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Highlights

- We recall the perturbation expansion for Michaelis-Menten kinetics.
- We then apply an alternative approach based on the renormalization group.
- We show that the uniform approximations better reproduce the numerical solutions of the original problem in a region encompassing the matching one.

An alternative approach to Michaelis-Menten kinetics that is based on the Renormalization Group.

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Abstract

We apply to Michaelis-Menten kinetics an alternative approach to the study of Singularly Perturbed Differential Equations, that is based on the Renormalization Group (SPDERG).¹ To this aim, we first rebuild the perturbation expansion for Michaelis-Menten kinetics, beyond the standard Quasi-Steady-State Approximation (sQSSA), determining the 2nd order contributions to the inner solutions, that are presented here for the first time to our knowledge. Our main result is that the SPDERG 2nd order uniform approximations reproduce the numerical solutions of the original problem in a better way than the known results of the perturbation expansion, even in the critical matching region. Indeed, we obtain analytical results nearly indistinguishable from the numerical solutions of the original problem in a large part of the whole relevant time window, even in the case in which the kinetic constants produce an expansion parameter value as large as $\varepsilon = 0.5$.

Keywords: Enzyme Kinetics, Singular Perturbation, Perturbation Expansion, Renormalization Group approach

1. Introduction

Michaelis-Menten (MM) kinetics, that characterizes enzymatic reactions [1, 2, 3, 4, 5], is a well known example in biomathematics [4, 5, 6, 7] of a system of ordinary differential equations (ODEs) characterized by two definitely different time scales. At the very beginning the complex rapidly reaches a pseudo-equilibrium with the substrate in a time

¹We used the following abbreviations (here listed in the order in which they appear in the text): sQSSA for standard Quasi-Steady-State Approximation; SPDERG for Singularly Perturbed Differential Equations by Renormalization Group; MM for Michaelis-Menten; ODE for Ordinary Differential Equation and ODEs for Ordinary Differential Equations; tQSSA for total Quasi-Steady-State Approximation; IC for Initial Condition and ICs for Initial Conditions.

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interval whose length can be taken as the first time scale to be considered. The second part of the reaction, that is important for the experimental observations, happens on a time scale that can be as longer as several orders of magnitude than the first one [8]. In fact, from the theoretical point of view [3, 4, 5, 9], MM kinetics is an example of boundary layer problem. In literature there are a lot of papers aiming at approximating the solutions of the system. In the *standard* Quasi-Steady-State Approximation (sQSSA) [1, 2, 3, 4, 5] the independent variables are chosen to be the substrate and the complex, with the complex evolution that depends algebraically on the substrate. It is the routinely taken starting point for investigating the system's dynamics. Nevertheless, different starting points can be taken into consideration in the literature [3, 4].

In the present work, we are interested in testing the correctness, in MM kinetics, of the approach to singularly perturbed differential equations that is based on the renormalization group (SPDERG) proposed by Chen, Goldenfeld and Oono in [10, 11], as an alternative to the perturbation expansion. In order to clarify similarities and differences between these two analytical ways of approximating the correct solutions, we focus here on the case of the perturbation expansion beyond the sQSSA, since the sQSSA appears the simplest starting point from the analytical point of view [3].

In fact, in the standard method, the solutions are approximated just by the perturbation expansion, in an appropriate parameter ε , of both the inner and the outer components of the two chosen independent variables, *i.e.*, of the solutions of systems of two ODEs with regular and singular perturbations, respectively, with the further imposition, at each order in ε , of the appropriate matching conditions. Within this framework, both the sQSSA [3, 4, 5, 12] and the *total* Quasi-Steady-State Approximation (tQSSA) [3, 13, 14, 15, 16, 17, 18, 19] represent the 0th order terms of the outer solutions. From the mathematical point of view, the correctness of applying the perturbation expansion to MM kinetics can be justified on the basis of the Tikhonov theorem [4, 12], as well as on the basis of different theoretical results [5], in both of the cases by assuming a small enough expansion parameter ε .

The perturbation expansion beyond the tQSSA, in which the independent variables are chosen to be the total substrate (*i.e.*, the sum of the substrate and of the complex) and the complex, has the advantage that the value of the expansion parameter is lower than $1/4$, for whatever the values of the kinetic constants and for whatever ICs [3, 13, 14, 15, 16].

Here, instead, in the sQSSA framework, we make the usual choice for the expansion parameter (*i.e.*, $\varepsilon = e_0/s_0$ with e_0 the initial enzyme concentration and s_0 the initial substrate one) [3, 4, 5, 6]. It can be shown that, in this case, the approximated solution in the substrate / complex phase space converges rapidly to the exact one, for reasonably small ε values [4].

Indeed, in this paper we are mainly interested in generally testing the SPDERG approach to MM kinetics, comparing it with the sQSSA, which is, among other approximations (PEA, WKB etc.), one of the most considered (see in particular [5, 6]). With this in mind, we: i) choose the usual expression for the expansion parameter ε (see, for example [24, 12]); ii) consider also kinetic constants and ICs that correspond to unfavorable cases for applying the sQSSA and going beyond it.

In fact, the SPDERG approach to the tQSSA seems at a first glance more difficult than to the sQSSA, for several reasons. It is our intent to apply in the future the SPDERG to this approximation, too. Therefore, the present work can also be seen as a

necessary first step in the direction of applying the same approach to the tQSSA, which is much more interesting than the results here obtained within the sQSSA framework in order to compare with the experiments, too [3].

In any event, the problem is complicated to be solved, even in the sQSSA framework, because both of the practical difficulty in explicitly finding the outer components, and of the matching conditions to be imposed. In fact, as usual in boundary layer problems [9, 11], the number of terms, to be considered in the matching conditions, increases with the order in the expansion [5]. Indeed, these difficulties are quite generally shared by other problems involving singular perturbations [9, 11]. Nevertheless, as we also clarify in the following, the problem presented by MM kinetics seems more demanding for applying the SPDERG approach than the boundary layer ones studied in detail in [11], at least from the point of view of the choice of the integration constants to be renormalized. This last reason made in fact hard a preliminary attempt to use this approach for going beyond the tQSSA [20]. Therefore, we adopt here an ad hoc new way that is different from the usual one, because we treat as different bare constants, to be renormalized, the contributions to the substrate IC at each order of perturbation, differently from the examples in [11], where 2nd order ODEs were studied, by introducing just two integration constants.

In the present application, we calculate in detail the SPDERG uniform approximations to the correct solutions up to 2nd order. Though the work could appear quite technical and cumbersome, the calculations do not imply particular difficulties, because of the use of a symbolic algebra system that made possible to partially automate them, too. On the other hand, the present application appears to allow to better understand both the working principles and the advantages / limits of the SPDERG approach in similar cases, besides highlighting analogies and differences with the standard perturbation expansion. Indeed, the study also makes possible to get some insights on the working principles of the perturbation expansion itself. Moreover, we deepen the knowledge of MM dynamics within the sQSSA framework, even only from the point of view of the 2nd order contributions to the inner solutions, that are presented here for the first time to our knowledge. From this last perspective, it is to be noticed that the calculation of the 2nd order inner contribution is not merely a technical exercise, but is fundamental for an in-depth understanding of the SPDERG scheme in the present case, as we show in the paper.

For anticipating our main results, just these 2nd order calculations allow us to verify the correctness of the present ad hoc new way of applying the SPDERG approach, to underline its usefulness, and to propose refined SPDERG 2nd order approximations that: i) are correctly asymptotically vanishing; ii) turn out to be better approximations to the correct numerical solutions than the not refined ones. Most importantly, the present detailed verifications can be taken for granted in possible future studies of similar cases, such as, in particular, the one of MM kinetics beyond the tQSSA.

The paper substantially consists of a first more introductive part, and of a second part in which we present and discuss our results. In detail, in the first part, we recall: in Section 2, the basis of MM kinetics and the sQSSA, by moreover introducing the particular kinetic constants and the two sets of ICs that we consider; in Section 3, the results of the standard perturbation expansion beyond the sQSSA, up to the known 1st order; in Section 4, the basis of the alternative SPDERG approach proposed in [10, 11], with attention to the case of boundary layer problems. In the second part, we present and

discuss: in Section 5, the derivation of the 1st order SPDERG uniform approximations; in Section 6, the calculation of the 2nd order contributions to the SPDERG uniform approximations; in Section 7, the refined 2nd order SPDERG uniform approximations that can be proposed; in Section 8, the comparison between the different best uniform approximations that we both recall and obtain. Finally, in Section 9, we present our conclusions. The paper is moreover completed by four Appendices: in Appendix A and in Appendix B we report the 1st order inner solution for the complex, and the 2nd order ones both for the substrate and the complex, respectively; in Appendix C we verify that the ODE obtained at the 2nd order from the study of the substrate is indeed the same ODE that one finds from the study of the complex. In Appendix D we recall a simple and illustrative example, that is taken from [11], of application of the SPDERG to a Cauchy Problem associated to a nonlinear differential equation of the second order.

2. The sQSSA

The sQSSA represents a milestone in the mathematical modelling of enzymatic reactions [1, 2, 3, 4, 5, 6, 7, 21, 22, 23, 24]. Here we just remind that the original paper by Michaelis and Menten dates back to more than one century ago [1, 2], that the idea was already present in the previous papers by Henri [21, 22, 23], and that the approach was further developed in particular by Briggs and Haldane [24]. Schematically [3, 4], one is modelling the reaction between the enzyme E , the substrate S , the complex C , and the product P :

that is reversible in the first part and irreversible in the second one, with associated kinetic constants k_1 , k_{-1} , and k_2 .

When introducing the concentrations e , s , c , and p , respectively, by using the mass action law, one arrives to describe the process by means of a system of four 1st order ODEs. Then, within the standard framework [3, 4], one starts by using the conservation law $e + c = e_0 + c_0$, that implies that the enzyme concentration, e , does only depends on the complex one, c . Moreover, one observes that the product concentration, p , can be obtained from the complex concentration, c , by integrating (equivalently, one can use the other conservation law, $s + c + p = s_0 + c_0 + p_0$). Finally, one assumes that the concentrations of the complex and of the product are zero at the beginning, as in typical experiments (*i.e.*, $c_0 = p_0 = 0$).

Hence, one ends up with the well known system of two 1st order ODEs (that we write in the same form as in [4]), that are to be obeyed by the variables s and c (with ICs $s(0) = s_0$, and $c(0) = 0$):

$$\begin{cases} \dot{s}(t) &= k_1[s(t) + K_D] \left[c(t) - \frac{e_0 s(t)}{s(t) + K_D} \right] \\ \dot{c}(t) &= -k_1[s(t) + K_M] \left[c(t) - \frac{e_0 s(t)}{s(t) + K_M} \right], \end{cases} \quad (2)$$

where the dot means the time derivative. Here $K_D = k_{-1}/k_1$ is the so-called dissociation constant, whereas $K_M = (k_{-1} + k_2)/k_1$ is the parameter that is generally known as

Michaelis constant. It can be further noticed that $K_M - K_D = k_2/k_1 = K$ is the Van Slyke-Cullen constant [25]. Though the original kinetic constants, k_1 , k_{-1} , and k_2 , are the key physical parameters for the studied system, only K_M , together with $V_{max} = k_2 e_0$, turns out to be experimentally measurable, in particular on the basis of the sQSSA.

The kinetic constants that we choose are (as in [3]):

$$k_1 = 1\mu M^{-1}s^{-1}; \quad k_{-1} = 4s^{-1}; \quad k_2 = 1s^{-1}; \quad (3)$$

As we anticipated, and as we clarify in the following, both this choice and the one of the two sets of ICs, that we are going to introduce, correspond to cases in which the sQSSA is a worse approximation than for different possible ones. Indeed, as also already outlined in the Introduction, we make these choices just because they are appropriate to the present analysis. In particular, these kinetic constants give $K_D = 4\mu M$, $K_M = 5\mu M$ and $K = 1\mu M$, whereas the two sets of ICs that we consider are:

$$e_0^a = 1\mu M; \quad e_0^b = 5\mu M; \quad s_0^a = s_0^b = 10\mu M; \quad (4)$$

In detail, we are taking different values of the initial enzyme concentration, e_0 , with $e_0^b > e_0^a$, by labelling a and b the two corresponding sets.

We plot in [Fig. 1] the solutions of Eqs. (2), obtained by numerically integrating the system, for these two sets of ICs, respectively. In the same figure, we compare the solutions with their sQSSA, by enlightening the fact that MM kinetics cannot be confused with the MM approximation (or sQSSA), that is expected to be valid only in the second, pseudo-equilibrium phase. The expected inadequacy of the sQSSA in the transient phase is enhanced by the use of the logarithmic scale for the time variable, which enlarges the transient phase. On the other hand, the logarithmic scale shrinks the intervals for large times, not allowing us to appreciate the bad approximation of the sQSSA for large times, when $\varepsilon = 0.5$.

The logarithmic scale in the figures enhances the typical presence of two definitely different time scales, with the concentration of the complex, c , that evolves very rapidly at the beginning, whereas it turns out to be in a *quasi-steady-state* or *pseudo-equilibrium* in the second part, of definitely longer duration [26]. Indeed, in logarithmic scale, the presence of a *plateau*, in which the complex is really roughly constant, is well more evident in case a , whereas in case b it displays a more or less symmetric behaviour around the maximum. Actually, as we are going to better discuss, this last choice of the ICs corresponds to a particularly unfavourable situation for applying the sQSSA.

In fact, in the sQSSA, one focuses on the second part, by assuming that the complex depends algebraically on the substrate. Indeed, this is equivalent to take $\dot{c} \sim 0$ in Eqs. (2). Therefore, from the mathematical point of view, the sQSSA appears quite a coarse approximation, that has been correspondingly largely criticized in the literature. In particular, we refer the reader to the detailed review [3], where the experimental cases, in which the sQSSA fails, are resumed, too, and to the work by Heineken, Tsuchiya and Aris [12], where the perturbation expansion beyond the sQSSA, with our choice of the ε expansion parameter, is originally presented. In any event, the sQSSA is clearly the more correct on the whole time window the more the time scale corresponding to the rapid transient phase of the complex, τ_c , is short with respect to the time scale τ_s , that rules the slow decay of the substrate.

Figure 1: **The numerical solutions, for the two considered sets of ICs, and its comparison with the sQSSA ones.** (Color online) In *A*) and in *C*) we present the behaviour of the concentrations of the substrate $s(t)$, whereas in *B*) and in *D*) we present the one of the concentrations of the complex $c(t)$, solutions of Eqs. (2), for the *a* and *b* sets of ICs given by (4), respectively. Notice that the time is in logarithmic scale. We plot the corresponding rough evaluations of the two different time scales involved, too, with τ_s describing the substrate decay time and τ_c the complex saturation time (see the text for details). Moreover, we present in advance the analytical solutions computed from the sQSSA ones (by using a standard numerical approximation to the Lambert function) as given by (8) and (10), whose derivation will be recalled in the following (from this point of view, notice that in *A*) and *B*) we are in the case in which the standard expansion parameter is $\varepsilon = \varepsilon^a = 0.1$, whereas in *C*) and *D*) we are in the one with $\varepsilon = \varepsilon^b = 0.5$).

To continue, let us note that one can argue about different time scale evaluations (see for instance the recent work in [27]). Here, we consider a simple approach in which the two most relevant time scales to the system's dynamics are just the initial complex saturation time, τ_c , and the final substrate decay time, τ_s . In fact, we are considering the evaluations of τ_s and τ_c given in [4], that indeed coincide with the ones obtained by quite detailed reasonings in [28]: on the one hand, from the assumption $\dot{c} \sim -(c - c_{eq})/\tau_c$, with $s \sim s_0$, one gets $\tau_c = 1/(k_1(s_0 + K_M))$; on the other hand, within the sQSSA, one has $\dot{s} \sim -k_2 e_0 s/(s + K_M)$, hence $\dot{s} \sim -s/\tau_s$, with $\tau_s = (s_0 + K_M)/(k_2 e_0)$, if one moreover assumes a final exponential substrate decay. These evaluations give the same values for the complex saturation times, $\tau_c^a = \tau_c^b = 0.0667s$, in our case, for the *a* and *b* sets of ICs, respectively, whereas the substrate decay times are $\tau_s^a = 15s$ and $\tau_s^b = 3s$, respectively, *i.e.*, τ_s is longer for the *a* set of ICs than for the *b* one.

As we are going to discuss, this approach seems to capture basic features of the observed dynamics, and it appears particularly intriguing from the point of view of better understanding the range of the kinetic constants and of the ICs in which the sQSSA approximates the correct solutions to the best of itself. Nevertheless, a more rigorous analysis and a possible comparison with different time scale evaluations is left

to future studies.

Let us now look more in detail at the behaviours displayed by the present numerical solutions of the original problem, given by Eqs. (2), when plotted in logarithmic scale. Indeed, in the case of the substrate, one observes, both in [Fig. 1A] and in [Fig. 1B], the presence of three inflection points. Importantly, this feature appears to depend on the present choices of the kinetic constants and of the ICs. We numerically checked that, for instance, in the case $k_1 = 1\mu M^{-1}s^{-1}$, $k_{-1} = 10s^{-1}$ and $k_2 = 20s^{-1}$, with the *a* set of ICs, as well as with the present kinetic constants, but by taking a definitely smaller value of $e_0 = 0.1\mu M$, one finds a (not shown) simpler behaviour than here, with only one inflection point in the curve of the substrate.

These observations confirm that we are considering situations in which the correct solutions are difficult to be analytically approximated, at least by the perturbation expansion that goes beyond the sQSSA, just since one has to reproduce a behaviour of the substrate curve that is particularly complicated. Correspondingly, our choice of the kinetic constants and of the two set of ICs is justified.

In light of the same observations, it is also even more interesting that, as can be seen from [Fig. 1], in logarithmic scale, the obtained estimation of τ_s captures quite accurately the last (*i.e.*, the third) inflection point in the curve of the substrate, that therefore appears, correctly, interpretable as the substrate decay time. On the other hand, the obtained estimation for τ_c captures quite accurately the first inflection point in the curve of the complex, that therefore appears, correctly, interpretable as the complex saturation time, too. In fact, the position of the third inflection point in the curve of the substrate roughly coincides with the one of the second inflection point in the curve of the complex. Correspondingly, both of the inflection points in the curve of the complex are captured by τ_c and τ_s , respectively (this is more evident in the case of the *a* set of ICs). Moreover, the complex saturation time τ_c turns out to be quite near to the first inflection point in the curve of the substrate.

Consistently, in the other previously mentioned cases, that display simpler behaviours than the present ones, the positions of the single substrate inflection points are more accurately captured by the corresponding substrate decay time τ_s than here. Moreover, both τ_c and τ_s more accurately capture the positions of the two inflection points in the complex curves than here, too.

Once again, it is because we are mainly interested in underlining similarities and differences between the perturbation expansion method and the SPDERG approach, that we find also useful for the reader to recall in some detail, though as briefly as possible, the various known stages of the perturbation expansion approximations to the correct solutions, from the sQSSA to the uniform approximations at the first order in ε , in the whole time window. This is indeed the reason that motivates the remaining of this Section and the following one.

With the aim of deepening the analysis, we are led to the problem of making dimensionless the system given by Eqs. (2). This involves the choice of the ε variable as the one giving the sQSSA condition for $\varepsilon = 0$. In fact, such a variable is clearly also the possible expansion parameter for going beyond the sQSSA. Here, within the two known possible schemes for making dimensionless the equations, and the two corresponding different choices of the ε variable [3, 4, 28], in the sQSSA case, we limit ourselves to study the one that is more largely considered in the literature [24, 3, 4, 6, 7, 5, 12], *i.e.*, $\varepsilon = e_0/s_0$.

Let us underline that the discussion about the correctness of the choice of the pertur-

bation parameter and of the adimensional variables is beyond the scopes of this paper, which is mainly devoted to test the SPDERG, comparing it to the sQSSA, as already stressed.

In detail (again following in particular [4], in the notation, too), one introduces the dimensionless parameters $m = K_D/s_0$, $M = K_M/s_0$, and one scales the time of a factor δ , $t \rightarrow \delta t$ with $\delta = k_1 e_0$. The substrate concentration is made dimensionless by taking $\tilde{s}(t) = s(t)/s_0$. Moreover, in the presently considered scheme, the complex concentration is made dimensionless by taking $\tilde{c}(t) = c(t)/e_0$ (that is a possible correct choice since, thanks to the first of the recalled conservation laws, $c(t) \leq e_0$).

Correspondingly, one obtains the (singular with respect to ε) system of ODEs:

$$\begin{cases} \dot{\tilde{s}}^{out}(t) &= [\tilde{s}^{out}(t) + m] \left[\tilde{c}^{out}(t) - \frac{\tilde{s}^{out}(t)}{\tilde{s}^{out}(t) + m} \right] \\ \varepsilon \dot{\tilde{c}}^{out}(t) &= -[\tilde{s}^{out}(t) + M] \left[\tilde{c}^{out}(t) - \frac{\tilde{s}^{out}(t)}{\tilde{s}^{out}(t) + M} \right]. \end{cases} \quad (5)$$

Here, the label *out* refers to the fact that these are, in fact, the ODEs that capture the long time behaviours, *i.e.*, the ones to be obeyed by the *outer* solutions. With the present kinetic constant choice (3), we have $m = 0.4$ and $M = 0.5$, respectively. On the other hand, the two sets of ICs given by (4) yield two different values for δ and for the expansion parameter ε :

$$\begin{aligned} \delta^a &= 1s^{-1}; & \delta^b &= 5s^{-1}; \\ \varepsilon^a &= 0.1; & \varepsilon^b &= 0.5; \end{aligned} \quad (6)$$

Thus, though the basic condition $\varepsilon < 1$ is verified in both of the cases, we are in the situation $\varepsilon^b > \varepsilon^a$, *i.e.*, the one expected to be appropriate to highlight differences between the approximations.

The system (5) should make evident that the sQSSA can be rigorously interpreted as the 0th order term of an asymptotic expansion in ε of this example of singular perturbation [3, 4, 5, 9], in which the original system is reduced to one ODE and one algebraic relation. For $\varepsilon = 0$, one has:

$$\begin{cases} \dot{\tilde{s}}_0^{out}(t) &= -\frac{M-m}{\tilde{s}_0^{out}(t) + M} \tilde{s}_0^{out}(t) \\ \tilde{c}_0^{out}(t) &= \frac{\tilde{s}_0^{out}(t)}{\tilde{s}_0^{out}(t) + M}. \end{cases} \quad (7)$$

It is to be noted that, in the numerator of the ODE to be obeyed by $\tilde{s}_0^{out}(t)$, the quantity $M - m$ is just the dimensionless Van Slyke-Cullen constant [25], K/s_0 . Here, the system is to be considered together with the substrate IC, $\tilde{s}_0^{out}(0) = 1$, in fact implying that the complex initial value is automatically fixed to $\tilde{c}_0^{out}(0) = 1/(1 + M)$.

The ODE for the dimensionless substrate concentration can be solved explicitly [3, 29], by means of the Lambert function $\omega(x)$ [30], that verifies the equation $\omega(x)e^{\omega(x)} = x$:

$$\tilde{s}_0^{out}(t) = M\omega(e^{-(M-m)t/M + 1/M}/M). \quad (8)$$

This solution does also satisfy the IC, $\tilde{s}_0^{out}(0) = 1$, since:

$$M\omega(e^{1/M}/M) = M\omega[\omega^{-1}(1/M)]. \quad (9)$$

Correspondingly, one gets:

$$\tilde{c}_0^{out}(t) = \frac{\omega(e^{-(M-m)t/M + 1/M/M})}{\omega(e^{-(M-m)t/M + 1/M/M}) + 1}, \quad (10)$$

with, in particular, $\tilde{c}_0^{out}(0) = 1/(1+M)$, as expected.

Hence, by using a standard numerical approximation to the Lambert function, we obtain the behaviours of $\tilde{s}_0^{out}(t)$ and $\tilde{c}_0^{out}(t)$, *i.e.*, the behaviours of the substrate and complex concentrations within the sQSSA. We already presented in [Fig. 1] our results for the two considered sets of ICs, in comparison with the numerical solution of the original problem, given by Eqs. (2).

We note, qualitatively, that the sQSSA gives definitely worse results for the *b* set of ICs ([Fig. 1C] and [Fig. 1D]), as predictable on the basis that $\varepsilon^b > \varepsilon^a$. In both cases, in these figures the logarithmic scale highlights that the complex very short transient time behaviour is not captured at all. Indeed, this is the well known failure of the sQSSA (that is shared by the tQSSA, too) that, as we already recalled, is quite largely criticized in the literature [3, 12]. From the mathematical point of view, it is to be stressed again that, whereas one can solve Eqs. (7) by choosing $\tilde{s}_0^{out}(0) = 1$, the original IC of the complex cannot *a priori* be satisfied within the present context. Therefore, the sQSSA is unable to predict the initial increase from zero of this quantity.

Noticeably, moreover, the presence of more than one inflection point in logarithmic scale in the curve of the substrate (hence the short time qualitative behaviour of this quantity) is not reproduced at all. In fact, also the maximum reached by the complex during its evolution is lower than its initial value within the sQSSA in both of the considered cases. This last feature is not observed in the other previously mentioned cases, that display simpler solution behaviours than the present ones, as we numerically checked. On this basis, one can indeed hypothesize that the various effects are related, though we left a more rigorous analysis to future studies. Presumably for the same reason, when taking $\varepsilon = \varepsilon^b = 0.5$ in the case *b*, it is naked-eye evident that the sQSSA fails in reproducing the long time behaviour, too (see [Fig. 1C] and [Fig. 1D]). Thus, our choices turn out to be even more appropriate than expected to the present analysis.

3. The perturbation expansion beyond the sQSSA

The standard perturbation expansion method, in the case of MM kinetics [3, 4, 5, 6, 7], too, is based on mathematical results for systems of ODEs with both singular and regular perturbations [9]. Within this framework, the system given by Eqs. (5) needs to be considered together with the system that one obtains with the transformation $t \rightarrow \tau = t/\varepsilon$, *i.e.*, in the opposite limit of short times, that is:

$$\begin{cases} \dot{\tilde{s}}^{in}(\tau) &= \varepsilon[\tilde{s}^{in}(\tau) + m] \left[\tilde{c}^{in}(\tau) - \frac{\tilde{s}^{in}(\tau)}{\tilde{s}^{in}(\tau) + m} \right] \\ \dot{\tilde{c}}^{in}(\tau) &= -[\tilde{s}^{in}(\tau) + M] \left[\tilde{c}^{in}(\tau) - \frac{\tilde{s}^{in}(\tau)}{\tilde{s}^{in}(\tau) + M} \right], \end{cases} \quad (11)$$

to be instead obeyed by the *inner* solutions.

Correspondingly [3, 4, 5, 6, 7, 9], one looks for solutions in the form:

$$\begin{cases} \tilde{s}^{in}(\tau) &= \sum_{i=0}^{\infty} \tilde{s}_i^{in}(\tau) \varepsilon^i; & \tilde{c}^{in}(\tau) &= \sum_{i=0}^{\infty} \tilde{c}_i^{in}(\tau) \varepsilon^i; \\ \tilde{s}^{out}(t) &= \sum_{i=0}^{\infty} \tilde{s}_i^{out}(t) \varepsilon^i; & \tilde{c}^{out}(t) &= \sum_{i=0}^{\infty} \tilde{c}_i^{out}(t) \varepsilon^i; \end{cases} \quad (12)$$

by requiring that $\{\tilde{s}_i^{in}(\tau), \tilde{c}_i^{in}(\tau)\}$ satisfy the system given by Eqs. (11), in the case of the inner solutions, and that $\{\tilde{s}_i^{out}(t), \tilde{c}_i^{out}(t)\}$ satisfy the system given by Eqs. (5), in the case of the outer solutions, at each order in ε . One then imposes the appropriate matching conditions and one takes, as uniform approximations to the correct solutions at a given order in ε , the sum of the inner and of the outer solutions at that order minus the common terms [3, 5].

The whole procedure is therefore a standard perturbation expansion method [9]. We, moreover, remind that the need for imposing appropriate matching conditions is due to the lack of ICs for the outer solutions; they can be determined from the behaviours of the inner ones in the large τ limit, that have to correspond to their behaviours in the small t limit (whereas the inner solutions are the ones that satisfy the original ICs of the problem) [3, 4, 5, 9].

In detail, in the present case of the perturbation expansion beyond the sQSSA, with $\varepsilon = e_0/s_0$, we reproduce the calculations as also in [3, 4] at the 0th order, whereas we follow both the original paper by Heineken, Tsuchiya and Aris [12], and the discussion in [5], for the complete 1st order contribution.

Let us, first of all, recall the 0th order inner solutions, obtained by setting $\varepsilon = 0$ in Eqs. (11), that thereby solve:

$$\begin{cases} \dot{\tilde{s}}_0^{in}(\tau) &= 0 \\ \dot{\tilde{c}}_0^{in}(\tau) &= -[\tilde{s}_0^{in}(\tau) + M] \left[\tilde{c}_0^{in}(\tau) - \frac{\tilde{s}_0^{in}(\tau)}{\tilde{s}_0^{in}(\tau) + M} \right], \end{cases} \quad (13)$$

with $\tilde{s}_0^{in}(0) = 1$, and $\tilde{c}_0^{in}(0) = 0$. The solutions are [3, 4]:

$$\begin{cases} \tilde{s}_0^{in}(\tau) &= 1 \\ \tilde{c}_0^{in}(\tau) &= \frac{1}{1+M} \left[1 - e^{-(1+M)\tau} \right]. \end{cases} \quad (14)$$

Let us continue by recalling also the 0th order outer solution of the system given by Eqs. (7), with IC $\tilde{s}_0^{out}(0) = \tilde{s}_0^{out*}$, where $\tilde{s}_0^{out*}$ needs to be determined by imposing the matching condition on the substrate. In the relatively simple 0th order case, one expects that the substrate solution verifies $\tilde{s}_0^{out*} = 1$. In fact, with this choice, one has:

$$\begin{cases} \lim_{\tau \rightarrow \infty} \tilde{s}_0^{in}(\tau) &= \frac{1}{1+M} &= \lim_{t \rightarrow 0} \tilde{s}_0^{out}(t) \\ \lim_{\tau \rightarrow \infty} \tilde{c}_0^{in}(\tau) &= \frac{1}{1+M} &= \lim_{t \rightarrow 0} \tilde{c}_0^{out}(t). \end{cases} \quad (15)$$

Hence, not only the substrate matching condition turns out to be satisfied, but, consistently [5], this condition (the only one to be freely enforceable) satisfies the complex matching condition, too.

Figure 2: **Comparison between the numerical solutions and the 0th order perturbation expansion uniform approximation, for the two considered sets of ICs, for the complex.** (Color online) In A) we present the behaviour of the concentration of the complex $c(t)$ for the a set of ICs given by (4), whereas in B) we present the one for the b set. Hence, it is $\varepsilon = \varepsilon^a = 0.1$ in the first case and $\varepsilon = \varepsilon^b = 0.5$ in the second one. We plot both the numerical solutions of Eqs. (2), already shown in the previous figure, and the analytical solutions computed from the dimensionless 0th order perturbation expansion uniform approximation (by using a standard numerical approximation to the Lambert function) as given by (16). We finally plot our corresponding rough evaluations of the two different time scales involved, too, with τ_s describing the substrate decay time and τ_c the complex saturation time. Notice that the time is in logarithmic scale.

In conclusion, the 0th order perturbation expansion uniform approximations (that we label u), are given by [3, 4]:

$$\begin{cases} \tilde{s}_0^u(t) = \tilde{s}_0^{in}(t/\varepsilon) + \tilde{s}_0^{out}(t) - 1 + O(\varepsilon) \\ \tilde{c}_0^u(t) = \tilde{c}_0^{in}(t/\varepsilon) + \tilde{c}_0^{out}(t) - \frac{1}{1+M} + O(\varepsilon). \end{cases} \quad (16)$$

We plot in [Fig. 2] our results on the complex concentrations (the uniform approximation to the substrate being coincident with the sQSSA one), for the two considered sets of ICs, in comparison with the numerical solutions of the original problem, given by Eqs. (2) (the same curves as in [Fig. 1]). The figures show that this approximation already captures the most characteristic features of the whole system's dynamics and, in particular, the rapid initial increase of the complex.

Nevertheless, the approximation over-evaluates the correct maximum values of the complex, as it is definitely more evident in case b , that corresponds to the higher value of the expansion parameter, $\varepsilon = \varepsilon^b = 0.5$, of the two set of ICs that we consider ([Fig. 2B]). On the other hand, as we already outlined, one can notice in the curves of the substrate ([Fig. 1A] and [Fig. 1C]) the sQSSA failure in capturing the presence of the first two inflection points (in logarithmic scale). The presently recalled results make clear that this failure is shared by the 0th order perturbation expansion uniform approximation, too.

Let us, finally, recall the calculation of the 1st order contribution [5, 12]. The 1st order inner solutions solve the system:

$$\begin{cases} \dot{\tilde{s}}_1^{in}(\tau) &= (1+m) \left[\tilde{c}_0^{in}(\tau) - \frac{1}{1+m} \right] \\ \dot{\tilde{c}}_1^{in}(\tau) &= -(1+M) \tilde{c}_1^{in}(\tau) - [\tilde{c}_0^{in}(\tau) - 1] \tilde{s}_1^{in}(\tau). \end{cases} \quad (17)$$

Here, we already used $\tilde{s}_0^{in}(\tau) = 1$, thus the ICs are $\tilde{s}_1^{in}(0) = \tilde{c}_1^{in}(0) = 0$. In fact, one has in particular to solve an ODE for $\tilde{c}_1^{in}$ in the form $\dot{y}(\tau) = -(1+M)y(\tau) + f(\tau)$, whose solution is $y(\tau) = a(\tau)e^{-(1+M)\tau}$, with $a(\tau) = \int_0^\tau f(z)e^{(1+M)z}dz$. One obtains [5, 12]:

$$\begin{cases} \tilde{s}_1^{in}(\tau) &= -\frac{M-m}{1+M}\tau - \frac{1+m}{(1+M)^2} [1 - e^{-(1+M)\tau}] \\ \tilde{c}_1^{in}(\tau) &= -\frac{M(M-m)}{(1+M)^3}\tau - \frac{M(1+2m-M)}{(1+M)^4} [1 - e^{-(1+M)\tau}] + \\ &\quad - \left[\frac{(1-M)(1+m)}{(1+M)^3}\tau + \frac{M-m}{(1+M)^2} \frac{\tau^2}{2} \right] e^{-(1+M)\tau} + \\ &\quad + \frac{(1+m)}{(1+M)^4} e^{-(1+M)\tau} [1 - e^{-(1+M)\tau}]. \end{cases} \quad (18)$$

On the other hand, the 1st order outer solutions are more complicated to be obtained than the inner ones, since they solve the system (that consists once again of one ODE and of one algebraic relation):

$$\begin{cases} \dot{\tilde{s}}_1^{out}(t) &= \frac{M(M-m)}{[\tilde{s}_0^{out}(t) + M]^4} \tilde{s}_0^{out}(t) [\tilde{s}_0^{out}(t) + m] - \frac{M(M-m)}{[\tilde{s}_0^{out}(t) + M]^2} \tilde{s}_1^{out}(t) \\ \tilde{c}_1^{out}(t) &= \frac{M(M-m)}{[\tilde{s}_0^{out}(t) + M]^4} + \frac{M}{[\tilde{s}_0^{out}(t) + M]^2} \tilde{s}_1^{out}(t), \end{cases} \quad (19)$$

in which $\tilde{s}_0^{out}(t)$ is reported, in terms of the Lambert function, in (8). One can verify that the solution for $\tilde{s}_1^{out}(t)$ is given by [5]:

$$\tilde{s}_1^{out}(t) = \frac{\tilde{s}_0^{out}(t)}{\tilde{s}_0^{out}(t) + M} \left\{ \frac{m}{M} \log \left[\frac{\tilde{s}_0^{out}(t) + M}{(1+M)\tilde{s}_0^{out}(t)} \right] - \frac{\tilde{s}_0^{out}(t) + m}{\tilde{s}_0^{out}(t) + M} \right\}. \quad (20)$$

Correspondingly, the 1st order outer solution for the complex is:

$$\tilde{c}_1^{out}(t) = \frac{\tilde{s}_0^{out}(t)}{[\tilde{s}_0^{out}(t) + M]^3} \left\{ m \log \left[\frac{\tilde{s}_0^{out}(t) + M}{(1+M)\tilde{s}_0^{out}(t)} \right] + \frac{2M(M-m)}{\tilde{s}_0^{out}(t) + M} - M \right\}. \quad (21)$$

Indeed, if we were to neglect the *secular* terms (*i.e.*, the terms proportional to τ in (18)), these solutions would also correctly satisfy the matching conditions, since one has:

$$\tilde{s}_1^{out}(0) = -\frac{1+m}{(1+M)^2}; \quad \tilde{c}_1^{out}(0) = -\frac{M(1+2m-M)}{(1+M)^4}, \quad (22)$$

that are the constant terms in the 1st order inner solutions.

From the point of view of the present work, it appears important to underline that one has, instead, to reasonably justify [5] the disappearance of the 1st order secular terms with the imposition of two term matching conditions, that involve the 1st order derivatives of the 0th order outer solutions, too. Moreover [5], one iteratively expects that, at higher orders in the expansion in ε , the divergences (*i.e.*, the expected presence of secular terms proportional to higher powers of τ in the inner solutions) could be absorbed by a possibly increasing number of terms in the corresponding matching conditions.

In detail, from Eqs. (7), one has:

$$\dot{\tilde{s}}_0^{out}(0) = -\frac{M-m}{(1+M)}; \quad \dot{\tilde{c}}_0^{out}(0) = -\frac{M(M-m)}{(1+M)^3}; \quad (23)$$

Figure 3: **Comparison between the numerical solutions and the 1st order perturbation expansion uniform approximations, for the two considered sets of ICs.** (Color online) In A) and C) we present the behaviour of the concentrations of the substrate $s(t)$, whereas in B) and D) we present the one of the concentrations of the complex $c(t)$ for the a and b sets of ICs given by (4), respectively. Hence, in A) and B) we are in the case with $\varepsilon = \varepsilon^a = 0.1$, whereas in C) and D) we are in the one with $\varepsilon = \varepsilon^b = 0.5$. We plot both the numerical solutions of Eqs. (2), already shown in the previous figures, and the analytical solutions computed from the 1st order perturbation expansion uniform approximations (by using a standard numerical approximation to the Lambert function), as given by (25). We finally plot our corresponding rough evaluations of the two different time scales involved, too, with τ_s describing the substrate decay time and τ_c the complex saturation time. Notice that the time is in logarithmic scale.

Correspondingly, they turn out to be verified the two term matching conditions, reported in detail in [5], that are more or less resumable as:

$$\begin{cases} \lim_{\tau \rightarrow \infty} \{ [\tilde{s}_0^{in}(\tau) + \varepsilon \tilde{s}_1^{in}(\tau)] - [\tilde{s}_0^{out}(0) + t \dot{\tilde{s}}_0^{out}(0) + \varepsilon \tilde{s}_1^{out}(0)] \} &= 0 \\ \lim_{\tau \rightarrow \infty} \{ [\tilde{c}_0^{in}(\tau) + \varepsilon \tilde{c}_1^{in}(\tau)] - [\tilde{c}_0^{out}(0) + t \dot{\tilde{c}}_0^{out}(0) + \varepsilon \tilde{c}_1^{out}(0)] \} &= 0. \end{cases} \quad (24)$$

Noticeably, it was also proved [5] that these 1st order matching conditions apply on a time interval (the matching region) that ranges from ε to $\sqrt{\varepsilon}$.

Therefore, one takes as perturbation expansion uniform approximations to the solutions at the 1st order in ε :

$$\begin{cases} \tilde{s}_1^u(t) &= [\tilde{s}_0^{in}(t/\varepsilon) + \tilde{s}_0^{out}(t)] + \varepsilon [\tilde{s}_1^{in}(t/\varepsilon) + \tilde{s}_1^{out}(t)] + \\ &- \left[1 - \varepsilon \frac{1+m}{(1+M)^2} - \frac{M-m}{(1+M)} t \right] + O(\varepsilon^2) \\ \tilde{c}_1^u(t) &= [\tilde{c}_0^{in}(t/\varepsilon) + \tilde{c}_0^{out}(t)] + \varepsilon [\tilde{c}_1^{in}(t/\varepsilon) + \tilde{c}_1^{out}(t)] + \\ &- \left[\frac{1}{1+M} - \varepsilon \frac{M(1+2m-M)}{(1+M)^4} - \frac{M(M-m)}{(1+M)^3} t \right] + O(\varepsilon^2). \end{cases} \quad (25)$$

Let us remark that in [5], at pp. 315/316, it was proved that the error between these approximations and the correct solutions is smaller than $a\varepsilon^2$, by assuming a small enough ε , for $t \in [0, \infty)$, where a is a constant independent of both ε and t (*i.e.* the error is uniformly $O(\varepsilon^2)$ for $t \in [0, \infty)$). The statement is mainly based on the results obtained in [31, 12, 32].

We plot in [Fig. 3] our results on the substrate and complex concentrations, for the two considered sets of ICs, in comparison with the numerical solutions of the original problem, given by Eqs. (2) (the same curves as in the previous figures). The figures make evident that in the case *a* ([Fig. 3A] and [Fig. 3B]), *i.e.*, for the relatively small $\varepsilon = \varepsilon^a = 0.1$, the 1st order perturbation expansion uniform approximations are indistinguishable, within the plot precision (and within our numerical precision, too), from the correct solution on the whole relevant time interval, despite of the particularly unfavourable situation, that is characterized both by the presence of three inflection points in the curve of the substrate and by a complex initial value, within the sQSSA, that is higher than its correct maximum.

On the other hand, in case *b*, *i.e.*, for $\varepsilon = \varepsilon^b = 0.5$, that is instead a quite large value, there is a naked-eye detectable difference between the approximation and the correct solution in the case of the substrate ([Fig. 3C]), for $t \sim 0.1 - 2$ s. This region actually encompasses the matching one, which is expected to extend here from $t = \varepsilon^b/\delta^b = 0.1$ s to $t = \sqrt{\varepsilon^b}/\delta^b \simeq 0.14$ s. Moreover, again in case *b*, when looking carefully at [Fig. 3D], one can notice that the approximation to the correct complex behaviour tends to zero still slightly too rapidly. In fact, also the maximum reached by the complex during its evolution is still slightly over-evaluated by the approximation. Both of these last observations, that concern the 1st order uniform approximation to the complex solution, within the perturbation expansion framework, will be made more evident by the following [Fig. 7C] and [Fig. 7D].

4. The SPDERG approach to boundary layer problems

The SPDERG approach [10, 11], and its connections with the renormalization group [33], with attention to the context of boundary layer problems, was extensively reviewed in [20]. In this last work, as already outlined, it is presented a preliminary attempt to apply the approach to MM kinetics, within the tQSSA framework, too. Moreover, a recent review of the general method, in a context that is instead different, can be found in [34]. Here, we limit ourselves to recall in some detail the original discussion in [10, 11], where the approach was generally proposed as a successful alternative to standard singular and reductive perturbation methods, in the case of the boundary layer ones.

As MM kinetics [3, 4, 5, 20], these problems [9, 11] are generally characterized by a boundary layer of a given small thickness (that is here $O(\varepsilon)$, but that could also be, for instance, $O(\sqrt{\varepsilon})$), in which the solution is rapidly varying. Correspondingly, in order to predict the system's dynamics, one needs to solve singularly perturbed ODEs and one usually resorts to the standard perturbation expansion method.

Let us attempt to sketch the general SPDERG procedure in these cases, by following in particular, in some detail, the examples of its application to boundary layer problems given in [11], one of which is recalled in Appendix D, in order to better illustrate the method:

- One faces the singular 2nd order ODE to be obeyed by the outer solution $y(t)$;
- One makes the transformation $t \rightarrow \tau = t/\varepsilon$, thereby solving the 2nd order ODE to be obeyed by the inner solution $Y(\tau)$, with given ICs (*i.e.*, Cauchy data) at $\tau = \tau_0$, and obtaining this last function;
- One identifies the part to be renormalized of the function $Y(\tau)$, *i.e.*, $Y_{div}(\tau)$. One moreover identifies, within $Y_{div}(\tau)$, the appropriate *bare* integration constants, that have to contain the ICs;
- When appropriately choosing these constants, their replacement with the renormalized ones, that are λ -depending, together with the replacement $(\tau - \tau_0) \rightarrow (\tau - \lambda) + (\lambda - \tau_0)$, allows to get the correct $Y_{div}(\tau, \lambda)$. Indeed, this function depends on τ in the same way as the original $Y_{div}(\tau)$. The differences are: i) the replacement $\tau_0 \rightarrow \lambda$; ii) the λ -dependence of the integration constants;
- One renormalizes $Y_{div}(\tau, \lambda)$ by imposing to this function to be independent of the *arbitrary* time λ , *i.e.*, $dY_{div}(\tau, \lambda)/d\lambda = 0$. This last requirement allows to get the ODEs to be obeyed by the renormalized integration constants;
- One makes the final transformation $\lambda \rightarrow \tau$;
- One adds to the obtained renormalized function the remaining part of the original inner solution $Y(\tau)$, in which the integration constants are not renormalized, one imposes the original ICs, and one looks at the result as a function of $\tau = t/\varepsilon$.

By this way, one ends up with a solution that indeed, usually:

- Contains the outer contribution up to the leading order in ε , too;
- Does not contain secular terms, hence does not diverge for $t \rightarrow \infty$;
- Does not require to cancel terms that otherwise would appear twice;
- Can be, for these reasons, regarded as the SPDERG uniform approximation to the correct solution;
- Can be expected to approximate better the correct solution to the original problem than the perturbation expansion uniform approximation at the leading order, at least in the matching region, since it contains the inner contribution at the following one.

More precisely [11], one chooses the part $Y_{div}(\tau)$, of the original inner solution $Y(\tau)$, by requiring that it contain the ICs, the other leading order terms, and the terms that do not tend to zero or to a constant value for $(\tau - \tau_0) \rightarrow \infty$ (*i.e.*, the secular terms). Moreover, the bare integration constants, let us say (following [11] also in the notation, as previously in this Section) $A_0(\tau_0)$ and $B_0(\tau_0)$, are renormalized as: $A_0(\tau_0) \rightarrow Z_1 A(\lambda)$, $B_0(\tau_0) \rightarrow Z_2 B(\lambda)$. In fact, the renormalization constants, Z_1 and Z_2 , depend both on τ_0 and λ , their basic role being to change, in the part to be renormalized of the function, the initial dependence on τ_0 of the ICs in a dependence on the arbitrary time λ .

In detail, they are assumed to have the expansion (with $a_0 = b_0 = 1$):

$$Z_1 = \sum_{n=0}^{\infty} a_n(\tau_0, \lambda) \varepsilon^n; \quad Z_2 = \sum_{n=0}^{\infty} b_n(\tau_0, \lambda) \varepsilon^n. \quad (26)$$

Since one can always take $(\tau - \tau_0) = (\tau - \lambda) + (\lambda - \tau_0)$, the secular terms in $(\lambda - \tau_0)$ are correspondingly absorbable in appropriate redefinitions of A_0 and B_0 , that have to be made by correctly choosing the coefficients $\{a_n\}$ and $\{b_n\}$. As it will become clear in the application that we are going to present, one can usually safely expect to be able to absorb in the coefficients of the renormalization constants also other possible secular terms, for instance those corresponding to higher powers of $(\tau - \tau_0)$. In particular, we will see in the present 2nd order calculations that, when writing $(\tau - \tau_0)^2 = (\tau - \lambda)^2 + (\lambda - \tau_0)^2 + 2(\tau - \lambda)(\lambda - \tau_0)$, only the second term is to be absorbed, whereas the last one is cancelled by the previously chosen 1st order renormalization coefficient, in the same way as in a case that is considered in [11] (see Section B, in that work).

Therefore [10, 11], the basic hypothesis, that is analogous to the *scaling* one in the renormalization group theory, is that the bare quantities need to be renormalized in such a way to get a solution independent of the arbitrary time λ , as it has reasonably to be. This is shown explicitly in the example in Appendix D, taken from [11] (see Section C, in that work). Evidently, λ plays a key role in the whole approach, and one can correspondingly think to it as the equivalent of the *unknown time*, at which the matching needs to be obeyed. From this point of view, we notice, therefore, an analogy with the imposition of the matching conditions, in the standard perturbation expansion method. This analogy can perhaps, first of all, be useful to the readers without particular knowledge of the renormalization group techniques. In fact, this analogy can be even more advantageous in order to better understand similarities and differences between the SPDERG approach and the perturbation expansion method. Nevertheless, it is not to be taken too rigorously, at least in cases as the present one, where, already at the 1st order, the matching requires two term conditions, and one expects that the correct matching could require even more terms at higher orders [5].

The previous attempt [20] of applying the SPDERG approach to MM kinetics, beyond the tQSSA, made evident that the here recalled prescriptions leave indeed with some freedom, in particular in the choice of the bare integration constants. As we are going to show, this seems indeed a hard choice in the case of MM kinetics, also when attempting to apply the approach beyond the sQSSA, despite the fact that this last starting point is analytically less complicated than the tQSSA.

To outline the main differences, we start by studying the system of two 1st order ODEs to be obeyed by the inner solutions, instead of looking at a single 2nd order possible one. Moreover, we choose as bare integration constants to be renormalized the ICs themselves (in detail, it turns out to be enough to renormalize the one of the substrate). Indeed, it was theoretically stated in [10, 11] that the direct renormalization of the ICs should have been equivalent to the SPDERG application, which is less intuitive and more technical, from a mathematical point of view. At a first glance, this prediction is not so evident. Thus, the present work aims also at being a detailed and analytical verification of the correctness of this prediction, at least in cases that are similar to the one here considered, in order to render as clear as possible the meaning of the predicted equivalence.

5. Results and discussion: i) First order contribution

Here we use, for the first time to our knowledge, the SPDERG approach to study MM kinetics, beyond the sQSSA, whose known uniform approximations we already recalled in Sections 2 and 3. As we were anticipating, we introduce an ad hoc new way of applying the SPDERG to the present case, that is different from the one considered in particular in [11], in other similar boundary layer problems.

In order to better explain why our different procedure seems indeed useful here, we start by noticing that one can rewrite the system, given by (11), for the inner solutions, in the form of a single 2nd order ODE (see [18, 19, 35] for the first studies of MM kinetics in terms of a 2nd order ODE), to be obeyed by the dimensionless substrate concentration:

$$\ddot{\tilde{s}}^{in}(\tau) - \frac{[\dot{\tilde{s}}^{in}(\tau)]^2}{\tilde{s}^{in}(\tau) + m} + [\tilde{s}^{in}(\tau) + M]\dot{\tilde{s}}^{in}(\tau) + \varepsilon \left[\frac{m}{\tilde{s}^{in}(\tau) + m} \dot{\tilde{s}}^{in}(\tau) + (M - m)\tilde{s}^{in}(\tau) \right] = 0, \quad (27)$$

with ICs (Cauchy data) $\tilde{s}^{in}(0) = 1$, and $\dot{\tilde{s}}^{in}(0) = -\varepsilon$. Analogously, one can write the same system, given by (11), in the form of a single 2nd order ODE, to be obeyed by the dimensionless complex concentration:

$$[1 - \tilde{c}^{in}(\tau)]\ddot{\tilde{c}}^{in}(\tau) + [\dot{\tilde{c}}^{in}(\tau)]^2 + M\tilde{c}^{in}(\tau)\dot{\tilde{c}}^{in}(\tau) + \varepsilon [1 - \tilde{c}^{in}(\tau)]^2 [\dot{\tilde{c}}^{in}(\tau) + (M - m)\tilde{c}^{in}(\tau)] = 0, \quad (28)$$

with ICs (Cauchy data) $\tilde{c}^{in}(0) = 0$, and $\dot{\tilde{c}}^{in}(0) = 1$.

Let us, in the meantime, observe that, at the 1st order in ε , the equations are satisfied by $\tilde{s}^{in}(\tau) = \tilde{s}_0^{in}(\tau) + \varepsilon \tilde{s}_1^{in}(\tau)$ and $\tilde{c}^{in}(\tau) = \tilde{c}_0^{in}(\tau) + \varepsilon \tilde{c}_1^{in}(\tau)$, with $\tilde{s}_0^{in}(\tau)$, $\tilde{c}_0^{in}(\tau)$ given by (14), and $\tilde{s}_1^{in}(\tau)$, $\tilde{c}_1^{in}(\tau)$ given by (18), respectively. On general basis, one expects that the solutions of these second order ODEs are the same as the ones of the system given by Eqs. (11), at each order in ε .

Nevertheless, the main difficulty, when attempting to apply the SPDERG approach scheme of [11] to the 2nd order ODE for the substrate, Eq. (27), or, equivalently, to the 2nd order one for the complex, Eq. (28), is that one faces the problem already encountered in [20], *i.e.*, that this scheme leaves with some freedom in the choice of the integration constants to be renormalized. In fact, to identify the most appropriate ones is seemingly more complicated in the case of MM kinetics than in the other boundary layer problems studied in [11].

Indeed, it is for these reasons that, as anticipated, we start by studying the SPDERG dimensionless substrate and complex concentrations, $\tilde{s}^{rg}(\tau)$ and $\tilde{c}^{rg}(\tau)$, that are solutions of the system given by Eqs. (11). The difference, with respect to the $\tilde{s}^{in}(\tau)$ and $\tilde{c}^{in}(\tau)$ that we previously recalled, within the perturbation expansion method, is that, here, the ICs are given at a time τ_0 , that we assume to be in principle different from zero, as $\tilde{s}^{rg}(\tau_0) = \tilde{s}^*$, and $\tilde{c}^{rg}(\tau_0) = \tilde{c}^*$, respectively. Correspondingly, we moreover take these ICs, hence $\tilde{s}^*$, and $\tilde{c}^*$, as the bare quantities to be renormalized, whereas the original ICs of the problem, *i.e.*, $\tilde{s}(0) = 1$, and $\tilde{c}(0) = 0$, will be taken into account after the renormalization procedure.

For the sake of clarity, at the cost of being somehow repetitive, at the 1st order in ε , we look again for solutions in the form:

$$\begin{cases} \tilde{s}^{rg}(\tau) = \tilde{s}_0^{rg}(\tau) + \varepsilon \tilde{s}_1^{rg}(\tau) \\ \tilde{c}^{rg}(\tau) = \tilde{c}_0^{rg}(\tau) + \varepsilon \tilde{c}_1^{rg}(\tau). \end{cases} \quad (29)$$

In these formulas, $\tilde{s}_0^{rg}(\tau)$ and $\tilde{c}_0^{rg}(\tau)$ solve as usual the 0th order system given by Eqs. (13), but the ICs are given at $\tau = \tau_0$, and their values are $\tilde{s}_0^{rg}(\tau_0) = \tilde{s}_0^*$ and $\tilde{c}_0^{rg}(\tau_0) = \tilde{c}_0^*$. These solutions are:

$$\begin{cases} \tilde{s}_0^{rg}(\tau) &= \tilde{s}_0^* \\ \tilde{c}_0^{rg}(\tau) &= \tilde{c}_0^* e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} + \frac{\tilde{s}_0^*}{\tilde{s}_0^* + M} \left[1 - e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} \right]. \end{cases} \quad (30)$$

On the other hand, $\tilde{s}_1^{rg}(\tau)$ and $\tilde{c}_1^{rg}(\tau)$ need to solve the 1st order system (that is slightly more complicated than Eqs. (17) because of the presence of $\tilde{s}_0^* \neq 1$):

$$\begin{cases} \dot{\tilde{s}}_1^{rg}(\tau) &= (\tilde{s}_0^* + m)\tilde{c}_0^{rg}(\tau) - \tilde{s}_0^* \\ \dot{\tilde{c}}_1^{rg}(\tau) &= -(\tilde{s}_0^* + M)\tilde{c}_1^{rg}(\tau) - [\tilde{c}_0^{rg}(\tau) - 1]\tilde{s}_1^{rg}(\tau), \end{cases} \quad (31)$$

with ICs, at $\tau = \tau_0$, $\tilde{s}_1^{rg}(\tau_0) = \tilde{s}_1^*$ and $\tilde{c}_1^{rg}(\tau_0) = \tilde{c}_1^*$. We obtain, in the case of the substrate:

$$\begin{aligned} \tilde{s}_1^{rg}(\tau) &= \tilde{s}_1^* - (M - m) \frac{\tilde{s}_0^*}{\tilde{s}_0^* + M} (\tau - \tau_0) + \\ &- \frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^2} [\tilde{s}_0^* - \tilde{c}_0^*(\tilde{s}_0^* + M)] \left[1 - e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} \right], \end{aligned} \quad (32)$$

whereas the solution for the complex, $\tilde{c}_1^{rg}(\tau)$, is given in Appendix A.

Let us continue by studying $\tilde{s}^{rg}(\tau)$. Following [11], we look at $\tilde{s}_{div}^{rg}(\tau)$, that contains only the substrate IC (*i.e.*, the terms that give $\tilde{s}^{rg}(\tau_0) = \tilde{s}_0^* + \varepsilon\tilde{s}_1^*$), the other possible leading terms at this order (that are absent, in the present case), and the secular terms (here, the one proportional to $(\tau - \tau_0)$ in $\tilde{s}_1^{rg}(\tau)$). Therefore, we write:

$$\tilde{s}^{rg}(\tau) = \tilde{s}_{div}^{rg}(\tau) + \varepsilon\mathcal{R}_1^s(\tau) + O(\varepsilon^2), \quad (33)$$

by grouping in $\mathcal{R}_1^s$ all the sub-leading terms that tend to zero or to a constant for $(\tau - \tau_0) \rightarrow \infty$ and that do not need to be renormalized. One has:

$$\tilde{s}_{div}^{rg}(\tau) = \tilde{s}_0^* + \varepsilon\tilde{s}_1^* - \varepsilon(M - m) \frac{\tilde{s}_0^*}{\tilde{s}_0^* + M} (\tau - \tau_0). \quad (34)$$

As previously recalled, the SPDERG approach [10, 11], at this point, is based on writing $(\tau - \tau_0) = (\tau - \lambda) + (\lambda - \tau_0)$, by correspondingly assuming, in the present case, that the secular term proportional to $(\lambda - \tau_0)$ can be absorbed in an appropriate redefinition of the bare substrate IC. In detail, by labelling $\tilde{s}_0^{rg*}$, and $\tilde{s}_1^{rg*}$, the contributions to the renormalized IC at the 0th, and at the 1st order, respectively, we put $\tilde{s}_0^* = Z_{s_0}\tilde{s}_0^{rg*}(\lambda)$, and $\tilde{s}_1^* = Z_{s_1}\tilde{s}_1^{rg*}(\lambda)$. The renormalization constants, Z_{s_0} , and Z_{s_1} , are assumed to have the same ε -expansions as the ones given by (26). These expansions, at the 1st order in ε , imply $\tilde{s}_0^* = [1 + \varepsilon z_{s_0,1}(\tau_0, \lambda)]\tilde{s}_0^{rg*}(\lambda)$ and $\tilde{s}_1^* = \tilde{s}_1^{rg*}(\lambda)$. Thus, the present secular term can be absorbed by choosing the first free coefficient in the expansions as:

$$z_{s_0,1}(\tau_0, \lambda) = \frac{(M - m)}{\tilde{s}_0^{rg*} + M} (\lambda - \tau_0). \quad (35)$$

Correspondingly, we end up to study:

$$\tilde{s}_{div}^{rg}(\tau, \lambda) = \tilde{s}_0^{rg*}(\lambda) + \varepsilon\tilde{s}_1^{rg*}(\lambda) - \varepsilon(M - m) \frac{\tilde{s}_0^{rg*}(\lambda)}{\tilde{s}_0^{rg*}(\lambda) + M} (\tau - \lambda). \quad (36)$$

Hence, by imposing the scaling condition [10, 11], $d\tilde{s}_{div}^{rg}(\tau, \lambda)/d\lambda = 0$, we get the 1st order ODEs, to be obeyed by the two terms that contribute to the renormalized IC.

In detail, at the 1st order in ε , *i.e.*, by disregarding in particular the part of the derivative of the last term that contains $d\tilde{s}_0^{rg*}(\lambda)/d\lambda$ (it will contribute to the 2nd order, as we show in the following), we obtain:

$$\frac{d\tilde{s}_0^{rg*}(\lambda)}{d\lambda} + \varepsilon \frac{d\tilde{s}_1^{rg*}(\lambda)}{d\lambda} + \varepsilon(M - m) \frac{\tilde{s}_0^{rg*}(\lambda)}{\tilde{s}_0^{rg*}(\lambda) + M} = 0. \quad (37)$$

Then, we separate the contributions by correctly taking into account, in advance, that, at the next step, one makes the transformation $\lambda \rightarrow \tau = t/\varepsilon$, and we get:

$$\begin{cases} \frac{d\tilde{s}_0^{rg*}(\lambda)}{d\lambda} &= -\varepsilon(M - m) \frac{\tilde{s}_0^{rg*}(\lambda)}{\tilde{s}_0^{rg*}(\lambda) + M} \\ \frac{d\tilde{s}_1^{rg*}(\lambda)}{d\lambda} &= 0. \end{cases} \quad (38)$$

Consistently, when indeed one makes the further transformation [11] $\lambda \rightarrow \tau = t/\varepsilon$, the first of these equations is just the ODE to be obeyed by the 0th order outer dimensionless substrate concentration, that we encountered in Eqs. (7). Its solution is therefore $\tilde{s}_0^{rg*}(t) = \tilde{s}_0^{out}(t)$, that is given by (8), by means of the Lambert function, and that satisfies the IC $\tilde{s}_0^{rg*}(0) = 1$, too.

Clearly, this result already suggests that, also in the present case of MM kinetics, the present ad hoc new way of applying the SPDERG approach turns out to be able to reproduce the leading order terms of the perturbation expansion uniform approximations.

On the other hand, the result $d\tilde{s}_1^{rg*}(\lambda)/d\lambda = 0$ is, here, to be interpreted as the verification that $\tilde{s}_1^{rg*}$ can be neglected at this order. In fact, we find $\tilde{s}_1^{rg*} = \text{const} = 0$ by imposing the original IC. More correctly, the bare IC, that is fixed, here, to the value $\tilde{s}(0) = 1$, should be imposed on the solution at the end, but this is not influential in the present case, since one generally has $\mathcal{R}(0) = 0$, for the appropriately calculated contribution of the parts not to be renormalized of the inner solutions.

Finally, we get the renormalized result:

$$\tilde{s}_1^{rg,u}(t) = \tilde{s}_0^{out}(t) + \varepsilon \mathcal{R}_1^s(t/\varepsilon) + O(\varepsilon). \quad (39)$$

Notice that, when we were considering $\tilde{s}^{rg}(\tau)$ as the inner solution, in (33), before applying the SPDERG approach, we knew that it was correct up to order $O(\varepsilon^2)$. Here, instead, the renormalized $\tilde{s}_1^{rg,u}(t)$ (that for this reason we label *rg,u*, by moreover making explicit that it is a 1st order approximation) is to be interpreted as the SPDERG uniform approximation to the solution of the original problem. Correspondingly, one has to bear in mind that, from this point of view, it is correct only up to order $O(\varepsilon)$. Actually, the renormalized $\tilde{s}_1^{rg,u}(t)$ in (39) is only expected [10, 11] to contain the leading order terms of the outer solution. It is indeed the case, by its comparison with (25).

Notice, moreover, that the terms in $\mathcal{R}_1^s$ (*i.e.*, the ones that do not need to be renormalized) are to be evaluated in $\tau_0 = 0$, by using the correct ICs, namely, the bare ones (*i.e.*, $\tilde{s}_0^* = 1$, $\tilde{s}_1^* = 0$, and $\tilde{c}_0^* = 0$). Thus, as expected [11], the SPDERG 1st order uniform approximation to the solution for the dimensionless substrate concentration does instead contain the 1st order terms of the perturbation expansion uniform approximation to the correct solution, *i.e.*, the ones that originate from $\tilde{s}_1^{in}(t/\varepsilon)$. On the other hand, the usual

asymptotic behaviour of the solution, that one finds when applying the recalled perturbation expansion method to MM kinetics (*i.e.*, $\lim_{t \rightarrow \infty} \tilde{s}(t) = 0$), is not verified here (one has $\lim_{t \rightarrow \infty} \tilde{s}_1^{rg,u}(t) = O(\varepsilon)$). We better discuss this failure of the present application of the SPDERG approach in the following subsections, by proposing a way to overcome it, too.

Let us now study the complex. First of all, despite of the presence of a large number of terms in (64) (the formula is given in Appendix A, with the coefficients reported in (65)), that describes the behaviour of the 1st order inner dimensionless complex concentration, within the SPDERG approach, $\tilde{c}_1^{rg}(\tau)$, the part of the function to be renormalized up to the 1st order in ε is as manageable as in the case of the substrate.

In detail, we write the same kind of expression as in (33):

$$\tilde{c}^{rg}(\tau) = \tilde{c}_{div}^{rg}(\tau) + \varepsilon \mathcal{R}_1^c(\tau) + O(\varepsilon^2), \quad (40)$$

by collecting in $\mathcal{R}_1^c$ all the sub-leading terms that tend to zero or to a constant for $(\tau - \tau_0) \rightarrow \infty$. Correspondingly, we find:

$$\tilde{c}_{div}^{rg}(\tau) = (\tilde{c}_0^* + \varepsilon \tilde{c}_1^*) e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} + \frac{\tilde{s}_0^*}{\tilde{s}_0^* + M} \varepsilon \frac{M(M-m)}{(\tilde{s}_0^* + M)^3} \tilde{s}_0^*(\tau - \tau_0). \quad (41)$$

In fact, here, we considered explicitly also the terms that give the original complex IC, (*i.e.*, $\tilde{c}_{div}^{rg}(0) = \tilde{c}_0^* + \varepsilon \tilde{c}_1^*$). Nevertheless, both the 0th order contribution, and the 1st order one, to this IC, are exponentially suppressed for $(\tau - \tau_0) \rightarrow \infty$. In particular from this point of view, the present case is similar to the example of the nonlinear boundary layer problem given in [11], that we recall in Appendix D. Correspondingly, $\tilde{c}_0^{rg*}(\lambda)$, when renormalizing, has to obey to the ODE $d\tilde{c}_0^{rg*}(\lambda)/d\lambda = 0$. Hence, one finds $\tilde{c}_0^{rg*}(\lambda) = const = 0$ when imposing the original (bare) IC (fixed, here, to $\tilde{c}(0) = 0$), at the end of the renormalization procedure. Namely, the contribution proportional to this term can be neglected. For the same reason, one also expects $\tilde{c}_1^{rg*}(\lambda) = const = 0$, a result that is even more predictable at this order, since we already verified that $\tilde{s}_1^{rg*}$ gives no contribution in the case of the substrate. Correspondingly, we assume that the contribution proportional to this last term can be neglected, too.

Accordingly, the function to be studied is further reduced to:

$$\tilde{c}_{div}^{rg}(\tau) \Big|_{\substack{\tilde{c}_0^*=0 \\ \tilde{c}_1^*=0}} = \frac{\tilde{s}_0^*}{\tilde{s}_0^* + M} - \varepsilon(M-m) \frac{M\tilde{s}_0^*}{(\tilde{s}_0^* + M)^3} (\tau - \tau_0). \quad (42)$$

As already recalled, in the context of the standard perturbation expansion method, the matching condition that is verified by the dimensionless substrate concentration does consistently also satisfy the matching of the inner and outer dimensionless complex concentrations. Alternatively, one can also remind that the SPDERG approach is usually applied to a 2nd order ODE (*i.e.*, here, on general basis, we could have chosen, equivalently, the one for the substrate, Eq. (27), or the one for the complex, Eq. (28)).

For these reasons, on the basis of the previously sketched analogy, too, we find not surprising that, when making the transformations $\{\tau_0 \rightarrow \lambda, \tilde{s}_0^* \rightarrow \tilde{s}_0^{rg*}(\lambda)\}$, the scaling condition $d\tilde{c}_{div}^{rg}(\tau, \lambda)/d\lambda = 0$ gives, once again, the same ODE to be obeyed by $\tilde{s}_0^{rg*}(\lambda)$ as the one that we just found in the study of $\tilde{s}_{div}^{rg}(\tau, \lambda)$ (*i.e.*, Eqs. (38)). Hence (with the transformation $\lambda \rightarrow \tau = t/\varepsilon$), we get, once again, $\tilde{s}_0^{rg*}(t) = \tilde{s}_0^{out}(t)$. In particular, one

can check that, since $d[\tilde{s}_0^*/(\tilde{s}_0^* + M)]/d\tilde{s}_0^* = M/(\tilde{s}_0^* + M)^2$, when renormalizing the bare 0th order contribution to the substrate IC, $\tilde{s}_0^*$, by using the value of the coefficient $z_{s_0,1}$, that is already fixed by (35), the contribution of the first term, in $\tilde{c}_{div}^{rg}(\tau, \lambda)$, to the order ε , is exactly equal to $\varepsilon(\lambda - \tau_0)M(M - m)\tilde{s}_0^{rg*}/(\tilde{s}_0^{rg*} + M)^2$, and, therefore, it suitably absorbs the secular term that is present in this case.

By recalling that $\tilde{c}_0^{out}(t) = \tilde{s}_0^{out}(t)/(\tilde{s}_0^{out}(t) + M)$ from Eqs. (7), the obtained SPDERG 1st order uniform approximation to the correct solution for the complex is:

$$\tilde{c}_1^{rg,u}(t) = \tilde{c}_0^{out}(t) + \varepsilon \mathcal{R}_1^c(t/\varepsilon) + O(\varepsilon), \quad (43)$$

with, as for the substrate, the terms in $\mathcal{R}_1^c$ to be evaluated in $\tau_0 = 0$, by using the original ICs (*i.e.*, $\tilde{s}_0^* = 1$, and $\tilde{s}_1^* = \tilde{c}_0^* = \tilde{c}_1^* = 0$).

Writing explicitly the contribution of the different terms, we obtain the following SPDERG 1st order uniform approximations to the correct solutions for the time behaviour of the dimensionless substrate concentration and of the dimensionless complex concentration, in MM kinetics, beyond the sQSSA, respectively (with ω the Lambert function):

$$\left\{ \begin{array}{l} \tilde{s}_1^{rg,u}(t) = M\omega(e^{-(M-m)t/M + 1/M/M}) + \\ \quad - \varepsilon \frac{1+m}{(1+M)^2} [1 - e^{-(1+M)t/\varepsilon}] + O(\varepsilon) \\ \tilde{c}_1^{rg,u}(t) = \frac{\omega(e^{-(M-m)t/M + 1/M/M})}{\omega(e^{-(M-m)t/M + 1/M/M}) + 1} - \frac{1}{1+M} e^{-(1+M)t/\varepsilon} + \\ \quad - \varepsilon \frac{M(1+2m-M)}{(1+M)^4} [1 - e^{-(1+M)t/\varepsilon}] + \\ \quad - \varepsilon \left[\frac{(1-M)(1+m)}{(1+M)^3} (t/\varepsilon) + \frac{M-m}{(1+M)^2} \frac{(t/\varepsilon)^2}{2} \right] e^{-(1+M)t/\varepsilon} + \\ \quad + \varepsilon \frac{(1+m)}{(1+M)^4} e^{-(1+M)t/\varepsilon} [1 - e^{-(1+M)t/\varepsilon}] + O(\varepsilon). \end{array} \right. \quad (44)$$

Here, we stress once again that these SPDERG uniform approximations are correct only up to $O(\varepsilon)$, since they lack the first order contributions of the outer solutions.

We plot in [Fig. 4] our corresponding results for the two considered sets of ICs, as usual, in comparison with the numerical solutions of the original problem, given by Eqs. (2) (the same curves as in the previous figures). The figure shows that, as expected, these results approximate more correctly the numerical solutions than the perturbation expansion 0th order uniform approximations ([Fig. 1A], [Fig. 2A] and [Fig. 1C], [Fig. 2B] for the results for the a and b sets of ICs, respectively). Nonetheless, these approximations are not as much correct as the perturbation expansion 1st order ones ([Fig. 3]).

Moreover, the figure also makes evident that, differently from the perturbation expansion results, the SPDERG approximations fail in particular in the large time region. Actually, also in the examples given in [11], the SPDERG was shown to give usually better results than the standard method in the matching region. Nevertheless, here we face the problem that both the substrate and the complex approach (physically meaningless) $O(\varepsilon)$ values for $t \rightarrow \infty$. In fact, from (44), one has $\lim_{t \rightarrow \infty} \tilde{s}_1^{rg,u}(t) = \tilde{s}_{1,\infty}^{rg,u} = -\varepsilon(1+m)/(1+M)^2$ and $\lim_{t \rightarrow \infty} \tilde{c}_1^{rg,u}(t) = \tilde{c}_{1,\infty}^{rg,u} = -\varepsilon M(1+2m-M)/(1+M)^4$. The corresponding asymptotic constants, for the two considered sets of ICs, are plotted in the figures, too. Both this unphysical outcome, and the lack the 1st order contribution

Figure 4: **Comparison between the numerical solutions and the 1st order SPDERG uniform approximations, for the two considered sets of ICs.** (Color online) In A) and C) we present the behaviour of the concentrations of the substrate $s(t)$, whereas in B) and D) we present the ones of the concentrations of the complex $c(t)$, for the a and b sets of ICs given by (4), respectively. Hence, in A) and B) we are in the case with $\varepsilon = \varepsilon^a = 0.1$, whereas in C) and D) we are in the one with $\varepsilon = \varepsilon^b = 0.5$. We plot both the numerical solutions of Eqs. (2), already shown in the previous figures, and the analytical solutions computed from the SPDERG 1st order uniform approximations (with a standard numerical approximation to the Lambert function), as given by (44). We plot moreover the (physically meaningless) limits for $t \rightarrow \infty$ of the analytical solutions: $s_0^a \bar{s}_{1,\infty}^{r,g,u} \simeq -0.622$ (μM), $e_0^a \bar{c}_{1,\infty}^{r,g,u} \simeq -0.0128$ (μM), and $s_0^b \bar{s}_{1,\infty}^{r,g,u} \simeq -3.11$ (μM), $e_0^b \bar{c}_{1,\infty}^{r,g,u} \simeq -0.305$ (μM), respectively. We finally plot our corresponding rough evaluations of the two different time scales involved, too, with τ_s describing the substrate decay time and τ_c the complex saturation time. Notice that the time is on logarithmic scale.

to the outer solution, are the most evident in the result for the substrate, in the case of the b set of ICs, corresponding to the quite large $\varepsilon = \varepsilon^b = 0.5$ ([Fig. 4C]).

On the other hand, the figure shows that the 1st order SPDERG approach, differently from the 0th order perturbation expansion method, is able to capture important features of the correct solutions. In detail, one can observe the presence of the three inflection points in the curves of the substrate both in [Fig. 4A] and in [Fig. 4C]. From the quantitative point of view, also the correct complex maximum values turn out to be better predicted than in the corresponding [Fig. 2], further confirming that the approach is particularly successful in the matching region and near it.

Therefore, on the basis of these initial results, that appear as a whole to support the SPDERG usefulness, in order both to further test its correctness and to possibly obtain better approximations to the correct solutions than the ones given by the perturbation expansion 1st order uniform approximations, we consider the 2nd order in ε , too.

6. Results and discussion: ii) Second order contribution

With the aim of simplifying the calculations, here we limit ourselves to study the case in which the contributions to the complex IC, at the considered orders in the expansion, in $\tau = \tau_0$, are fixed at $\tilde{c}_0^* = \tilde{c}_1^* = \tilde{c}_2^* = 0$ from the beginning, for every τ_0 . This could seem unrealistic, but it is not expected to influence the result, for two reasons. On the one hand, we already showed that both $\tilde{c}_0^*$ and $\tilde{c}_1^*$ were negligible at the previous order, whereas $\tilde{c}_2^*$ should be negligible here at least in the same way as $\tilde{s}_1^*$ at the previous order. On the other hand, since one is interested in taking as initial time $\tau_0 = 0$, we expect that, as at the 1st order, the renormalization of s implies the correct renormalization of c . Thus it appears reasonable to set $\tilde{c}_0^* = \tilde{c}_1^* = \tilde{c}_2^* = 0$.

Once again, this last expectation can be intuitively understood, first of all, within the analogy with the matching in the perturbation expansion, where there is freedom for fixing only one of the two conditions, whereas the other turns out to be consistently satisfied, too. Moreover, also the observation that, within the SPDERG approach scheme as applied to different boundary layer problems in [11], one should be able to limit the study to one of the 2nd order equations for the inner components (here, Eq. (27), or Eq. (28)), points towards the same direction.

We anyway verify in detail, in the following, that indeed one gets the same ODE to be obeyed by $\tilde{s}_1^{rg}$ both from the study of the substrate and from the study of the complex.

Moreover, we take $\tilde{s}_2^* = 0$ from the beginning, too, since we expect that it can be anyway neglected within this approach at the 2nd order, in the same way as $\tilde{s}_1^*$ turned out to be negligible at the 1st order. Notice that we should instead allow for $\tilde{s}_2^* \neq 0$, if we were to use these solutions to calculate the 3rd order contribution, too.

Clearly, one looks for 2nd order solutions in the form:

$$\begin{cases} \tilde{s}^{rg}(\tau) = \tilde{s}_0^{rg}(\tau) + \varepsilon \tilde{s}_1^{rg}(\tau) + \varepsilon^2 \tilde{s}_2^{rg}(\tau) + O(\varepsilon^3) \\ \tilde{c}^{rg}(\tau) = \tilde{c}_0^{rg}(\tau) + \varepsilon \tilde{c}_1^{rg}(\tau) + \varepsilon^2 \tilde{c}_2^{rg}(\tau) + O(\varepsilon^3). \end{cases} \quad (45)$$

Here, $\tilde{s}_0^{rg}(\tau)$ and $\tilde{c}_0^{rg}(\tau)$ are still given by (30), with $\tilde{c}_0^* = 0$ in the case of the complex. Moreover, $\tilde{s}_1^{rg}(\tau)$ and $\tilde{c}_1^{rg}(\tau)$ are still given by (32), and (64), respectively, with $\tilde{c}_1^* = 0$ in the case of the complex, whereas the condition $\tilde{c}_0^* = 0$ does apply to the solution for the substrate, too.

Correspondingly, we end up to study the system:

$$\begin{cases} \dot{\tilde{s}}_2^{rg}(\tau) = (\tilde{s}_0^* + m)\tilde{c}_1^{rg}(\tau) + [\tilde{c}_0^{rg}(\tau) - 1]\tilde{s}_1^{rg}(\tau) \\ \dot{\tilde{c}}_2^{rg}(\tau) = -(\tilde{s}_0^* + M)\tilde{c}_2^{rg}(\tau) - [\tilde{c}_0^{rg}(\tau) - 1]\tilde{s}_2^{rg}(\tau) - \tilde{s}_1^{rg}(\tau)\tilde{c}_1^{rg}(\tau), \end{cases} \quad (46)$$

whose solutions, $\tilde{s}_2^{rg}(\tau)$, and $\tilde{c}_2^{rg}(\tau)$, with ICs, at $\tau = \tau_0$, $\tilde{s}_2^{rg}(\tau_0) = 0$, and $\tilde{c}_2^{rg}(\tau_0) = 0$, are given in Appendix B.

The obtained formulas are anyway cumbersome, as one could expect: in fact, they contain both (implicitly) the 1st order contributions to the outer solutions and (explicitly) the 2nd order contributions to the inner ones. As anticipated, these last 2nd order contributions are calculated, in the present work, for the first time to our knowledge.

By carrying on the study as in the previous Section, we start from the part to be renormalized of the substrate solution. The first three terms in the solution $\tilde{s}_2^{rg}(\tau)$, given by (66), are the secular ones, whose coefficients are reported in (67). The correct function, $\tilde{s}_{div}^{rg}(\tau)$, needs also to contain the constant term that appears in $\tilde{s}_1^{rg}(\tau)$ (given

by (32)), since this is a leading order term at the 2nd order. In fact, it depends on the 0th order contribution to the bare substrate IC (*i.e.*, $\tilde{s}_0^*$), and it does not tend to zero for $\tau \rightarrow \infty$.

Hence, one finds:

$$\begin{aligned}\tilde{s}_{div}^{rg}(\tau) &= \tilde{s}_0^* + \varepsilon \tilde{s}_1^* - \varepsilon \frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^2} \tilde{s}_0^* - \varepsilon \frac{(M - m) \tilde{s}_0^*}{\tilde{s}_0^* + M} (\tau - \tau_0) + \\ &+ \varepsilon^2 \frac{2M(M - m) \tilde{s}_0^*}{(\tilde{s}_0^* + M)^4} (\tilde{s}_0^* + m) (\tau - \tau_0) - \varepsilon^2 \frac{M(M - m) \tilde{s}_1^*}{(\tilde{s}_0^* + M)^2} (\tau - \tau_0) + \\ &+ \varepsilon^2 \frac{M(M - m)^2 \tilde{s}_0^*}{2(\tilde{s}_0^* + M)^3} (\tau - \tau_0)^2.\end{aligned}\quad (47)$$

Then, we replace the bare constants with the renormalized ones, *i.e.*:

$$\begin{cases} \tilde{s}_0^* &= Z_{s_0}(\tau_0, \lambda) \tilde{s}_0^{rg*}(\lambda) \\ \tilde{s}_1^* &= Z_{s_1}(\tau_0, \lambda) \tilde{s}_1^{rg*}(\lambda), \end{cases}\quad (48)$$

with, at the 2nd order in ε :

$$\begin{cases} Z_{s_0}(\tau_0, \lambda) &= 1 + \varepsilon z_{s_0,1}(\tau_0, \lambda) + \varepsilon^2 z_{s_0,2}(\tau_0, \lambda), \\ Z_{s_1}(\tau_0, \lambda) &= 1 + \varepsilon z_{s_1,1}(\tau_0, \lambda). \end{cases}\quad (49)$$

Correspondingly, we write $(\tau - \tau_0) = (\tau - \lambda) + (\lambda - \tau_0)$ in (47), and we absorb the secular terms in $(\lambda - \tau_0)$ by appropriately choosing the renormalization constant coefficients. In detail, $z_{s_0,1}(\tau_0, \lambda)$ is already fixed by (35). Nevertheless, the contributions proportional to this coefficient to the third term, and to the fourth one, in (47) are to be taken carefully into account, since they turn out to be $O(\varepsilon^2)$.

In particular, in the case of the third term, when renormalizing $\tilde{s}_0^*$, one has:

$$-\varepsilon \frac{(\tilde{s}_0^* + m) \tilde{s}_0^*}{(\tilde{s}_0^* + M)^2} = -\varepsilon \frac{(\tilde{s}_0^{rg*} + m) \tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^2} - \varepsilon^2 \left\{ \frac{d}{d\tilde{s}_0^*} \left[\frac{(\tilde{s}_0^* + m) \tilde{s}_0^*}{(\tilde{s}_0^* + M)^2} \right] \Big|_{\tilde{s}_0^* = \tilde{s}_0^{rg*}} \right\} z_{s_0,1}(\tau_0, \lambda) \tilde{s}_0^{rg*}, \quad (50)$$

with:

$$\begin{aligned}& -\varepsilon^2 \left\{ \frac{d}{d\tilde{s}_0^*} \left[\frac{(\tilde{s}_0^* + m) \tilde{s}_0^*}{(\tilde{s}_0^* + M)^2} \right] \Big|_{\tilde{s}_0^* = \tilde{s}_0^{rg*}} \right\} z_{s_0,1}(\tau_0, \lambda) \tilde{s}_0^{rg*} = \\ &= -\varepsilon^2 \left[\frac{(M - m) \tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^3} + \frac{M(\tilde{s}_0^{rg*} + m)}{(\tilde{s}_0^{rg*} + M)^3} \right] z_{s_0,1}(\tau_0, \lambda) \tilde{s}_0^{rg*} = \\ &= -\varepsilon^2 \left[\frac{(M - m)^2 (\tilde{s}_0^{rg*})^2}{(\tilde{s}_0^{rg*} + M)^4} + \frac{M(M - m) \tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^4} (\tilde{s}_0^{rg*} + m) \right] (\lambda - \tau_0).\end{aligned}\quad (51)$$

In fact, both of these two terms contribute, and they have to be taken into account in the definition of $z_{s_0,2}(\tau_0, \lambda)$. Let us note, moreover, that $d[\tilde{s}_0^*/(\tilde{s}_0^* + M)]/d\tilde{s}_0^* = M/(\tilde{s}_0^* + M)^2$. Thus, one can check that the 2nd order contribution proportional to the same coefficient, $z_{s_0,1}(\tau_0, \lambda)$ (that originates from the fourth term in $\tilde{s}_{div}^{rg}$, in the same way as we just explained in detail with the formulas (50) and (51)), partially absorbs the term proportional to $(\tau - \lambda)(\lambda - \tau_0)$ (that originates from the last term), and partially contributes to $z_{s_0,2}(\tau_0, \lambda)$.

Thus, by taking:

$$\begin{cases} z_{s_0,2}(\tau_0, \lambda) &= \left[\frac{(M-m)^2 \tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^4} - \frac{M(M-m)}{(\tilde{s}_0^{rg*} + M)^4} (\tilde{s}_0^{rg*} + m) \right] (\lambda - \tau_0) + \\ &+ \frac{M(M-m)^2}{2(\tilde{s}_0^{rg*} + M)^3} (\lambda - \tau_0)^2 \\ z_{s_1,1}(\tau_0, \lambda) &= \frac{M(M-m)}{(\tilde{s}_0^{rg*} + M)^2} (\lambda - \tau_0), \end{cases} \quad (52)$$

we end up with an expression for $\tilde{s}_{div}^{rg}(\tau, \lambda)$ that is exactly the same as the one given by (47), with $\tilde{s}_0^* \rightarrow \tilde{s}_0^{rg*}(\lambda)$, $\tilde{s}_1^* \rightarrow \tilde{s}_1^{rg*}(\lambda)$ and $\tau_0 \rightarrow \lambda$. Moreover, though we wrote explicitly the first two terms in $z_{s_0,2}$ to make evident the different origins of the contributions, their sum can be simplified in such a way that the coefficient of the term proportional to $(\lambda - \tau_0)$ is simply equal to $-m(M-m)/(\tilde{s}_0^{rg*} + M)^3$.

Therefore, we avoid to write explicitly $\tilde{s}_{div}^{rg}(\tau, \lambda)$, and we study directly its derivative with respect to λ . We obtain, at the 2nd order:

$$\begin{aligned} \frac{d\tilde{s}_{div}^{rg}(\tau, \lambda)}{d\lambda} &= \frac{d\tilde{s}_0^{rg*}(\lambda)}{d\lambda} + \varepsilon \frac{d\tilde{s}_1^{rg*}(\lambda)}{d\lambda} + \varepsilon \frac{(M-m)\tilde{s}_0^{rg*}(\lambda)}{\tilde{s}_0^{rg*}(\lambda) + M} + \\ &+ \varepsilon^2 \frac{(M-m)^2 [\tilde{s}_0^{rg*}(\lambda)]^2}{[\tilde{s}_0^{rg*}(\lambda) + M]^4} + \varepsilon^2 \frac{M(M-m)\tilde{s}_0^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^4} [\tilde{s}_0^{rg*}(\lambda) + m] + \\ &+ \varepsilon^2 \frac{M(M-m)^2 \tilde{s}_0^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^3} (\tau - \lambda) - \varepsilon^2 \frac{2M(M-m)\tilde{s}_0^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^4} [\tilde{s}_0^{rg*}(\lambda) + m] + \\ &+ \varepsilon^2 \frac{M(M-m)\tilde{s}_1^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^2} - \varepsilon^2 \frac{M(M-m)^2 \tilde{s}_0^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^3} (\tau - \lambda). \end{aligned} \quad (53)$$

In fact, one already makes use of the known 1st order result on $d\tilde{s}_0^{rg*}/d\lambda$, given by Eqs. (38), in the derivation of this equation.

Here, for the sake of clarity, we also wrote explicitly both of the 2nd order terms proportional to $(\tau - \lambda)$, that obviously cancel each other. In fact, this appears a quite consistent result of the present approach, since they have completely different origins. Indeed, the first of these terms originates from part of the derivative with respect to λ of the 1st order term, proportional to $(\tau - \lambda)$, in $\tilde{s}_{div}^{rg}(\tau, \lambda)$ (*i.e.*, from the term that is equal to $-\varepsilon(M-m)\{d[\tilde{s}_0^{rg*}/(\tilde{s}_0^{rg*} + M)]/d\lambda\}(\tau - \lambda)$). The second of these terms originates, instead, from the derivative with respect to λ of the last term in $\tilde{s}_{div}^{rg}(\tau, \lambda)$, that is proportional to $(\tau - \lambda)^2$.

Interestingly, the second term proportional to ε^2 (part of the contribution that originates from the constant term in $\tilde{s}_1^{rg}(\tau)$), letting aside a factor 2, is the same as the one that is found when deriving with respect to λ the first of the terms proportional to $\varepsilon^2(\tau - \lambda)$ in (47), *i.e.*, the term in $\tilde{s}_{div}^{rg}(\tau, \lambda)$ that corresponds to the fourth term proportional to ε^2 here, but it has opposite sign.

In fact, both of these results are obtained in a similar way to the one that we previously described in detail, in the context of the derivation of the appropriate renormalization constants. Indeed, from Eqs. (38), one has $(\lambda - \tau_0)d\tilde{s}_0^{rg*}/d\lambda = -\varepsilon z_{s_0,1}(\tau_0, \lambda)\tilde{s}_0^{rg*}$.

Finally, by imposing the scaling condition $d\tilde{s}_{div}^{rg}(\tau, \lambda)/d\lambda = 0$, and by correctly grouping the terms in ε , and in ε^2 , we derive the two ODEs to be obeyed by $\tilde{s}_0^{rg*}(\lambda)$, and $\tilde{s}_1^{rg*}(\lambda)$,

respectively:

$$\left\{ \begin{aligned} \frac{d\tilde{s}_0^{rg*}(\lambda)}{d\lambda} &= -\varepsilon \frac{(M-m)\tilde{s}_0^{rg*}(\lambda)}{\tilde{s}_0^{rg*}(\lambda) + M} \\ \frac{d\tilde{s}_1^{rg*}(\lambda)}{d\lambda} &= \varepsilon \left\{ -\frac{(M-m)^2 [\tilde{s}_0^{rg*}(\lambda)]^2}{[\tilde{s}_0^{rg*}(\lambda) + M]^4} + \frac{M(M-m)\tilde{s}_0^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^4} [\tilde{s}_0^{rg*}(\lambda) + m] + \right. \\ &\quad \left. - \frac{M(M-m)\tilde{s}_1^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^2} \right\} = \\ &= \varepsilon \left\{ \frac{m(M-m)\tilde{s}_0^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^3} - \frac{M(M-m)\tilde{s}_1^{rg*}(\lambda)}{[\tilde{s}_0^{rg*}(\lambda) + M]^2} \right\}. \end{aligned} \right. \quad (54)$$

The first of these ODEs is just the already known 1st order result for $d\tilde{s}_0^{rg*}(\lambda)/d\lambda$ reported in Eqs. (38). Actually, at the 2nd order, the interesting ODE is the one to be obeyed by $\tilde{s}_1^{rg*}(\lambda)$.

Let us remark that, when making the final transformation $\lambda \rightarrow \tau = t/\varepsilon$, and when recalling that $\tilde{s}_0^{rg*}(t) = \tilde{s}_0^{out}(t)$ (given by (8)), the ODE to be obeyed by $\tilde{s}_1^{rg*}(t)$ turns out to be different from the one for the 1st order outer substrate within the perturbation expansion method, reported in Eqs. (19). Here, we wrote the equation both with and without the simplification, that is due to the sum of the first two terms, just in order to make evident the difference, since it is the first term in the not simplified expression that was absent there. Indeed, to get in particular the same coefficient as in the ODE in Eqs. (19), for the second term in the present not simplified expression, it is essential to correctly take into account the constant in $\tilde{s}_1^{rg}(\tau)$ in the part to be renormalized of the function (at the 2nd order). In fact, as outlined, the contribution of the only term proportional to ε^2 would give an incorrect (twice larger) coefficient.

Most interestingly, the present ODE turns out to be simpler than the one encountered in the perturbation expansion method. One can check that the solution is given by:

$$\tilde{s}_1^{rg*}(t) = \frac{m\tilde{s}_0^{out}(t)}{M[\tilde{s}_0^{out}(t) + M]} \log \left[\frac{\tilde{s}_0^{out}(t) + M}{(1+M)\tilde{s}_0^{out}(t)} \right], \quad (55)$$

with the choice $\tilde{s}_1^{rg*}(0) = 0$, that is reasonable in this context, since it allows to get, correctly, $\tilde{s}_2^{rg,u}(0) = 1$. It is also important to stress that the solution also satisfies the asymptotic condition $\lim_{t \rightarrow \infty} \tilde{s}_1^{rg*}(t) = 0$, though this in fact implies $\lim_{t \rightarrow \infty} \tilde{s}_2^{rg,u}(t) = O(\varepsilon^2)$.

On the other hand, when adding the 1st order term that originates from the replacement, $\tilde{s}_0^* \rightarrow \tilde{s}_0^{rg*}(\lambda)$, in the 1st order constant term, in the part to be renormalized of the function, the total 1st order *outer* contribution to the SPDERG 2nd order uniform approximation to the correct solution, in the case of the substrate, is just:

$$\tilde{s}_1^{rg,out}(t) = -\frac{[\tilde{s}_0^{out}(t) + m]\tilde{s}_0^{out}(t)}{[\tilde{s}_0^{out}(t) + M]^2} + \tilde{s}_1^{rg*}(t) = \tilde{s}_1^{out}(t). \quad (56)$$

Thus, one recovers the 1st order outer contribution to the perturbation expansion uniform approximation reported in (20). As we discuss more in detail in the following, this was not a result to be taken for granted [11]. In particular, the result implies that $\tilde{s}_1^{rg,out}(0) = -(1+m)/(1+M)^2$.

Hence, we recall that $\mathcal{R}_2^s(\tau)$ is to be evaluated from the remaining part of the solution in $\tilde{s}_0^* = 1$, $\tilde{s}_1^* = 0$, and $\tau_0 = 0$. It is given by (see (66), and (68), in Appendix B):

$$\begin{aligned} \mathcal{R}_2^s(\tau) = & D_{s_2^{rg}}(1) + \left[F_{s_2^{rg}}(1) + H_{s_2^{rg}}(1)\tau + J_{s_2^{rg}}(1)\tau^2 \right] e^{-(1+M)\tau} + K_{s_2^{rg}}(1)e^{-2(1+M)\tau} = \\ & = -\frac{1}{2(1+M)^5} [2M^2(2m+1) - M(6m^2+5m+3) - m^2+m] + \\ & + \frac{1}{(1+M)^5} [M^2(2m+1) - M(3m^2+3m+2) - m^2-m-1] e^{-(1+M)\tau} + \\ & - \left\{ \frac{1}{(1+M)^4} [M^2+M(m^2+1)-2m-1]\tau - \frac{(M-m)}{2(1+M)^3} (m+1)\tau^2 \right\} e^{-(1+M)\tau} + \\ & + \frac{(m+1)}{2(1+M)^5} (M+m+2) e^{-2(1+M)\tau}. \end{aligned} \quad (57)$$

Here we used, in particular, the coefficient values reported in (68).

Correspondingly, we get the complete result for the SPDERG 2nd order uniform approximation to the dimensionless substrate solution:

$$\tilde{s}_2^{rg,u}(t) = \tilde{s}_1^{rg,u}(t) - \varepsilon \left\{ \frac{\tilde{s}_0^{out}(t)+m}{[\tilde{s}_0^{out}(t)+M]^2} \tilde{s}_0^{out}(t) - \frac{1+m}{(1+M)^2} \tilde{s}_1^{rg*}(t) \right\} + \varepsilon^2 \mathcal{R}_2^s(t/\varepsilon) + O(\varepsilon^2), \quad (58)$$

with $\tilde{s}_1^{rg,u}(t)$ given by (44), $\tilde{s}_0^{out}(t) = \tilde{s}_0^{rg*}(t)$ given by (8), and $\tilde{s}_1^{rg*}(t)$, $\mathcal{R}_2^s(t/\varepsilon)$, given by (55), (57), respectively. We wrote the solution in the present form with the aim to make as evident as possible analogies and differences with the 1st order perturbation expansion result. In particular, the constant term that is equal to $-(1+m)/(1+M)^2$ originates, here, from the constant term depending on $\tilde{s}_0^*$ that appeared (calculated in $\tilde{s}_0^* = 1$) in $\tilde{s}_1^{rg,u}(t)$, the one that has been now included in $\tilde{s}_{div}^{rg}$, at the 2nd order. Moreover, one can notice that the result implies, as expected, $\lim_{t \rightarrow \infty} \tilde{s}_2^{rg,u}(t) = \tilde{s}_2^{rg,u} = \varepsilon^2 D_{s_2^{rg}}(1) = O(\varepsilon^2)$, where $D_{s_2^{rg}}(1)$ is the first of the terms in (57), reported in Appendix B.

For the complex, the 2nd order terms to be added to the part of the solution to be renormalized are the three ones that appear in $\tilde{c}_{2,div}^{rg}(\tau)$, that is reported in (70), in Appendix B. Moreover, we have again to take into account also the constant term in $\tilde{c}_1^{rg}(\tau)$, *i.e.*, the one that corresponds to the coefficient $B_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*)$, that is reported in (65), in Appendix B, and that needs to be calculated in $\tilde{c}_0^* = 0$. We obtain:

$$\begin{aligned} \tilde{c}_{div}^{rg}(\tau) = & \frac{\tilde{s}_0^*}{\tilde{s}_0^*+M} - \varepsilon \frac{M(\tilde{s}_0^*-M+2m)}{(\tilde{s}_0^*+M)^4} \tilde{s}_0^* + \varepsilon \frac{M\tilde{s}_1^*}{(\tilde{s}_0^*+M)^2} - \varepsilon \frac{M(M-m)\tilde{s}_0^*}{(\tilde{s}_0^*+M)^3} (\tau - \tau_0) + \\ & + \varepsilon^2 A_{c_{2,div}^{rg}}(\tilde{s}_0^*)(\tau - \tau_0) + \varepsilon^2 B_{c_{2,div}^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*)(\tau - \tau_0) + \varepsilon^2 C_{c_{2,div}^{rg}}(\tilde{s}_0^*)(\tau - \tau_0)^2, \end{aligned} \quad (59)$$

Here, the coefficients $A_{c_{2,div}^{rg}}$, $B_{c_{2,div}^{rg}}$, and $C_{c_{2,div}^{rg}}$, of the three 2nd order secular terms, are given by (71), once again in Appendix B.

The proof, that is reported in Appendix C (see Eqs. (77)-(80) and the following discussion), involves quite complicated calculations. Nevertheless, one can check that here one obtains a function $\tilde{c}_{div}^{rg}(\tau, \lambda)$ exactly corresponding to (59), with $\tilde{s}_0^* \rightarrow \tilde{s}_0^{rg*}(\lambda)$, $\tilde{s}_1^* \rightarrow \tilde{s}_1^{rg*}(\lambda)$, and $\tau_0 \rightarrow \lambda$, in the same way as we showed in detail in the study of the substrate, with the same renormalization coefficients of the bare substrate IC ($z_{s_0,1}$ already fixed by (35), and $z_{s_0,2}$, $z_{s_1,1}$ already fixed by (52), respectively). This was in fact

the expected result, both from the point of view of the analogy with the matching in the perturbation expansion, and from the observation that it should have been alternatively possible to limit the study to Eq. (27), or Eq. (28).

Moreover, as expected within the same context, we verify that, when imposing the scaling condition, $d\tilde{c}_{div}^{rg}(\tau, \lambda)/d\lambda = 0$, one recovers, once again, the two ODEs given by (54), to be obeyed by $\tilde{s}_0^{rg*}(\lambda)$, and $\tilde{s}_1^{rg*}(\lambda)$. Thus, one obtains, in particular, the same result on $\tilde{s}_1^{rg*}(\lambda)$ (as reported in Appendix C, too, see Eq. (83)).

In detail, also in the case of the complex, one needs to use the known 1st order result on $d\tilde{s}_0^{rg*}(\lambda)/d\lambda$, in the derivation of the 2nd order one on $d\tilde{s}_1^{rg*}(\lambda)/d\lambda$. Also here, the result on the derivative with respect to λ is obtained in a very similar way to the proof of the correspondence between $\tilde{c}_{div}^{rg}(\tau, \lambda)$ and the original $\tilde{c}_{div}^{rg}(\tau)$, given by (59).

Clearly, in the present case, there is a definitely larger number of relevant terms that anyway either cancel each other or contribute in the correct way to the final result. Therefore, the verification, reported in Appendix C, of the correctness of the expectations we made, appears to give further consistency to the whole approach.

Correspondingly, we obtain a 1st order *outer* contribution to the SPDERG 2nd order uniform approximation, for the dimensionless complex concentration, that turns out to be exactly equal to the 1st order perturbation expansion outer contribution, given by (21). It is obtained, here, from an algebraic relation, that could appear different from the one reported in Eqs. (19), but that is, in fact, equivalent. This becomes evident when writing $\tilde{s}_1^{rg*}(t)$ in terms of $\tilde{s}_0^{out}(t)$, and $\tilde{s}_1^{out}(t)$, by means of (56):

$$\tilde{c}_1^{rg, out}(t) = -\frac{M(\tilde{s}_0^{rg*}(t) - M + 2m)}{[\tilde{s}_0^{rg*}(t) + M]^4} \tilde{s}_0^{rg*}(t) + \frac{M\tilde{s}_1^{rg*}(t)}{[\tilde{s}_0^{rg*}(t) + M]^2} = \tilde{c}_1^{out}(t). \quad (60)$$

The equality can also be checked by reminding that $\tilde{s}_0^{rg*}(t) = \tilde{s}_0^{out}(t)$, and by using the known result for $\tilde{s}_1^{rg*}(t)$, reported in (55).

The SPDERG 2nd order uniform approximation for the complex is then obtainable by taking into account also the remaining part of the 2nd order inner solution, and it is given by:

$$\begin{aligned} \tilde{c}_2^{rg, u}(t) = & \tilde{c}_1^{rg, u}(t) - \varepsilon \left\{ \frac{M(\tilde{s}_0^{rg*}(t) - M + 2m)}{[\tilde{s}_0^{rg*}(t) - M]^4} \tilde{s}_0^{rg*}(t) - \frac{M\tilde{s}_1^{rg*}(t)}{[\tilde{s}_0^{rg*}(t) + M]^2} - \frac{M(1 - M + 2m)}{(1 + M)^4} \right\} + \\ & + \varepsilon^2 \mathcal{R}_2^c(t/\varepsilon) + O(\varepsilon^2). \end{aligned} \quad (61)$$

Here, we attempt to outline once more similarities and differences with the perturbation expansion result. In fact, because of (60), one can equivalently write the terms in curly brackets as $\tilde{c}_1^{out}(t)$ minus the constant terms that in the standard perturbation expansion method appear twice.

In detail, the various terms that appear in (61) are reported: $\tilde{c}_1^{rg, u}(t)$ in (44); $\tilde{s}_0^{rg*}(t) = \tilde{s}_0^{out}(t)$ in (8); $\tilde{s}_1^{rg*}(t)$ in (55); and $\mathcal{R}_2^c(\tau)$, correctly evaluated at $\tau_0 = 0$, $\tilde{s}_0^* = 1$ and $\tilde{s}_1^* = 0$ in (72), with the coefficients given by (74), in Appendix B.

This uniform approximation verifies the IC $\tilde{c}_2^{rg, u}(0) = 0$, whereas one finds:

$$\lim_{t \rightarrow \infty} \tilde{c}_2^{rg, u}(t) = \tilde{c}_{2, \infty}^{rg, u} = \varepsilon^2 A_{\mathcal{R}_2^c}(1, 0) = O(\varepsilon^2). \quad (62)$$

Here, $A_{\mathcal{R}_2^c}(1, 0)$ is the constant term in $\mathcal{R}_2^c(\tau)$, whose detailed dependence on $\tilde{s}_0^*$, and $\tilde{s}_1^*$, is reported in (73), and that is calculated in $\tilde{s}_0^* = 1$, $\tilde{s}_1^* = 0$ in (74), in Appendix B.

Figure 5: **Comparison between the numerical solutions and the 2nd order SPDERG uniform approximations, for the two considered sets of ICs.** (Color online) In A) and C) we present the behaviour of the concentrations of the substrate $s(t)$, whereas in B) and D) we present the one of the concentrations of the complex $c(t)$ for the a and b sets of ICs given by (4), respectively. Hence, in A) and B) we are in the case with $\varepsilon = \varepsilon^a = 0.1$, whereas in C) and D) we are in the one with $\varepsilon = \varepsilon^b = 0.5$. We plot both the numerical solutions of Eqs. (2), already shown in the previous figures, and the analytical solutions computed from the SPDERG 2nd order uniform approximations (with a standard numerical approximation to the Lambert function), as given by (58), and (61), respectively. We plot moreover the (physically meaningless) asymptotic limits of these analytical solutions: $s_0^a \bar{s}_{2,\infty}^{rg,u} \simeq 0.0012$ (μM), $e_0^a \bar{c}_{2,\infty}^{rg,u} \simeq -0.00023$ (μM), and $s_0^b \bar{s}_{2,\infty}^{rg,u} \simeq 0.3$ (μM), $e_0^b \bar{c}_{2,\infty}^{rg,u} \simeq -0.029$ (μM), for the a and b sets of ICs, respectively. We finally plot our corresponding rough evaluations of the two different time scales involved, too, with τ_s describing the substrate decay time and τ_c the complex saturation time. Notice that the time is in logarithmic scale.

We plot in [Fig. 5] our numerical results on the SPDERG 2nd order uniform approximations for the substrate and the complex, respectively, for the two considered sets of ICs. The plots are, as usual, in comparison with the numerical solutions of the original problem, given by Eqs. (2) (the same curves as in the previous figures).

Since they contain the 2nd order terms of the inner solutions (this is indeed the only difference), these are definitely better approximations than the 1st order perturbation expansion uniform approximations, in a region that encompasses the matching one. Indeed, the results here are nearly indistinguishable, within our numerical precision, from the correct ones on a definitely larger time window. This is true also in the particularly unfavourable case of the substrate in [Fig. 5C], and the outcome is clearly different from the one observed in the same case at the 1st order, when applying the standard perturbation expansion method, that is reported in [Fig. 3C].

Nevertheless, one can still note a minor discrepancy at large times, that is at least partially to be related to the failure of the approximations in reproducing the asymptotically vanishing solutions. Actually, on the basis of the results that we already obtained in the present study, this failure seems correctable in a reasonable way. In the following Section, we just introduce refined SPDERG 2nd order uniform approximations that satisfy the asymptotic conditions $\lim_{t \rightarrow \infty} s(t) = \lim_{t \rightarrow \infty} c(t) = 0$, too.

7. Results and discussion: iii) Refined SPDERG second order uniform approximations

Within the framework of the already obtained results, by assuming that the found solution behaviours could be iterated, one can hypothesize that, in the actual SPDERG approach, the constant term at a given order will contribute to the outer component of the solution at the following one. Actually, this appears to us the SPDERG approach ingredient that is equivalent to take into account both a part of the matching conditions and the removing of one of the constants that otherwise would appear twice in the uniform approximations of the standard perturbation expansion method, though the observation needs to be better formalized for investigating its possible generalizations.

In fact, in the present case, when passing from the 2nd to the 3rd order, these iteratively expected solution behaviours should be obtainable by means of the substitutions $\tilde{s}_0^* \rightarrow \tilde{s}_0^{rg*}(t)$ and $\tilde{s}_1^* \rightarrow \tilde{s}_1^{rg*}(t)$ in the constant terms $D_{s_2^{rg}}(\tilde{s}_0^*) + E_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*)$ and $A_{\mathcal{R}_2}(\tilde{s}_0^*, \tilde{s}_1^*)$. These terms appear in the 2nd order inner solution for the substrate and the complex, respectively, that are given by (68), and (73), in Appendix B. We notice that, despite of the substitutions, they remain terms of 2nd order, in agreement with the general consideration that, at the n -th order, within the SPDERG approach, one in fact obtains the $(n - 1)$ -th order outer components of the corresponding perturbation expansion uniform approximations, *i.e.*, their leading order terms [10, 11].

Therefore, we can finally consider as refined SPDERG 2nd order uniform approximations the functions $\tilde{s}_{2,r}^{rg,u}(t)$, and $\tilde{c}_{2,r}^{rg,u}(t)$, that satisfy by construction the physically correct asymptotic conditions $\lim_{t \rightarrow \infty} \tilde{s}_{2,r}^{rg,u}(t) = \lim_{t \rightarrow \infty} \tilde{c}_{2,r}^{rg,u}(t) = 0$. These are given by:

$$\begin{cases} \tilde{s}_{2,r}^{rg,u}(t) = \tilde{s}_2^{rg,u}(t) + \varepsilon^2 \left\{ D_{s_2^{rg}}[\tilde{s}_0^{rg*}(t)] + E_{s_2^{rg}}[\tilde{s}_0^{rg*}(t), \tilde{s}_1^{rg*}(t)] - D_{s_2^{rg}}(1) \right\} + O(\varepsilon^2) \\ \tilde{c}_{2,r}^{rg,u}(t) = \tilde{c}_2^{rg,u}(t) + \varepsilon^2 \left\{ A_{\mathcal{R}_2}[\tilde{s}_0^{rg*}(t), \tilde{s}_1^{rg*}(t)] - A_{\mathcal{R}_2}(1, 0) \right\} + O(\varepsilon^2), \end{cases} \quad (63)$$

Figure 6: **Comparison between the numerical solutions and the refined 2nd order SPDERG uniform approximations, for the two considered sets of ICs.** (Color online) In A) and C) we present the behaviour of the concentrations of the substrate $s(t)$, whereas in B) and D) we present the one of the concentrations of the complex $c(t)$ for the a and b sets of ICs given by (4), respectively. Hence, in A) and B) we are in the case with $\varepsilon = \varepsilon^a = 0.1$, whereas in C) and D) we are in the one with $\varepsilon = \varepsilon^b = 0.5$. We plot both the numerical solutions of Eqs. (2), already shown in the previous figures, and the analytical solutions computed from the refined SPDERG 2nd order uniform approximations (with a standard numerical approximation to the Lambert function), as given by (63). We finally plot our corresponding rough evaluations of the two different time scales involved, too, with τ_s describing the substrate decay time and τ_c the complex saturation time. Notice that the time is in logarithmic scale.

We remind that $E_{s_2^{rg}}(1, 0) = 0$, whereas $\tilde{s}_2^{rg,u}(t)$ and $\tilde{c}_2^{rg,u}(t)$ are reported in (58) and (61), respectively, $\tilde{s}_0^{rg*}(t) = \tilde{s}_0^{out}(t)$ in (20), and $\tilde{s}_1^{rg*}(t)$ in (55).

It is not to be taken for granted that these approximations could turn out to be better than the previously considered ones, since they, anyway, lack a part of the 2nd order outer contributions. On the other hand, these appear to us the most refined SPDERG 2nd order uniform approximations that one can propose, by exploiting as much as possible the obtained results.

We present the corresponding substrate and complex behaviours, as usual for the two different considered sets of ICs, in [Fig. 6]. The plots are, once more, in comparison with the numerical solutions of the original problem, given by Eqs. (2) (the same curves as in the previous figures), too.

In fact, one could already observe in the previous [Fig. 5A], [Fig. 5B] that there was no detectable difference between the SPDERG 2nd order uniform approximations and the correct solutions in the case of the a set of ICs. Indeed, this set corresponds to the relatively small $\varepsilon = \varepsilon^a = 0.1$, and the perturbation expansion 1st order uniform approximations showed no detectable difference with respect to the correct solutions for this set of ICs ([Fig. 3A], [Fig. 3B]), too. In this case, we limit ourselves to underline that the here proposed SPDERG 2nd order approximations, that are presented in [Fig. 6A]

for the substrate concentration and in [Fig. 6B] for the complex one, respectively, are, moreover, also rigorously asymptotically vanishing. This implies, in particular, that they are nearly indistinguishable from the correct solutions, within our numerical precision, as much as the perturbation expansion 1st order results.

On the other hand, when looking at [Fig. 6C], and [Fig. 6D], that show the behaviour of the substrate and complex concentration, respectively, for the b case of ICs, *i.e.*, for the quite large value of the expansion parameter $\varepsilon = \varepsilon^b = 0.5$, the plots turn out to be not enough detailed for making evident the differences between the present approximated solutions and the ones without the refinement. Both for this reason and for roughly quantifying our various qualitative observations, we are led to a more careful study.

8. Results and discussion: iv) A conclusive comparison

We show in [Fig. 7] the detailed time depending behaviours of the substrate concentration, $s(t)$, and of the complex one, $c(t)$, for the case that corresponds to the quite large value of the expansion parameter $\varepsilon = \varepsilon^b = 0.5$. First of all, we plot separately and differently the two relevant parts of the time window, *i.e.*, the time is in logarithmic scale only in the first part. Here, we compare the different *best* approximations that we both recall and obtain in the present work: i) the perturbation expansion 1st order uniform approximations (as given by (25), already presented in [Fig. 3C], [Fig. 3D]); ii) the SPDERG 2nd order uniform approximations, (as given by (58), (61), already presented in [Fig. 5C], [Fig. 5D]); iii) the refined SPDERG 2nd order uniform approximations (as given by (63), already presented in [Fig. 6C], [Fig. 6D]).

In detail, we neglect the initial time interval, up to $t = 0.03s$ for the substrate, and to $t = 0.08s$ for the complex, respectively. Indeed, in this interval, the different results are indistinguishable, within our numerical precision, both each other and with the correct numerical solutions. Instead, we show with higher definition than previously, as usual in logarithmic time scale, the central intervals, *i.e.*, the ones that encompass the matching region. These intervals are $t \sim 0.03 - 3.5 s$ for the substrate ([Fig. 7A]) and $t \sim 0.08 - 2.5 s$ for the complex ([Fig. 7C]), respectively. Finally, we present in non logarithmic time scale the relevant large time window, [Fig. 7B], and [Fig. 7D], for the substrate and for the complex, respectively. In fact, this window ranges up to $t \sim 12s$ for the substrate, and up to $t \sim 14s$ for the complex, since at longer times (as it is clear from [Fig. 7B], in particular) the solutions have already reached, within our numerical precision, their asymptotic values (that are different from zero in the case of the non refined SPDERG).

Once more, the curves shown in [Fig. 7A] make evident that, in the case of the substrate, both of the present SPDERG 2nd order uniform approximations are definitely better approximations to the correct solutions than the perturbation expansion 1st order ones, both in the matching region and near it. They, moreover, allow to naked-eye evaluate the range in which this happens. In fact, this range corresponds to $t \sim 0.05 - 2 s$, hence it covers about the 15% of the whole relevant time window, in the case without refinement. Instead, this range corresponds to $t \sim 0.05 - 3 s$ (notice that the longer time is of the same order of τ_s^b), hence it covers about the 25% of the whole relevant time window, in the case with the refinement. On the other hand, for $t \gtrsim 3s$ ([Fig. 7B]), the refined SPDERG 2nd order uniform approximation appears to tend to zero slightly too rapidly, with respect both to the correct solution and to the perturbation expansion 1st

Figure 7: Comparison between the numerical solutions, the 1st order perturbation expansion uniform approximations, the 2nd order SPDERG uniform approximations, and the refined 2nd order SPDERG uniform approximations, for the more unfavourable of the two considered sets of ICs. (Color online) In A) (respectively C)) we present the behaviour of the concentration of the substrate $s(t)$ (respectively of the complex $c(t)$) in the central part of the time window, in logarithmic time scale, whereas in B) (respectively D)) we present the large time behaviour of these two quantities. The results are for the b set of ICs given by (4), *i.e.*, the one that corresponds to $\varepsilon = \varepsilon^b = 0.5$. We plot the numerical solutions of Eqs. (2), already shown in the previous figures, and we compare with these correct behaviours: i) the perturbation expansion 1st order uniform approximations (as given by (25), already presented in [Fig. 3C], [Fig. 3D]); ii) the SPDERG 2nd order uniform approximations (as given by (58), (61), already presented in [Fig. 5C], [Fig. 5D]); iii) the refined SPDERG 2nd order uniform approximations (as given by (63), already presented in [Fig. 6C], [Fig. 6D]). All these uniform approximations are computed by means of the same standard numerical approximation to the Lambert function. When they belong to the time window, we finally plot our corresponding rough evaluations of the two different time scales involved, too, with τ_s^b describing the substrate decay time and τ_c^b the complex saturation time.

order result, though it is correctly asymptotically vanishing and, moreover, it makes a smaller error than the same SPDERG approximation without the refinement.

In the case of the complex, as already anticipated, the curves shown in [Fig. 7C] make clear that the perturbation expansion 1st order uniform approximation slightly over-evaluates the value of its maximum. In fact, it appears to over-evaluate the complex dynamical behaviour in the whole range $t \sim 0.25 - 0.7$ s, that is a time interval roughly centered around the maximum abscissa (in logarithmic time scale). On the other hand, both of the SPDERG 2nd order uniform approximations are successful in correctly capturing the maximum value of the complex numerical solution. In particular, the refined SPDERG approximation turns out to be the one more in agreement with the correct result up to the larger time $t \sim 2$ s, *i.e.*, in about the 15% of the whole relevant time window. It is moreover both as much correct as the 1st order result of the standard method (though going to zero slightly more rapidly than the correct solution) and definitely better than the same approximation without refinement at large times. In particular, this is true for $t \sim 9 - 14$ s, that covers about a remaining 35% of the whole relevant time window. Nevertheless, the refined SPDERG approximation turns out to be the one that makes the largest error, by over-evaluating the correct complex concentration behaviour, in the remaining part of the relevant time window (in detail, for $t \sim 2.5 - 6.5$ s).

Thus, the present refined SPDERG 2nd order uniform approximations successfully capture the correct dynamical behaviours in a large part of the relevant time windows, despite of the considered case ($\varepsilon \sim 0.5$) being very unfavourable. First of all, this further confirms both the correctness and the utility of the SPDERG approach in general. Moreover, these findings support the effectiveness of the present proposed method for obtaining asymptotically vanishing solutions, that exploits as much as possible the results, too. At least within our way of applying the SPDERG, the proposed refined uniform approximations appear easily generalizable to other similar cases. At the same time, the present analysis makes clear that the remaining part, to be analytically calculated, of the 2nd order outer contributions, would be important for an approximation to MM kinetics, beyond the sQSSA, that could give correct results in the whole relevant time window, also in cases as unfavourable as the here considered one, from the point of view of the values of the kinetic constants and of the expansion parameter.

9. Conclusions

In the present work, we start by recalling the singular perturbation expansion method in the case of MM kinetics, beyond the sQSSA [3, 4, 5, 12], *i.e.*, the analytical method that is often used to deal with the problem of approximating, as correctly as possible, the solutions of Eqs. (2), that can be seen as an example of a singular system of ODEs and, in particular, as an example of a boundary layer problem [9]. As an alternative, we are able to successfully apply the SPDERG approach [10, 11], in detail, by following the examples of its application to boundary layer problems given in [11], by clarifying similarities and differences with the standard method.

The procedure that we choose for applying the SPDERG is based on a statement made in [10, 11], *i.e.*, that to renormalize appropriate integration constants that contain the ICs of the problem should be equivalent to renormalize directly the ICs. In fact, the case of MM kinetics is seemingly more demanding than the other boundary layer problems

considered in [11], at least from the point of view of the choice of these integration constants. Here, we show that this observation, made possible from a preliminary attempt to apply the SPDERG approach within the tQSSA framework [20], appears correct when starting from the sQSSA, too. Indeed, this can be seen from the 2nd order ODEs to be obeyed by the substrate and the complex, respectively.

For these reasons, we study the system of two 1st order ODEs to be obeyed by the inner solutions, with ICs given at a generic time, and we take as integration constants, to be renormalized, the ICs themselves. We advance in the calculations up to the 2nd order, by generally outlining as much as possible similarities and differences with respect to the perturbation expansion. To this aim, we explicitly write down all the terms that contribute to the results and underline the contribution of the single terms at every order of the approximations.

In the standard perturbation expansion method, the matching condition to be imposed on the complex is consistently verified by the one to be imposed on the substrate. Thus, in particular on the basis of the possible analogy with the matching conditions that we outlined, it appears reasonable to expect that the only IC to be renormalized is the one of the substrate (the renormalized complex solution being determined correspondingly, too). In any event, we found also essential, as we did, to verify and confirm in detail our expectation.

Nonetheless, it is important to underline that, within our way of applying the SPDERG, we treat as different bare constants, to be renormalized, all the contributions to the substrate IC at each order. From this point of view, our approach is definitely different from the examples in [11], where 2nd order ODEs were studied, by introducing just two integration constants.

In conclusion, though our reasonings could be better formalized in the future, the present verifications can be taken for granted in other similar studies.

Among our main results, in particular, we are able to show that one gets exactly the same outer component, as in the standard perturbation expansion 1st order uniform approximation, for the substrate (thus, also for the complex). This result was not predictable. In fact, in the context of the boundary layer problems studied in [11], it was shown the possibility to find by the SPDERG approach not exactly the same terms as in the corresponding perturbation expansion uniform approximation, though anyway the SPDERG solutions approximated better than this last one the correct behaviours in the matching region.

At the same time, at least within our application, the SPDERG approach turns out, as expected [10, 11], to make possible to correctly manage both the secular terms and the constant ones, without the imposition of matching conditions. Actually, this can be intuitively understood as a result of the analogy with the matching conditions of the standard method we were referring to. Indeed, we suggested this analogy on the basis of the observation that the key ingredient, here, *i.e.*, the fact that the renormalized part of the solution has to be independent of the arbitrary time λ , looks similar to the imposition of the matching conditions at an unknown time.

On the one hand, within the SPDERG approach, it is necessary to advance in the calculations up to the 2nd order for recovering the 1st order outer contribution of the standard perturbation expansion method. This allowed us to present the 2nd order contribution of the inner solutions of the standard perturbation expansion method, beyond the sQSSA [5, 12], for the first time to our knowledge.

Most importantly, assuming that the observed solution behaviours could be iterated to successive orders, allowed us to hypothesize that the constant terms at a given order, not to be renormalized, play the role of a part of the outer component at the following order. Indeed, this looks equivalent to both the imposition of the first term of the matching conditions and the need for cancelling one of the constant terms that otherwise would appear twice in the uniform approximations, within the perturbation expansion. It is reasonable to expect that this is a general characteristic of the SPDERG approach to boundary layer problems, at least in the present way of applying it, by directly renormalizing the ICs.

The possibility to make such an hypothesis was essential in order to overcome a failure of the SPDERG approach in our case, *i.e.*, the fact that one is unable to impose the correct asymptotically vanishing behaviours to the solutions. Thus, we propose refined SPDERG 2nd order uniform approximations. These last ones contain the parts of the 2nd order outer components that are correspondingly predictable, and are, thus, asymptotically vanishing, too.

At last, we presented a conclusive comparison among the best different approximations that we both recalled and obtained, for the more unfavourable ICs of the two studied sets (the one that corresponds to a quite large value of the expansion parameter $\varepsilon = \varepsilon^b = 0.5$, too).

Such a comparison makes evident that, in any event, the SPDERG approach allows to better approximate the correct numerical solutions in a time window definitely encompassing the matching one, that is even larger in the refined case. Moreover, apart from being correctly asymptotically vanishing, the refined 2nd order SPDERG uniform approximations, when looking in particular at the complex, turn out to be as correct as the 1st order perturbation expansions at large times, too. Nevertheless, the calculation of the remaining part of the outer 2nd order contributions would remain necessary for efficiently approximating the correct solutions in the whole time window, in cases as unfavourable as this one.

Let us still highlight an interesting advantage of the present way of applying the SPDERG approach, *i.e.*, that, at least in the considered case, at the 2nd order, in order to obtain the 1st order outer substrate and complex component, one needs to solve a simpler ODE, than the corresponding one in the standard perturbation expansion method, just because the other part of the outer contribution is already known. Such an advantage could turn out to be particularly useful when attempting to apply the same procedure within the different framework of the tQSSA. In fact, in this case, the outer solutions are not known neither explicitly, nor in terms of the Lambert function, not only at the 1st order but even at the 0th order [14, 15, 16].

As anticipated in the Introduction, the application of the SPDERG approach in the tQSSA framework, that we foresee to deal with in the future, could allow to obtain analytical results more meaningful than the present ones from the experimental point of view, too. In fact, in this case, the SPDERG could allow to obtain approximations to the correct solutions exploitable in order to fit experimental time courses, even in the worst possible experimental situations, in which it is needed to go beyond the known standard perturbation expansion that takes the tQSSA as starting point [16]. This would make possible, in particular, a better understanding of the relations between the kinetic constants that appear in MM kinetics and the quantities that instead are usually experimentally measured (see, for instance, [36], and references therein, for a similar

analysis on a related subject).

Finally, we notice that, despite of their being quite technical and cumbersome, there is no particular difficulty in the present calculations. From this point of view, we underline that the use of a symbolic algebra system allowed us to partially automate them, greatly simplifying the work. Nevertheless, the ODE to be solved in order to obtain the outer solutions remains the most evident obstacle to a complete automatization, to easily determine higher orders in the expansion.

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A. The complex 1st order SPDERG inner solution

We report the solution $\tilde{c}_1^{rg}(\tau)$ of the system given by Eqs. (31), *i.e.*, the 1st order inner solution for the dimensionless complex concentration in MM kinetics, beyond the sQSSA, within the SPDERG approach. Here, the ICs to be renormalized are fixed to $\tilde{s}^{rg}(\tau_0) = \tilde{s}_0^* + \varepsilon \tilde{s}_1^*$, and $\tilde{c}^{rg}(\tau_0) = \tilde{c}_0^* + \varepsilon \tilde{c}_1^*$, at $\tau = \tau_0$. In detail, we distinguish the terms corresponding to different functions of $(\tau - \tau_0)$. We find:

$$\begin{aligned} \tilde{c}_1^{rg}(\tau) &= A_{c_1^{rg}}(\tilde{s}_0^*)(\tau - \tau_0) + B_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*) + C_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*, \tilde{c}_1^*)e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} + \\ &+ \left[D_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*)(\tau - \tau_0) + E_{c_1^{rg}}(\tilde{s}_0^*, \tilde{c}_0^*)(\tau - \tau_0)^2 \right] e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} + \\ &+ F_{c_1^{rg}}(\tilde{s}_0^*, \tilde{c}_0^*)e^{-2(\tilde{s}_0^* + M)(\tau - \tau_0)}, \end{aligned} \quad (64)$$

with:

$$\begin{aligned} A_{c_1^{rg}}(\tilde{s}_0^*) &= -\frac{M(M-m)}{(\tilde{s}_0^* + M)^3} \tilde{s}_0^*; \\ B_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*) &= -\frac{M(\tilde{s}_0^* - M + 2m)}{(\tilde{s}_0^* + M)^4} \tilde{s}_0^* + \frac{M}{(\tilde{s}_0^* + M)^2} \tilde{s}_1^* + \frac{M(\tilde{s}_0^* + m)}{(\tilde{s}_0^* + M)^3} \tilde{c}_0^*; \\ C_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*, \tilde{c}_1^*) &= \tilde{c}_1^* + \frac{M(\tilde{s}_0^* - M + 2m)}{(\tilde{s}_0^* + M)^4} \tilde{s}_0^* + \frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^4} (\tilde{s}_0^*)^2 - \frac{M}{(\tilde{s}_0^* + M)^2} \tilde{s}_1^* + \\ &- \frac{(2\tilde{s}_0^* + M)(\tilde{s}_0^* + m)}{(\tilde{s}_0^* + M)^3} \tilde{c}_0^* + \frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^2} (\tilde{c}_0^*)^2; \\ D_{c_1^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*, \tilde{c}_0^*) &= -\frac{(\tilde{s}_0^* + m)(\tilde{s}_0^* - M)}{(\tilde{s}_0^* + M)^3} \tilde{s}_0^* + \frac{\tilde{s}_0^* \tilde{s}_1^*}{\tilde{s}_0^* + M} - \frac{\tilde{s}_1^* \tilde{c}_0^*}{(\tilde{s}_0^* + M)^2} + \frac{(\tilde{s}_0^* + m)(2\tilde{s}_0^* - M)}{(\tilde{s}_0^* + M)^2} \tilde{c}_0^* + \\ &- \frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^2} (\tilde{c}_0^*)^2; \\ E_{c_1^{rg}}(\tilde{s}_0^*, \tilde{c}_0^*) &= -\frac{(M-m)}{2(\tilde{s}_0^* + M)^2} (\tilde{s}_0^*)^2 + \frac{(M-m)}{2(\tilde{s}_0^* + M)} \tilde{s}_0^* \tilde{c}_0^*; \\ F_{c_1^{rg}}(\tilde{s}_0^*, \tilde{c}_0^*) &= -\frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^4} (\tilde{s}_0^*)^2 + 2\frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^3} \tilde{s}_0^* \tilde{c}_0^* - \frac{\tilde{s}_0^* + m}{(\tilde{s}_0^* + M)^2} (\tilde{c}_0^*)^2. \end{aligned} \quad (65)$$

In particular, one can check that it is, correctly, $\tilde{c}_1^{rg}(\tau_0) = B_{c_1^{rg}} + C_{c_1^{rg}} + F_{c_1^{rg}} = \tilde{c}_1^*$. Moreover, for $\tilde{s}_0^* = 1$, $\tilde{s}_1^* = \tilde{c}_0^* = \tilde{c}_1^* = 0$, and $\tau_0 = 0$, the result on $\tilde{c}_1^{in}$ reported in (18) is correctly reproduced, too.

B. The substrate and complex 2nd order SPDERG inner solutions

We report the solutions $\tilde{s}_2^{rg}(\tau)$ and $\tilde{c}_2^{rg}(\tau)$ of the system given by Eqs. (46), *i.e.*, the 2nd order inner solutions for the dimensionless substrate and complex concentrations in MM kinetics, beyond the sQSSA, within the SPDERG approach. Here, the ICs are anyway already fixed, for the sake of simplicity, to $\tilde{s}_2^{rg}(\tau_0) = \tilde{s}_0^* + \varepsilon \tilde{s}_1^*$, and $\tilde{c}_2^{rg}(\tau_0) = 0$, at $\tau = \tau_0$. As discussed in the text, this choice is made on the basis of the expectation, to be verified, that the only quantities that need to be renormalized at the present order are $\tilde{s}_0^*$ (in agreement with the previously obtained result), and $\tilde{s}_1^*$.

Let us start with $\tilde{s}_2^{rg}(\tau)$. Notice that, here, we separate the terms that are different functions of $(\tau - \tau_0)$, and the terms that depend only on $\tilde{s}_0^*$, or both on $\tilde{s}_0^*$ and on $\tilde{s}_1^*$:

$$\begin{aligned} \tilde{s}_2^{rg}(\tau) = & \left[A_{s_2^{rg}}(\tilde{s}_0^*) + B_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) \right] (\tau - \tau_0) + C_{s_2^{rg}}(\tilde{s}_0^*) (\tau - \tau_0)^2 + D_{s_2^{rg}}(\tilde{s}_0^*) + E_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) + \\ & + \left\{ \left[F_{s_2^{rg}}(\tilde{s}_0^*) + G_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) \right] + \left[H_{s_2^{rg}}(\tilde{s}_0^*) + I_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) \right] (\tau - \tau_0) \right\} e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} + \\ & + J_{s_2^{rg}}(\tilde{s}_0^*) (\tau - \tau_0)^2 e^{-(\tilde{s}_0^* + M)(\tau - \tau_0)} + K_{s_2^{rg}}(\tilde{s}_0^*) e^{-2(\tilde{s}_0^* + M)(\tau - \tau_0)}. \end{aligned} \quad (66)$$

In fact, only the first three terms contribute to the part to be renormalized of the whole function, $\tilde{s}_2^{rg}(\tau)$, at the 2nd order. Their coefficients are:

$$\begin{aligned} A_{s_2^{rg}}(\tilde{s}_0^*) &= \frac{2M(M-m)\tilde{s}_0^*}{(\tilde{s}_0^* + M)^4} (\tilde{s}_0^* + m); & B_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) &= -\frac{M(M-m)\tilde{s}_1^*}{(\tilde{s}_0^* + M)^2}; \\ C_{s_2^{rg}}(\tilde{s}_0^*) &= \frac{M(M-m)^2\tilde{s}_0^*}{2(\tilde{s}_0^* + M)^3}. \end{aligned} \quad (67)$$

For the sake of completeness, we give the explicit dependence on $\tilde{s}_0^*$, and $\tilde{s}_1^*$, of the other terms, too. One finds:

$$\begin{aligned} D_{s_2^{rg}}(\tilde{s}_0^*) &= \frac{\tilde{s}_0^*}{2(\tilde{s}_0^* + M)^5} [(\tilde{s}_0^*)^2(3M-m) - \tilde{s}_0^*(2M^2 - 5Mm - m^2) - 2Mm(2M-3m)]; \\ E_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) &= -G_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) = -\frac{\tilde{s}_1^*}{(\tilde{s}_0^* + M)^3} [\tilde{s}_0^*(2M-m) + Mm]; \\ F_{s_2^{rg}}(\tilde{s}_0^*) &= -\frac{\tilde{s}_0^*}{(\tilde{s}_0^* + M)^5} [(\tilde{s}_0^*)^3 + (\tilde{s}_0^*)^2(2M+m) - \tilde{s}_0^*(M^2 - 3Mm - m^2) - Mm(2M-3m)]; \\ H_{s_2^{rg}}(\tilde{s}_0^*) &= \frac{\tilde{s}_0^*}{(\tilde{s}_0^* + M)^4} [(\tilde{s}_0^*)^3 - (\tilde{s}_0^*)^2(M-2m) - \tilde{s}_0^*M^2 - Mm^2]; \\ I_{s_2^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) &= -\frac{\tilde{s}_0^*\tilde{s}_1^*}{(\tilde{s}_0^* + M)^2} (\tilde{s}_0^* + m); & J_{s_2^{rg}}(\tilde{s}_0^*) &= \frac{(\tilde{s}_0^*)^2(M-m)}{2(\tilde{s}_0^* + M)^3} (\tilde{s}_0^* + m); \\ K_{s_2^{rg}}(\tilde{s}_0^*) &= \frac{(\tilde{s}_0^*)^2(\tilde{s}_0^* + m)}{2(\tilde{s}_0^* + M)^5} (2\tilde{s}_0^* + M + m). \end{aligned} \quad (68)$$

One can check that, correctly, $\tilde{s}_2^{rg}(\tau_0) = D_{s_2^{rg}} + E_{s_2^{rg}} + F_{s_2^{rg}} + G_{s_2^{rg}} + K_{s_2^{rg}} = 0$. Notice, moreover, that, when calculating the $\mathcal{R}_2^s(\tau)$ contribution to the SPDERG 2nd order uniform approximation, with the renormalized divergent part, one is interested in evaluating this quantity in $\tau_0 = 0$, for $\tilde{s}_0^* = 1$, and $\tilde{s}_1^* = 0$. Hence, one immediately gets $E_{s_2^{rg}} = G_{s_2^{rg}} = I_{s_2^{rg}} = 0$, since all of these coefficients are proportional to $\tilde{s}_1^*$. The other coefficients can be easily calculated for $\tilde{s}_0^* = 1$, and the corresponding $\mathcal{R}_2^s$ is reported in (57).

In the case of $\tilde{c}_2^{rg}(\tau)$, since the complete formula is uselessly cumbersome, we limit ourselves to report explicitly the dependence on $\tilde{s}_0^*$, and $\tilde{s}_1^*$, only for the part of the whole function that needs to be renormalized (*i.e.*, in the coefficients of the terms that are proportional to $(\tau - \tau_0)$, and to $(\tau - \tau_0)^2$).

Correspondingly, we write from the beginning:

$$\tilde{c}_2^{rg}(\tau) = \tilde{c}_{2,div}^{rg}(\tau) + \mathcal{R}_2^c(\tau). \quad (69)$$

In fact, we are collecting in $\tilde{c}_{2,div}^{rg}(\tau)$ just the secular terms:

$$\tilde{c}_{2,div}^{rg}(\tau) = \left[A_{c_{2,div}^{rg}}(\tilde{s}_0^*) + B_{c_{2,div}^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) \right] (\tau - \tau_0) + C_{c_{2,div}^{rg}}(\tilde{s}_0^*) (\tau - \tau_0)^2, \quad (70)$$

with, in detail:

$$\begin{aligned} A_{c_{2,div}^{rg}}(\tilde{s}_0^*) &= -\frac{M(M-m)\tilde{s}_0^*}{(\tilde{s}_0^*+M)^6} [2(\tilde{s}_0^*)^2 - 5\tilde{s}_0^*(M-m) + M^2 - 3Mm]; \\ B_{c_{2,div}^{rg}}(\tilde{s}_0^*, \tilde{s}_1^*) &= \frac{M(M-m)\tilde{s}_1^*}{(\tilde{s}_0^*+M)^4} (2\tilde{s}_0^* - M); \quad C_{c_{2,div}^{rg}}(\tilde{s}_0^*) = -\frac{M(M-m)^2\tilde{s}_0^*}{2(\tilde{s}_0^*+M)^5} (2\tilde{s}_0^* - M). \end{aligned} \quad (71)$$

On the other hand, $\mathcal{R}_2^c(\tau)$ contains all the terms that remain constant or tend to zero in the large $(\tau - \tau_0)$ limit, and it gives the 2nd order contribution of the inner solution to the SPDERG uniform approximation (that is $O(\varepsilon^2)$). For $\tilde{s}_0^* = 1$, and $\tilde{s}_1^* = 0$, by also coherently evaluating it in $\tau_0 = 0$, one finds:

$$\begin{aligned} \mathcal{R}_2^c(\tau) \Big|_{\substack{\tilde{s}_0^*=1 \\ \tilde{s}_1^*=0}} &= A_{\mathcal{R}_2^c} + [B_{\mathcal{R}_2^c} + C_{\mathcal{R}_2^c}\tau + D_{\mathcal{R}_2^c}\tau^2 + E_{\mathcal{R}_2^c}\tau^3 + F_{\mathcal{R}_2^c}\tau^4] e^{-(1+M)\tau} + \\ &+ [G_{\mathcal{R}_2^c} + H_{\mathcal{R}_2^c}\tau + I_{\mathcal{R}_2^c}\tau^2] e^{-2(1+M)\tau} + J_{\mathcal{R}_2^c} e^{-3(1+M)\tau}. \end{aligned} \quad (72)$$

Actually, it is useful to report also the complete dependence on $\tilde{s}_0^*$, $\tilde{s}_1^*$, M , and m , of the coefficient $A_{\mathcal{R}_2^c}$ (the constant term in the original $\tilde{c}_{2,div}^{rg}(\tau)$), since it allows to propose a refined SPDERG 2nd order uniform approximation. We find:

$$\begin{aligned} A_{\mathcal{R}_2^c}(\tilde{s}_0^*, \tilde{s}_1^*) &= -\frac{M(\tilde{s}_0^*)^4}{(\tilde{s}_0^*+M)^7} + \frac{M(\tilde{s}_0^*)^3(9M-11m)}{2(\tilde{s}_0^*+M)^7} - \frac{M(\tilde{s}_0^*)^2}{2(\tilde{s}_0^*+M)^7} (12M^2 - 27Mm + 13m^2) + \\ &+ \frac{M^2\tilde{s}_0^*(M^2 - 6mM + 6m^2)}{(\tilde{s}_0^*+M)^7} + \frac{M\tilde{s}_1^*}{(\tilde{s}_0^*+M)^5} [2(\tilde{s}_0^*)^2 - \tilde{s}_0^*(5M-6m) + M(1-2m)] + \\ &- \frac{M(\tilde{s}_1^*)^2}{(\tilde{s}_0^*+M)^3}, \end{aligned} \quad (73)$$

whereas the dependence on M and m of all the coefficients, calculated in $\tilde{s}_0^* = 1$, and $\tilde{s}_1^* = 0$, is given by:

$$\begin{aligned} A_{\mathcal{R}_2^c} &= \frac{M^4 - 6M^3(m+1)}{(1+M)^7} + \frac{3M^2(4m^2+9m+3)}{2(1+M)^7} - \frac{M(13m^2+11m+2)}{2(1+M)^7}; \\ B_{\mathcal{R}_2^c} &= -\frac{M^4 - 6M^3(m+1)}{(1+M)^7} - \frac{M^2(6m^2+10m+3)}{(1+M)^7} + \frac{M(m-7) - 9m^2 - m}{4(1+M)^7}; \\ C_{\mathcal{R}_2^c} &= \frac{M^3(2m+1)}{(1+M)^6} - \frac{M^2(3m^2+7m+5)}{(1+M)^6} + \frac{M(12m^2+15m+5)}{2(1+M)^6} + \frac{3m^2+3m+2}{2(1+M)^6}; \\ D_{\mathcal{R}_2^c} &= -\frac{1}{2(1+M)^5} [2M^3 + M^2(m^2-6m-3) + M(4m^2-m-3) + 2m^2+3m+1]; \\ E_{\mathcal{R}_2^c} &= \frac{(M-m)}{6(1+M)^4} [M^2 + M(2m+3) - 3(m+1)]; \quad F_{\mathcal{R}_2^c} = -\frac{(M-m)^2}{8(1+M)^3}; \\ G_{\mathcal{R}_2^c} &= -\frac{M^2(7m+3)}{2(1+M)^7} + \frac{M(13m^2+11m+6)}{2(1+M)^7} + \frac{3m^2+2m+1}{(1+M)^7}; \\ H_{\mathcal{R}_2^c} &= \frac{1}{(1+M)^6} [M^2 + M(2m^2+m+1) - 3m-2]; \\ I_{\mathcal{R}_2^c} &= -\frac{(M-m)}{(1+M)^5} (m+1); \quad J_{\mathcal{R}_2^c} = -\frac{(m+1)}{4(1+M)^7} (M+3m+4). \end{aligned} \quad (74)$$

One can check that, correctly, $\mathcal{R}_2^c(0) = A_{\mathcal{R}_2^c} + B_{\mathcal{R}_2^c} + G_{\mathcal{R}_2^c} + J_{\mathcal{R}_2^c} = 0$.

C. The study of the complex at the 2nd order within the SPDERG approach

Let us relabel $T_1(\tilde{s}_0^*)$, $T_2(\tilde{s}_0^*)$, $T_3(\tilde{s}_0^*, \tilde{s}_1^*)$, and $T_4(\tilde{s}_0^*)$, the coefficients of the first four terms in $\tilde{c}_{div}^{rg}(\tau)$, at the 2nd order, given by (59). Hence, one has:

$$\tilde{c}_{div}^{rg}(\tau) = T_1(\tilde{s}_0^*) + \varepsilon T_2(\tilde{s}_0^*) + \varepsilon T_3(\tilde{s}_0^*, \tilde{s}_1^*) + \varepsilon T_4(\tilde{s}_0^*)(\tau - \tau_0) +$$

$$+ \varepsilon^2 A_{c_{2,div}}^{rg}(\tilde{s}_0^*)(\tau - \tau_0) + \varepsilon^2 B_{c_{2,div}}^{rg}(\tilde{s}_0^*, \tilde{s}_1^*)(\tau - \tau_0) + \varepsilon^2 C_{c_{2,div}}^{rg}(\tilde{s}_0^*)(\tau - \tau_0)^2, \quad (75)$$

with:

$$\begin{aligned} T_1(\tilde{s}_0^*) &= \frac{\tilde{s}_0^*}{\tilde{s}_0^* + M}; & T_2(\tilde{s}_0^*) &= -\frac{M(\tilde{s}_0^* - M + 2m)}{(\tilde{s}_0^* + M)^4} \tilde{s}_0^*; \\ T_3(\tilde{s}_0^*, \tilde{s}_1^*) &= \frac{M\tilde{s}_1^*}{(\tilde{s}_0^* + M)^2}; & T_4(\tilde{s}_0^*) &= -\frac{M(M - m)\tilde{s}_0^*}{(\tilde{s}_0^* + M)^3}; \end{aligned} \quad (76)$$

Here, in detail: T_1 is the coefficient of the 0th order term, that was already present in $\tilde{c}_0^{rg}(\tau)$, given by (30); $T_2 + T_3 = B_{c_1}^{rg}$, with $B_{c_1}^{rg}$ (calculated in $\tilde{c}_0^* = 0$) the constant term in $\tilde{c}_1^{rg}(\tau)$, given by (65); $T_4 = A_{c_1}^{rg}$, with $A_{c_1}^{rg}$ the coefficient of the single 1st order secular term in $\tilde{c}_1^{rg}(\tau)$, given again by (65); $A_{c_{2,div}}^{rg}$, $B_{c_{2,div}}^{rg}$, and $C_{c_{2,div}}^{rg}$, are instead the coefficients of the three 2nd order secular terms in $\tilde{c}_2^{rg}(\tau)$, given by (71), respectively.

When renormalizing the bare substrate IC, $\tilde{s}^* = \tilde{s}_0^* + \tilde{s}_1^*$, by $\tilde{s}_0^* = (1 + \varepsilon z_{s0,1} + \varepsilon^2 z_{s0,2})\tilde{s}_0^{rg*}$, and $\tilde{s}_1^* = (1 + \varepsilon z_{s0,1})\tilde{s}_1^{rg*}$, respectively (with the already chosen $z_{s0,1}$, given by (35), and $z_{s0,2}$, $z_{s1,1}$, given by (52)), one finds (up to order ε^2):

$$\begin{aligned} T_1(\tilde{s}_0^*) - T_1(\tilde{s}_0^{rg*}) &= \left[\frac{dT_1(\tilde{s}_0^*)}{d\tilde{s}_0^*} \right]_{\tilde{s}_0^* = \tilde{s}_0^{rg*}} (\varepsilon z_{s0,1} + \varepsilon^2 z_{s0,2}) \tilde{s}_0^{rg*} + \frac{1}{2} \left[\frac{d^2 T_1(\tilde{s}_0^*)}{d(\tilde{s}_0^*)^2} \right]_{\tilde{s}_0^* = \tilde{s}_0^{rg*}} (\varepsilon z_{s0,1})^2 (\tilde{s}_0^{rg*})^2 = \\ &= \varepsilon \frac{M(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^3} (\lambda - \tau_0) - \varepsilon^2 Mm \frac{(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^5} (\lambda - \tau_0) + \\ &\quad - \varepsilon^2 M \frac{(M-m)^2 \tilde{s}_0^{rg*}}{2(\tilde{s}_0^{rg*} + M)^5} (2\tilde{s}_0^{rg*} - M)(\lambda - \tau_0)^2 = \\ &= -\varepsilon T_4(\tilde{s}_0^{rg*})(\lambda - \tau_0) - \varepsilon^2 Mm \frac{(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^5} (\lambda - \tau_0) + \varepsilon^2 C_{c_{2,div}}^{rg}(\tilde{s}_0^{rg*})(\lambda - \tau_0)^2; \end{aligned} \quad (77)$$

$$\begin{aligned} \varepsilon [T_2(\tilde{s}_0^*) - T_2(\tilde{s}_0^{rg*})] &= \varepsilon \left[\frac{dT_2(\tilde{s}_0^*)}{d\tilde{s}_0^*} \right]_{\tilde{s}_0^* = \tilde{s}_0^{rg*}} (\varepsilon z_{s0,1}) \tilde{s}_0^{rg*} = \\ &= \varepsilon^2 \frac{M(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^6} [2(\tilde{s}_0^{rg*})^2 - (5M - 6m)\tilde{s}_0^{rg*} + M(M - 2m)] (\lambda - \tau_0) = \\ &= -\varepsilon^2 A_{c_{2,div}}^{rg}(\tilde{s}_0^{rg*})(\lambda - \tau_0) + \varepsilon^2 Mm \frac{(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^5} (\lambda - \tau_0); \end{aligned} \quad (78)$$

$$\begin{aligned} \varepsilon [T_3(\tilde{s}_0^*, \tilde{s}_1^*) - T_3(\tilde{s}_0^{rg*}, \tilde{s}_1^{rg*})] &= \varepsilon \left[\frac{\partial T_3(\tilde{s}_0^*, \tilde{s}_1^*)}{\partial \tilde{s}_0^*} \right]_{\substack{\tilde{s}_0^* = \tilde{s}_0^{rg*} \\ \tilde{s}_1^* = \tilde{s}_1^{rg*}}} (\varepsilon z_{s0,1}) \tilde{s}_0^{rg*} + \varepsilon \left[\frac{\partial T_3(\tilde{s}_0^*, \tilde{s}_1^*)}{\partial \tilde{s}_1^*} \right]_{\substack{\tilde{s}_0^* = \tilde{s}_0^{rg*} \\ \tilde{s}_1^* = \tilde{s}_1^{rg*}}} (\varepsilon z_{s1,1}) \tilde{s}_1^{rg*} = \\ &= \varepsilon^2 \left[-\frac{2M(M-m)\tilde{s}_1^{rg*}}{(\tilde{s}_0^{rg*} + M)^4} \tilde{s}_0^{rg*} + \frac{M^2(M-m)}{(\tilde{s}_0^{rg*} + M)^4} \tilde{s}_1^{rg*} \right] (\lambda - \tau_0) = \\ &= -\varepsilon^2 B_{c_{2,div}}^{rg}(\tilde{s}_0^{rg*}, \tilde{s}_1^{rg*})(\lambda - \tau_0); \end{aligned} \quad (79)$$

$$\begin{aligned} \varepsilon [T_4(\tilde{s}_0^*) - T_4(\tilde{s}_0^{rg*})] &= \varepsilon \left[\frac{dT_4(\tilde{s}_0^*)}{d\tilde{s}_0^*} \right]_{\tilde{s}_0^* = \tilde{s}_0^{rg*}} (\varepsilon z_{s0,1}) \tilde{s}_0^{rg*} = \varepsilon^2 \frac{M(M-m)^2 \tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^4} (2\tilde{s}_0^{rg*} - M)(\lambda - \tau_0) = \\ &= -2\varepsilon^2 C_{c_{2,div}}^{rg}(\tilde{s}_0^{rg*})(\lambda - \tau_0). \end{aligned} \quad (80)$$

Therefore, when moreover writing $(\tau - \tau_0) = (\tau - \lambda) + (\lambda - \tau_0)$, since obviously $(\tau - \tau_0)^2 = (\tau - \lambda)^2 + 2(\tau - \lambda)(\lambda - \tau_0) + (\lambda - \tau_0)^2$, one gets exactly the same form of $\tilde{c}_{div}^{rg}(\tau, \lambda)$ given by (59), with $\tau_0 \rightarrow \lambda$, $\tilde{s}_0^* \rightarrow \tilde{s}_0^{rg*}(\lambda)$, and $\tilde{s}_1^* \rightarrow \tilde{s}_1^{rg*}(\lambda)$.

Let us now remind that the 1st order scaling condition on the renormalized substrate IC, given by Eqs. (38), implies the relation $d\tilde{s}_0^{rg*}/d\lambda = -\varepsilon z_{s_0,1} \tilde{s}_0^{rg*}/(\lambda - \tau_0)$, too. Correspondingly, one can make partially use again of the previous formulas in the study of the derivative with respect to λ of $\tilde{c}_{div}^{rg}(\tau, \lambda)$:

$$\begin{aligned} \frac{d\tilde{c}_{div}^{rg}(\tau, \lambda)}{d\lambda} &= \frac{dT_1(\tilde{s}_0^{rg*})}{d\tilde{s}_0^{rg*}} \frac{d\tilde{s}_0^{rg*}}{d\lambda} + \varepsilon \frac{dT_2(\tilde{s}_0^{rg*})}{d\tilde{s}_0^{rg*}} \frac{d\tilde{s}_0^{rg*}}{d\lambda} + \varepsilon \frac{\partial T_3(\tilde{s}_0^{rg*}, \tilde{s}_1^{rg*})}{\partial \tilde{s}_0^{rg*}} \frac{d\tilde{s}_0^{rg*}}{d\lambda} + \\ &+ \varepsilon \frac{\partial T_3(\tilde{s}_0^{rg*}, \tilde{s}_1^{rg*})}{\partial \tilde{s}_1^{rg*}} \frac{d\tilde{s}_1^{rg*}}{d\lambda} + \varepsilon \frac{dT_4(\tilde{s}_0^{rg*})}{d\tilde{s}_0^{rg*}} \frac{d\tilde{s}_0^{rg*}}{d\lambda} (\tau - \lambda) - \varepsilon T_4(\tilde{s}_0^{rg*}) + \\ &- \varepsilon^2 A_{c_{2,div}^{rg}}(\tilde{s}_0^{rg*}) - \varepsilon^2 B_{c_{2,div}^{rg}}(\tilde{s}_0^{rg*}, \tilde{s}_1^{rg*}) - 2\varepsilon^2 C_{c_{2,div}^{rg}}(\tilde{s}_0^{rg*})(\tau - \lambda). \end{aligned} \quad (81)$$

In detail, one can notice, first of all, that, to get $d\tilde{c}_{div}^{rg}(\tau, \lambda)/d\lambda = 0$, the 1st order known result on $d\tilde{s}_0^{rg*}/d\lambda$, needs to be once again satisfied. From this point of view, see in particular Eqs. (77): indeed, the contribution that comes from the term $dT_1(\tilde{s}_0^{rg*})/d\tilde{s}_0^{rg*}$, in the same way as the first term in that formula, and the one that is equal to $-\varepsilon T_4(\tilde{s}_0^{rg*})$ are the only contributions to be proportional to ε ; thus, they obviously need to cancel each other.

Then, by further exploiting the just recalled relation, $d\tilde{s}_0^{rg*}/d\lambda = -\varepsilon z_{s_0,1} \tilde{s}_0^{rg*}/(\lambda - \tau_0)$, one finds that the term involving the derivative of T_2 is partially cancelled by the one proportional to $A_{c_{2,div}^{rg}}$, leaving a contribution equal to $-\varepsilon^2 Mm(M-m)\tilde{s}_0^{rg*}/(\tilde{s}_0^{rg*} + M)^5$, as can be seen from Eqs. (78). Moreover, the two terms proportional to $(\tau - \lambda)$ cancel each other, too, as can be seen from Eqs. (80).

Therefore, by using $d\tilde{s}_0^{rg*}(\lambda)/d\lambda = -\varepsilon(M-m)\tilde{s}_0^{rg*}/(\tilde{s}_0^{rg*} + M)$, by imposing the scaling condition $d\tilde{c}_{div}^{rg}(\tau, \lambda)/d\lambda = 0$ at the 2nd order, and by making partially use of Eqs. (79), we end up with the equation:

$$-\varepsilon \frac{Mm(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^5} + \varepsilon \frac{2M(M-m)\tilde{s}_0^{rg*}\tilde{s}_1^{rg*}}{(\tilde{s}_0^{rg*} + M)^4} + \frac{M}{(\tilde{s}_0^{rg*} + M)^2} \frac{d\tilde{s}_1^{rg*}}{d\lambda} - \varepsilon \frac{M(M-m)\tilde{s}_1^{rg*}}{(\tilde{s}_0^{rg*} + M)^4} (2\tilde{s}_0^{rg*} - M) = 0. \quad (82)$$

Hence, we get the expected result:

$$\frac{d\tilde{s}_1^{rg*}}{d\lambda} = \varepsilon \left[\frac{m(M-m)\tilde{s}_0^{rg*}}{(\tilde{s}_0^{rg*} + M)^3} - \frac{M(M-m)\tilde{s}_1^{rg*}}{(\tilde{s}_0^{rg*} + M)^2} \right], \quad (83)$$

that completes the present verification. In fact, this is the same ODE, to be obeyed by $\tilde{s}_1^{rg*}(\lambda)$, that we previously obtained in the study of the substrate, and that is reported in Eqs. (54).

D. An example of application of the SPDERG to boundary layer problems

The example is taken from [11]. In detail, it is given in the Section C in that work, as an application of the SPDERG approach to a nonlinear boundary layer problem, as in the present case of MM kinetics.

Let us consider the 2nd order ODE:

$$\begin{aligned} \varepsilon \ddot{y}(t) + 2\dot{y}(t) + e^{y(t)} &= 0 \\ y(0) &= y(1) = 0. \end{aligned} \quad (84)$$

This example is characterized by a boundary layer, that is in particular of thickness ε (again, as in the present case of MM kinetics), at $t = 0$. In order to study the transient phase, we rescale the independent variable: $\tau = t/\varepsilon$ and rename the dependent variable: $Y(\tau) = y(t)$. Thus we have:

$$\frac{d^2 Y(\tau)}{d\tau^2} + 2 \frac{dY(\tau)}{d\tau} = -\varepsilon e^{Y(\tau)}. \quad (85)$$

This can be considered the analogous of the inner equation. We solve the equation by means of the expansion $Y(\tau) = Y_0 + \varepsilon Y_1(\tau) + O(\varepsilon^2)$, obtaining, in the large τ limit:

$$Y(\tau) \sim A_0 + B_0 e^{-2\tau} - \varepsilon \left[\frac{1}{2} e^{A_0} (\tau - \tau_0) + \mathcal{R} \right] + O(\varepsilon^2), \quad (86)$$

where A_0 and B_0 are integration constants and $\mathcal{R}$ contains all the terms asymptotically regular for $(\tau - \tau_0) \rightarrow +\infty$. In order to outline the difference with the application of the SPDERG method in the present work, it is interesting to notice that here one faces directly a second order differential equation,

that is solved by introducing two appropriate integration constants. Hence, one has consistently a single time τ_0 at which these two integration constants need to satisfy the two given ICs, at the end of the procedure.

In detail, the part to be renormalized of the function, $Y_{div}(\tau)$, is the one in which the contribution due to $\mathcal{R}$ is neglected. Its divergence can be controlled by renormalizing the two integration constants as $A_0(\tau_0) \rightarrow Z_1 A(\lambda)$ and $B_0(\tau_0) \rightarrow Z_2 B(\lambda)$, respectively. The renormalization constants, Z_1 and Z_2 , are assumed to depend both on τ_0 and λ , with the aim of changing, in $Y_{div}(\tau)$, the initial dependence on τ_0 of the ICs in a dependence on the arbitrary time λ .

Generally, for a boundary layer of thickness ε , one moreover chooses, for Z_1 and Z_2 , the expansion (with $a_0 = b_0 = 1$) that we already reported in (26), and that we repeat here for the sake of clarity:

$$Z_1 = \sum_{n=0}^{\infty} a_n(\tau_0, \lambda) \varepsilon^n; \quad Z_2 = \sum_{n=0}^{\infty} b_n(\tau_0, \lambda) \varepsilon^n. \quad (87)$$

Hence, at the first order in ε :

$$Z_1 = 1 + a_1(\tau_0, \lambda) \varepsilon + O(\varepsilon^2); \quad Z_2 = 1 + b_1(\tau_0, \lambda) \varepsilon + O(\varepsilon^2). \quad (88)$$

In this example, it is important to outline that the term proportional to $e^{-\tau}$ is anyway suppressed in the large τ limit. From this point of view, the case is similar to the one that we discussed in the text in the context of our SPDERG study of the complex. Therefore, at the next step of the procedure, *i.e.*, when replacing $(\tau - \tau_0)$ with $(\tau - \lambda) + (\lambda - \tau_0)$, the only constant to be fixed is a_1 . One chooses its value exactly in order to obtain a τ_0 -independent function, which implies:

$$a_1 = \frac{1}{2} e^{A_0} (\lambda - \tau_0) / A_0. \quad (89)$$

Consistently, one arrives at the renormalized perturbation result

$$Y_{div}(\tau, \lambda) = A(\lambda) + B(\lambda) e^{-2\tau} - \varepsilon \frac{1}{2} e^{A(\lambda)} (\tau - \lambda) + O(\varepsilon^2). \quad (90)$$

Imposing the renormalization group condition of invariance $dY/d\lambda = 0$ brings to the equations, up to order ε :

$$\begin{aligned} \frac{dA(\lambda)}{d\lambda} + \varepsilon \frac{1}{2} e^{A(\lambda)} &= 0 \\ \frac{dB(\lambda)}{d\lambda} &= 0. \end{aligned} \quad (91)$$

Therefore, one obtains:

$$A(\lambda) = \log \left(\frac{2}{\varepsilon \lambda + C_1} \right); \quad B(\lambda) = C_2, \quad (92)$$

where C_1 and C_2 are two integration constants to be determined by means of the boundary values. To better outline the difference with our SPDERG results on the complex, we recall that, in our context, a constant renormalized complex IC implied instead a zero value for this quantity, hence the possibility to neglect the terms proportional to it.

Equating λ and τ in (90) and rewriting $t = \varepsilon \tau$, we obtain the SPDERG uniform expansion:

$$y(t) \sim \log \left(\frac{2}{t + C_1} \right) + C_2 e^{-2t/\varepsilon} + O(\varepsilon). \quad (93)$$

Finally, by imposing the boundary conditions given in (84) and by taking into account the limit $\varepsilon \rightarrow 0^+$, we arrive at the approximation:

$$y(t) \sim \log \left(\frac{2}{t + 1} \right) + \log(2) e^{-2t/\varepsilon} + O(\varepsilon). \quad (94)$$

The result reproduces, at the leading order, the solution obtained in [9], (Example 1, pp. 463–464, formula (9.7.6)) in terms of singular perturbations and matching techniques.

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