\begin{aligned} \frac{dx_1}{dt} &= k_{21} - k_{12}x_1 + k_{43}x_1x_2 - k_{65}x_1(E - x_4) + k_{56}x_4 \\ \frac{dx_2}{dt} &= -k_{43}x_1x_2 + k_76x_4 \\ \frac{dx_4}{dt} &= -k_{56}x_4 + k_{65}x_1(E - x_4) - k_{76}x_4 \end{aligned} \tag{7}$$

0.4.2 Non-dimensionalization of the problem

The next step in the analysis is to determine which are the variables which are varying on the time-scale of interest. We proceed as in section 0.2.

Step 1: Scale concentrations From the conservation relation it is clear that $x_4 \leq E$ for all $t \geq 0$. Bounds for x_1 and x_2 are not so easy since the network is not closed (i.e there is an in and outflux of calcium from the cytosol). To determine them it is necessary to use a comparison lemma [7]. Using the bound for x_4 and that all concentrations are non-negative yields

$$\begin{aligned} \frac{dx_1}{dt} &\leq k_{21} - k_{12}x_1 + k_{43}x_1x_2 + k_{56}E \\ \frac{dx_2}{dt} &\leq -k_{43}x_1x_2 + k_{76}E \end{aligned} \tag{8}$$

Hence by comparing (7) with the system

$$\begin{aligned}\frac{dz_1}{dt} &= k_{21} - k_{12}z_1 + k_{43}z_1z_2 + k_{56}E \\ \frac{dz_2}{dt} &= -k_{43}z_1z_2 + k_{76}E\end{aligned} \tag{9}$$

with initial conditions $z_1(0) = X_1$ and $z_2(0) = X_2$ it is trivial to prove that bounds for z_1 and z_2 will also be bounds for x_1 and x_2. From the phase portrait of system (9) shown in figure 2 it seems clear that the trajectories are bounded and in fact converge to the fixed point independent of the initial conditions. This is in fact the case as can be shown using continuity arguments to define an invariant region. Although the bounds cannot be found explicitely in this case it is clear that they will depend on the initial conditions (and of course the parameters) and hence we will denote them by $F(X_1, X_2)$ and $G(X_1, X_2)$ respectively for x_1 and x_2.

Substituting in $y_1 = \frac{x_1}{F(X_1,X_2)}$, $y_2 = \frac{x_2}{G(X_1,X_2)}$ and $y_4 = \frac{x_4}{E}$ gives

$$\begin{aligned}\frac{dy_1}{dt} &= \frac{k_{21}}{F} - k_{12}y_1 + k_{43}Gy_1y_2 - k_{65}Ey_1(1-y_4) + \frac{k_{56}E}{F}y_4 \\ \frac{dy_2}{dt} &= -k_{43}Fy_1y_2 + \frac{k_{76}}{G}y_4 \\ \frac{dy_4}{dt} &= -(k_{56}+k_{76})y_4 + k_{65}Fy_1(1-y_4)\end{aligned} \tag{10}$$

Step 2 and 3: Determining Relative Time-Scales and Time-Scale of Interest In order to do this some assumptions have to be introduced on the parameters. Here it is assumed (as in common when considering systems involving enzymes) that $E \ll X_1, X_2$. Noting that $X_1 \leq F$ and $X_2 \leq G$ the relative time-scales of each equation are $\frac{1}{k_{43}G}$, $\frac{1}{k_{43}F}$ and $\frac{1}{k_{65}F}$ for y_1, y_2 and y_4 respectively. For this example the time-scale of interest will be that of T_{y_1} since it is the calcium in the cytosol which exhibits oscillations. Hence dividing each equation by its relative time-scale and rescaling time by the time-scale of interest gives

$$\begin{aligned}\frac{dy_1}{dt} &= \frac{k_{21}}{F} - k_{12}y_1 + k_{43}Gy_1y_2 - k_{65}Ey_1(1-y_4) + \frac{k_{56}E}{F}y_4 \\ \frac{G}{F}\frac{dy_2}{dt} &= -k_{43}Gy_1y_2 + \frac{k_{76}}{F}y_4 \\ \frac{k_{43}G}{k_{65}F}\frac{dy_4}{dt} &= -\frac{k_{43}G}{k_{65}F}(k_{56}+k_{76})y_4 + k_{65}Gy_1(1-y_4)\end{aligned} \tag{11}$$

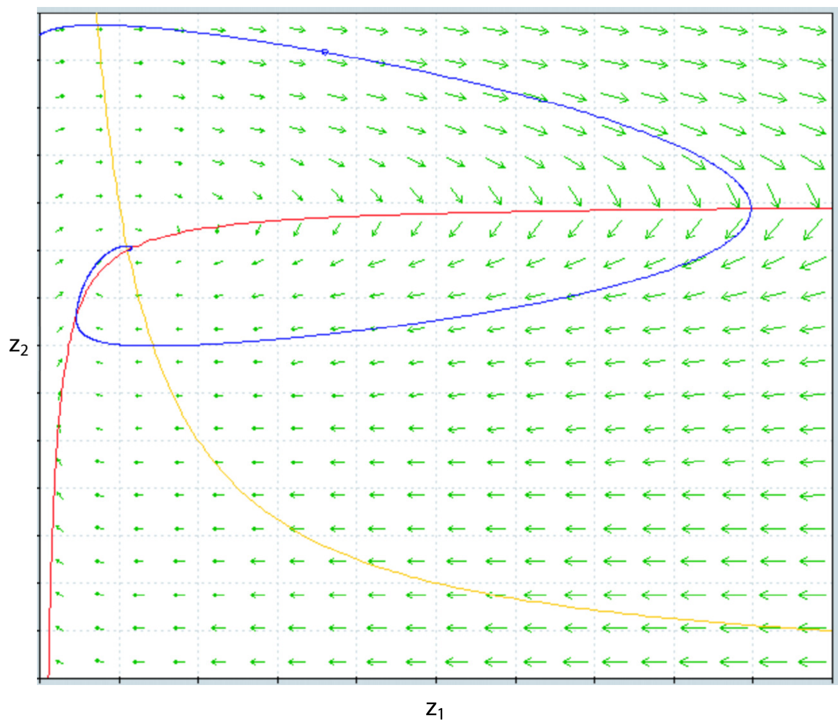

Figure 2: The phase portrait of system (9). The red line is the z_1 nullcline, the yellow line the z_2 nullcline and the blue an example of a trajectory. The green arrows show the vector field.

Step 4: Classify variables Assuming $k_{43} \ll k_{65}$ and $G \approx F$ gives that y_1 and y_2 are changing on the time-scale of interest and that y_4 is a fast variable. Thus provided that the assumptions of Tichonov's theorem are satisfied the equation for y_4 can be reduced to an algebraic one and the system reduced to a two-dimensional ODE.

0.4.3 Applying Tichonov's theorem

Letting $\frac{G}{F} = 1$ and defining $\epsilon := \frac{k_{43}}{k_{65}}$ the problem becomes

$$\begin{aligned}
\frac{dy_1}{dt} &= \frac{k_{21}}{F} - k_{12}y_1 + k_{43}Gy_1y_2 - k_{65}Ey_1(1-y_4) + \frac{k_{56}E}{F}y_4 \\
\frac{dy_2}{dt} &= -k_{43}Gy_1y_2 + \frac{k_{76}}{F}y_4 \\
\epsilon\frac{dy_4}{dt} &= -\frac{k_{43}G}{k_{65}F}(k_{56}+k_{76})y_4 + k_{65}Gy_1(1-y_4)
\end{aligned} \tag{12}$$

with initial conditions $y_1(0) = \frac{X_1}{F}$, $y_2(0) = \frac{X_2}{G}$ and $y_4(0) = 0$. The adjoint in this case is

$$\frac{dy_4}{d\tau} = -\frac{k_{43}G}{k_{65}F}(k_{56}+k_{76})y_4 + k_{65}Gy_1(1-y_4) \tag{13}$$

Clearly the first hypothesis is satisfied trivially on $\Omega = \mathbf{R}^n \times \mathbf{R}^m$. In fact this is generally true when the ODEs are derived from mass-action kinetics since the right hand side of the equations will just be polynimials. To satisfy the second assumption we need to find a root for g that is defined on a compact set. In this case it is simple as it can just be computed. It is easy to check that

$$\Phi(y_1, y_2) = \frac{k_{65}Fy_1}{k_{56} + k_{76} + k_{65}Fy_1} \tag{14}$$

satisfies $g(y_1, y_2, \Phi(y_1, y_2)) = 0$ on all of $\mathbf{R}^2$. In general if mass-action kinetics are assumed this can be shown using the Implicit Function Theorem provided $\frac{\partial g}{\partial y_4} \neq 0$ on a compact set since g is a polynomial and hence continuously differentiable. The isolation of the root also follows from the Implicit Function Theorem again provided that $\frac{\partial g}{\partial y_4} \neq 0$. This we check:

$$\begin{aligned}
\frac{\partial g}{\partial y_4} &= -\tfrac{k_{43}G(k_{56}+k_{76})}{k_{65}F} - k_{43}Gy_1 \\
&< 0 \qquad\qquad \forall y_1, y_2 \geq 0
\end{aligned}$$

This also proves hypothesis 4 i.e that the equilibrium of the adjoint is stable. Hypothesis 5 is ensured by the Basic Theorem of ODEs. This follows for the full problem since the right hand side of the equations are polynomials they are continuously differentiable and hence locally Lipshitz. It holds for the reduced problem since the Implicit Function Theorem guarantees Φ is continuously differentiable and so the existence and uniqueness of solutions follows by the same argument. Finally it remains to check that $(\frac{X_1}{F}, \frac{X_2}{G}, 0) \in \Omega$ and $(\frac{X_1}{F}, \frac{X_2}{G}) \in K$ and $(\frac{X_1}{F}, \frac{X_2}{G}, 0)$ lies in the domain of influence of the stable root $y_4 = \Phi(y_1, y_2)$. The two former conditions are obvious. Defining the parameter in the adjoint as $(\frac{X_1}{F}, \frac{X_2}{G})$ gives

$$\frac{dy_4}{d\tau} = -\frac{k_{43}G}{k_{65}F}(k_{56} + k_{76})y_4 + k_{65}G\frac{X_1}{F}(1 - y_4)$$

which is just an ODE of the form

$$\frac{dy_4}{d\tau} = -Ay_4 + B \tag{15}$$

with $A = \frac{k_{43}G(k_{56}+k_{76}+k_{65}X_1)}{k_{65}F}$ and $\frac{k_{43}GX_1}{F}$. Equation (15) has solutions of the form

$$y_4(\tau) = \frac{B}{A}(1 - e^{-A\tau}) \tag{16}$$

which tends to $\frac{B}{A} = \frac{k_{65}X_1}{k_{56}+k_{76}+k_{65}X_1}$ as $\tau \to \infty$. Now all is left to show is that $\Phi\left(\frac{X_1}{F}, \frac{X_2}{G}\right) = \frac{k_{65}X_1}{k_{56}+k_{76}+k_{65}X_1}$ but this is clear on substitution of the initial values in (14).

We can now use Tichonov's theorem for sufficiently small ϵ and reduce the system of ODEs to

$$\begin{aligned}
\frac{dy_1}{dt} &= \frac{k_{21}}{F} - k_{12}y_1 + k_{43}Gy_1y_2 - k_{65}Ey_1\left(1 - \frac{k_{65}Fy_1}{k_{56} + k_{76} + k_{65}Fy_1}\right) \\
&\quad + \frac{k_{65}k_{56}Ey_1}{k_{56} + k_{76} + k_{65}Fy_1} \\
\frac{dy_2}{dt} &= -k_{43}Gy_1y_2 + \frac{k_{65}k_{76}y_1}{k_{56} + k_{76} + k_{65}Fy_1} \\
y_4 &= \frac{k_{65}Fy_1}{k_{56} + k_{76} + k_{65}Fy_1}
\end{aligned} \tag{17}$$

Converting back to the original variables the problem becomes

$$
\begin{aligned}
\frac{dx_1}{dt} &= k_{21} - k_{12}x_1 + k_{43}x_1x_2 - k_{65}Ex_1\left(1 - \frac{k_{65}x_1}{k_{56}+k_{76}+k_{65}x_1}\right) \\
&\quad + \frac{k_{65}k_{56}Ex_1}{k_{56}+k_{76}+k_{65}x_1} \\
\frac{dx_2}{dt} &= -k_{43}x_1x_2 + \frac{k_{65}k_{76}Ex_1}{k_{56}+k_{76}+k_{65}x_1} \\
x_4 &= \frac{k_{65}Ex_1}{k_{56}+k_{76}+k_{65}Ex_1}
\end{aligned}
\tag{18}
$$

0.5 Conclusions and Final Remarks

Tichonov's theorem is one way of reducing chemical reaction systems using time-scale arguments. It is a specific form of the slow-manifold theorem. The form presented here can be generalised to include a number of different small parameters, namely when the system is of the form

$$
\begin{aligned}
\frac{dx_1}{dt} &= f_1(x_1,\ldots,x_n) \\
\epsilon_1\frac{dx_2}{dt} &= f_2(x_1,\ldots,x_n) \\
&\vdots \\
\epsilon_{n-1}\frac{dx_n}{dt} &= f_n(x_1,\ldots,x_n)
\end{aligned}
\tag{19}
$$

(20)

with $\epsilon_1 > \epsilon_2 > \ldots > \epsilon_{n-1}$. Tichonov's Second Theorem investigates the behaviour of the solutions when $\epsilon_j \to 0$ in such a way that $\epsilon_{j+1}/\epsilon_j \to 0$ (see [3]).

Bibliography

[1] TIKHONOV A.N. 1985 *Differential Equations* Springer-Verlag

[2] WASOV W. 2002 *Asymptotic Expansions for Ordinary Differential Equations* John-Wiley and sons

[3] KLONOWSKI W. 1983 Simplifying Principles for Chemical and Enzyme Reaction Kinetics *Biophysical Chemistry* 18:73-87

[4] SENSSE A. 2002 *Algebraic Methods for the Analysis of Hopf Bifurcations in Biochemical Networks* (Masters Thesis)

[5] GOLDBETER A. and DUPONT G. 1990 Allosteric Regulation, Cooperativity and Biochemical Oscillations *Biophysical Chemistry* 37:341-353

[6] GOLDBETER A. 1996 *Biochemical Oscillations and Cellular Rhythms* Cambridge University Press

[7] DELILLO N.J. 1982 *Advanced Calculus with Applications* Macmillan Publishing Co.