Perturbation theory and TQSSA

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Abstract

Perturbation theory has a long history. In recent decades we have seen many applications in enzymatic kinetics. We start with some basic polynomial examples of regular perturbation theory, progress to singular perturbation and a boundary-value problem of differential equation, and then tackle a real application in the form of Total Quasi Steady State from enzyme kinetics.

To Anna, Margo, and Yishao

Contents

1 Introduction

Perturbation theory has its roots in celestial mechanics and aerodynamics. There are two particularly interesting victories that perturbation theory has enabled. The first was the discovery of Neptune, and the second was the theoretical foundation for aerodynamics.

The promise of perturbation theory is that it allows us to find approximate solutions to a larger class of problems, for example, in differential equations, than we could otherwise with analytical methods. It does this by giving us approximate but rigorous solutions. In this article we will guide the reader from a very simple and familiar example, a quadratic equation, all the way to a useful research example in system biology: the total quasi steady state in enzyme kinetics.

The article has been written with the goal that any student with a basic understanding of calculus, differential equations and linear algebra will be able to follow along. All the relevant biology and perturbation theory will be explained as it becomes necessary.

2 A regular perturbation

We are going to start with one of the simplest non-trivial examples imaginable, a quadratic equation:

$$x^2 - 2x + \epsilon = 0. \tag{1}$$

We know how to solve this analytically. The roots of the equation are $x_1 = 1 + \sqrt{1-\epsilon}$ and $x_2 = 1 - \sqrt{1-\epsilon}$.

The case we are interested in is the one where ϵ is very small. In this case, we can see that setting $\epsilon = 0$ produces the roots $x = 0$ and $x = 2$ respectively. In fact, for any given small ϵ we notice that the solution changes very little. In that sense it's a very "boring" and predictable problem.

Can we make more rigorous the observation that a small change in ϵ only brings about a small change in the solution? One way is to rewrite the part of the solution containing ϵ as a *Taylor series*. Recall the definition of a Taylor series for a function $f(x)$ around a point a is

$$f(x) = \sum_{n=0}^{\infty} \frac{f^n(a)}{n!}(x-a)^n. \tag{2}$$

The Taylor series for $f(\epsilon) = (1-\epsilon)^{1/2}$ around 0 (since we assume that ϵ is very small) is thus

$$\sqrt{1-\epsilon} = 1 - \frac{\epsilon}{2} - \frac{\epsilon^2}{8} + O(\epsilon^3), \tag{3}$$

where $O(\epsilon^3)$ is some expression with a term ϵ^3 in it. This is called *Big-Oh* notation and it is commonly used to describe the limiting behaviour of a function. If we take the limit of this expression as $\epsilon \to 0$, it's obvious that

our intuition is correct. That is, a small change in ϵ only brings about a small change in the solution. We get

$$x_1 = 2 - \frac{\epsilon}{2} - \frac{\epsilon^2}{8} + O(\epsilon^3), \tag{4}$$

$$x_2 = \frac{\epsilon}{2} + \frac{\epsilon^2}{8} + O(\epsilon^3). \tag{5}$$

What is the point of all this? We said in the beginning that perturbation theory allows us to find approximate solutions to a larger class of problems, but what we have done so far hasn't given any indication of that being true. After all, we already have an analytical formula for the quadratic equation.

Let's start over, but this time let's assume we don't have the quadratic formula at our disposal. We will outline a method which would allow us to get arbitrarly good approximations for polynomials of any degree.

Let's assume the solutions of (1) in terms of x can be expressed in the form of some power series of ϵ, where ϵ is a small number:

$$\sum_{0}^{\infty} a_k \epsilon^k = a_0 + a_1\epsilon + a_2\epsilon^2 + ... \tag{6}$$

Another name for this type of series is *perturbation series*. We will now insert this perturbation series into (1), and then expand that expression in terms of powers of ϵ. We only have to do this for the first few terms of the perturbation series to get a decent approximation. If we want to we can always add more terms and get a more accurate approximation. We have

$$(a_0 + a_1\epsilon + a_2\epsilon^2 + ...)^2 - 2(a_0 + a_1\epsilon + a_2\epsilon^2 + ...) + \epsilon = 0. \tag{7}$$

We expand the expression using Big-Oh algebra. For example, for the first term, we get: $(a_0 + a_1\epsilon + a_2\epsilon^2)^2 = a_0^2 + 2a_0a_1\epsilon + (a_1^2 + 2a_0a_2)\epsilon^2 + O(\epsilon^3)$. The whole expression becomes

$$a_0^2 - 2a_0 + (2a_0a_1 - 2a_1 + 1)\epsilon + (a_1^2 + 2a_0a_2 - 2a_2)\epsilon^2 = O(\epsilon^3), \epsilon \to 0. \quad (8)$$

Now we turn to the problem of determining the coefficients a_0, a_1 etc. Since ϵ is treated as a variable, as opposed to as a parameter, we see that the coefficients before each power of ϵ separately all have to be equal to zero. We thus get the following system of equations for solving the coefficients:

$$a_0^2 - 2a_0 = 0, \quad (9)$$

$$2a_0a_1 - 2a_1 + 1 = 0, \quad (10)$$

$$a_1^2 + 2a_0a_2 - 2a_2 = 0. \quad (11)$$

Solving these equations in turn gives us, starting with the first equation, $a_0 = 0$ or $a_0 = 2$. For $a_0 = 0$ we have $a_1 = \frac{1}{2}$ and $a_2 = \frac{1}{8}$. For $a_0 = 2$ we have $a_1 = -\frac{1}{2}$ and $a_2 = -\frac{1}{8}$.

We said at the beginning that we assume the solution is in the form of a perturbation series. We have two options for the coefficients of this perturbation series, and these corresponds to the two approximate solutions of the original equation. From the above and (6) we get

$$x_1 = \frac{1}{2}\epsilon + \frac{1}{8}\epsilon^2 + O(\epsilon^3), \quad (12)$$

$$x_2 = 2 - \frac{1}{2}\epsilon - \frac{1}{8}\epsilon^2 + O(\epsilon^3). \quad (13)$$

This is exactly the same as our previous solutions in (4) and (5), without the use of the quadratic formula. There was nothing we did that assumed a

second degree polynomial. We have thus found a general method for finding approximate solutions to polynomials of any degree with a small parameter ϵ.

3 A singular perturbation

In the last section we dealt with a so called regular perturbation problem. In this section we will deal with a singular perturbation problem. What is the difference? In a singular perturbation problem, the small ϵ *matters* for the solution. In general, singular problems are interesting precisely because their solutions can change significantly with just a small change in circumstances. More precisely, a singular perturbation problem is one where setting ϵ to 0 doesn't give us a good approixmate solution.

A way to get some intuition in the matter is to imagine balancing a pen on a table. It's possible to get the pen to stay upright, but just a slight perturbation of the pen results in it falling in one of many directions.

As before, we will use a quadratic equation to illustrate how this works,

$$\epsilon x^2 - 2x + 1 = 0, \tag{14}$$

where ϵ is a very small number. This equation has the solutions

$$x_1 = \frac{1 + \sqrt{1 - \epsilon}}{\epsilon}, \tag{15}$$

$$x_2 = \frac{1 - \sqrt{1 - \epsilon}}{\epsilon}. \tag{16}$$

The first thing we notice is that even though ϵ is very small, we can't set it to zero. If we were to do it in (14), we would only get a one degree polynomial. The fact that we are losing solutions is a qualitative change and is indicative that we are dealing with a singular perturbation problem.

Let's try using the same method as we did before. We assume x can be expressed in the form of a perturbation series. Inserting this in our equation

gives us

$$\epsilon(a_0 + a_1\epsilon + a_2\epsilon^2)^2 - 2(a_0 + \epsilon a_1 + a_2\epsilon^2) + 1 = 0, \tag{17}$$

which gets expanded into

$$(-2a_0 + 1) + (a_0^2 - 2a_1)\epsilon + (2a_0a_1 - 2a_2)\epsilon^2 + O(\epsilon^3), \tag{18}$$

and leads to

$$-2a_0 + 1 = 0, \tag{19}$$

$$a_0^2 - 2a_1 = 0, \tag{20}$$

$$2a_0a_1 - 2a_2 = 0. \tag{21}$$

The only solution to this system of equations is $a_0 = \frac{1}{2}$, $a_1 = \frac{1}{8}$, $a_2 = \frac{1}{16}$. This gives us only one of the roots,

$$x_1 = \frac{1}{2} + \frac{1}{8}\epsilon + O(\epsilon^2). \tag{22}$$

Note that the a_2 coefficient is included in the $O(\epsilon^2)$ expression. By the *Fundamental Theorem of Algebra*, we would expect to see two solutions. What happened to the other root? We missed it because it's not on the form of a perturbation series. That is, the other solution diverges as $\epsilon \to 0$. So what do we do?

The key here is that we can do a change in variable to turn the problem into a regular perturbation problem:

$$x(\epsilon) = \frac{y(\epsilon)}{\delta(\epsilon)}. \tag{23}$$

Here we are treating x as a function, $y(\epsilon)$ is $O(1)$ and we want to determine the re-scaling factor function $\delta(\epsilon)$. Our original equation becomes

$$\frac{\epsilon}{\delta^2}y^2 - \frac{2}{\delta}y + 1 = 0. \tag{24}$$

Our goal is to simplify this equation. We do this by dropping insignificant terms. As we have seen, it turns out that the first term in the equation is not insignificant, so we have to leave it in. Is there some other term that we, to a first approximation, can drop?

All three terms in the above equation have some order of magnitude. The method of dominant balance tells us to look for pairs that balance ($\sim$), where balance means they are of the same order of magnitude. We have already determined that the first term can't be dropped, so we have two possibilities.

The first possibility is that $\frac{\epsilon}{\delta^2}y^2 \sim 1$, with $\frac{2}{\delta}$ being insignificant. $\frac{\epsilon}{\delta^2} = 1 \implies \delta = \epsilon^{\frac{1}{2}}$. But then $\frac{2}{\delta} = \frac{2}{\sqrt{\epsilon}}$ which isn't small as $\epsilon \to 0$.

The second possibility is that $\frac{\epsilon}{\delta^2}y^2 \sim \frac{2}{\delta}y$, with 1 being insignificant. This means $\frac{\epsilon}{\delta^2} = \frac{1}{\delta}$ which implies that $\delta = \epsilon$. This seems correct as both expressions are $O(\frac{1}{e})$, and 1 is small compared to this when $\epsilon \to 0$. We get

$$P(x) = \epsilon x^2 - 2x + 1, \tag{25}$$

$$\epsilon P\Big(\frac{y}{\epsilon}\Big) = y^2 - 2y + \epsilon, \tag{26}$$

where the last part is exactly the same as our regular perturbation problem in equation (1). As before, this gives us

$$y_1 = \frac{1}{2}\epsilon + \frac{1}{8}\epsilon^2 + O(\epsilon^3), \tag{27}$$

$$y_2 = 2 - \frac{1}{2}\epsilon - \frac{1}{8}\epsilon^2 + O(\epsilon^3), \tag{28}$$

which means that

$$x_1 = \frac{1}{2} + \frac{1}{8}\epsilon + O(\epsilon^2), \tag{29}$$

$$x_2 = \frac{2}{\epsilon} - \frac{1}{2} + \frac{1}{8}\epsilon + O(\epsilon^2). \tag{30}$$

The first root approaches $\frac{1}{2}$ as $\epsilon \to 0$, and the second root is our missing solution that approaches ∞ as $\epsilon \to 0$. This is the essence of singular perturbation theory - to find the singular behavior and do a change of variable to turn it into a regular perturbation problem.

4 ODE and boundary theory

Boundary layer theory has its origins in aerodynamics and the work of Prandtl. He discovered that fluids, like air around a plane and water around some obstacle flow, are almost completely void of viscosity, or stickiness, except for in a very thin region near the boundary of the plane of the obstacle. This observation meant that one could treat these two phenomena as separate problems - one where viscosity can be discarded, and one where it matters a lot - as opposed to treating it as one big complex problem. This simplified calculations greatly.

We will now give a basic example of this in the form of a *boundary value problem* with differential equations. Recall that a boundary value problem is one where we have some set of constraints that have to be fulfilled, called boundary conditions. We will again look at a problem which we could solve explicitly, but which we will instead use perturbation theory to analyze. In a boundary value problem, we have two boundary value conditions and, in a first approximation, they can't both be satisfied at the same time. The strategy we use is to split the problem in two - one where we are in a very thin region at $t = 0$ (where we have a boundary condition), the so called "inner region", and one where we are in an "outer region", which is everywhere else. This strategy is generalizable to multiple layers.

We start by looking for the outer solution, then the inner solution, then we match them together into one unified solution.

4.1 Outer solution

We are now going to look at a differential equation

$$\epsilon y'' + 2y' + y, \;\; y(0) = 0, \;\; y(1) = 1, \;\; 0 < x < 1. \tag{31}$$

If we naively set $\epsilon = 0$ we see that the resulting equation $2y' + y$ has the general solution $Ce^{-\frac{1}{2}x}$. This can't satisfy both boundary conditions at once. If it satisfies $y(0) = 0$ we have $y = 0$ as the only solution, and if it satisfies $y(1) = 1$ we have

$$y_O = e^{\frac{1}{2}(1-x)}. \tag{32}$$

We are going to assume this is a good approximation somewhere. It is valid for the $y(1) = 1$ boundary condition, so we call this the *outer solution*.

Like the example in the last section, we missed something when we set $\epsilon = 0$. We have found one of the two solutions and now we want to the find the other one with the help of pairwise balancing.

4.2 Inner solution

We are assuming the boundary layer is near 0, and that it has a thickness $\delta(\epsilon)$. By thickness we simply mean the order of magnitude where the approximation is valid. For example, in Figure 2 (see section 4.4) we can see that at $x = \delta(\epsilon) = \epsilon$ (not derived until later in this section), the difference between the approximation and the solution is negliable.

We introduce a re-scaling variable

$$\overline{x} = \frac{x}{\delta}. \tag{33}$$

Having two scales like this is typical for singular perturbation problems. Our original equation (31) becomes

$$\frac{\epsilon}{\delta^2}\frac{d^2y}{d\overline{x}^2} + \frac{2}{\delta}\frac{dy}{d\overline{x}} + y = 0. \tag{34}$$

We now do pairwise balancing, as before. Looking at the coefficients of the above equation, we have the following orders of magnitude

$$O\Big(\frac{\epsilon}{\delta^2}\Big), O\Big(\frac{1}{\delta}\Big), O(1). \tag{35}$$

We must have $\frac{\epsilon}{\delta^2}$ present, so the question is if it balance one of the other terms with one being insignificant, and if so, which one is insignificant. There are two possibilities. Either we have

$$\frac{\epsilon}{\delta^2} \sim 1 \implies \delta = \epsilon^{\frac{1}{2}}, \tag{36}$$

but then $\frac{1}{\delta}$ is big compared to 1. Or we have

$$\frac{\epsilon}{\delta^2} \sim \frac{1}{\delta} \implies \delta = \epsilon, \tag{37}$$

in which case 1 is indeed insignificant.

We have, multiplying by ϵ, the inner equation

$$\frac{d^2y}{d\overline{x}^2} + 2\frac{dy}{d\overline{x}} + \epsilon y = 0. \tag{38}$$

To a first approximation we can neglect the last term, so we have

$$\frac{d^2y}{d\overline{x}^2} + 2\frac{dy}{d\overline{x}} = 0. \tag{39}$$

Together with the other initial condition $y(0) = 0$ we get the general inner solution, valid in a region of thickness ϵ close to $x = 0$,

$$y_I = C(1 - e^{-2\overline{x}}). \tag{40}$$

We now have an outer and inner solution, and we turn to matching these to determine the value of the constant C.

4.3 Matching and uniform approximation

The idea behind *matching* is that there is some edge or region between the inner and outer solution, a region where both solutions are valid approximations. We find a *uniform approximation* by piecing together our inner and outer solution, so that we have one single expression of the solution that is valid everywhere in our interval.

The procedure we will follow works in this case, but it's worth noting that it's not always this straightforward. For more details, consult a good textbook such as Bender and Orszag [1].

If we imagine a particle tracing the x-axis rightward, as we exit the boundary layer, i.e. as $\overline{x} \to \infty$, the value of y_I should be equal to the value of y_O as $x \to 0$, that is

$$\lim_{\overline{x}\to\infty} y_I = \lim_{x\to 0+} y_O \iff \lim_{\overline{x}\to\infty} C(1 - e^{-2\overline{x}}) = \lim_{x\to 0+} e^{\frac{1}{2}(1-x)}. \tag{41}$$

This is called a *matching condition*. The right-hand side equals $e^{\frac{1}{2}}$, and thus the left-hand side gives us that $C = e^{\frac{1}{2}}$.

We now have two separate approximations. We would like to have one single approximation that is valid everywhere. We do this by adding the two approximations together and removing their common part to avoid double counting. Intuitively, one of the approximations is great close to one of the boundary conditions, ok in the middle, and terrible close to the other boundary conditions. The other approximation is exactly the opposite. By combining them, we get a smooth approximation of the whole solution:

$$y_U = y_o(x) + y_I\Big(\frac{x}{\delta}\Big) - e^{\frac{1}{2}}. \tag{42}$$

The common part comes from the matching condition earlier in this section. In the inner region the other terms are negliable, and vice versa in the outer region,

$$y_U = e^{\frac{1}{2}(1-x)} + e^{\frac{1}{2}}(1 - e^{\frac{-2x}{\epsilon}}) - e^{\frac{1}{2}} \tag{43}$$

$$= e^{\frac{1}{2}}(e^{\frac{-x}{2}} - e^{\frac{-2x}{\epsilon}}). \tag{44}$$

This is our uniform approximation for the whole solution. We can compare this to the exact solution and see that it is indeed a good approximation.

4.4 Comparison with exact solution

We saw in the previous section what a good approximation to the solution is. Our original equation (31) can however be solved exactly, so let's do that.

The *characteristic polynomial* $\epsilon r^2 + 2r + 1 = 0$ has the solutions $\frac{-1\pm\sqrt{1-\epsilon}}{\epsilon}$. We have that

$$y_\epsilon(x) = c_1 e^{\frac{-1+\sqrt{1-\epsilon}}{\epsilon}x} + c_2 e^{\frac{-1-\sqrt{1-\epsilon}}{\epsilon}x}. \tag{45}$$

With the help of the boundary conditions $y(0) = 0, y(1) = 1$ we see that

$$c_2 = -c_1 = -\frac{1}{e^{\frac{-1+\sqrt{1-\epsilon}}{\epsilon}} - e^{\frac{-1-\sqrt{1-\epsilon}}{\epsilon}}}. \tag{46}$$

We use a Taylor expansion as before and define

$$\alpha_1 = \frac{1-\sqrt{1-\epsilon}}{\epsilon} = \frac{1}{2} + O(\epsilon), \tag{47}$$

$$\alpha_2 = 1 + \sqrt{1-\epsilon} = 2 + O(\epsilon). \tag{48}$$

We can then express the solution as

$$y_\epsilon(x) = \frac{1}{e^{-\alpha_1(\epsilon)} - e^{\frac{-\alpha_2(\epsilon)}{\epsilon}}}\left(e^{-\alpha_1(\epsilon)x} - e^{\frac{-\alpha_2(\epsilon)x}{\epsilon}}\right). \tag{49}$$

There are two terms in this solution. As $\epsilon \to 0+$, for fixed $x \in (0,1)$, all the expressions involving division by ϵ disappear, i.e. all the a_2 terms. The solution becomes

$$y_\epsilon(x) \to \frac{e^{\frac{-x}{2}}}{e^{\frac{-1}{2}}} = e^{\frac{1}{2}(1-x)}. \tag{50}$$

This is exactly the outer solution we got before in (32), satisfying $y(1) = 1$ but not $y(0) = 0$.

Notice that the above is just valid for a fixed x, as we will see below. If we instead take (49) and notice that, for arbitrarily small ϵ, $e^{-\frac{\alpha_2(\epsilon)}{\epsilon}}$ is 0. The exact solution is thus (we distinguish between an approximation of the exact solution, and the outer approximation):

$$y_\epsilon(x) \approx e^{\frac{1}{2}}(e^{-\frac{x}{2}} - e^{-\frac{2x}{\epsilon}}), \quad 0 < \epsilon \ll 1. \tag{51}$$

When we graph (50) and (51) for any given ϵ we see that, outside of a small region near 0, the outer approximation is indeed a good approximation. We get the second graph by doing the same thing for the inner solution.

For the first graph, note that the outer approximation starts at $y(0) = e^{\frac{1}{2}}$, and thus misses the contribution ϵ has on the solution for very small x values.

For the second graph, notice the agreement between the exact and inner approximation in a region close to $x = 0$ (which we can move arbitrarily closer by using a smaller ϵ).

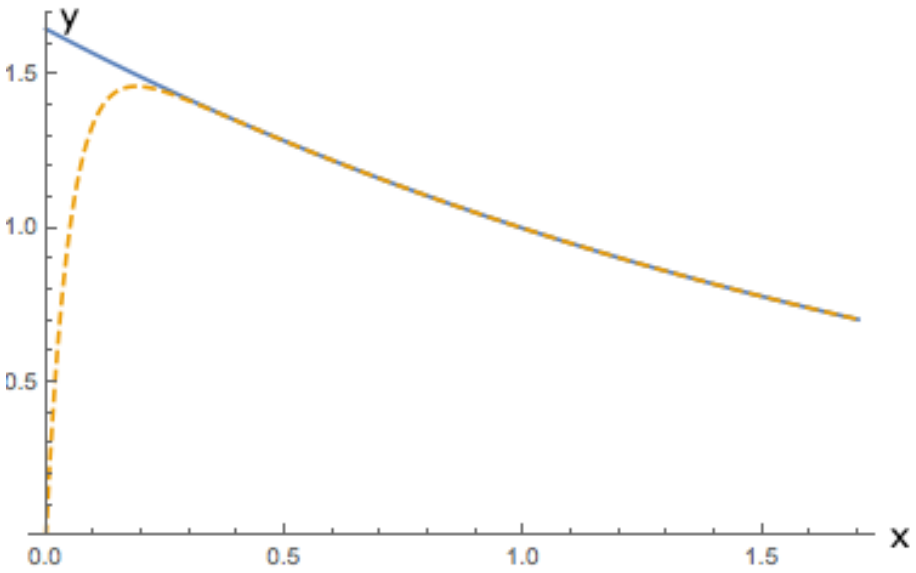

Figure 1: The full line is the outer approximation, $\epsilon = 0.1$.

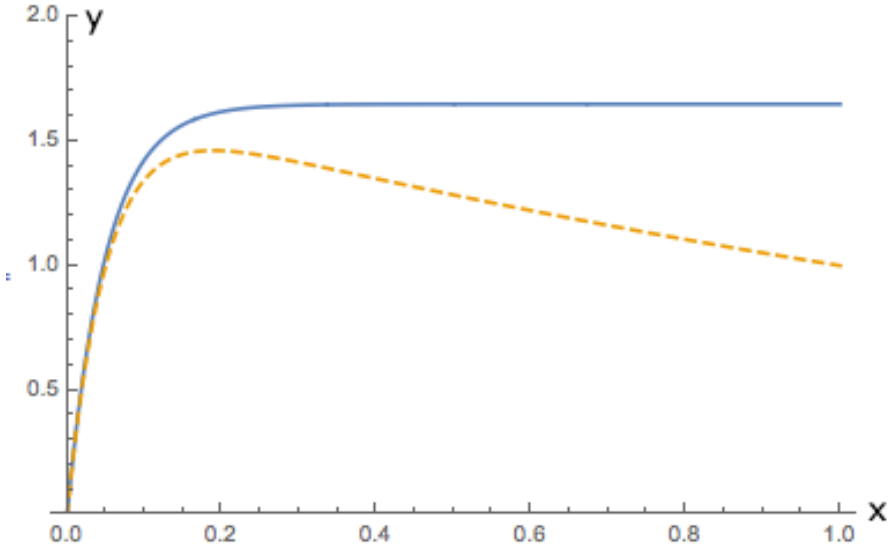

Figure 2: The full line is the inner approximation, $\epsilon = 0.1$.

5 Total Quasi Steady State

5.1 A biological problem

In enzyme kinetics we often come across chemical reactions like

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \xrightarrow{k_2} E + P \tag{52}$$

This is an enzyme E and substrate S that combine, reversibly, to form a complex C, which in turn gives us a product P and enzyme E back. k_1, k_{-1}, k_2 are rate constants. We won't bother with the biological details too much, but will instead look at how we can analyze the above as a dynamical system.

The *law of mass action* tells us that two molecules A and B forming complex C, $A + B \xrightarrow{k} C$ are governed by $\frac{dC}{dt} = kAB$. That is, the greater concentration of A or B we have, the faster the complex C is formed. This has been experimentally verified by Guldberg and Waage in 1867, and many times since.

With this law, we can translate our chemical reaction into a system of differential equations:

$$\frac{dE}{dt} = -k_1 ES + k_{-1} C + k_2 C, \tag{53}$$

$$\frac{dS}{dt} = -k_1 ES + k_{-1} C, \tag{54}$$

$$\frac{dC}{dt} = k_1 ES - k_{-1} C - k_2 C, \tag{55}$$

$$\frac{dP}{dt} = k_2 C. \tag{56}$$

In the study of enzyme kinetics, we normally have some initial conditions to help us out: $S(0) = S_0, E(0) = E_0, C(0) = 0, P(0) = 0$.

We see immediately that

$$\frac{dE}{dt} + \frac{dC}{dt} = 0. \tag{57}$$

Together with the initial conditions we get that

$$E + C = E_0, \tag{58}$$

which we can use to eliminate E from the equation. This is called a conservation law. We also don't care about P, as it doesn't feed back into the other equations. We are left with

$$\frac{dS}{dt} = -k_1(E_0 - C)S + k_{-1}C, \tag{59}$$

$$\frac{dC}{dt} = k_1(E_0 - C)S - k_{-1}C - k_2C. \tag{60}$$

This is a two-dimensional system, which is much easier to deal with. Can we do better? It turns out we can.

Very often, in practice, the substrate has a much higher concentration than the enzyme. This means that C can be treated as constant after a short initial period. By exploiting this fact, we can reduce the system to one equation. This is called the *Quasi-Steady State approximation.*

Assume that C is constant $\iff \frac{dC}{dt} = 0$ after a short period of time. Then we write

$$\frac{dS}{dt} = -k_2C \tag{61}$$

with

$$C = \frac{E_0S}{K_m + S}, \tag{62}$$

where $K_m = \frac{k_{-1}+k_2}{k_1}$ is the so called Michaelis-Menten constant. We have

$$\frac{dS}{dt} = -\frac{k_2E_0S}{K_m + S} \tag{63}$$

together with $S(0) = S_0$ as initial condition. This is what is normally considered the QSSA, valid after some short amount of time has passed.

We can justify this with a procedure similar to one in the previous section, as done by for example Lin and Segel [5]. Instead we are going to look at a slight variation of this, namely what happens when the amount of substrate isn't much bigger than the amount of enzyme. This is the *Total Quasi Steady State assumption*, discovered by Borghans and Segel 1996 [2].

5.2 TQSSA

The basic idea behind TQSSA is to perform a change of variable

$$\overline{S} = S + C. \tag{64}$$

This change of variable makes the approximation valid not just when the substrate has a much higher concentration than the enzyme, but also, under certain conditions, when they are roughly equal. This makes the TQSSA valid for a wider range of parameters. We will see in the next few sections what those conditions are.

We get the following system of equations from (59), (60) and (64)

$$\frac{d\overline{S}}{dt} = -k_2 C, \tag{65}$$

$$\frac{dC}{dt} = k_1(E_0 - C)(\overline{S} - C) - (k_{-1} + k_2)C. \tag{66}$$

Together with initial conditions $\overline{S}(0) = S_0, C(0) = 0$, these are the rate equations for the TQSSA.

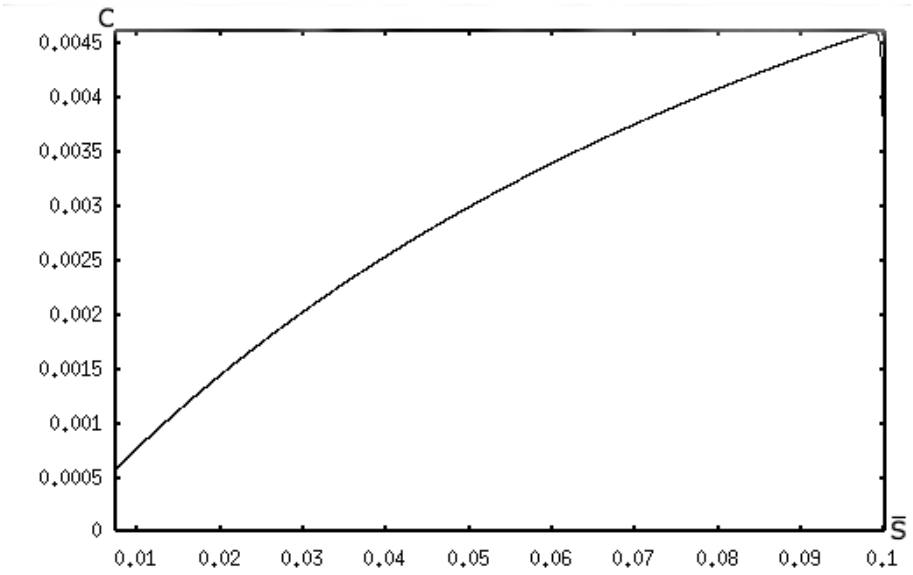

Figure 3: TQSSA phase plane. Initial state is $\overline{S}(0) = 0.1, C(0) = 0$. $E = 0.01, k_1 = 10, k_{-1} = 1, k_2 = 0.1$.

We get some intuition of the behavior by inspecting the phase plane of the above equations. With the help of XPP (see appendix for the source code used), we can numerically simulate the system, as seen in Figure 3. There are two things to note: (1) the steady state is at (0,0) (not shown in graph due to numerical rounding error, but this can easily be seen looking at the equations above) and (2) from the initial state there's a rapid increase of concentration in the complex C, after which it slowly decreases (quasi-steady state) until it reaches steady state

The rapid increase of concentration in the complex C is just barely visible in the top right corner. It can also be seen by looking at the initial conditions, and then noticing that right after that the line is in the top right corner.

5.3 Timescales

To analyze the problem rigorously using perturbation theory, we need to find an expression that estimates these two time scales that the system is operating with, t_C for the fast initial period and $t_{\overline{S}}$ for the slow quasi-steady state period.

One way to get some intuition behind the use of different time scales is to think about the difference between seconds and years. Some phenomena happens on the scale of seconds or less, like many chemical reaction, whereas the development of cities happens on a scale of years. If you blink, the city landscape isn't going to change before your eyes. Using different time scales is a way to capture that observation in a rigorous fashion.

We are first going to calculate the timescales for the normal QSSA, to get some intuition for the concept. We will then extend this to the TQSSA. Exactly why these timescales are good is not obviously, but as we move into the next section on Scaling the reasons will hopefully become more clear. Essentially it's about finding good approximations for when the (T)QSSA is valid.

To get the fast time scale, we can estimate S as S_0 since in that time period the substrate concentration won't change much and we just care about rough orders of magnitudes for the timescales. From (60) we get

$$\frac{dC}{dt} = k_1 E_0 S_0 - (k_1 S_0 + k_{-1} + k_2)C. \tag{67}$$

With the help of the initial condition $C(0) = 0$, we get the solution

$$C(t) = A(1 - e^{\lambda x}), \quad \lambda = (-S_0 k_1 + k_{-1} + k_2), \quad A = \frac{k_1 E_0 S_0}{S_0 k_1 + k_{-1} + k_2}. \tag{68}$$

The timescale here is $t_C = |\lambda^{-1}|$, which we can rewrite as

$$t_C = \frac{1}{k_1(S_0 + K_m)}. \tag{69}$$

To get the other time scale we first use that $dC/dt = 0$ after some period of time, which is the time period we care about. We get t_s with the help of an estimation technique by Segel [6]. This technique tells us to take $S_{\max} - S_{\min} = S_0$ divided by the maximum of $|dS/dt|$ using $S = S_0$ in (63). This gives us

$$t_s = \frac{S_{\max} - S_{\min}}{|dS/dt|_{\max}} \tag{70}$$

$$= \frac{K_m + S_0}{k_2 E_0}. \tag{71}$$

So far we have only derived timescales for the normal QSSA. To get the timescales for TQSSA, we use the substitution from (64). By doing so, and assuming $\frac{dC}{dt} = 0$ as before, (66) becomes

$$C^2 - (E_0 + K_m + \overline{S})C + E_0\overline{S} = 0. \tag{72}$$

We define a function f with the goal of solving for C as

$$f(C) = C^2 - (E_0 + K_m + \overline{S})C + E_0\overline{S}. \tag{73}$$

If we have a quadratic equation $x^2 + bx + c$, assuming there are two roots x_1 and x_2, then the quadratic equation can be factored into $(x - x_1)(x - x_2)$, where

$$x_1 x_2 = c. \tag{74}$$

Is there a unique positive solution to (74)? No. We know $f(0) = E_0\overline{S} > 0$, since a concentration can never be less than 0, and we know from the above identity that $c_1c_2 = E_0\overline{S}$. Thus, assuming c_1, c_2 are solutions, $c_1c_2 > 0$, which in turn implies that both roots are positive or both roots are negative.

Are there positive solutions? Yes. We have:

$$f(0) = E_0\overline{S} > 0, \tag{75}$$

$$f(E_0) = E_0^2 - (E_0 + K_m + \overline{S})E_0 + E_0\overline{S} \tag{76}$$

$$= -K_mE_0 < 0. \tag{77}$$

Using the Intermediate Value Theorem for continuous functions, there must be a number $c_1 \in (0, E_0)$, such that $f(c_1) = 0$ is a solution. Moreover, since we are dealing with a real polynomial, the Complex Conjugate Root Theorem says that the complex roots appear in pair. Together with what we saw above, this implies that both c_1 and c_2 are positive.

With this we get the following inequalities. First, the discriminant of f(c) is positive:

$$(E_0 + K_m + \overline{S})^2 - 4E_0\overline{S} > 0. \tag{78}$$

For a quadratic equation x^2+bx+c, we have another identity for its roots:

$$x_1 + x_2 = \frac{-b + \sqrt{b^2 - 4c}}{2} + \frac{-b - \sqrt{b^2 - 4c}}{2} = -b. \tag{79}$$

Hence

$$c_1 + c_2 = E_0 + K_m + \overline{S} \iff c_2 = E_0 + K_m + \overline{S} - c_1. \tag{80}$$

And we have our second set of inequalities:

$$c_1 < E_0 \qquad \implies c_2 > K_m + \overline{S}, \tag{81}$$

$$c_1 > 0 \qquad \implies c_2 < E_0 + K_m + \overline{S}. \tag{82}$$

With these inequalities, we can position the roots as follows:

$$0 < c_1 < E_0, \tag{83}$$

$$0 < K_m + \overline{S} < c_2 < E_0 + K_m + \overline{S}. \tag{84}$$

If $E_0 < K_m + \overline{S}$ there is only one solution that satisfies the conservation law (58), since for c_2 we would have a contradiction (since E can't be negative):

$$0 < E_0, \;\; E_0 = E + c_2, \tag{85}$$

$$E_0 < K_m + \overline{S} < c_2 \implies E < 0. \tag{86}$$

Assuming that the condition above holds, we thus have as our only solution

$$c_1(\overline{S}) = \frac{E_0 + K_m + \overline{S} - \sqrt{(E_0 + K_m + \overline{S})^2 - 4E_0\overline{S}}}{2}. \tag{87}$$

We want to investigate what happens when $\overline{S}$ is very large. Multiplying both sides with the conjugate we get

$$c_1(\overline{S}) = \frac{E_0\overline{S}}{E_0 + K_m + \overline{S} + \sqrt{(E_0 + K_m + \overline{S})^2 - 4E_0\overline{S}}}, \tag{88}$$

$$= \frac{2E_0}{\frac{E_0+K_m}{\overline{S}} + 1 + \sqrt{(\frac{E_0+K_m}{\overline{S}} + 1)^2 - \frac{4E_0}{\overline{S}}}} \to E_0 \text{ as } \overline{S} \to \infty. \tag{89}$$

Since we always have that $(E_0 + K_m + \overline{S})^2 \geq E_0\overline{S}$ we can rewrite (89),

$$c_1 = \frac{2E_0\overline{S}}{(E_0 + K_m + \overline{S}) + (E_0 + K_m + \overline{S})\sqrt{1 - \frac{4E_0\overline{S}}{(E_0+K_m+\overline{S})^2}}} \tag{90}$$

$$= \frac{2E_0\overline{S}}{\Big(E_0 + K_m + \overline{S}\Big)\Big(1 + \sqrt{1 - \frac{4E_0\overline{S}}{(E_0+K_m+\overline{S})^2}}\Big)}. \tag{91}$$

Recall that for an expression like $\sqrt{1-x}$ the Taylor expansion around $x = 0$ is $1 - O(x)$. This converges for $|x| < 1$. In our case that means we can simplify the above as

$$c_1 = \frac{2E_0\overline{S}}{\Big(E_0 + K_m + \overline{S}\Big)\Big(1 + \Big(1 - O\Big(\frac{4E_0\overline{S}}{(E_0+K_m+\overline{S})^2}\Big)\Big)\Big)} \tag{92}$$

$$\approx \frac{E_0\overline{S}}{E_0 + K_m + \overline{S}}. \tag{93}$$

Let's now look at when the following inequality holds

$$(E_0 + K_m + \overline{S})^2 \gg E_0\overline{S}. \tag{94}$$

This is equivalent to

$$1 \ll \frac{(E_0 + K_m + \overline{S})^2}{E_0\overline{S}} = \frac{(E_0 + K_m + \overline{S})}{E_0}\frac{(E_0 + K_m + \overline{S})}{\overline{S}} \tag{95}$$

$$= \Big(1 + \frac{K_m}{E_0} + \frac{\overline{S}}{E_0}\Big)\Big(1 + \frac{E_0}{\overline{S}} + \frac{K_m}{\overline{S}}\Big). \tag{96}$$

This is true both when $\overline{S}$ is sufficiently large and when it is sufficiently small compared to E_0.

If $\overline{S} = E_0$ then

$$\Big(1 + \frac{K_m}{E_0} + \frac{\overline{S}}{E_0}\Big)\Big(1 + \frac{E_0}{\overline{S}} + \frac{K_m}{\overline{S}}\Big) = \Big(2 + \frac{K_m}{E_0}\Big)\Big(2 + \frac{K_m}{E_0}\Big) \gg 1. \tag{97}$$

So if $E_0 < K_m + \overline{S}$ our approximation (94) is possible.

Doing calucations similar to what we did in beginning of this section, using equation (94), we eventually end up with these two slightly modified time-scales:

$$t_C = \frac{1}{k_1(E_0 + S_0 + K_m)}, \tag{98}$$

$$t_{\overline{S}} = \frac{E_0 + S_0 + K_m}{k_2 + E_0}, \tag{99}$$

with $K_m = \frac{k_{-1}+k_2}{k_1}$ as before. We will now analyze this problem like we did in section 4. But first, we have to scale the system using our newly discovered timescales.

5.4 Scaling

Lin and Segel defines *scaling* as follows:

Scaling amounts to nondimensionalizing so that relative magnitude of each term is indicated by a dimensionless factor preceding that term [5].

We will now introduce scaled, dimensionless variables. We get these variables by dividing by their respective scales. We have the two time variables

$$\tau = \frac{t}{t_C}, \tag{100}$$

$$T = \frac{t}{t_{\overline{S}}}, \tag{101}$$

where τ is the fast time scale, and T the slow one. We also scale C and $\overline{S}$ by

their maximum:

$$c = \frac{C}{C_0}, \tag{102}$$

$$s = \frac{\overline{S}}{S_0}. \tag{103}$$

S_0 is max since S starts from some constant value S_0 and then turns into the complex C, as we saw before. We derive C's max, C_0, by using the approximation we got for C in (94) and $S = S_0$:

$$C_0 = \frac{E_0 S_0}{E_0 + S_0 + K_m}. \tag{104}$$

5.5 Outer solution

Now we need a small parameter ϵ to begin looking for the outer solution, when the complex changes slowly. A necessary condition for the TQSSA to hold is $0 < \epsilon \ll 1$ where

$$\epsilon = \frac{t_C}{t_{\overline{S}}} = \frac{k_2 E_0}{k_1 (E_0 + S_0 + K_m)^2}. \tag{105}$$

This comes from Borghans, and it makes sense given what we have learned about timescales - you can only treat a city landscape as static if you are looking at it on a short timescale. Assuming $t_C \ll t_{\overline{S}}$ we will calculate for the outer region, using the procedure by Khoo and Heglund [4]. Translating equation (65) and (66) with the help of the above equations and the chain rule,

$$\frac{dc}{dT} = \frac{dC}{dt} \frac{dt}{dT} \frac{dc}{dC}, \tag{106}$$

we get

$$\frac{dc}{dT} = \frac{t_{\overline{S}}}{C_0}\Big[k_1\Big(E_0S_0s - (E_0 + S_0s + K_m)C_0c + (C_0c)^2\Big)\Big] \tag{107}$$

$$= \frac{(E_0 + S_0 + K_m)^2k_1}{(k_2 + E_0)}\Big(s - \frac{E_0 + S_0s + K_m}{E_0 + S_0 + K_m}c + \frac{(C_0)^2}{E_0S_0}c^2\Big) \tag{108}$$

$$= \frac{1}{\epsilon}\Big(s - \frac{E_0 + S_0s + K_m}{E_0 + S_0 + K_m}c + \gamma c^2\Big) \tag{109}$$

with

$$\gamma = \frac{(C_0)^2}{E_0S_0} = \frac{E_0S_0}{(E_0 + S_0 + K_m)^2}. \tag{110}$$

We now have an equation of the form

$$\epsilon\frac{dc}{dT} = \gamma c^2 - \frac{E_0 + S_0s + K_m}{E_0 + S_0 + K_m}c + s. \tag{111}$$

We also note that as $\gamma \to 0$, $\epsilon \to 0$.

Similarly to what we saw in Section 3, as $\epsilon \to 0$, we have that

$$\gamma c^2 - \frac{E_0 + S_0s + K_m}{E_0 + S_0 + K_m}c + s = 0. \tag{112}$$

As justified in (95) to (98), $\gamma \ll 1$ when $\overline{S}$ is sufficiently large or small compared to E_0. Recall what we learned in Section 3. We have established that, under certain conditions, the quadratic equation has only one solution. Our above quadratic is, to a first approximation, thus

$$s - \frac{E_0 + S_0s + K_m}{E_0 + S_0 + K_m}c = 0. \tag{113}$$

Thus we obtain our outer solution (note the subscript 'O' as in the author's first name):

$$c_O = \frac{E_0 + S_0 + K_m}{E_0 + S_0s + K_m}s. \tag{114}$$

If we substitute this into equation (65), after scaling for the slow timescale, we get an expression for the outer solution of s:

$$\frac{ds}{dT} = -\frac{E_0 + S_0 + K_m}{E_0 + S_0 s + K_m} s, \;\; s(0) = 1. \tag{115}$$

We can solve this by separation of variables:

$$\int \frac{E_0 + S_0 s + K_m}{(E_0 + S_0 + K_m)s} ds = \int -dT. \tag{116}$$

The left hand side is an equation of the form:

$$\int \frac{a + bx + c}{(a + b + c)x} dx \quad [\text{u = a + bx + c}] \tag{117}$$

$$\iff \frac{1}{a + b + c} \int \frac{u}{u - a - c} du \tag{118}$$

$$\iff \frac{1}{a + b + c} \int \Big(\frac{a + c}{u - a - c} + 1 \Big) du \tag{119}$$

$$\iff \frac{a + c}{a + b + c} \int \frac{1}{u - a - c} du + \frac{1}{a + b + c} \int 1 du \tag{120}$$

$$\iff \frac{(a + c) \ln x}{a + b + c} + \frac{bx}{a + b + c} + \text{constant}. \tag{121}$$

This makes the solution to (117)

$$\frac{E_0 + K_m}{E_0 + S_0 + K_m} \ln s + \frac{S_0}{E_0 + S_0 + K_m} s = -T + \text{constant}. \tag{122}$$

Using the initial condition $s(0) = 1$, and the fact that $t = 0$, we get the constant

$$\frac{S_0}{E_0 + S_0 + K_m}. \tag{123}$$

This gives us the outer solution for s, s_O:

$$(E_0 + K_m) \ln s_O(T) + S_0(s_O(T) - 1) + (E_0 + S_0 + K_m)T = 0. \tag{124}$$

5.6 Inner solution

The outer solution can't satisfy the initial conditions for our problem, which is why we have an inner solution where the complex changes quickly. Proceeding as with the outer solution, we scale (65):

$$\frac{ds}{d\tau} = \frac{t_C}{S_0}\Big(- k_2 C_0 c\Big) \tag{125}$$

$$= \frac{-k_2 E_0}{k_1(E_0 + S_0 + K_m)^2} c \tag{126}$$

$$= \epsilon c. \tag{127}$$

As $\epsilon \to 0$, the above becomes $\frac{ds}{d\tau} = 0$. That is, s is approximately constant at this fast time scale. Together with the initial condition $s(0) = 1$, we have the inner solution for s

$$s_I(\tau) = s(0) = 1. \tag{128}$$

For c we get, using $s = s_I = 1$,

$$\frac{dc}{d\tau} = \frac{t_C}{C_0}\Big(k_1 E_0 S_0 s - k_1 C_0 (E_0 + S_0 s + K_m)c + k_1 C_0^2 c^2\Big) \tag{129}$$

$$= -\gamma c^2 - c + 1. \tag{130}$$

We solve this by separation of variables, like before:

$$\frac{dc}{-\gamma c^2 - c + 1} = d\tau. \tag{131}$$

By Bézout's identity for polynomials, there exists polynomials C and D such that

$$\frac{1}{P(x)Q(x)} = \frac{C}{Q(x)} + \frac{D}{P(x)}, \tag{132}$$

where $CP+DQ=1$. We will use this in the partial fraction step below.

Let $\Delta = 1+4\gamma$. We investigate the denominator in (132):

$$-\gamma c^2 - c + 1 = -\gamma\Big(c - \frac{-1+\sqrt{\Delta}}{2\gamma}\Big)\Big(c + \frac{1+\sqrt{\Delta}}{2\gamma}\Big) \tag{133}$$

$$\implies \frac{1}{-\gamma c^2 - c + 1} = \frac{1}{-\gamma\Big(c - \frac{-1+\sqrt{\Delta}}{2\gamma}\Big)\Big(c + \frac{1+\sqrt{\Delta}}{2\gamma}\Big)} \tag{134}$$

$$= -\frac{1}{\sqrt{\Delta}}\left(\frac{1}{c - \frac{-1+\sqrt{\Delta}}{2\gamma}} - \frac{1}{c + \frac{1+\sqrt{\Delta}}{2\gamma}}\right) \quad \text{(see above identity).} \tag{135}$$

Integrating (132) we get

$$\frac{-1}{\sqrt{\Delta}}\Big(\int \frac{dc}{c - \frac{\sqrt{\Delta}-1}{2\gamma}} - \int \frac{dc}{c + \frac{\sqrt{\Delta}+1}{2\gamma}}\Big) = \tau + \text{constant} \tag{136}$$

$$\iff \frac{-1}{\sqrt{\Delta}} \ln\left|\frac{c - \frac{\sqrt{\Delta}-1}{2\gamma}}{c + \frac{\sqrt{\Delta}+1}{2\gamma}}\right| = \tau + \text{constant} \tag{137}$$

$$\iff \frac{1}{\sqrt{\Delta}} \ln\left|\frac{c + \frac{\sqrt{\Delta}+1}{2\gamma}}{c - \frac{\sqrt{\Delta}-1}{2\gamma}}\right| = \tau + \text{constant} \tag{138}$$

$$\iff \ln\left|\frac{2\gamma c + \sqrt{\Delta} + 1}{2\gamma c - \sqrt{\Delta} + 1}\right| = (\tau + \text{constant})\sqrt{\Delta}. \tag{139}$$

Note that $|-\sqrt{\Delta}+1| = \sqrt{\Delta}-1$. $c(0)=0$ makes the constant

$$\frac{1}{\sqrt{\Delta}} \ln\frac{\sqrt{\Delta}+1}{\sqrt{\Delta}-1}, \tag{140}$$

which gives us

$$\ln\left|\frac{2\gamma c + \sqrt{\Delta} + 1}{2\gamma c - \sqrt{\Delta} + 1}\right| = \tau\sqrt{\Delta} + \ln\frac{\sqrt{\Delta}+1}{\sqrt{\Delta}-1} \tag{141}$$

$$\implies \left|\frac{2\gamma c + \sqrt{\Delta} + 1}{2\gamma c - \sqrt{\Delta} + 1}\right| = \frac{\sqrt{\Delta}+1}{\sqrt{\Delta}-1} \mathrm{e}^{\sqrt{\Delta}\tau}. \tag{142}$$

Note that $2\gamma c + \sqrt{\Delta} + 1 > 1 > 0$ and $2\gamma c - \sqrt{\Delta} + 1 < 0$. That the second inequality is true is not obvious, but we will see that this is indeed the case in the next section.

We then have:

$$(2\gamma c + \sqrt{\Delta} + 1)(\sqrt{\Delta} - 1) = (\sqrt{\Delta} - 2\gamma c - 1)(\sqrt{\Delta} + 1)e^{\sqrt{\Delta}\tau} \tag{143}$$

$$\iff 2\gamma c(\sqrt{\Delta} - 1) + 4\gamma = \Big(- 2\gamma c(\sqrt{\Delta} + 1) + 4\gamma\Big)e^{\sqrt{\Delta}\tau} \tag{144}$$

$$\iff c(\sqrt{\Delta} - 1) + c(\sqrt{\Delta} + 1)e^{\sqrt{\Delta}\tau} = 2(e^{\sqrt{\Delta}\tau} - 1) \tag{145}$$

$$\implies c_I(\tau) = \frac{2(e^{\sqrt{\Delta}\tau} - 1)}{(\sqrt{\Delta} + 1)e^{\sqrt{\Delta}\tau} + (\sqrt{\Delta} - 1)} \tag{146}$$

$$\iff c_I(\tau) = \frac{2(e^{\sqrt{1+4\gamma}\tau} - 1)}{(\sqrt{1+4\gamma} + 1)e^{\sqrt{1+4\gamma}\tau} + \sqrt{1+4\gamma} - 1}, \tag{147}$$

which is our inner solution for c. Note that this is a different result from what Khoo and Heglund got. It seems as if their result is incorrect.

5.7 Matching and uniform approximation

As before in section 4.3, we are looking for a common limit, and our matching condition as $\epsilon \to 0$, $\tau \to \infty$, and $T \to 0$ is

$$\lim_{\epsilon \to 0}[y_O(T)|_{T=0}] = \lim_{\epsilon \to 0}[y_I(\tau)|_{\tau=\infty}]. \tag{148}$$

For the substrate s this is

$$\lim_{\epsilon \to 0}[s_O(T)|_{T=0}] = \lim_{\epsilon \to 0}[s_I(\tau)|_{\tau=\infty}] \tag{149}$$

$$\iff \lim_{\epsilon \to 0}[s_O(T)|_{T=0}] = \lim_{\epsilon \to 0} 1. \tag{150}$$

We don't have an explicit expression for s_O, but the right hand side above is obviously 1, and evaluating the implicit expression for $s_O(0)$ from (125) we see that $s_O(0) = 1$ is indeed a solution:

$$(E_0 + K_m) \ln s_O(0) + S_0(s_O(0) - 1) = 0. \tag{151}$$

The matching condition in (149) is thus simply equal to 1.

For the complex c we have

$$\lim_{\epsilon \to 0}[c_O(T)|_{T=0}] = \lim_{\epsilon \to 0}[c_I(\tau)|_{\tau=\infty}]. \tag{152}$$

For $c_O(T)$ at $T = 0$ we have

$$c_O(0) = \frac{E_0 + S_0 + K_m}{E_0 + S_0 s(0) + K_m} s(0) \tag{153}$$

$$= \frac{E_0 + S_0 + K_m}{E_0 + S_0 + K_m} \tag{154}$$

$$= 1 \text{ as } \epsilon \to 0. \tag{155}$$

As we established earlier, $\gamma \ll 1$.We use this to proceed similarly to how we did in (92) to (94), and approximate the expression $\sqrt{1+4\gamma}$ as $1+O(1+4\gamma) \approx 1$ as $\gamma \to 0$. We then have for $c_I(\tau)$:

$$c_I(\tau) = \frac{2(e^{\sqrt{1+4\gamma}\tau} - 1)}{(\sqrt{1+4\gamma}+1)e^{\sqrt{1+4\gamma}\tau} + \sqrt{1+4\gamma} - 1} \tag{156}$$

$$= \frac{2(e^{(1+O(1+4\gamma))\tau} - 1)}{(2+O(1+4\gamma))e^{(1+O(1+4\gamma))\tau} + O(1+4\gamma)} \tag{157}$$

$$\approx \frac{2(e^{\tau} - 1)}{(2+O(1+4\gamma))e^{\tau}} \tag{158}$$

$$= \frac{2(1 - \frac{1}{e^{\tau}})}{2+O(1+4\gamma)} \tag{159}$$

$$= \frac{2(1 - \frac{1}{e^{\tau}})}{1+\sqrt{1+4\gamma}} \to \frac{2}{1+\sqrt{1+4\gamma}} \quad \text{as } \tau \to \infty. \tag{160}$$

Even though the expressions for c_O and c_I look different, they are both equal to 1 in the limiting case as (161) $\to 1$ as $\tau \to 0$ and $\gamma \to 0$. This corresponds to how well the TQSSA approximation works. Note that this would not be the case if we chose differently in the inequality after equation (142). Equation (153) is thus

$$\approx \frac{2}{1+\sqrt{1+4\gamma}}. \tag{161}$$

We note that Khoo finds the following for equation (153):

$$\approx \frac{2}{1+\sqrt{1-4\gamma}}. \tag{162}$$

Now we turn to the matter of finding an uniform approximation. We proceed as we did before in section 4.3, taking the common part and subtracting the difference:

$$s_u = s_O + s_I - 1 = s_O, \tag{163}$$

$$c_u = c_O + c_I - 2(1+\sqrt{1+4\gamma})^{-1}. \tag{164}$$

This is our uniform solution to the problem posed in the beginning of this section. We have thus found a single approximation of to substrate S and complex C in equation (52), valid when $0 < \epsilon \ll 1$.

Chemical reactions like (52) arise all the time in the field of enzyme kinetics, and $0 < \epsilon \ll 1$ is surprisingly often true in practice, or *in vivo*, which is what biologists call observations of living organisms. By simplifying a system of differential equations into (163) and (164) as we have done, calculations are greatly simplified in a rigorous fashion. This has many practical applications, but these are outside the scope of this article.

6 References

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7 Appendix

7.1 TQSSA XPP code

```
# tqssa.ode
# k = k1, l=k_1, m=k2
#
s'=-m*c
c'=k*(e-c)*(s-c)-(l+m)*c
par e=0.01, k=10, l=1, m=0.1
init s=0.1, c=0
@xp=s, yp=c
# xlo=0, ylo=0, xhi=1, yhi=1
@ total=400
@ nmesh=51
done
```

To reproduce, download XPP and load the above code. Press "V 2" and choose S on the x-axis for the phase plane, press "I G" to simulate from the initial conditions, then "W F" to fit the resulting graph to the window. If we press "S G" we get a confirmation that there's a steady state at at (0,0) to a rounding error becuase of numerical errors, and that it is stable. For more information, consult the official XPP manual available online.

7.2 Mathematica code

```
f[x_] := E^((1/2) (1 - x)) (* outer approx *)
g[x_] := E^(1/2) (E^(-x/2) - E^(-2 x/err)) (* exact *)
h[x_] := E^(1/2) * (1 - E^(-2*x/err)) (* inner approx *)
err = 0.1

Plot[{f[x], g[x]}, {x, 0, 1.7}, PlotRange -> {0, 1.7}, PlotStyle ->
 {Dashing, Directive[Dashed], Directive[Thick]}]

Plot[{h[x], g[x]}, {x, 0, 1}, PlotRange -> {0, 2},
 PlotStyle -> {Dashing, Directive[Dashed], Directive[Thick]}]
```