

Approximation of enzyme kinetics for high enzyme concentration by a first order perturbation approach

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Abstract This contribution presents an approximate solution of the enzyme kinetics problem for the case of excess of an enzyme over the substrate. A first order perturbation approach is adopted where the perturbation parameter is the relation of the substrate concentration to the total amount of enzyme. As a generalization over existing solutions for the same problem, the presented approximation allows for nonzero initial conditions for the substrate and the enzyme concentrations as well as for nonzero initial complex concentration. Nevertheless, the approximate solution is obtained in analytical form involving only elementary functions like exponentials and logarithms. The presentation discusses all steps of the procedure, starting from amplitude and time scaling for a non-dimensional representation and for the identification of the perturbation parameter. Suitable time constants lead to the short term and long term behaviour, also known as the inner and outer solution. Special attention is paid to the matching process by the definition of a suitable intermediate layer. The results are presented in concise form as a summary of the required calculations. An extended example compares the zero order and first order perturbation approximations for the short term and long term solution as well as the uniform solution. A comparison to the numerical solution of the initial set of nonlinear ordinary differential equations demonstrates the achievable accuracy.

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1 Introduction

1.1 Review of previous work

Enzyme reactions have been under investigation for more than hundred years. In the simplest form they consist of an initial substance (the substrate) which binds an enzyme to form a complex. The complex decomposes again into another chemical substance (the product), thereby releasing the enzyme which can again react with the remaining substrate. The kinetics of these reactions are described by rate expressions which can be expressed as a set of nonlinear differential equations.

Solutions of the rate expressions have been obtained under simplifying assumptions. The purpose of these assumptions is twofold: At first, they enable theoretical insight by capturing the essential chemical or biological behaviour. Secondly, they turn the set of differential equations into simpler nonlinear equations or even into a linear relation.

The rich and mature research in the kinetics of enzyme reactions has always been concerned with finding the most suitable and valid assumptions for the case under study and with the derivation of the correct conclusions and solutions from these assumptions. Only a few recent publications are referenced here which also contain historical remarks and more references.

Initially the following two assumptions have been studied: At first, that the concentration of the substrate is much higher than the enzyme concentration, and secondly, that a certain steady state is reached. These assumptions greatly simplify the mathematical description and lead to classical models like the well-known Michaelis–Menten model [19]. References to original work in the early twentieth century by Henri, Michaelis and Menten, Briggs and Haldane, and reviews thereof are given e.g. in [3, 22].

Recently, signal transduction in biological systems is being investigated. Here the substrate serves as carrier of information and its concentration may be rather low compared to the amount of enzyme in the environment. The same is true for approaches to molecular communication which are currently envisioned, see Sect. 1.2.

In this case, the classical assumptions do not hold anymore. At first, the concentration of the substrate is now much lower than the enzyme concentration. Secondly, information is carried by transients rather than by static behaviour. Consequently, it has been observed that the classical approximations do not hold for low substrate concentrations, see [23].

The classical assumption that the complex concentration is constant after a short initial transient (standard quasi steady state assumption) has been reconsidered in [5]. There, the differential equations for the enzyme kinetics were rewritten by replacing the free substrate concentration by the total substrate concentration which includes the free substrate and the substrate bound in the complex. Then also the standard quasi steady state assumption is replaced by a total quasi steady state assumption. It has

been shown in [5] that the total quasi steady state assumption has a wider range of validity, including also an excess of enzyme. This range of validity has been revisited and reformulated by [27].

Standard and total quasi steady state assumptions have been compared in [23] and the total quasi steady state assumption has been recommended over the standard one. The assumptions (1) that either the substrate or the enzyme is in excess and (2) that the concentration of the substance in excess is constant lead to simplified rate expressions in the form of pseudo first-order kinetics, which have been investigated e.g. in [22].

Since the quasi steady state assumptions are related to a zero order perturbation approach, it is tempting to use also higher order perturbation approaches to get away from overly limiting assumptions. A first order perturbation approach has been applied in [4] for the case of enzyme excess. Consequently, the so-called small parameter is the relation between the small initial substrate concentration and the relatively high total enzyme concentration. Closed form first order approximations for the short term and the long term behaviour have been derived for the case of zero initial complex concentration. Other perturbation approaches for enzyme kinetics are e.g. [10, 17, 18]. Recently, a perturbation solution has been presented in a so-called total framework which is valid for any set of kinetic parameters [9]. Nevertheless, all these approaches have been derived under the restriction that the initial complex concentration is zero.

1.2 Motivation

This publication reviews enzyme kinetics from a view point of molecular communications. Here, information is transmitted over small distances by particles rather than by electromagnetic or acoustic waves. In terms of information theory, the release of particles is the source and the receptor which senses the particle concentration in some small distance is the receiver. The environment between source and receiver is the information channel. Releasing a number of particles triggered by a certain event carries information from the source to the receiver. However, the repeated release of particles would eventually flood the channel and overdrive the receptor.

To avoid this situation, Noel et al. [21] have proposed to gradually reduce the particle concentration by an enzyme reaction. In this setting, the information carrying particles are the substrate which is turned into the product by the enzyme reaction. The receptor at the receiver side is sensitive to the substrate, but not to the enzyme, the complex, or the product. Similar approaches can be found in [2, 7, 13].

Practical applications of molecular communication are mostly visionary and published results are based on more or less simplified models and idealizing assumptions, see e.g. [8, 11, 20, 21, 24, 25]. Reaction models for molecular communication serve to design the chemical or biological implementation of the communication channel.

The number of released substance particles may be very low for a single event. Therefore, the potential enzyme reactions suitable for molecular communications are characterized by an excess of enzyme. The initial conditions may adopt arbitrary values, since a repeated release of substrate may happen for certain nonzero concentrations of substrate, complex, and free enzyme left over from the previous release. It is thus necessary to study enzyme reaction kinetics for arbitrary initial conditions and reactions with an excess of enzyme.

1.3 Preview

This article is structured as follows: The familiar enzyme reaction and a mathematical model with amplitude and time scaling are presented in Sect. 2. The extreme cases of high substrate and high enzyme concentration are discussed in Sect. 3. For a first order perturbation approach to the case of high enzyme concentration, Sect. 4 collects the nonlinear differential equations for nonzero initial conditions of substrate, enzyme, and complex. These equations are solved in Sect. 5 separately for the long term and the short term behaviour (also called inner and outer solution). Both solutions are matched in Sect. 6 and combined to the uniform solutions in Sect. 7. The relation to previous work in this field is shown in Sect. 8. Finally, the results are demonstrated by an example in Sect. 9.

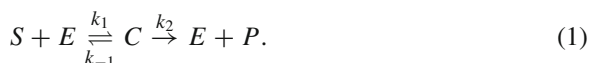
This article is an extended and corrected version of some parts of [26]. Its novel contributions are contained in Sects. 5 to 7.

2 Mathematical model

This section quotes the standard enzyme reaction and gives a derivation of a mathematical model in the form of coupled nonlinear ordinary differential equations. Amplitude and time scaling are used for a representation in dimensionless variables. The presentation is rather concise, details can be found e.g. in [19] and references therein.

2.1 Reaction model

The enzyme kinetics of the following chemical reaction are studied



The substrate S and the enzyme E form a complex C at a rate k_1 . In turn, the complex decomposes again into S and E at a rate k_{-1} and into E and the product P at a rate k_2 . This type of enzyme reaction is well investigated especially for high substrate concentrations, see e.g. [19].

2.2 Differential equations

The concentrations of the substrate, the enzyme and the complex are functions of time t . They are denoted by $s(t)$, $e(t)$, and $c(t)$, respectively. Their time evolution is governed by the following set of nonlinear ordinary differential equations

$$\dot{s}(t) = -k_1 s(t) e(t) + k_{-1} c(t) \quad (2)$$

$$\dot{e}(t) = -k_1 s(t) e(t) + k_{-1} c(t) + k_2 c(t) \quad (3)$$

$$\dot{c}(t) = k_1 s(t) e(t) - k_{-1} c(t) - k_2 c(t) \quad (4)$$

with the time derivatives $\dot{s}(t)$ etc. and the initial concentrations

$$s(0) = s_0, \quad e(0) = e_0, \quad c(0) = c_0. \tag{5}$$

Note, that none of the initial concentrations is assumed to be zero. In a closed system, the total amount of enzyme e_T is constant

$$e(t) + c(t) = e_0 + c_0 = e_T, \tag{6}$$

so that one of the Eqs. (2)–(4) can be eliminated. E.g. (3) is removed by setting $e(t) = e_T - c(t)$. The remaining equations are

$$\dot{s}(t) = -k_1 e_T s(t) + k_{-1} c(t) + k_1 s(t) c(t), \tag{7}$$

$$\dot{c}(t) = k_1 e_T s(t) - (k_{-1} + k_2) c(t) - k_1 s(t) c(t). \tag{8}$$

The further analysis is simplified when these equations are made dimensionless by amplitude and time scaling.

2.3 Amplitude scaling

The concentrations $s(t)$ and $c(t)$ are made dimensionless by introducing the scaled concentrations $\mu(t)$ and $\nu(t)$ as

$$\mu(t) = \frac{s(t)}{s_0}, \quad \nu(t) = \frac{c(t)}{e_T}. \tag{9}$$

The time constants

$$T_e = \frac{1}{k_1 e_T}, \quad T_s = \frac{1}{k_1 s_0}, \tag{10}$$

and the dimensionless constants

$$\rho = k_{-1} T_s, \quad \lambda = k_2 T_s, \quad K = \rho + \lambda, \tag{11}$$

lead to the representation in scaled concentrations

$$T_e \dot{\mu}(t) = -\mu(t) + \rho \nu(t) + \mu(t) \nu(t), \tag{12}$$

$$T_s \dot{\nu}(t) = \mu(t) - K \nu(t) - \mu(t) \nu(t), \tag{13}$$

As an abbreviation for the introduction of different time scales in Sect. 2.4 the functions

$$f(\mu(t), \nu(t)) = -\mu(t) + \rho \nu(t) + \mu(t) \nu(t), \tag{14}$$

$$g(\mu(t), \nu(t)) = \mu(t) - K \nu(t) - \mu(t) \nu(t), \tag{15}$$

are defined. Then a short notation for the amplitude-scaled equations reads as

$$T_e \dot{\mu}(t) = f(\mu(t), v(t)), \quad (16)$$

$$T_s \dot{v}(t) = g(\mu(t), v(t)), \quad (17)$$

with the scaled initial conditions

$$\mu(0) = 1, \quad v(0) = v_0 = \frac{c_0}{e_T} = 1 - \frac{e_0}{e_T} \leq 1. \quad (18)$$

The concentrations $\mu(t)$ and $v(t)$ have a dimension of unity but their argument is still the time t in seconds.

2.4 Time scaling

Time scaling does not only allow a further simplification of (16), (17). It serves also to highlight the short term behaviour and the long term behaviour of the reaction dynamics. These different kinds of behaviour appear in the extreme cases of high substrate concentration or high enzyme concentration discussed in Sect. 3.

Two different time scales are considered here. They are characterized by the reference times T_e and T_s or through (10) by the concentrations e_T and s_0 . The respective scaled time variables are defined as

$$\tau = \frac{t}{T_e} = k_1 e_T t \quad \text{and} \quad \theta = \frac{t}{T_s} = k_1 s_0 t \quad \text{where} \quad \frac{\tau}{\theta} = \frac{T_s}{T_e} = \frac{e_T}{s_0}. \quad (19)$$

The time-scaled variables with respect to (w.r.t.) T_e are

$$\sigma_e(\tau) = \mu(t) \quad \gamma_e(\tau) = v(t), \quad (20)$$

with

$$\frac{d}{d\tau} \sigma_e(\tau) = \sigma_e'(\tau) = \frac{d}{dt} \mu(t) \frac{dt}{d\tau} = \dot{\mu}(t) T_e, \quad (21)$$

and similar for $\gamma_e(\tau)$. In the same way, the time-scaled variables w.r.t. T_s are introduced as $\sigma_s(\theta)$ and $\gamma_s(\theta)$. Their definitions and derivatives w.r.t. the respective time variables are compiled here as

$$\sigma_e(\tau) = \mu(t) \quad \sigma_e'(\tau) = T_e \dot{\mu}(t), \quad (22)$$

$$\gamma_e(\tau) = v(t) \quad \gamma_e'(\tau) = T_e \dot{v}(t), \quad (23)$$

$$\sigma_s(\theta) = \mu(t) \quad \sigma_s'(\theta) = T_s \dot{\mu}(t), \quad (24)$$

$$\gamma_s(\theta) = v(t) \quad \gamma_s'(\theta) = T_s \dot{v}(t). \quad (25)$$

Applying these relations to the amplitude-scaled equations (16), (17) gives two versions of fully amplitude- and time-scaled systems of differential equations with either the reference time T_e

$$\sigma'_e(\tau) = f(\sigma_e(\tau), \gamma_e(\tau)), \tag{26}$$

$$\frac{T_s}{T_e} \gamma'_e(\tau) = g(\sigma_e(\tau), \gamma_e(\tau)), \tag{27}$$

or the reference time T_s

$$\frac{T_e}{T_s} \sigma'_s(\theta) = f(\sigma_s(\theta), \gamma_s(\theta)), \tag{28}$$

$$\gamma'_s(\theta) = g(\sigma_s(\theta), \gamma_s(\theta)). \tag{29}$$

For a further simplification, the relations between the reference times are abbreviated as

$$\frac{T_s}{T_e} = \frac{e_T}{s_0} = \varepsilon, \qquad \frac{T_e}{T_s} = \frac{s_0}{e_T} = \delta = \frac{1}{\varepsilon}. \tag{30}$$

Then (26, 27) can be represented in two different versions as

$$\sigma'_e(\tau) = f(\sigma_e(\tau), \gamma_e(\tau)) \qquad \sigma'_e(\tau) = f(\sigma_e(\tau), \gamma_e(\tau)), \tag{31}$$

$$\varepsilon \gamma'_e(\tau) = g(\sigma_e(\tau), \gamma_e(\tau)) \qquad \gamma'_e(\tau) = \delta g(\sigma_e(\tau), \gamma_e(\tau)), \tag{32}$$

and similar for (28, 29)

$$\delta \sigma'_s(\theta) = f(\sigma_s(\theta), \gamma_s(\theta)) \qquad \sigma'_s(\theta) = \varepsilon f(\sigma_s(\theta), \gamma_s(\theta)), \tag{33}$$

$$\gamma'_s(\theta) = g(\sigma_s(\theta), \gamma_s(\theta)) \qquad \gamma'_s(\theta) = g(\sigma_s(\theta), \gamma_s(\theta)). \tag{34}$$

Note that the left hand side (l.h.s.) and the r.h.s of (31, 32) are identical due to the reciprocal relationship between ε and δ in (30). In the same way also the l.h.s and the r.h.s of (33, 34) are identical. Furthermore, the two relations in (31, 32) and in (33, 34) represent the same system of differential equations, differing only in the scale of the time axis.

Nevertheless, in the extreme cases of either high substrate concentration or high enzyme concentration, these equivalent formulations give rise to different approximations for either the short term behaviour or the long term behaviour of the enzyme reaction system (1). These extreme cases are discussed in the next section.

3 Extreme cases

The derivation of systems of differential equations above did not make any assumptions on the relation between the amounts of substrate and enzyme in the reaction. However, different application fields are characterized by either a high substrate concentration or a high enzyme concentration. In these cases, the relations between the reference times according to Eq. (30), ε or δ , can be used as small parameters in the sense of perturbation theory. Therefore, these two extreme cases are discussed below, the first one shortly for historical reasons, the second one because of its importance in molecular communications, see Sect. 1.2.

The application of perturbation approaches is not restricted to these extreme cases. If the relation between the amounts of substrate and enzyme is not determined by the application at hand, then other, more general approaches are available for the selection of the small parameter. One example is the total framework proposed in [9]. Another possibility is the homotopy method [1, 12] where the small parameter describes the transition from a linear problem to a nonlinear one. Nevertheless, for the application field described in Sect. 1.2, the case of high enzyme concentration is the most natural choice.

3.1 High substrate concentration

The classical application is to convert a raw material (the substrate S) into a chemical product. To produce large quantities, the amount of substrate S should be high. The concentration of the enzyme can be as low as possible for a reasonable yield.

The condition for a high substrate concentration $e_T \ll s_0$ induces from (30)

$$\frac{e_T}{s_0} = \varepsilon \ll 1 \quad \text{and} \quad T_s \ll T_e. \quad (35)$$

The latter relation for the reference times shows that the scaled time variables from (19) describe

τ	long term behaviour with reference time T_e ,
θ	short term behaviour with reference time T_s .

A suitable starting point for an approximation are those two pairs of equations from (31 to 34) which contain the multiplier ε

$$\begin{aligned} \sigma_e'(\tau) &= f(\sigma_e(\tau), \gamma_e(\tau)) & \sigma_s'(\theta) &= \varepsilon f(\sigma_s(\theta), \gamma_s(\theta)), \\ \varepsilon \gamma_e'(\tau) &= g(\sigma_e(\tau), \gamma_e(\tau)) & \gamma_s'(\theta) &= g(\sigma_s(\theta), \gamma_s(\theta)). \end{aligned}$$

Setting ε to zero and adopting certain steady state assumptions greatly simplifies these relations and leads to the classical Michaelis–Menten model [3, 19].

3.2 High enzyme concentration

The condition for a high enzyme concentration $s_0 \ll e_T$ induces from (30)

$$\frac{s_0}{e_T} = \delta \ll 1 \quad \text{and} \quad T_e \ll T_s. \quad (36)$$

The relation for the reference times shows that the scaled time variables from (19) describe now

τ	short term behaviour with reference time T_e ,
θ	long term behaviour with reference time T_s .

The starting point for an approximation are the two pairs of equations from (31 to 34) which contain the multiplier δ

$$\sigma'_e(\tau) = f(\sigma_e(\tau), \gamma_e(\tau)) = -\sigma_e(\tau) + \rho \gamma_e(\tau) + \sigma_e(\tau)\gamma_e(\tau), \tag{37}$$

$$\gamma'_e(\tau) = \delta g(\sigma_e(\tau), \gamma_e(\tau)) = \delta(\sigma_e(\tau) - K \gamma_e(\tau) - \sigma_e(\tau)\gamma_e(\tau)), \tag{38}$$

and

$$\delta \sigma'_s(\theta) = f(\sigma_s(\theta), \gamma_s(\theta)) = -\sigma_e(\tau) + \rho \gamma_e(\tau) + \sigma_e(\tau)\gamma_e(\tau), \tag{39}$$

$$\gamma'_s(\theta) = g(\sigma_s(\theta), \gamma_s(\theta)) = \sigma_e(\tau) - K \gamma_e(\tau) - \sigma_e(\tau)\gamma_e(\tau). \tag{40}$$

The behaviour described by these differential equations is investigated in detail in Sect. 4.

4 Perturbation approaches for high enzyme concentration

No exact analytical solution is known for the systems of nonlinear differential equations in the form of either (37, 38) or (39, 40). However, approximate solutions by perturbation approaches are possible. The idea is to solve the short term and long term behaviour separately by suitable approximations, and to combine these partial solutions into a unified solution which is valid for both time scales [14, 16].

This approach has been adopted by many researchers as referenced in Sect. 1. E.g. in [4, 22, 27] it is shown that (37–40) can be solved separately for short term behaviour $(\sigma_e(\tau), \gamma_e(\tau))$ and long term behaviour $(\sigma_s(\theta), \gamma_s(\theta))$ by considering δ as a perturbation parameter. A zero order approximation is obtained by simply setting $\delta = 0$. This approach is extended here to the case where not only the initial substrate and enzyme concentration but also the initial complex concentration is nonzero, see (5).

4.1 First order perturbation approach

4.1.1 Formulation of the first order perturbation approach

The perturbation approach referenced above expands the solution of Eqs. (37–40) into a power series in δ . This series converges fast for small values of δ . Considering the zero order term and the first order term, the unknown functions in (37–40) can be written as

$$\sigma_e(\tau) = \sigma_{e,0}(\tau) + \delta \sigma_{e,1}(\tau) + \mathcal{O}(\delta^2), \tag{41}$$

$$\gamma_e(\tau) = \gamma_{e,0}(\tau) + \delta \gamma_{e,1}(\tau) + \mathcal{O}(\delta^2), \tag{42}$$

$$\sigma_s(\theta) = \sigma_{s,0}(\theta) + \delta \sigma_{s,1}(\theta) + \mathcal{O}(\delta^2), \tag{43}$$

$$\gamma_s(\theta) = \gamma_{s,0}(\theta) + \delta \gamma_{s,1}(\theta) + \mathcal{O}(\delta^2), \quad (44)$$

where $\mathcal{O}(\delta^2)$ denotes all terms with δ^n for $n \geq 2$.

4.1.2 Initial conditions

Short Term Behaviour The initial conditions of the short term behaviour are the values of the variables in Eqs. (41) and (42) for $\tau = 0$. They are well defined by the initial conditions (5) of the unscaled problem or (18) after amplitude scaling. Thus, the initial values for the short term behaviour do not depend on the perturbation parameter δ . Therefore, the initial values $\sigma_e(0)$ and $\gamma_e(0)$ are represented by the initial values $\sigma_{e,0}(0)$ and $\gamma_{e,0}(0)$ of the zero-order terms. The initial values of the first-order terms are zero.

These relations for the initial conditions are summarized below, where the abbreviations σ_{e0} and γ_{e0} for the zero order terms are introduced

$$\sigma_{e,0}(0) = \sigma_e(0) = \sigma_{e0} \quad \gamma_{e,0}(0) = \gamma_e(0) = \gamma_{e0}, \quad (45)$$

$$\sigma_{e,1}(0) = 0 \quad \gamma_{e,1}(0) = 0. \quad (46)$$

From Eq. (18) follows that

$$\sigma_{e0} = 1, \quad \gamma_{e0} = \nu_0. \quad (47)$$

However, for better comparison with the initial conditions for the long term behaviour, the designations σ_{e0} and γ_{e0} are kept for the moment.

Long Term Behaviour The initial conditions of the short term behaviour are the values of the variables in Eqs. (43) and (44) for $\theta = 0$. Since the long term behaviour is not a good approximation for $\theta = 0$ the initial conditions $\sigma_{s,0}(0)$, $\sigma_{s,1}(0)$, $\gamma_{s,0}(0)$, and $\gamma_{s,1}(0)$ cannot be inferred directly as for the short term behaviour. In particular, it cannot be assumed that one or more of these terms are zero. Instead they have to be determined from the solution of the short term behaviour by process called matching (see Sect. 6). For the further calculations these initial conditions are abbreviated by

$$\sigma_{s,0}(0) = \sigma_{s0} \quad \gamma_{s,0}(0) = \gamma_{s0}, \quad (48)$$

$$\sigma_{s,1}(0) = \sigma_{s1} \quad \gamma_{s,1}(0) = \gamma_{s1}. \quad (49)$$

4.2 Application to the case of high enzyme concentration

Inserting the perturbation approach from Eqs. (41)–(44) into the equations for the case of high enzyme concentration (37)–(40) and collecting the resulting terms by powers of δ gives a set of four first order non-linear differential equations for the short term behaviour and another set for the long term behaviour.

Short Term Behaviour For the short term behaviour, the following set of first order differential equations results

$$\sigma'_{e,0}(\tau) = -\sigma_{e,0}(\tau) + \rho\gamma_{e,0}(\tau) + \sigma_{e,0}(\tau)\gamma_{e,0}(\tau), \tag{50}$$

$$\gamma'_{e,0}(\tau) = 0, \tag{51}$$

$$\sigma'_{e,1}(\tau) = -\sigma_{e,1}(\tau) + \rho\gamma_{e,1}(\tau) + \sigma_{e,0}(\tau)\gamma_{e,1}(\tau) + \sigma_{e,1}(\tau)\gamma_{e,0}(\tau), \tag{52}$$

$$\gamma'_{e,1}(\tau) = \sigma_{e,0}(\tau) - K\gamma_{e,0}(\tau) - \sigma_{e,0}(\tau)\gamma_{e,0}(\tau). \tag{53}$$

Long Term Behaviour The corresponding set of equations for the long term behaviour is given by

$$0 = -\sigma_{s,0}(\theta) + \rho\gamma_{s,0}(\theta) + \sigma_{s,0}(\theta)\gamma_{s,0}(\theta), \tag{54}$$

$$\gamma'_{s,0}(\theta) = \sigma_{s,0}(\theta) - K\gamma_{s,0}(\theta) - \sigma_{s,0}(\theta)\gamma_{s,0}(\theta), \tag{55}$$

$$\sigma'_{s,0}(\theta) = -\sigma_{s,1}(\theta) + \rho\gamma_{s,1}(\theta) + \sigma_{s,0}(\theta)\gamma_{s,1}(\theta) + \sigma_{s,1}(\theta)\gamma_{s,0}(\theta), \tag{56}$$

$$\gamma'_{s,1}(\theta) = \sigma_{s,1}(\theta) - K\gamma_{s,1}(\theta) - \sigma_{s,0}(\theta)\gamma_{s,1}(\theta) - \sigma_{s,1}(\theta)\gamma_{s,0}(\theta). \tag{57}$$

The zero on the left hand side of Eq. (54) and the structure of terms on the right hand sides of Eqs. (54)–(57) suggest an alternate set of equations. It results from replacing Eq. (55) by the sum of (54) and (55) and Eq. (57) by the sum of (56) and (57). The resulting four equations read

$$0 = -\sigma_{s,0}(\theta) + \rho\gamma_{s,0}(\theta) + \sigma_{s,0}(\theta)\gamma_{s,0}(\theta), \tag{58}$$

$$\gamma'_{s,0}(\theta) = -\lambda\gamma_{s,0}(\theta), \tag{59}$$

$$\sigma'_{s,0}(\theta) = -\sigma_{s,1}(\theta) + \rho\gamma_{s,1}(\theta) + \sigma_{s,0}(\theta)\gamma_{s,1}(\theta) + \sigma_{s,1}(\theta)\gamma_{s,0}(\theta), \tag{60}$$

$$\gamma'_{s,1}(\theta) = -\lambda\gamma_{s,1}(\theta) - \sigma'_{s,0}(\theta). \tag{61}$$

5 Solution of the differential equations

This section describes the solution of the two sets of nonlinear differential equations for the short term behaviour Eqs. (50–53) and the long term behaviour Eqs. (58–61). In the parlance of perturbation theory, the solutions for the short term and long term behaviour are also called the inner and the outer solution, respectively [14, 16]. To keep the following equations manageable, some abbreviations are introduced along the way.

5.1 Short term behaviour

The solution of the differential equations for the short term behaviour (50)–(53) follows the procedure shown graphically in Fig. 1.

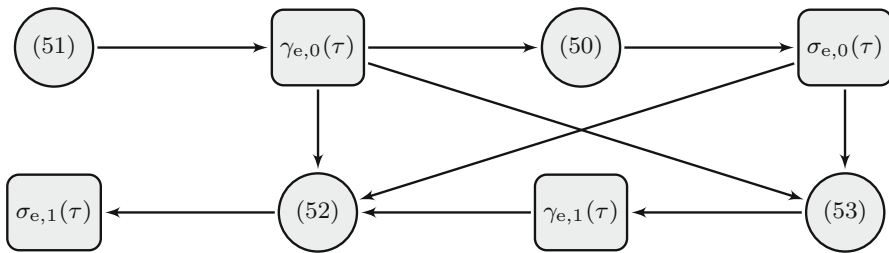


Fig. 1 Sequence of the calculations for solving the set of nonlinear differential equations (50)–(53) for the short time behaviour. Circles denote the Eqs. (50)–(53). Boxes denote the resulting variables. The detailed calculations are given in Sect. 5.1.1

5.1.1 Individual solutions

Solution of Eq. (51): The most simple equation is (51) with the solution

$$\gamma_{e,0}(\tau) = \gamma_{e0}. \quad (62)$$

Solution of Eq. (50): Inserting this result into (50) gives the linear differential equation

$$\sigma'_{e,0}(\tau) + (1 - \gamma_{e0}) \sigma_{e,0}(\tau) = \sigma'_{e,0}(\tau) + \frac{1}{\tau_0} \sigma_{e,0}(\tau) = \rho \gamma_{e0}, \quad (63)$$

where the abbreviation

$$\tau_0 = \frac{1}{1 - \gamma_{e0}}, \quad (64)$$

has been used. The solution of Eq. (63) follows directly from Eq. (171) in Appendix A.1 as

$$\sigma_{e,0}(\tau) = \rho \gamma_{e0} \tau_0 + r_0 \exp\left(-\frac{\tau}{\tau_0}\right). \quad (65)$$

Here, the abbreviation r_0 has been introduced

$$r_0 = \sigma_{e0} - \rho \gamma_{e0} \tau_0. \quad (66)$$

The abbreviation (64) allows to express all occurrences of γ_{e0} by τ_0 and vice versa. Nevertheless mixed representations with both γ_{e0} and τ_0 in the same equation are sometimes used for the sake of conciseness.

Solution of Eq. (53): Inserting (65) into (53) gives an algebraic expression for $\gamma'_{e,1}(\tau)$ as

$$\gamma'_{e,1}(\tau) = \frac{r_0}{\tau_0} \exp\left(-\frac{\tau}{\tau_0}\right) - \lambda \gamma_{e0}, \quad (67)$$

which can be solved by integration

$$\gamma_{e,1}(\tau) = r_0 \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) - \lambda \gamma_{e0} \tau. \quad (68)$$

Setting $\tau = 0$ shows that the initial value vanishes $\gamma_{e,1}(0) = 0$, as has been presumed in Eq. (46).

Solution of Eq. (52):

Inserting the above results into Eq. (52) gives

$$\sigma'_{e,1}(\tau) + \frac{1}{\tau_0} \sigma_{e,1}(\tau) = (\rho + \sigma_{e,0}(\tau)) \gamma_{e,1}(\tau) = m(\tau), \tag{69}$$

where the right hand side has been abbreviated by $m(\tau)$. Thus, the solution of this first order differential equation is given by Eq. (171) as

$$\sigma_{e,1}(\tau) = \exp\left(-\frac{\tau}{\tau_0}\right) \int_0^\tau m(\tau') \exp\left(\frac{\tau'}{\tau_0}\right) d\tau', \tag{70}$$

since the initial value $\sigma_{e,1}(0)$ is zero according to Eq. (46).

It remains to evaluate the right hand side $m(\tau)$ and to solve the integral in Eq. (70). These steps require only basic algebra and some standard integrals, but the calculations are somewhat involved. Therefore suitable abbreviations are introduced and the main intermediate results are stated.

Inserting Eqs. (65) and (68) into the expression for $m(\tau)$ in (69) and sorting terms with Eq. (64) allows to express $m(\tau)$ in the form

$$m(\tau) = a_0 + b_0 \tau + c_0 \exp\left(-\frac{\tau}{\tau_0}\right) + d_0 \tau \exp\left(-\frac{\tau}{\tau_0}\right) + e_0 \exp\left(-\frac{2\tau}{\tau_0}\right), \tag{71}$$

with the abbreviations

$$\begin{aligned} a_0 &= \rho \tau_0 r_0, & b_0 &= -\rho \lambda \gamma_{e0} \tau_0, & c_0 &= r_0(r_0 - \rho \tau_0), \\ d_0 &= -\lambda \gamma_{e0} r_0, & e_0 &= -r_0^2. \end{aligned} \tag{72}$$

Multiplication with the exponential term inside of the integral gives

$$m(\tau) \exp\left(\frac{\tau}{\tau_0}\right) = a_0 \exp\left(\frac{\tau}{\tau_0}\right) + b_0 \tau \exp\left(\frac{\tau}{\tau_0}\right) + c_0 + d_0 \tau + e_0 \exp\left(-\frac{\tau}{\tau_0}\right). \tag{73}$$

Now the integral in Eq. (70) can be evaluated

$$\begin{aligned} \int_0^\tau m(\tau') \exp\left(\frac{\tau'}{\tau_0}\right) d\tau' &= \tau_0(a_0 - b_0 \tau_0) \left(\exp\left(\frac{\tau}{\tau_0}\right) - 1\right) + c_0 \tau + \frac{1}{2} d_0 \tau^2 \\ &\quad + \tau_0 e_0 \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) + \tau_0 b_0 \tau \exp\left(\frac{\tau}{\tau_0}\right). \end{aligned} \tag{74}$$

Another multiplication with the exponential outside of the integral in (70) finally gives

$$\begin{aligned}\sigma_{e,1}(\tau) &= \tau_0(a_0 - b_0\tau_0) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) + \left(c_0\tau + \frac{1}{2}d_0\tau^2\right) \exp\left(-\frac{\tau}{\tau_0}\right) \\ &\quad + \tau_0 e_0 \exp\left(-\frac{\tau}{\tau_0}\right) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) + \tau_0 b_0 \tau.\end{aligned}\quad (75)$$

Again, the initial value turns out to be $\sigma_{e,1}(0) = 0$. Finally, the abbreviations from Eq. (72) can be re-substituted

$$\begin{aligned}\sigma_{e,1}(\tau) &= \rho\tau_0^2(r_0 + \lambda\gamma_{e0}\tau_0) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) \\ &\quad + r_0 \left((r_0 - \rho\tau_0)\tau - \frac{1}{2}\lambda\gamma_{e0}\tau^2\right) \exp\left(-\frac{\tau}{\tau_0}\right) \\ &\quad - r_0^2\tau_0 \exp\left(-\frac{\tau}{\tau_0}\right) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) - \rho\lambda\gamma_{e0}\tau_0^2\tau.\end{aligned}\quad (76)$$

5.1.2 Summary of the short term behaviour

The above results for the solution of the short term behaviour (aka the inner solution) are summarized as

$$\sigma_{e,0}(\tau) = \rho\gamma_{e0}\tau_0 + r_0 \exp\left(-\frac{\tau}{\tau_0}\right), \quad (77)$$

$$\gamma_{e,0}(\tau) = \gamma_{e0}, \quad (78)$$

$$\begin{aligned}\sigma_{e,1}(\tau) &= \rho\tau_0^2(r_0 + \lambda\gamma_{e0}\tau_0) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) \\ &\quad + r_0 \left((r_0 - \rho\tau_0)\tau - \frac{1}{2}\lambda\gamma_{e0}\tau^2\right) \exp\left(-\frac{\tau}{\tau_0}\right) \\ &\quad - r_0^2\tau_0 \exp\left(-\frac{\tau}{\tau_0}\right) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) - \rho\lambda\gamma_{e0}\tau_0^2\tau,\end{aligned}\quad (79)$$

$$\gamma_{e,1}(\tau) = r_0 \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) - \lambda\gamma_{e0}\tau. \quad (80)$$

5.2 Long term behaviour

The solution of the differential equations for the long term behaviour (58)–(61) follows the procedure shown graphically in Fig. 2.

5.2.1 Individual solutions

Solution of Eq. (59):

The most simple differential equation is Eq. (59) with the solution

$$\gamma_{s,0}(\theta) = \gamma_{s0}e^{-\lambda\theta}. \quad (81)$$

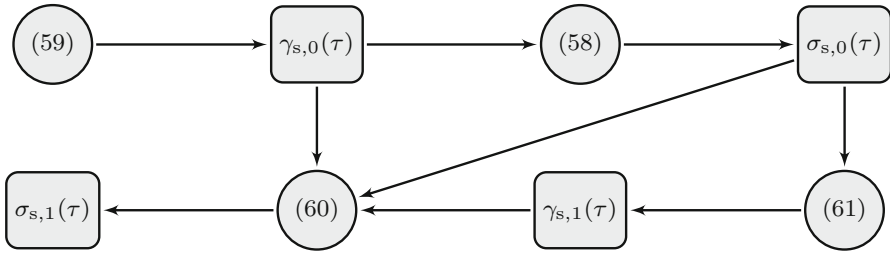


Fig. 2 Sequence of the calculations for solving the set of nonlinear differential equations (58)–(61) for the long term behaviour. Circles denote the Eqs. (58)–(61). Boxes denote the resulting variables. The detailed calculations are given in Sect. 5.2.1

Solution of Eq. (58):

The further calculations are simplified by introducing the function $w(\theta)$ with the following properties

$$w(\theta) = 1 - \gamma_{s,0}(\theta), \quad w'(\theta) = \lambda(1 - w(\theta)), \quad w''(\theta) = -\lambda w'(\theta), \quad (82)$$

$$w(\theta)w''(\theta) - (w'(\theta))^2 = w''(\theta) = -\lambda w'(\theta). \quad (83)$$

Inserting Eq (81) into Eq. (58) and solving for $\sigma_{s,0}(\theta)$ gives

$$\sigma_{s,0}(\theta) = \rho \frac{\gamma_{s,0}(\theta)}{1 - \gamma_{s,0}(\theta)} = \frac{\rho}{\lambda} \frac{w'(\theta)}{w(\theta)}. \quad (84)$$

Solution of Eq. (61):

Eq. (61) requires the derivative of $\sigma_{s,0}(\theta)$

$$\sigma'_{s,0}(\theta) = -\rho \frac{w'(\theta)}{w^2(\theta)} = -l(\theta), \quad (85)$$

where (83) has been used. The function $l(\theta)$ can be expressed with (84) as

$$l(\theta) = -\sigma'_{s,0}(\theta) = \rho \frac{w'(\theta)}{w^2(\theta)} = \frac{\lambda}{w(\theta)} \sigma_{s,0}(\theta). \quad (86)$$

Now Eq. (61) can be written as a first order differential equation

$$\gamma'_{s,1}(\theta) + \lambda\gamma_{s,1}(\theta) = -\sigma'_{s,0}(\theta) = l(\theta), \quad (87)$$

with the solution from Eq. (171)

$$\gamma_{s,1}(\theta) = e^{-\lambda\theta} \left(\int_0^\theta l(\theta')e^{\lambda\theta'} d\theta' + \gamma_{s1} \right). \quad (88)$$

The integrand can be written as

$$l(\theta)e^{\lambda\theta} = \rho \frac{w'(\theta)}{w^2(\theta)} e^{\lambda\theta} = \rho \gamma_{s0} \frac{\lambda}{w^2(\theta)}, \quad (89)$$

such that

$$\gamma_{s,1}(\theta) = \rho \gamma_{s0} e^{-\lambda\theta} \int_0^\theta \frac{\lambda}{w^2(\theta')} d\theta' + \gamma_{s1} e^{-\lambda\theta}. \quad (90)$$

The integral in (90) has the closed form solution (see Appendix A.2)

$$\begin{aligned} \int_0^\theta \rho \gamma_{s0} \frac{\lambda}{w^2(\theta')} d\theta' &= \left[\ln w(\theta') - \frac{1}{w(\theta')} + \lambda\theta' \right] \Big|_0^\theta \\ &= \ln \frac{w(\theta)}{w(0)} - \frac{1}{w(\theta)} + \frac{1}{w(0)} + \lambda\theta. \end{aligned} \quad (91)$$

Inserting this solution into (90) and using (81) gives

$$\gamma_{s,1}(\theta) = \rho \gamma_{s,0}(\theta) \left(\ln \frac{w(\theta)}{w(0)} - \frac{1}{w(\theta)} + \frac{1}{w(0)} + \lambda\theta \right) + \gamma_{s1} e^{-\lambda\theta}. \quad (92)$$

Solution of Eq. (60):

It remains to determine $\sigma_{s,1}(\theta)$ from Eq. (60)

$$(1 - \gamma_{s,0}(\theta)) \sigma_{s,1}(\theta) = (\rho + \sigma_{s,0}(\theta)) \gamma_{s,1}(\theta) - \sigma'_{s,0}(\theta). \quad (93)$$

Evaluating

$$\rho + \sigma_{s,0}(\theta) = \rho \left(1 + \frac{\gamma_{s,0}(\theta)}{1 - \gamma_{s,0}(\theta)} \right) = \rho \frac{1}{1 - \gamma_{s,0}(\theta)} = \frac{\rho}{w(\theta)}, \quad (94)$$

and using (82) and (86) gives

$$\sigma_{s,1}(\theta) = \frac{1}{w^2(\theta)} \left(\lambda \sigma_{s,0}(\theta) + \rho \gamma_{s,1}(\theta) \right). \quad (95)$$

5.2.2 Summary of the long term behaviour

The above results for the solution of the long term behaviour (aka the outer solution) are summarized as

$$\gamma_{s,0}(\theta) = \gamma_{s0}e^{-\lambda\theta}, \tag{96}$$

$$w(\theta) = 1 - \gamma_{s,0}(\theta), \tag{97}$$

$$\sigma_{s,0}(\theta) = \rho \frac{\gamma_{s,0}(\theta)}{w(\theta)}, \tag{98}$$

$$\gamma_{s,1}(\theta) = \rho \gamma_{s,0}(\theta) \left(\ln \frac{w(\theta)}{w(0)} - \frac{1}{w(\theta)} + \frac{1}{w(0)} + \lambda\theta \right) + \gamma_{s1} e^{-\lambda\theta}, \tag{99}$$

$$\sigma_{s,1}(\theta) = \frac{1}{w^2(\theta)} \left(\lambda\sigma_{s,0}(\theta) + \rho\gamma_{s,1}(\theta) \right). \tag{100}$$

Setting $\theta = 0$ in (98) and in (100) gives the initial values of $\sigma_{s,0}(0)$ and $\sigma_{s,1}(0)$ in terms of the initial values γ_{s0} and γ_{s1} . However, these initial values for the long term behaviour are still unrelated to the initial values of the short term behaviour and thus to the initial values in (5).

6 Matching of short and long term behaviour

The missing relation between the initial values of the short term and the long term behaviour can be established by a process called matching [14, 16]. At first sight, the expressions in Eqs. (77)–(80) and in Eqs. (96)–(100) look quite different. Moreover, they are defined on different time scales, represented by the variables τ and θ , respectively.

The basic approach is now to express both, the short and long term behaviour by polynomials and to match their coefficients up to a certain order. This is not possible on a global time scale due to the different nature of the inner and outer solutions. But it is possible for a certain time range which is large w.r.t. the short term behaviour and small w.r.t the long term behaviour. This time range is also called the intermediate layer. It can be described in more detail for the short term and the long term behaviour separately.

The equations for the short term behaviour (77)–(80) contain terms which are constant or linear in τ and exponentially decaying terms. For values of τ which are sufficiently large, the exponential terms can be neglected and the short term behaviour can be approximated by a first order polynomial in τ . There is also a polynomial approximation for the equations for the long term behaviour (96)–(100). It is obtained by a Taylor series expansion w.r.t. θ which holds for sufficiently small values of θ . The details of this procedure are now discussed in detail.

6.1 Short term behaviour

The solution for the short term behaviour from Eqs. (77)–(80) is rewritten here in a more concise form. The exponential terms which can be neglected for $\tau \gg \tau_0$ are abbreviated by EXP. These terms are a special case of the transcendentally small terms from [16]

$$\sigma_{e,0}(\tau) = \rho\gamma_{e0}\tau_0 + \text{EXP}, \tag{101}$$

$$\gamma_{e,0}(\tau) = \gamma_{e0}, \quad (102)$$

$$\sigma_{e,1}(\tau) = \rho\tau_0^2(r_0 + \lambda\gamma_{e0}\tau_0) - \rho\lambda\gamma_{e0}\tau_0^2\tau + \text{EXP}, \quad (103)$$

$$\gamma_{e,1}(\tau) = r_0 - \lambda\gamma_{e0}\tau + \text{EXP}. \quad (104)$$

For the purpose of matching, only the terms which are constant or linear in τ are of interest.

6.2 Long term behaviour

The solutions for the long term behaviour can be expressed as first order polynomials by expansion into a Taylor series with [compare (48)]

$$\sigma_{s,0}(0) = \sigma_{s0}, \quad \sigma'_{s,0}(0) = \sigma'_{s0}. \quad (105)$$

and similar for $\gamma_{s,0}(\theta)$, $\sigma_{s,1}(\theta)$, and $\gamma_{s,1}(\theta)$ at $\theta = 0$

$$\sigma_{s,0}(\theta) = \sigma_{s0} + \sigma'_{s0}\theta + \mathcal{O}(\theta^2), \quad (106)$$

$$\gamma_{s,0}(\theta) = \gamma_{s0} + \gamma'_{s0}\theta + \mathcal{O}(\theta^2), \quad (107)$$

$$\sigma_{s,1}(\theta) = \sigma_{s1} + \sigma'_{s1}\theta + \mathcal{O}(\theta^2), \quad (108)$$

$$\gamma_{s,1}(\theta) = \gamma_{s1} + \gamma'_{s1}\theta + \mathcal{O}(\theta^2). \quad (109)$$

Both, the short term behaviour for large values of τ in (101)–(104) and the long term behaviour for small values of θ in (106)–(109) now have the form of first order polynomials. However, the time scales for τ and θ are still unrelated.

6.3 Intermediate layer

The intermediate layer is the region where the polynomial approximations of the short term and the long term behaviour can be compared. It is characterized by its own frequency variable ψ and scaling factor η which is related to both τ and θ by

$$\tau = \frac{\theta}{\delta} = \frac{\eta\psi}{\delta}, \quad \tau\delta = \theta = \eta\psi. \quad (110)$$

A natural choice is $\psi = t$ and $\eta = k_1s_0 = 1/T_s$, but also a differently scaled time variable is possible. No special choice is assumed for generality as in [14, 16].

To compare the short term and the long term behaviour in the intermediate layer, the variables τ and θ are replaced by ψ according to (110). This procedure is carried out for the substrate concentration and for the complex concentration.

6.3.1 Intermediate layer for the substrate concentration

The short term solution $\sigma_e(\eta \psi/\delta)$ and the long term solution $\sigma_s(\eta \psi)$ of the substrate concentration are required to be equal in the intermediate layer

$$\lim_{\delta \downarrow 0} \sigma_e\left(\eta \frac{\psi}{\delta}\right) = \lim_{\delta \downarrow 0} \sigma_s(\eta \psi). \tag{111}$$

With (41), (43), (106), and (108) the left hand side (l.h.s.) and the right hand side (r.h.s.) can be written as

$$\lim_{\delta \downarrow 0} \sigma_e\left(\eta \frac{\psi}{\delta}\right) = \lim_{\delta \downarrow 0} \left[\sigma_{e,0}\left(\eta \frac{\psi}{\delta}\right) + \delta \sigma_{e,1}\left(\eta \frac{\psi}{\delta}\right) \right], \tag{112}$$

$$\lim_{\delta \downarrow 0} \sigma_s(\eta \psi) = \sigma_{s0} + \eta \psi \sigma'_{s0} + \delta \sigma_{s1} + \delta \eta \psi \sigma'_{s1}. \tag{113}$$

In the limit, the terms of $\mathcal{O}(\delta^2)$ vanish but the other terms need further evaluation.

Evaluation of σ_e : First $\sigma_e(\eta \psi/\delta)$ is evaluated with the results from (101) and (103)

$$\begin{aligned} \sigma_e\left(\eta \frac{\psi}{\delta}\right) &= \sigma_{e,0}\left(\eta \frac{\psi}{\delta}\right) + \delta \sigma_{e,1}\left(\eta \frac{\psi}{\delta}\right) \\ &= \rho \gamma_{e0} \tau_0 + \delta \left(\rho \tau_0^2 (r_0 + \lambda \gamma_{e0} \tau_0) - \rho \lambda \gamma_{e0} \tau_0^2 \eta \frac{\psi}{\delta} \right) + \mathcal{O}(\delta^2) + \text{EXP} \\ &= \rho \gamma_{e0} \tau_0 - \rho \lambda \gamma_{e0} \tau_0^2 \eta \psi + \delta \rho \tau_0^2 (r_0 + \lambda \gamma_{e0} \tau_0) + \mathcal{O}(\delta^2) + \text{EXP}. \end{aligned} \tag{114}$$

In the limit $\delta \downarrow 0$ the terms of $\mathcal{O}(\delta^2)$ and the exponential terms vanish [14, 16]

$$\lim_{\delta \downarrow 0} \sigma_e\left(\eta \frac{\psi}{\delta}\right) = \rho \gamma_{e0} \tau_0 - \rho \lambda \gamma_{e0} \tau_0^2 \eta \psi + \delta \rho \tau_0^2 (r_0 + \lambda \gamma_{e0} \tau_0). \tag{115}$$

Evaluation of σ_s : For the evaluation of $\sigma_s(\eta \psi)$ it is assumed that the limit for $\delta \downarrow 0$ is such that the terms of $\mathcal{O}(\delta \psi)$ vanish. Then the last term in Eq. (113) can be omitted

$$\lim_{\delta \downarrow 0} \sigma_s(\eta \psi) = \sigma_{s0} + \eta \psi \sigma'_{s0} + \delta \sigma_{s1}. \tag{116}$$

6.3.2 Intermediate layer for the complex concentration

The relations of the complex concentration in the intermediate layer are calculated in the same way as for the substrate concentration. In the intermediate layer it is required that

$$\lim_{\delta \downarrow 0} \gamma_c\left(\eta \frac{\psi}{\delta}\right) = \lim_{\delta \downarrow 0} \gamma_s(\eta \psi). \tag{117}$$

With (42), (44), (107), and (109) both sides of this equation turn into

$$\lim_{\delta \downarrow 0} \gamma_e \left(\eta \frac{\psi}{\delta} \right) = \lim_{\delta \downarrow 0} \left[\gamma_{e,0} \left(\eta \frac{\psi}{\delta} \right) + \delta \gamma_{e,1} \left(\eta \frac{\psi}{\delta} \right) \right], \quad (118)$$

$$\lim_{\delta \downarrow 0} \gamma_s (\eta \psi) = \gamma_{s0} + \eta \psi \gamma'_{s0} + \delta \gamma_{s1} + \delta \eta \psi \gamma'_{s1}. \quad (119)$$

Evaluation of γ_e : At first $\gamma_e(\eta \psi/\delta)$ is evaluated with the results from (102) and (104)

$$\begin{aligned} \gamma_e \left(\eta \frac{\psi}{\delta} \right) &= \gamma_{e,0} \left(\eta \frac{\psi}{\delta} \right) + \delta \gamma_{e,1} \left(\eta \frac{\psi}{\delta} \right) \\ &= \gamma_{e0} + \delta \left(r_0 - \lambda \gamma_{e0} \eta \frac{\psi}{\delta} \right) + \mathcal{O}(\delta^2) + \text{EXP} \\ &= \gamma_{e0} - \lambda \gamma_{e0} \eta \psi + \delta r_0 + \mathcal{O}(\delta^2) + \text{EXP}. \end{aligned} \quad (120)$$

In the limit $\delta \downarrow 0$ the terms of $\mathcal{O}(\delta^2)$ and the exponential terms vanish

$$\lim_{\delta \downarrow 0} \gamma_e \left(\eta \frac{\psi}{\delta} \right) = \gamma_{e0} - \lambda \gamma_{e0} \eta \psi + \delta r_0. \quad (121)$$

Evaluation of γ_s : With the same assumption as for (116) the the evaluation of $\gamma_s(\eta \psi)$ yields

$$\lim_{\delta \downarrow 0} \gamma_s (\eta \psi) = \gamma_{s0} + \eta \psi \gamma'_{s0} + \delta \gamma_{s1}. \quad (122)$$

6.4 Matching of the terms in the intermediate layer

Now, the short term and the long term solutions of the substrate concentration and the complex concentration within the intermediate layer have been determined. The next step is to match the corresponding terms for equal orders of δ .

6.4.1 Matching of the substrate concentration

The matching process of the substrate concentration is performed separately for the terms of $\mathcal{O}(1)$ and $\mathcal{O}(\delta)$. A comparison of the respective terms from (115) and (116) yields the identities

$$\mathcal{O}(1) \quad \rho \gamma_{e0} \tau_0 - \rho \lambda \gamma_{e0} \tau_0^2 \eta \psi = \sigma_{s0} + \sigma'_{s0} \eta \psi, \quad (123)$$

$$\mathcal{O}(\delta) \quad \rho \tau_0^2 (r_0 + \lambda \gamma_{e0} \tau_0) = \sigma_{s1}. \quad (124)$$

Matching of the terms of order $\mathcal{O}(1)$: The terms of order $\mathcal{O}(1)$ from (123) can be separated into constant terms and terms proportional to $\eta \psi$. For these terms two separate identities

$$(\eta \psi)^0 \quad \sigma_{s0} = \rho \gamma_{e0} \tau_0, \quad (125)$$

$$(\eta \psi)^1 \quad \sigma'_{s0} = -\rho \lambda \gamma_{e0} \tau_0^2 \quad (126)$$

follow. The value σ'_{s0} is obtained from (85) for $\theta = 0$ as

$$\sigma'_{s0} = \sigma'_{s,0}(0) = -\rho \frac{w'(0)}{w^2(0)} = -\rho \frac{\lambda\gamma_{s,0}}{(1 - \gamma_{s,0})^2}. \tag{127}$$

Insertion into (126) using (64) yields

$$-\frac{1}{\rho\lambda} \sigma'_{s0} = \frac{\gamma_{s,0}}{(1 - \gamma_{s,0})^2} = \frac{\gamma_{e,0}}{(1 - \gamma_{e,0})^2}. \tag{128}$$

This identity holds for

$$\gamma_{s,0} = \gamma_{e,0}. \tag{129}$$

Matching of the terms of order $\mathcal{O}(\delta)$: Eq. (124) states directly

$$\sigma_{s1} = \rho\tau_0^2(r_0 + \lambda\gamma_{e0}\tau_0). \tag{130}$$

6.4.2 Matching of the complex concentration

Using Eqs. (121) and (122) the zero and first order terms are obtained in the same way as in Eqs. (123) and (124)

$$\mathcal{O}(1) \qquad \gamma_{e0} - \lambda\gamma_{e0} \eta\psi = \gamma_{s0} + \gamma'_{s0} \eta\psi, \tag{131}$$

$$\mathcal{O}(\delta) \qquad r_0 = \gamma_{s1}. \tag{132}$$

Matching of the terms of order $\mathcal{O}(1)$: Again, a separation into the powers of $\eta\psi$ gives

$$(\eta\psi)^0 \qquad \gamma_{s0} = \gamma_{e0}, \tag{133}$$

$$(\eta\psi)^1 \qquad \gamma'_{s0} = -\lambda\gamma_{e0}. \tag{134}$$

From (81) follows

$$\gamma'_{s0} = \gamma'_{s,0}(0) = -\lambda\gamma_{s0}. \tag{135}$$

Insertion into (134) confirms (129).

Matching of the terms of order $\mathcal{O}(\delta)$: From (132) follows with (66)

$$\gamma_{s1} = r_0 = \sigma_{e0} - \rho\gamma_{e0}\tau_0. \tag{136}$$

Thus the abbreviation r_0 from (66) turns out to be equal to the initial value of the $\mathcal{O}(\delta)$ term of the long term solution of the complex concentration γ_{s1} .

6.5 Summary of the matching process

After the tedious matching of corresponding terms for equal powers of δ and of $\eta\psi$ for both the substrate and the complex concentration, the individual results from Eqs. (125), (129), (136), (130), (136), (126), (135) are summarized here

$$\sigma_{s0} = \rho\gamma_{e0}\tau_0 = \rho \frac{\gamma_{e0}}{1 - \gamma_{e0}}, \quad (137)$$

$$\gamma_{s0} = \gamma_{e0}, \quad (138)$$

$$\gamma_{s1} = r_0 = \sigma_{e0} - \sigma_{s0} = \sigma_{e0} - \rho\gamma_{e0}\tau_0, \quad (139)$$

$$\sigma_{s1} = \rho\tau_0^2(r_0 + \lambda\gamma_{e0}\tau_0), \quad (140)$$

$$\sigma'_{s0} = -\rho\lambda\gamma_{e0}\tau_0^2, \quad (141)$$

$$\gamma'_{s0} = \gamma'_{s,0}(0) = -\lambda\gamma_{s0}, \quad (142)$$

$$\sigma_{s1} = \tau_0(\rho\gamma_{s1}\tau_0 - \sigma'_{s0}). \quad (143)$$

Some conclusions can be drawn from these results:

The abbreviation r_0 introduced previously in (66) can be expressed in various ways by γ_{s1} as well as by σ_{e0} and σ_{s0} in (139). Also the matching result for σ_{s1} in (140) can be rephrased in terms of the other results in concise form as (143).

Eqs. (137)–(142) allow to express the initial values σ_{s0} , γ_{s0} , σ_{s1} , γ_{s1} and the initial derivatives σ'_{s0} , γ'_{s0} of the long term solution entirely by the two initial values σ_{e0} and γ_{e0} of the short term solution. Nevertheless, the initial values of the long term solution constitute concise and meaningful abbreviations for the more lengthy expressions that arise from using only the initial values σ_{e0} and γ_{e0} of the short term solution. Therefore, the initial values of the long term solution will still be used as abbreviations for the sake of conciseness.

6.6 Matched solutions for the short term and long term behaviour

The matching process described in this section so far has succeeded in expressing the initial values σ_{s0} , σ_{s1} , γ_{s0} , γ_{s1} of the long term solution by the initial values of the short term solution and thus by the initial values of the rate Eq. (5). Thus, the solutions for the short term behaviour and for the long term behaviour are compiled here as the outcome of the matching process. For conciseness, the initial values of the long term solution are still used but now as abbreviations defined in Eqs. (137)–(142).

6.6.1 Short term behaviour

The short term behaviour is given by Eqs. (77)–(80)

$$\sigma_{e,0}(\tau) = \sigma_{s0} + \gamma_{s1} \exp\left(-\frac{\tau}{\tau_0}\right), \quad (144)$$

$$\gamma_{e,0}(\tau) = \gamma_{e0}, \quad (145)$$

$$\begin{aligned} \sigma_{e,1}(\tau) &= \sigma_{s1} \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) \\ &\quad + \gamma_{s1} \left((\gamma_{s1} - \rho\tau_0)\tau - \frac{1}{2}\lambda\gamma_{e0}\tau^2\right) \exp\left(-\frac{\tau}{\tau_0}\right) \\ &\quad - \gamma_{s1}^2\tau_0 \exp\left(-\frac{\tau}{\tau_0}\right) \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right) + \sigma'_{s0}\tau, \end{aligned} \quad (146)$$

$$\gamma_{e,1}(\tau) = -\lambda\gamma_{e0}\tau + \gamma_{s1} \left(1 - \exp\left(-\frac{\tau}{\tau_0}\right)\right). \quad (147)$$

6.6.2 Long term behaviour

In the same way follows from Eqs. (96)-(100)

$$\gamma_{s,0}(\theta) = \gamma_{e0} e^{-\lambda\theta}, \tag{148}$$

$$w(\theta) = 1 - \gamma_{s,0}(\theta), \tag{149}$$

$$w(0) = 1 - \gamma_{s0} = \frac{1}{\tau_0}, \tag{150}$$

$$\sigma_{s,0}(\theta) = \rho \frac{\gamma_{s,0}(\theta)}{w(\theta)}, \tag{151}$$

$$\gamma_{s,1}(\theta) = \rho \gamma_{s,0}(\theta) \left(\ln(w(\theta)\tau_0) - \frac{1}{w(\theta)} + \lambda\theta + \tau_0 \right) + \gamma_{s1} e^{-\lambda\theta}, \tag{152}$$

$$\sigma_{s,1}(\theta) = \frac{1}{w^2(\theta)} (\rho \gamma_{s,1}(\theta) + \lambda \sigma_{s,0}(\theta)). \tag{153}$$

7 Uniform solutions

As the final step, the equations for the short term behaviour and the long term behaviour (aka the inner and outer solutions) are combined to the so-called uniform solution. It consists not only of the sum of the short term and the long term solution but also of a subtractive common term. This common term contains those parts which are common to the short term and long term behaviour and which are counted twice in their summation. The common term is most simply expressed by a limit value of the long term behaviour [14, 16].

The uniform solution is written in dependency of the short term variable τ with the long term variable θ replaced by $\theta = \tau\delta = \eta\psi$ from (110).

7.1 Substrate concentration

For the substrate concentration follows from Eqs. (41), (43) and (116)

$$\begin{aligned} \sigma_u(\tau) &= \sigma_e(\tau) + \sigma_s(\tau\delta) - \lim_{\delta \downarrow 0} \sigma_s(\tau\delta) \\ &= \sigma_{e,0}(\tau) + \delta\sigma_{e,1}(\tau) + \sigma_{s,0}(\tau\delta) + \delta\sigma_{s,1}(\tau\delta) - (\sigma_{s0} + \delta\sigma_{s1} + \sigma'_{s0} \tau\delta) \\ &= \sigma_{u,0}(\tau) + \delta \sigma_{u,1}(\tau) \end{aligned} \tag{154}$$

with

$$\sigma_{u,0}(\tau) = \sigma_{e,0}(\tau) + \sigma_{s,0}(\tau\delta) - \sigma_{s0} \tag{155}$$

$$\sigma_{u,1}(\tau) = \sigma_{e,1}(\tau) + \sigma_{s,1}(\tau\delta) - (\sigma_{s1} + \sigma'_{s0} \tau). \tag{156}$$

The functions $\sigma_{e,0}(\tau)$, $\sigma_{e,1}(\tau)$, $\sigma_{s,0}(\tau\delta)$, $\sigma_{s,1}(\tau\delta)$ and the initial values σ_{s0} , σ_{s1} , σ'_{s0} can be inserted from Eqs. (144), (146), (151), (153) and (137), (140), (141), respectively.

Note that the initial values cancel the corresponding terms in (146) and (147) as a result of the matching procedure.

7.2 Complex concentration

For the substrate concentration follows from Eqs. (42), (44) and (122)

$$\begin{aligned}\gamma_u(\tau) &= \gamma_e(\tau) + \gamma_s(\tau\delta) - \lim_{\delta \downarrow 0} \gamma_s(\tau\delta) \\ &= \gamma_{e,0}(\tau) + \delta\gamma_{e,1}(\tau) + \gamma_{s,0}(\tau\delta) + \delta\gamma_{s,1}(\tau\delta) - (\gamma_{s0} + \delta\gamma_{s1} + \gamma'_{s0} \tau\delta) \\ &= \gamma_{u,0}(\tau) + \delta\gamma_{u,1}(\tau)\end{aligned}\quad (157)$$

with

$$\gamma_{u,0}(\tau) = \gamma_{e,0}(\tau) + \gamma_{s,0}(\tau\delta) - \gamma_{s0} \quad (158)$$

$$\gamma_{u,1}(\tau) = \gamma_{e,1}(\tau) + \gamma_{s,1}(\tau\delta) - (\gamma_{s1} + \gamma'_{s0} \tau) \quad (159)$$

The functions $\gamma_{e,0}(\tau)$, $\gamma_{e,1}(\tau)$, $\gamma_{s,0}(\tau\delta)$, $\gamma_{s,1}(\tau\delta)$ and the initial values γ_{s0} , γ_{s1} , γ'_{s0} can be inserted from Eqs. (145), (147), (148), (152) and (138), (139), (142), respectively. Again, the subtraction of the initial terms reflects the matching procedure.

7.3 Summary of the calculations

The uniform solutions can be written entirely in terms of exponential functions, logarithms and powers of the time variable by inserting the initial conditions from Sect. 6.5 and equations from Sect. 6.6 as described above in Sect. 7. However, the resulting expressions for the general case are rather lengthy and are not reproduced here. For a simplified case they are shown in Sect. 8.

A summary of the calculations for the general case is listed in Table 1. It specifies an algorithm for the computation of the solution of the enzyme kinetics according to the presented first order perturbation approach. A code example in the programming environment MATLAB is provided in [15].

The calculation starts with the collection of the given values. The rate constants are defined with respect to the natural time axis in seconds or fractions thereof. The initial values are given in terms of amount of substance per volume. Then, the dimensionless time axes and the dimensionless rate constants are calculated. These serve to express also the initial values in dimensionless form.

The core of the algorithm is the calculation of the short term and long solutions and their combination into the uniform solutions simply by evaluation of Eqs. (144)–(159). Finally, the physical dimensions of the various concentrations are recovered by inversion of the initial time and amplitude scaling.

Table 1 Summary of the calculations for the enzyme kinetics with a first order perturbation approach. See Sect. 7.3 for a detailed explanation

Given:	Equations:
time axis t	
rate constants k_1, k_{-1}, k_2	(2)–(4)
initial concentrations s_0, e_0, c_0	(5)
Constants and scaled time axes	
$e_T = e_0 + c_0$	(6)
$T_e = \frac{1}{k_1 e_T}, T_s = \frac{1}{k_1 s_0}, \delta = \frac{T_e}{T_s}$	(10), (30)
$\rho = k_{-1} T_s, \lambda = k_2 T_s, K = \rho + \lambda, v_0 = \frac{c_0}{e_T}, \tau_0 = \frac{1}{1 - v_0}$	(11), (18), (64)
$\tau = \frac{t}{T_e}, \theta = \tau \delta$	(19)
Initial values	(18), (137)–(142)
$\sigma_{s0} = \rho v_0 \tau_0, \gamma_{s0} = \gamma_{e0} = v_0,$	
$\gamma_{s1} = 1 - v_0, \sigma_{s1} = \rho \tau_0^2 (1 - v_0 + \lambda v_0 \tau_0)$	
$\sigma'_{s0} = -\rho \lambda v_0 \tau_0^2, \gamma'_{s0} = -\lambda v_0$	
Short term and long term solutions	
$\sigma_{e,0}(\tau), \gamma_{e,0}(\tau), \sigma_{e,1}(\tau), \gamma_{e,1}(\tau)$	(144)–(147)
$\gamma_{s,0}(\theta), w(\theta), \sigma_{s,0}(\tau), \gamma_{s,1}(\theta), \sigma_{s,1}(\theta)$	(148)–(153)
Uniform solutions	
$\sigma_{u,0}(\tau), \sigma_{u,1}(\tau), \gamma_{u,0}(\theta), \gamma_{u,1}(\theta), \sigma_u(\tau), \gamma_u(\theta)$	(154)–(159)
Physical dimensions for time and amplitudes	
$s(t) = s_0 \sigma_u(t/T_e), c(t) = e_T \gamma_u(t/T_e), e(t) = e_T - c(t)$	(9), (19), (6)

8 Relation to previous work in this field

As already noted in Sect. 1, the above enzyme kinetics have been investigated before for the case of zero initial complex concentration. The obtained solutions are included in the uniform solution from Sect. 7 as a special case.

Using (18), (64), and (137)–(142) the simplified relations for a vanishing initial complex concentration $c(0)$ can be obtained

$$\sigma_{e0} = 1, \quad \gamma_{e0} = v_0 = 0, \quad \tau_0 = 1, \quad (160)$$

$$\sigma_{s0} = 0, \quad \gamma_{s0} = 0, \quad \gamma_{s1} = 1, \quad (161)$$

$$\sigma_{s1} = \rho, \quad \sigma'_{s0} = 0, \quad \gamma'_{s0} = 0. \quad (162)$$

The short term solutions (144)–(147) become

$$\sigma_{e,0}(\tau) = e^{-\tau}, \quad \sigma_{e,1}(\tau) = \rho (1 - e^{-\tau}) + (1 - \rho) \tau e^{-\tau} - e^{-\tau} (1 - e^{-\tau}) \quad (163)$$

$$\gamma_{e,0}(\tau) = 0, \quad \gamma_{e,1}(\tau) = 1 - e^{-\tau}. \quad (164)$$

From (81) and (82) follows with $\gamma_{s0} = 0$ that also $w(\theta) = 1$. The long term solutions (148)–(153) are now

$$\sigma_{s,0}(\theta) = 0, \quad \sigma_{s,1}(\theta) = \rho e^{-\lambda\theta}, \quad \gamma_{s,0}(\theta) = 0, \quad \gamma_{s,1}(\theta) = e^{-\lambda\theta}. \quad (165)$$

The uniform solutions for zero initial complex concentration are

$$\sigma_u(\tau) = e^{-\tau} + \delta \left(e^{-2\tau} + [(1 - \rho)\tau - (1 + \rho)]e^{-\tau} + \rho e^{-\lambda\tau\delta} \right), \quad (166)$$

$$\gamma_u(\tau) = \delta \left(e^{-\lambda\tau\delta} - e^{-\tau} \right). \quad (167)$$

Returning to physical dimensions for time and concentration finally gives the substrate and complex concentrations [see Table 1 and Eqs. (9), (19), (30)]

$$s(t) = s_0 e^{-k_1 e_T t} + \frac{s_0^2}{e_T} \left(e^{-2k_1 e_T t} + \left[(k_1 s_0 - k_{-1}) \frac{e_T}{s_0} t - \left(1 + \frac{K_D}{s_0} \right) \right] e^{-k_1 e_T t} + \frac{K_D}{s_0} e^{-k_2 t} \right), \quad (168)$$

$$c(t) = s_0 \left(e^{-k_2 t} - e^{-k_1 e_T t} \right). \quad (169)$$

These relations coincide with the results obtained in [4, Eq. (21)] with the dissociation constant $K_D = k_{-1}/k_1$.

9 Example

The uniform solutions from Sect. 7 have been calculated according to Table 1 with the parameter values listed in Table 2. They are compared to the numerical solution of the Eqs. (7,8) which is calculated by the MATLAB ODE solver `ode15s` with the relative tolerance set to $\delta^2/10$. The program code for the generation of this example is available at [15].

Table 2 Parameter values for the example in Sect. 9. The top row contains the values for the rate constants and the initial concentrations according to the top section in Table 1. The bottom row shows the numerical values that have been calculated according to the second section in Table 1. The initial concentrations are given in a suitable unit (amount of substance per volume). The rate constants k_{-1} and k_2 are given in inverse time. The values for the reference times T_e and T_s follow in the corresponding time unit

s_0	e_0	c_0		k_1		k_{-1}		k_2
0.03	0.5	1		$\frac{100}{3}$		0.1		1
e_T	T_e	T_s	δ	ρ	λ	K	ν_0	τ_0
1.5	0.02	1	0.02	0.1	1	1.1	$\frac{2}{3}$	3

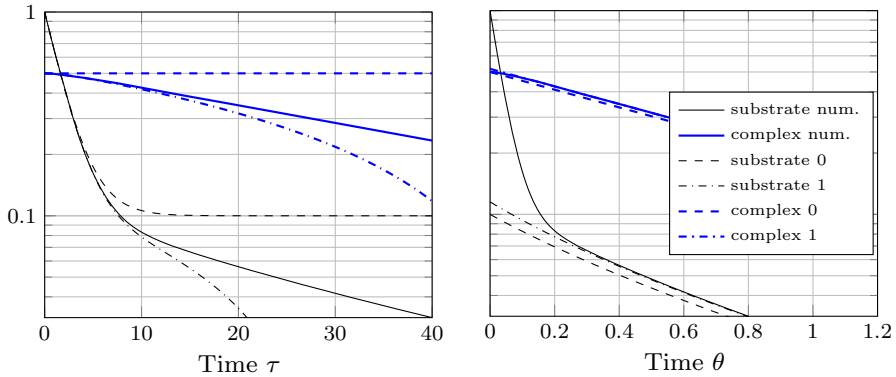


Fig. 3 Short term (left) and long term (right) behaviour for the substrate concentration (thin) and the complex concentration (thick) for order zero and one along with the respective numerical solutions. Horizontal axis: dimensionless time τ (left) and dimensionless time θ (right). Vertical axis: dimensionless concentration

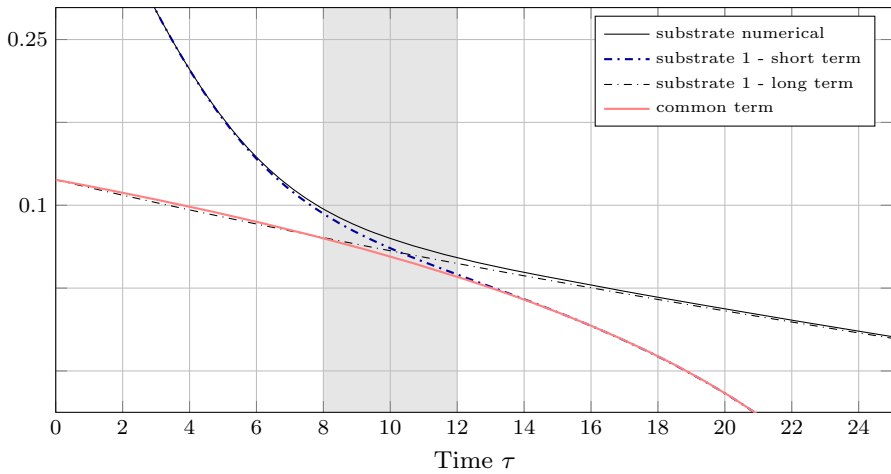


Fig. 4 Short term behaviour and long term behaviour for the substrate concentration and common term for first order along with the numerical solution. Horizontal axis: dimensionless time τ . Vertical axis: dimensionless concentration. The grey shaded area indicates the approximate position of the intermediate layer

Figure 3 (left) shows the short term behaviour for the perturbation approaches of order 0 and 1. The first order approach approximates the numerical solution quite well for $0 < \tau < 10$. The long term behaviour is shown in Fig. 3 (right). The zero order approach deviates visibly from the numerical solution for all values of θ while the first order approach is a good approximation for $\theta > 0.2$. Note that $\tau = 10$ corresponds to $\theta = 0.2$ due to $\delta = 0.2$ (see Table 2) and Eq. (110).

Figure 4 shows both the short term and the long term behaviour for the substrate concentration as well as the so-called common part of both first order approximations. This common part approximates those regions of the short term behaviour and of the long term behaviour which deviate from the true solution. These regions are $0 < \theta <$

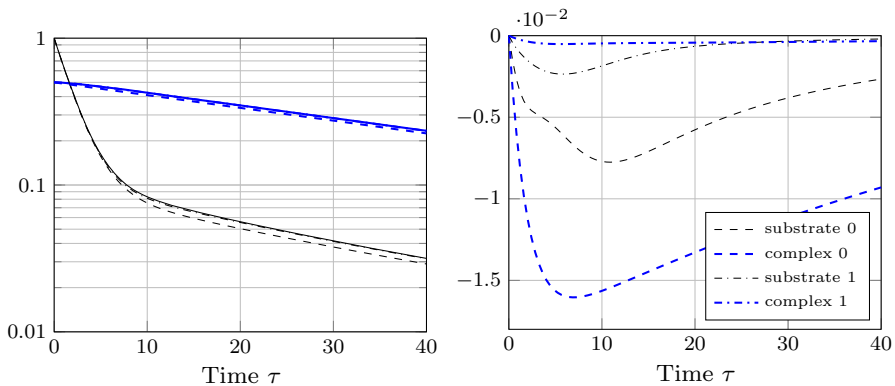


Fig. 5 Left: Uniform solutions for the substrate concentration (thin) and the complex concentration (thick). Right: Differences between the zero order and first order approximations and the numerical solution for the substrate and the complex concentration. Horizontal axis: dimensionless time τ . Vertical axis: dimensionless concentration difference

0.2 for the long term behaviour and $0.2 < \theta$ for the short term behaviour. Subtracting the common part in (154) corrects for these poor approximations.

The uniform solution for the substrate and the complex concentration and for the perturbation approaches of order 0 and 1 are shown in Fig. 5 (left). The zero order approximation is reasonably good although some deviations are visible. The first order approximation can hardly be distinguished from the numerical solution. The differences between the zero order resp. first order approximation and the numerical solution are shown in Fig. 5 (right). The deviations of the zero order approximation for substrate and complex concentration is about 1%. The first order approximation exhibits a deviation which is about one order of magnitude less.

Finally, the complex concentration is plotted against the substrate concentration in the style of a phase diagram in Fig. 6. The perturbation approximation is of first order. In similar representations (e.g. [Figs. 3–6] [10]), the time evolution starts at a complex concentration of zero, but here an arbitrary initial complex concentration is possible. The short term behaviour is characterized by a quick decrease of the substrate with an almost constant complex concentration. When less than 10% of the initial substrate is left, the decomposition of the complex is dominant over the formation of new complex. The corresponding faster decrease of the complex characterizes the long term behaviour.

10 Conclusions

An approximate solution of the classical enzyme kinetics problem by a perturbation approach has been presented. The adopted definition of the perturbation parameter δ is suitable whenever there is an excess of enzyme over substrate. This choice is motivated by potential applications in molecular communications, where few substrate particles act as carriers of information.

As a generalization over existing solutions of the same problem, the presented approximation allows for nonzero initial conditions of the substrate and the enzyme

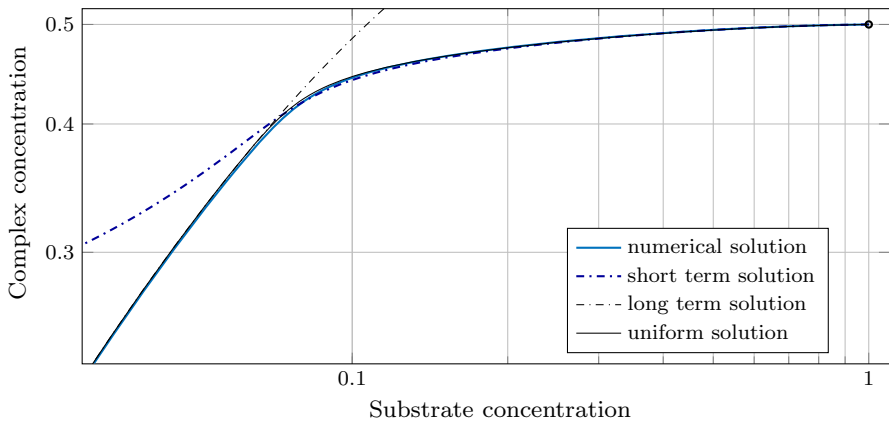


Fig. 6 Complex concentration versus substrate concentration: Numerical solution, short term, long term, and uniform solution for first order perturbation. The time evolution starts at the initial values denoted by a small circle at (1, 0.5) and proceeds towards decreasing values of both concentrations

concentrations as well as for nonzero initial complex concentration. Nevertheless, the approximate solution has been obtained in analytical form involving only elementary functions like exponentials and logarithms.

Crucial in the derivation and presentation of the approximation is the choice of meaningful intermediate quantities. Here the time constant τ_0 and the function $w(\theta)$ have been proven useful to express the first order perturbation solution in a concise form.

Further work in this direction may extend the proposed framework to other definitions of the perturbation parameter suitable for other regimes of concentration relations. Of interest is also a comparison to the homotopy method [12].

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

A Appendix

A.1 Solution of a linear first order differential equation

The linear ordinary differential equation of first order with initial condition

$$y'(t) + \frac{1}{t_0} y(t) = v(t), \quad y(0) = y_0 \tag{170}$$

has the solution [6]

$$y(t) = \exp\left(-\frac{t}{t_0}\right) \left[\int_0^t v(t') \exp\left(\frac{t'}{t_0}\right) dt' + y_0 \right]. \tag{171}$$

A.2 Integration of Eq. (90)

For the function $w(\theta)$ from Eq. (82) holds

$$\int \frac{\lambda}{w^2(\theta)} d\theta = \ln w(\theta) - \frac{1}{w(\theta)} + \lambda\theta + \text{const} \quad (172)$$

since

$$\begin{aligned} \frac{d}{d\theta} \left[\ln w(\theta) - \frac{1}{w(\theta)} + \lambda\theta \right] &= \frac{w'(\theta)}{w(\theta)} + \frac{w'(\theta)}{w^2(\theta)} + \lambda \\ &= \frac{1}{w^2(\theta)} \left[w'(\theta)(1 + w(\theta)) + \lambda w^2(\theta) \right] = \frac{\lambda}{w^2(\theta)}, \end{aligned} \quad (173)$$

where the relations (82) and (83) have been used.

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