# Trend to equilibrium for a reaction-diffusion system modelling reversible enzyme reaction

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**Abstract**

A spatio-temporal evolution of chemicals appearing in a reversible enzyme reaction and modelled by a four component reaction-diffusion system with the reaction terms obtained by the law of mass action is considered. The large time behaviour of the system is studied by means of entropy methods.

*Keywords:* enzyme reaction; reaction-diffusion system; entropy method.

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## 1 Introduction

In eukaryotic cells, responses to a variety of stimuli consist of chains of successive protein interactions where enzymes play significant roles, mostly by accelerating reactions. Enzymes are catalysts that facilitate a conversion of molecules (generally proteins) called substrates into other molecules called products, but they themselves are not changed by the reaction. In the reaction scheme proposed by Michaelis and Menten [26] in 1913, an enzyme $E$ converts a substrate $S$ into a product $P$ through a two step process, schematically written as

$$S+E \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C \overset{k_{p+}}{\longrightarrow} E+P, \tag{1}$$

where $C$ is an intermediate complex and $k_+, k_-$ and $k_{p+}$ are positive kinetic rates of the reaction (1). In 1925, the enzyme reaction (1) was analysed by Briggs and Haldane [6] by using ordinary differential equations (ODE) derived from mass action kinetics. In their quasi-steady-state approximation (QSSA), the complex is assumed to reach a steady state quickly, i.e., there is no change in its concentration $n_C = [C]$ in time ($\mathrm{d}n_C/\mathrm{d}t = 0$). The analysis yields an algebraic

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expression for $n_C$, the so-called Michaelis-Menten function, and a simple, though nonlinear, ODE for the concentration of substrate $n_S = [S]$, namely

$$\frac{\mathrm{d}n_S}{\mathrm{d}t} = -k_{p+}\frac{e_0 n_S}{K_m + n_S}, \tag{2}$$

where $e_0$ denotes the true enzyme molarity and $K_m = (k_- + k_{p+})/k_+$ is the Michaelis constant, [10]. The kinetics of enzyme reactions described by Briggs and Haldane is sometimes called the Michealis-Menten kinetics. Further details on the existing approximation techniques can be found in [10, 37, 38, 39, 40], a validation of the QSSA also in [32].

Many important reactions in biochemistry are, however, reversible in the sense that a significant amount of the product $P$ exists in the reaction mixture due to a reaction of $P$ with the enzyme $E$, [10]. Therefore, the Michaelis-Menten mechanism (1) is incomplete for these reactions and should be rather replaced by

$$S + E \underset{k_-}{\overset{k_+}{\rightleftharpoons}} C \underset{k_{p-}}{\overset{k_{p+}}{\rightleftharpoons}} E + P, \tag{3}$$

where $k_+, k_-, k_{p+}$ and $k_{p-}$ are positive kinetic rates.

Almost the entire mathematical modelling of the enzyme reactions (1) and (3) taken with mass-action kinetics is usually done by means of ODEs, thus assuming that the substrate-enzyme reaction takes place in a homogeneous medium, [10, 38, 39, 40]. However, protein pathways occur in living cells, heterogeneous spatial structure of which has an impact on the enzyme efficiency [36]. Indeed, the cellular crowdedness and subcellular organisation regulate many metabolic pathways in the cells and such regulation is often achieved through the compartmentalisation of biochemical reactions in various intracellular organelles. In eukaryotic cells, a small molecule, such as a substrate, diffuses rapidly. Therefore, we may consider the concentration of such small molecules to be distributed relatively uniformly throughout the compartments. On the other hand, enzymes and other macromolecules diffuse relatively slowly in the cytosol, in part because they interact with many other macromolecules [1]. Besides the relatively slow mobility of enzymes, limiting diffusion to a confined space and sequestration of enzyme activities within compartments protect the cell from toxic byproducts of such specific enzyme reactions [9]. Protein-tyrosine phosphatase PTP1B, which is an enzyme confined to the endoplasmic reticulum and which acts as an inhibitor of the receptor tyrosine kinases, may serve as an example of spatial regulation of the enzyme-substrate activity [42]. Other examples and further discussion on the spatio-temporal regulation of protein signalling networks can be found, for example, in [23]. Interactions between diffusion and spatial heterogeneity from a viewpoint of mathematical analysis are studied, for example, in [29].

In this paper, a spatial reaction-diffusion system for the reversible enzyme reaction (3) is studied without any kind of quasi-steady-state approximation. Instead, we focus on the asymptotic behaviour of a system of four equations for the concentrations of the species appearing in (3) with the reaction terms obtained by the law of mass action. Moreover, we assume that each species can diffuse freely and randomly (modelled by linear diffusion) with a constant diffusion rate. Thus, we consider the system

$$\begin{aligned}
\frac{\partial n_S}{\partial t} - D_S \Delta n_S &= k_- n_C - k_+ n_S n_E, \\
\frac{\partial n_E}{\partial t} - D_E \Delta n_E &= (k_- + k_{p+}) n_C - k_+ n_S n_E - k_{p-} n_E n_P, \\
\frac{\partial n_C}{\partial t} - D_C \Delta n_C &= k_+ n_S n_E - (k_- + k_{p+}) n_C + k_{p-} n_E n_P, \\
\frac{\partial n_P}{\partial t} - D_P \Delta n_P &= k_{p+} n_C - k_{p-} n_E n_P.
\end{aligned} \tag{4}$$

We assume that $n_i = n_i(t,x)$ for each $i \in \{S,E,C,P\}$ is defined in the time-space cylinder $Q_T = I \times \Omega$ where $I = (0,T)$ for $0 < T < \infty$ and $\Omega$ is an open, bounded and connected subset of $\mathbb{R}^d$, $d \geq 1$, with a sufficiently smooth boundary $\partial\Omega$ (e.g., $C^2$). Without loss of generality, we assume $|\Omega| = 1$. The reaction rates $k_+, k_-, k_{p+}$ and $k_{p-}$ as well as the diffusion coefficients $D_i$, $i \in \{S,E,C,P\}$, are supposed to be positive constants, possibly different from each other. Further, we assume that there exist nonnegative functions $n_i^0 \in L^\infty(\Omega)$ such that

$$n_i(0,x) = n_i^0(x) \ \text{ in } \Omega, \qquad \int_\Omega n_i^0(x)\,\mathrm{d}x > 0, \quad \forall i \in \{S,E,C,P\}. \tag{5}$$

Finally, the system is coupled with the zero-flux boundary conditions

$$\nabla n_i \cdot \nu = 0, \quad \forall t \in I,\ x \in \partial\Omega,\ i \in \{S,E,C,P\}, \tag{6}$$

where $\nu$ is a unit normal vector pointed outward from the boundary $\partial\Omega$.

Two linearly independent conservation laws can be observed, in particular,

$$\int_\Omega (n_E + n_C)(t,x)\,\mathrm{d}x = \int_\Omega (n_E^0 + n_C^0)(x)\,\mathrm{d}x = M_1, \tag{7}$$

$$\int_\Omega (n_S + n_C + n_P)(t,x)\,\mathrm{d}x = \int_\Omega (n_S^0 + n_C^0 + n_P^0)(x)\,\mathrm{d}x = M_2, \tag{8}$$

for each $t \geq 0$, where $M_1 > 0, M_2 > 0$. Note that there is often $M_1 \ll M_2$ [10], however, we will not assume any relation between $M_1$ and $M_2$.

The conservation laws (7) and (8) imply the uniform $L^1$ bounds on the solutions of (4)-(6) which are insufficient for the existence of global solutions. A global weak solution in all space dimensions ($d \geq 1$), however, can be deduced from a combination of a duality argument (reviewed in Appendix A), which provides estimates on the (at most quadratic) nonlinearities of the system, and an approximation method developed in [34, 15], which justifies rigorously the existence of the weak solution to (4)-(6) built up from the solutions of the approximating systems. The existence of the global weak solution with the total mass conserved by means of (7) and (8) can be shown constructively by the semi-implicit (Rothe) method [35, 16], a method suitable for numerical simulations. We also refer to [4] where a proof of the existence of the unique, global-in-time solution to (4)-(6) with the concentration dependent diffusivities and $d \leq 9$ is obtained by a combination of duality and bootstrapping arguments. Therefore, we do not give any rigorous results on the existence of solutions; instead, we focus on the large time behaviour of the solution as $t \to \infty$. However, we derive a-priori estimates which make all the integrals that will appear (e.g., entropy functional) well defined.

In particular, by a direct application of a duality argument, we deduce that whenever $n_i^0 \in L^2(\log L)^2(\Omega)$, then $n_i \in L^2(\log L)^2(Q_T)$ for each $0 < T < \infty$, $i \in \{S,E,C,P\}$. With the $L^2(\log L)^2$ estimates at hand, the solution $n_i$ for $i \in \{S,E,C,P\}$ can be shown, as in [4, 14], to belong to $L^\infty([0,\infty) \times \overline{\Omega})$ in all space dimensions given that the initial data and the boundary $\partial\Omega$ are sufficiently regular. Indeed, since the nonlinearities contain a linear term, namely $n_C$ multiplied by a constant, the smoothing properties of the heat kernel allow us to study the regularity of some of the $n_i$ with the linear term separately, and then use this regularity to obtain the regularity of the other ones [14]. Thus again, we can deduce the global-in-time existence of the classical solution by the standard results for reaction-diffusion systems [24]. The function spaces used in the article are briefly recalled at the beginning of Section 2.

The main result of this paper is a quantitative analysis of the large time behaviour of the solution $n_i$, $i \in \{S,E,C,P\}$, to (4)-(6). It can be stated as follows:

**Theorem 1.1.** *Let $(n_S, n_E, n_C, n_P)$ be a solution to (4)-(6) satisfying (7) and (8). Then there exist two explicitly computable constants $C_1$ and $C_2$ such that*

$$\sum_{i \in \{S,E,C,P\}} \|n_i - n_{i,\infty}\|^2_{L_1(\Omega)} \leq C_2 e^{-C_1 t} \tag{9}$$

*where $n_{i,\infty}$ is the unique, positive, detailed balance steady state defined in (12).*

In other words we show the exponential $L^1$-convergence of the solution $n_i$, $i \in \{S,E,C,P\}$, of (4)-(6) to the steady state $n_{i,\infty}$, $i \in \{S,E,C,P\}$, at the rate $C_1/2$. The result is important for two reasons:

- As soon as an enzyme reaction occurs in a connected spatial domain and there is no flow of the species through the boundary, the constant steady state is always reached for arbitrary positive diffusion and kinetic rates in any space dimension.
- The steady state is attained exponentially fast with explicitly computable rates.

The latter result seems to be new even though the computed rates of exponential convergence may not be optimal.

We remark that the general theory of the detailed balance systems, e.g., [18] and references therein, implies the existence of a unique detailed balance equilibrium to the system (4)-(6) satisfying the conservation laws

$$n_{E,\infty} + n_{C,\infty} = M_1, \quad n_{S,\infty} + n_{C,\infty} + n_{P,\infty} = M_2, \tag{10}$$

and the detailed balance conditions

$$k_- n_{C,\infty} = k_+ n_{S,\infty} n_{E,\infty}, \quad k_{p+} n_{C,\infty} = k_{p-} n_{P,\infty} n_{E,\infty}. \tag{11}$$

It is easy to show that the unique strictly positive equilibrium $\mathbf{n}_\infty = (n_{S,\infty}, n_{E,\infty}, n_{C,\infty}, n_{P,\infty})$ is then

$$\begin{gathered} n_{C,\infty} = \frac{1}{2}\left(M + K - \sqrt{(M+K)^2 - 4M_1M_2}\right), \\ n_{E,\infty} = M_1 - n_{C,\infty}, \quad n_{S,\infty} = \frac{k_- n_{C,\infty}}{k_+ n_{E,\infty}}, \quad n_{P,\infty} = \frac{k_{p+} n_{C,\infty}}{k_{p-} n_{E,\infty}}, \end{gathered} \tag{12}$$

where $M = M_1 + M_2$ and $K = k_-/k_+ + k_{p+}/k_{p-}$.

Theorem 1.1 is proved by means of entropy methods, which are based on an idea to measure the distance between the solution and the stationary state by the (monotone in time) entropy of the system. This entropy method has been developed mainly in the framework of the scalar diffusion equations and the kinetic theory of the spatially homogeneous Boltzmann equation, see [2, 8, 41] and references therein. The method has been already used to obtain explicit rates for the exponential decay to equilibrium in the case of reaction-diffusion systems modelling chemical reactions $2A_1 \rightleftharpoons A_2$, $A_1 + A_2 \rightleftharpoons A_3$, $A_1 + A_2 \rightleftharpoons A_3 + A_4$ and $A_1 + A_2 \rightleftharpoons A_3 \rightleftharpoons A_4 + A_5$ in [11, 12, 13, 18]. The large time behaviour of a solution to a general detailed balance reaction-diffusion system counting $R$ reversible reactions involving $N$ chemicals,

$$\alpha_1^j A_1 + \ldots + \alpha_N^j A_N \rightleftharpoons \beta_1^j A_1 + \ldots + \beta_N^j A_N \tag{13}$$

with the nonnegative stoichiometric coefficients $\alpha_1^j, \ldots, \alpha_N^j$, $\beta_1^j, \ldots, \beta_N^j$, for $j = 1, \ldots, R$, was also studied in [18]. However, the convergence rates could not be explicitly calculated without knowing explicit structure of the mass conservation laws in the general case.

The present paper extends the application of the proposed entropy method for the reversible enzyme reaction (3) counting two single reversible reactions. The difficulty comes from a chemical (an enzyme) that appears in both reactions which makes (3) different from the reaction $A_1 + A_2 \rightleftharpoons A_3 \rightleftharpoons A_4 + A_5$ studied in [18], in particular, in the structure of the conservation laws that is essential in the computation of the rates of convergence. Further, even though the convergence rates are obtained through a chain of rather simple but lengthy calculations in [11, 12, 13, 18], we simplify them by means of the inequality (32) in Lemma 3.4. In particular, if we denote $N_i = \sqrt{n_i}$, $N_{i,\infty} = \sqrt{n_{i,\infty}}$ and $\overline{N_i} = \int_\Omega N_i(x)\,\mathrm{d}x$ for some chemical $n_i$ and its equilibrium state $n_{i,\infty}$, the expansion used in [11, 12, 13, 18] (c.f., equation (2.29) in [18]) to measure the distance between $\overline{N_i}$ and $N_{i,\infty}$ is of the form

$$\overline{N_i} = N_{i,\infty}(1 + \mu_i) - \frac{\overline{N_i^2} - \overline{N_i}^2}{\sqrt{\overline{N_i^2}} + \overline{N_i}}$$

for some constant $\mu_i \geq -1$. The fraction in this expansion may become unbounded when $\overline{N_i^2}$ approaches zero, which has to be carefully treated. On the other hand, Lemma 3.4 allows different expansions that consequently lead to easier calculations.

For the sake of completeness, we mention that a different approach based on a convexification argument is used in [27] to study the large time behaviour of the reaction-diffusion system for (13). However, it is difficult to derive explicit convergence rates even for a bit more complex chemical reaction such as (3) by using this convexification argument. First order chemical reaction networks have been recently analysed in [17].

The rest of the paper is organised as follows. In Section 2, we introduce entropy and entropy dissipation functionals and provide first estimates including $L^2$ and $L^2(\log L)^2$ bounds. A main ingredient for the a-priori estimates is a duality argument that is presented in Appendix A. The large time behaviour of the solution as $t \to \infty$ studied by the entropy method is given in Section 3 with technical calculations placed to Appendix B.

## 2 Entropy, entropy dissipation and a-priori estimates

Let $\Omega$ be a measurable subset of the Euclidean space $\mathbb{R}^d$. By $L^p(\Omega,\mathbb{R}^d)$ we will denote the set of all measurable functions $u:\Omega\to\mathbb{R}^d$ such that $\|u\|_{L^p(\Omega,\mathbb{R}^d)}<\infty$, where

$$\|u\|_{L^p(\Omega,\mathbb{R}^d)} = \begin{cases} \left(\int_\Omega |u(x)|^p \,\mathrm{d}x\right)^{1/p} & \text{for } 1\le p<\infty, \\ \text{ess sup}_{x\in\Omega}|u(x)| & \text{for } p=\infty \end{cases}$$

and $|\cdot|$ is the Euclidean norm on $\mathbb{R}^d$. We will write $L^p(\Omega)=L^p(\Omega,\mathbb{R}^1)$. By $L^p(\log L)^p(\Omega)$ we will denote the set of all measurable functions $u:\Omega\to\mathbb{R}$ such that $\|u\log u\|_{L^p(\Omega)}<\infty$ for $p\ge 1$. By $W^{1,p}(\Omega)$ we will denote the Sobolev space $W^{1,p}(\Omega)=\{u\in L^p(\Omega);\nabla u\in L^p(\Omega,\mathbb{R}^d)\}$ equipped with the norm $\|u\|_{W^{1,p}(\Omega)}=\left(\|u\|^p_{L^p(\Omega)}+\|\nabla u\|^p_{L^p(\Omega,\mathbb{R}^d)}\right)^{1/p}$ for $1\le p<\infty$ and $\|u\|_{W^{1,\infty}(\Omega)}=\max\{\|u\|_{L^\infty(\Omega)},\|\nabla u\|_{L^\infty(\Omega,\mathbb{R}^d)}\}$. Finally, for a Banach space $X$ and an interval $I=(0,T)$, by $L^p(I;X)$ we will denote the set of all measurable functions $u:I\to X$ with the norm $\|u\|_{L^p(I;X)}=\left(\int_0^T\|u(t)\|^p_X\right)^{1/p}$ for $1\le p<\infty$ and $\|u\|_{L^\infty(I;X)}=\text{ess sup}_{t\in I}\|u(t)\|_X$.

Let us first mention a simple result on the non-negativity of solutions of (4)-(6) which follows from the so-called quasi-positivity property of the right hand sides of (4), see [33].

**Lemma 2.1.** *Let $n_i^0\ge 0$ in $\Omega$, then $n_i\ge 0$ everywhere in $Q_T$ for each $i\in\{S,E,C,P\}$.*

In the sequel, we will write shortly $\mathbf{n}=(n_S,n_E,n_C,n_P)$. The entropy functional $E(\mathbf{n}):[0,\infty)^4\to[0,\infty)$ and the entropy dissipation $D(\mathbf{n}):[0,\infty)^4\to[0,\infty)$ are defined, respectively, by

$$E(\mathbf{n}) = \sum_{i=\{S,E,C,P\}} \int_\Omega (n_i\log(\sigma_i n_i) - n_i + 1/\sigma_i)\,\mathrm{d}x \tag{14}$$

and

$$\begin{aligned} D(\mathbf{n}) = &\sum_{i=\{S,E,C,P\}} 4D_i \int_\Omega |\nabla\sqrt{n_i}|^2\,\mathrm{d}x \\ &+ \int_\Omega [(k_+n_Sn_E - k_-n_C)(\log(\sigma_S\sigma_E n_Sn_E) - \log(\sigma_C n_C)) \\ &+ (k_{p-}n_En_P - k_{p+}n_C)(\log(\sigma_E\sigma_P n_En_P) - \log(\sigma_C n_C))]\,\mathrm{d}x, \end{aligned} \tag{15}$$

where $\sigma_S$, $\sigma_E$, $\sigma_C$ and $\sigma_P$ depend on the kinetic rates $k_+,k_-,k_{p+}$ and $k_{p-}$. The first integral of the entropy dissipation (15) is known as the relative Fisher information in information theory and as the Dirichlet form in the theory of large particle systems, since

$$4\int|\nabla\sqrt{n_i}|^2 = \int\frac{|\nabla n_i|^2}{n_i} = \int n_i\,|\nabla(\log n_i)|^2,$$

see [41], p. 278.

Note that the function $x\log x - x + 1$ is nonnegative and strictly convex on $[0,\infty)$. Thus, the entropy $E(\mathbf{n})$ is nonnegative along the solution $\mathbf{n}(t,\cdot)$ for each $t\ge 0$. Also, the entropy dissipation $D(\mathbf{n})$ is nonnegative along the solution $\mathbf{n}(t,\cdot)$ for $\alpha,\beta > 0$ such that

$$\begin{aligned} \sigma_C = \alpha k_-, \quad \sigma_S\sigma_E = \alpha k_+, \\ \sigma_C = \beta k_{p+}, \quad \sigma_E\sigma_P = \beta k_{p-}. \end{aligned} \tag{16}$$

Indeed, with (16) the last two integrands in (15) have a form of $(x-y)(\log x - \log y)$ which is nonnegative for all $x,y \in \mathbb{R}_+$. One can choose $\alpha = 1$ and $\beta = k_-/k_{p+}$ to obtain

$$\sigma_C = \sigma_E = k_-,\ \sigma_S = \frac{k_+}{k_-} \ \text{ and } \ \sigma_P = \frac{k_{p-}}{k_{p+}}, \tag{17}$$

though other options are possible.

It is straightforward to verify that $D(\mathbf{n}) = -\partial_t E(\mathbf{n})$, which implies that $E(\mathbf{n})$ is decreasing along the solution $\mathbf{n}(t,\cdot)$ and that there exists a limit of $E(\mathbf{n}(t,\cdot))$ as $t \to \infty$. By integrating this simple relation over $[t_1,t_2]$ ($t_2 > t_1 > 0$) we obtain

$$E(\mathbf{n}(t_1,x)) - E(\mathbf{n}(t_2,x)) = \int_{t_1}^{t_2} D(\mathbf{n}(s,x))\mathrm{d}s$$

which implies that

$$\lim_{t\to\infty} \int_t^\infty D(\mathbf{n}(s,x))\mathrm{d}s = 0. \tag{18}$$

Hence, if the solution $\mathbf{n}(t,x)$ tends to some $\mathbf{n}_\infty(x)$ as $t \to \infty$, then $D(\mathbf{n}_\infty(x)) = 0$ and $\mathbf{n}_\infty$ is spatially homogeneous due to the Fisher information in (15). In fact, it holds that

$$D(\mathbf{n}(t,x)) = 0 \Longleftrightarrow \mathbf{n}(t,x) = \mathbf{n}_\infty \tag{19}$$

where $\mathbf{n}_\infty$ is given by (10) and (11). Let us remark that the entropy $E(\mathbf{n})$ is “D-diffusively convex Lyapunov functional” for (4)-(6) which implies that diffusion added to the system of ODEs is irrelevant to its long-term dynamics and that there cannot exist other (non-constant) equilibrium to (4)-(6) than (12), [19].

Further, we can write

$$E(\mathbf{n}(t,x)) + \int_0^t D(\mathbf{n}(s,x))\mathrm{d}s = E(\mathbf{n}(0,x)) \tag{20}$$

for all $t > 0$. Since the entropy and entropy dissipation are both nonnegative, we can deduce from (20) and the conservation laws (7) and (8) that

$$\sup_{t\in[0,\infty)} \|n_i \log n_i\|_{L^1(\Omega)} \le C, \tag{21}$$

i.e., $n_i \in L^\infty([0,\infty); L(\log L)(\Omega))$ for each $i \in \{S,E,C,P\}$, and

$$\|\nabla\sqrt{n_i}\|^2_{L^2((0,\infty);L^2(\Omega,\mathbb{R}^d))} \le C, \tag{22}$$

i.e., $\sqrt{n_i} \in L^2((0,\infty); W^{1,2}(\Omega))$ for each $i \in \{S,E,C,P\}$.

In addition to the above estimates, let us introduce nonnegative entropy density variables $z_i = n_i \log(\sigma_i n_i) - n_i + 1/\sigma_i$. Then, the system (4)-(6) implies

$$\frac{\partial z}{\partial t} - \Delta(Az) \le 0 \text{ in } \Omega, \quad \nabla(Az)\cdot\nu = 0 \text{ on } \partial\Omega \tag{23}$$

where $z = \sum_i z_i$, $z_d = \sum_i D_i z_i$ (sums go through $i \in \{S,E,C,P\}$) and $A = z_d/z \in [\underline{D},\overline{D}]$ for $\underline{D} = \min_{i\in\{S,E,C,P\}}\{D_i\}$ and $\overline{D} = \max_{i\in\{S,E,C,P\}}\{D_i\}$. Indeed, after some algebra we obtain

$$\begin{aligned}\frac{\partial z}{\partial t} - \Delta(Az) = &-\sum_i D_i \frac{|\nabla n_i|^2}{n_i}\\ &-(k_+ n_S n_E - k_- n_C)(\log(\sigma_S\sigma_E n_S n_E) - \log(\sigma_C n_C))\\ &-(k_{p-} n_E n_P - k_{p+} n_C)(\log(\sigma_E\sigma_P n_E n_P) - \log(\sigma_C n_C))\end{aligned} \tag{24}$$

where the *r.h.s.* of (24) is nonpositive for the constants $\sigma_i$ given by (17). The boundary condition in (23) can be also easily verified.

Hence, a duality argument developed in [34, 33] and reviewed in Appendix A implies for each $j \in \{S,E,C,P\}$ that

$$\|n_j \log(\sigma_j n_j) - n_j + 1/\sigma_j\|_{L^2(Q_T)} \le C \left\| \sum_i n_i^0 \log(\sigma_i n_i^0) - n_i^0 + 1/\sigma_i \right\|_{L^2(\Omega)} \tag{25}$$

where $C = C(\Omega, \underline{D}, \overline{D}, T)$. We deduce from (25) that $n_i \in L^2(\log L)^2(Q_T)$ as soon as $n_i^0 \in L^2(\log L)^2(\Omega)$ for each $i \in \{S,E,C,P\}$.

Moreover, the same duality argument implies $L^2(Q_T)$ bounds by taking into account $n_i^0 \in L^2(\Omega)$ for each $i \in \{S,E,C,P\}$ and $z = n_S + n_E + 2n_C + n_P$, $z_d = D_S n_S + D_E n_E + 2D_C n_C + D_P n_P$ and $A = z_d/z$ for which we directly obtain (23).

# 3 Exponential convergence to equilibrium: an entropy method

Let us first describe briefly a basic idea of the method. Consider an operator $A$, which can be linear or nonlinear and can involve derivatives or integrals, and an abstract problem

$$\partial_t \rho = A\rho.$$

Assume that we can find a Lyapunov functional $E := E(\rho)$, usually called the entropy, such that $D(\rho) = -\partial_t E(\rho) \ge 0$ and

$$D(\rho) \ge \Phi(E(\rho) - E(\rho_{eq})) \tag{26}$$

along the solution $\rho$ where $\Phi$ is a continuous function strictly increasing from 0 and $\rho_{\mathbf{eq}}$ is a state independent of the time $t$, [2, 41]. The inequality (26) between the entropy dissipation $D(\rho)$ and the relative entropy $E(\rho) - E(\rho_{eq})$ is known as the entropy-entropy dissipation inequality (EEDI). The EEDI (26) and the Gronwall inequality then imply the convergence in the relative entropy $E(\rho) \to E(\rho_{eq})$ as $t \to \infty$ that can be either exponential if $\Phi(x) = \lambda x$ or polynomial if $\Phi(x) = x^\alpha$; in both cases $\lambda$ and $\alpha$ can be found explicitly. In the second step, the relative entropy $E(\rho) - E(\rho_{eq})$ is bounded from below by the distance $\rho - \rho_{eq}$ in some topology.

In our reaction-diffusion setting, the relative entropy $E(\mathbf{n}|\mathbf{n}_\infty) := E(\mathbf{n}) - E(\mathbf{n}_\infty)$ for the entropy functional defined in (14) can be written as

$$E(\mathbf{n}|\mathbf{n}_\infty) = \sum_{i=\{S,E,C,P\}} \int_\Omega n_i \log \frac{n_i}{n_{i,\infty}} - (n_i - n_{i,\infty})\,\mathrm{d}x \geq 0. \tag{27}$$

This is a consequence of the conservation laws (7) and (8) which together with (10) and (11) imply

$$\sum_{i=\{S,E,C,P\}} (\overline{n_i} - n_{i,\infty}) \log(\sigma_i n_{i,\infty}) = 0. \tag{28}$$

Note that the relative entropy (27), known also as the Kullback-Leibler divergence, is universal in the sense that it is independent of the reaction rate constants, [20]. The relative entropy (27) can be then estimated from below by using the Cziszár-Kullback-Pinsker (CKP) inequality known from information theory that can be stated as follows.

**Lemma 3.1** (Cziszár-Kullback-Pinsker, [18])**.** *Let $\Omega$ be a measurable domain in $\mathbb{R}^d$ and $u, v : \Omega \to \mathbb{R}_+$ measurable functions. Then*

$$\int_\Omega u \log \frac{u}{v} - (u - v)\,\mathrm{d}x \geq \frac{3}{2\|u\|_{L^1(\Omega)} + 4\|v\|_{L^1(\Omega)}} \|u - v\|^2_{L^1(\Omega)}. \tag{29}$$

Let us mention some other tools that will be later recalled in the proof of the first step.

**Lemma 3.2** (Logarithmic Sobolev inequality, [13])**.** *Let $\Omega \in \mathbb{R}^d$ be a bounded domain such that $|\Omega| \geq 1$. Then,*

$$\int_\Omega u^2 \log u^2\,\mathrm{d}x - \left(\int_\Omega u^2\,\mathrm{d}x\right) \log\left(\int_\Omega u^2\,\mathrm{d}x\right) \leq L \int_\Omega |\nabla u|^2 \tag{30}$$

*that holds for some $L = L(\Omega, d)$ positive, whenever the integrals on both sides of the inequality exist.*

**Lemma 3.3** (Poincaré-Wirtinger inequality, [32])**.** *Let $\Omega \in \mathbb{R}^d$ be a bounded domain. Then*

$$P(\Omega) \int_\Omega |u(x) - \overline{u}|^2 \leq \int_\Omega |\nabla u|^2, \quad \forall u \in H^1(\Omega) \tag{31}$$

*where $\overline{u} = \int_\Omega u(x)\,\mathrm{d}x$ and $P(\Omega)$ is the first non-zero eigenvalue of the Laplace operator with a Neumann boundary condition.*

The following lemma is a technical consequence of the Jensen inequality.

**Lemma 3.4.** *Let $\Omega \in \mathbb{R}^d$ be such that $|\Omega| = 1$, $u, v \in L^1(\Omega)$ be nonnegative functions, $\overline{u} = \int_\Omega u(x)\,\mathrm{d}x$ and $\overline{v} = \int_\Omega v(x)\,\mathrm{d}x$. Then*

$$\left(\sqrt{\overline{u}} - \sqrt{\overline{v}}\right)^2 \leq (\overline{\sqrt{u}} - \sqrt{\overline{v}})^2 + \|\sqrt{u} - \overline{\sqrt{u}}\|^2_{L^2(\Omega)}, \tag{32}$$

*where equality occurs for $v \equiv 0$.*

*Proof.* Let us define an expansion of $\sqrt{u}$ around its spatial average $\overline{\sqrt{u}}$ by $\sqrt{u} = \overline{\sqrt{u}} + \delta_u(x)$ which implies immediately that $\overline{\delta_u} = 0$,

$$\|\sqrt{u} - \overline{\sqrt{u}}\|^2_{L^2(\Omega)} = \|\delta_u\|^2_{L^2(\Omega)} = \overline{\delta_u^2} \quad \text{and} \quad \overline{u} = \overline{\sqrt{u}}^2 + \overline{\delta_u^2}.$$

Then, with the Jensen inequality $\overline{\sqrt{u}} \leq \sqrt{\overline{u}}$ we can write

$$\begin{aligned}\left(\sqrt{\overline{u}} - \sqrt{\overline{v}}\right)^2 &= \overline{u} - 2\sqrt{\overline{u}}\sqrt{\overline{v}} + \overline{v} \\ &\leq \overline{\sqrt{u}}^2 - 2\overline{\sqrt{u}}\sqrt{\overline{v}} + \overline{v} + \overline{\delta_u^2} \\ &= (\overline{\sqrt{u}} - \sqrt{\overline{v}})^2 + \overline{\delta_u^2}\end{aligned}$$

which concludes the proof. $\square$

In fact, with the ansatz $\sqrt{v} = \overline{\sqrt{v}} + \delta_v(x)$, we can deduce that

$$\begin{aligned}\left(\sqrt{\overline{u}} - \sqrt{\overline{v}}\right)^2 &\leq (\overline{\sqrt{u}} - \overline{\sqrt{v}})^2 + \|\sqrt{u} - \overline{\sqrt{u}}\|^2_{L^2(\Omega)} + \|\sqrt{v} - \overline{\sqrt{v}}\|^2_{L^2(\Omega)} \\ &\leq \|\sqrt{u} - \sqrt{v}\|^2_{L^2(\Omega)} + \frac{1}{P(\Omega)}(\|\nabla\sqrt{u}\|^2_{L^2(\Omega)} + \|\nabla\sqrt{v}\|^2_{L^2(\Omega)})\end{aligned}$$

by the Jensen and Poincaré-Wirtinger inequalities.

Recall that we assume $|\Omega| = 1$, $\underline{D} = \min_i\{D_i\}$, $\overline{D} = \max_i\{D_i\}$ and we write shortly $\mathbf{n} = (n_S, n_E, n_C, n_P)$, $\mathbf{n}_\infty = (n_{S,\infty}, n_{E,\infty}, n_{C,\infty}, n_{P,\infty})$ and $\overline{\mathbf{n}}(t) = (\overline{n_S}, \overline{n_E}, \overline{n_C}, \overline{n_P})$ where $\overline{n_i} = \int_\Omega n_i \, \mathrm{d}x$ for each $i \in \{S, E, C, P\}$. In the summations we will omit $i \in \{S, E, C, P\}$ from the notation.

Following the introduction to entropy methods at the beginning of Section 3, first we have to establish the EEDI (26).

**Lemma 3.5** (EEDI)**.** *Let $\boldsymbol{n}$ be a solution to (4)-(6) satisfying (7) and (8). Then there exists a positive constant $C_1$ such that*

$$D(\boldsymbol{n}) \geq C_1 E(\boldsymbol{n}|\boldsymbol{n}_\infty), \tag{33}$$

*where $\boldsymbol{n}_\infty$ is given by (12).*

*Proof.* We split the relative entropy so that

$$E(\mathbf{n}|\mathbf{n}_\infty) = E(\mathbf{n}|\overline{\mathbf{n}}) + E(\overline{\mathbf{n}}|\mathbf{n}_\infty),$$

and estimate both terms separately. For the first term we obtain that

$$E(\mathbf{n}|\overline{\mathbf{n}}) = \sum_i \int_\Omega n_i \log n_i \, \mathrm{d}x - \overline{n_i} \log \overline{n_i} \leq L \sum_i \int_\Omega |\nabla\sqrt{n_i}|^2 \, \mathrm{d}x \tag{34}$$

by the logarithmic Sobolev inequality (30). Hence, when compared with the entropy dissipation (15), we conclude that $D(\mathbf{n}) \geq \overline{C}_1 E(\mathbf{n}|\overline{\mathbf{n}})$ for the constant $\overline{C}_1 = 4\underline{D}/L$.

For the second term $E(\overline{\mathbf{n}}|\mathbf{n}_\infty)$ we use (28) and an elementary inequality $x\log x - x + 1 \leq (x-1)^2$, which holds true for $x \geq 0$, to obtain

$$
\begin{aligned}
E(\overline{\mathbf{n}}|\mathbf{n}_\infty) &= \sum_i \overline{n_i} \log \frac{\overline{n_i}}{n_{i,\infty}} - \overline{n_i} + n_{i,\infty} \\
&\leq \sum_i \frac{1}{n_{i,\infty}} (\overline{n_i} - n_{i,\infty})^2 \\
&\leq C \sum_i \left(\sqrt{\overline{n_i}} - \sqrt{n_{i,\infty}}\right)^2 \\
&\leq C \left( \sum_i \left(\overline{\sqrt{n_i}} - \sqrt{n_{i,\infty}}\right)^2 + \sum_i \|\sqrt{n_i} - \overline{\sqrt{n_i}}\|^2_{L^2(\Omega)} \right)
\end{aligned}
\tag{35}
$$

where the last inequality is due to (32) (for $u = n_i$ and $v = \overline{v} = n_{i,\infty}$) and the constant $C = 2\max_i\{1/n_{i,\infty}\}\max\{2M_1, 2M_2, M_1 + M_2\}$ is deduced from (7) and (8).

On the other hand, the entropy dissipation $D(\mathbf{n})$ given by (15) can be estimated from below by the Poincaré-Wirtinger inequality (31) and an elementary inequality $(x-y)(\log x - \log y) \geq 4(\sqrt{x} - \sqrt{y})^2$, which holds true for $x, y \in \mathbb{R}_+$. We obtain

$$
\begin{aligned}
D(\mathbf{n}) \geq 4\min\{P(\Omega)\underline{D}, 1\} \Big( &\sum_i \|\sqrt{n_i} - \overline{\sqrt{n_i}}\|^2_{L^2(\Omega)} \\
&+ \|\sqrt{k_+ n_S n_E} - \sqrt{k_- n_C}\|^2_{L^2(\Omega)} + \|\sqrt{k_{p-} n_E n_P} - \sqrt{k_{p+} n_C}\|^2_{L^2(\Omega)} \Big).
\end{aligned}
\tag{36}
$$

We can conclude the proof once we find two constants $C_3$ and $C_4$ such that

$$
\begin{aligned}
\sum_i \left(\overline{\sqrt{n_i}} - \sqrt{n_{i,\infty}}\right)^2 + \sum_i \|\sqrt{n_i} - \overline{\sqrt{n_i}}\|^2_{L^2(\Omega)} &\leq C_3 \sum \|\sqrt{n_i} - \overline{\sqrt{n_i}}\|^2_{L^2(\Omega)} \\
+ C_4 \left( \|\sqrt{k_+ n_S n_E} - \sqrt{k_- n_C}\|^2_{L^2(\Omega)} + \|\sqrt{k_{p-} n_E n_P} - \sqrt{k_{p+} n_C}\|^2_{L^2(\Omega)} \right),
\end{aligned}
\tag{37}
$$

since in this case, by combining (35)-(37), we obtain

$$
\frac{1}{C} E(\overline{\mathbf{n}}(t)|\mathbf{n}_\infty) \leq \frac{\max\{C_3, C_4\}}{4\min\{P(\Omega)\underline{D}, 1\}} D(\mathbf{n}).
$$

Hence, we can derive a constant $\widetilde{C}_1$ such that $D(\mathbf{n}) \geq \widetilde{C}_1 E(\overline{\mathbf{n}}|\mathbf{n}_\infty)$ and thus the convergence rate $C_1$ in the EEDI (33), e.g., $C_1 = \min\{\overline{C}_1, \widetilde{C}_1\}/2$. The missing inequality (37) is proved in the following Lemma 3.6. □

For the sake of simplicity, let us denote $N_i = \sqrt{n_i}$ and $N_{i,\infty} = \sqrt{n_{i,\infty}}$ and thus rewrite (37) into the form

$$
\begin{aligned}
\sum_i \left(\overline{N_i} - N_{i,\infty}\right)^2 + \sum_i \|N_i - \overline{N_i}\|^2_{L^2(\Omega)} &\leq C_3 \sum_i \|N_i - \overline{N_i}\|^2_{L^2(\Omega)} \\
+ C_4 \left( \|\sqrt{k_+} N_S N_E - \sqrt{k_-} N_C\|^2_{L^2(\Omega)} + \|\sqrt{k_{p-}} N_E N_P - \sqrt{k_{p+}} N_C\|^2_{L^2(\Omega)} \right).
\end{aligned}
\tag{38}
$$

**Lemma 3.6.** *Let $N_i$, $i \in \{S,E,C,P\}$, be measurable functions from $\Omega$ to $\mathbb{R}_+$ satisfying the conservation laws (7) and (8), i.e.*

$$\overline{N_C^2} + \overline{N_E^2} = M_1 \quad \text{and} \quad \overline{N_S^2} + \overline{N_C^2} + \overline{N_P^2} = M_2, \tag{39}$$

*and let $n_{i,\infty} = N_{i,\infty}^2$ be defined by (10) and (11). Then there exist constants $C_3$ and $C_4$, cf. (74) and (75), such that (38) is satisfied.*

*Proof.* Let us use the expansion of $N_i$ around the spatial average $\overline{N_i}$ from Lemma 3.4,

$$N_i = \overline{N_i} + \delta_i(x), \quad \overline{\delta}_i = 0, \quad i \in \{S,E,C,P\}, \tag{40}$$

which implies $\overline{N_i^2} = \overline{N_i}^2 + \overline{\delta_i^2}$ for each $i \in \{S,E,C,P\}$ and

$$\sum_i \|N_i - \overline{N_i}\|^2_{L^2(\Omega)} = \sum_i \overline{\delta_i^2}. \tag{41}$$

With (40) at hand, we can expand the remaining terms in (38). In particular, we obtain

$$\begin{aligned} \|\sqrt{k_+}N_S N_E - \sqrt{k_-}N_C\|^2_{L^2(\Omega)} &= \left(\sqrt{k_+}\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\overline{N_C}\right)^2 \\ &\quad + 2\sqrt{k_+}\left(\sqrt{k_+}\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\overline{N_C}\right)\overline{\delta_S\delta_E} \\ &\quad + \|\sqrt{k_+}\left(\overline{N_S}\delta_E + \overline{N_E}\delta_S + \delta_S\delta_E\right) - \sqrt{k_-}\delta_C\|^2_{L^2(\Omega)} \\ &\geq \left(\sqrt{k_+}\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\overline{N_C}\right)^2 - \sqrt{k_+}K_1\sum_i \overline{\delta_i^2}, \end{aligned} \tag{42}$$

since the third term in (42) is nonnegative and the second term in (42) can be estimated as follows,

$$\begin{aligned} 2\left(\sqrt{k_+}\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\overline{N_C}\right)\overline{\delta_S\delta_E} &\geq -2\left|\sqrt{k_+}\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\overline{N_C}\right|\int_\Omega \delta_S\delta_E\,\mathrm{d}x \\ &\geq -K_1(\overline{\delta_S^2} + \overline{\delta_E^2}) \geq -K_1\sum_i \overline{\delta_i^2}, \end{aligned}$$

where $K_1 = \sqrt{k_+M_1M_2} + \sqrt{k_-(M_1+M_2)/2}$ is deduced from the Jensen inequality $\overline{N_i^2} \geq \overline{N_i}^2$ and (39). Analogously, we deduce for $K_2 = \sqrt{k_{p-}M_1M_2} + \sqrt{k_{p+}(M_1+M_2)/2}$ that

$$\|\sqrt{k_{p-}}N_P N_E - \sqrt{k_{p+}}N_C\|^2_{L^2(\Omega)} \geq \left(\sqrt{k_{p-}}\overline{N_P}\,\overline{N_E} - \sqrt{k_{p+}}\overline{N_C}\right)^2 - \sqrt{k_{p-}}K_2\sum_i \overline{\delta_i^2}. \tag{43}$$

We see that with (41)–(43) it is sufficient to find $C_3$ and $C_4$ such that

$$\begin{aligned} \sum_i(\overline{N_i} - N_{i,\infty})^2 + \sum_i \overline{\delta_i^2} &\leq \left(C_3 - C_4(\sqrt{k_+}K_1 + \sqrt{k_{p-}}K_2)\right)\sum_i \overline{\delta_i^2} \\ &\quad + C_4\left(\left(\sqrt{k_+}\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\overline{N_C}\right)^2 + \left(\sqrt{k_{p-}}\overline{N_P}\,\overline{N_E} - \sqrt{k_{p+}}\overline{N_C}\right)^2\right) \end{aligned} \tag{44}$$

from which (38) (and so (37)) directly follows.

Next, we study how far the spatial average $\overline{N_i}$ can be from the equilibrium state $N_{i,\infty}$ for each $i \in \{S,E,C,P\}$, i.e., we consider a substitution

$$\overline{N_i} = N_{i,\infty}(1+\mu_i) \tag{45}$$

for some $-1 \leq \mu_i \leq \mu_{i,max}$, $i \in \{S,E,C,P\}$. We obtain

$$\sum_i \left(\overline{N_i} - N_{i,\infty}\right)^2 = \sum_i N_{i,\infty}^2 \mu_i^2 \tag{46}$$

and, by using (11), namely $\sqrt{k_+} N_{S,\infty} N_{E,\infty} = \sqrt{k_-} N_{C,\infty}$ and $\sqrt{k_{p-}} N_{P,\infty} N_{E,\infty} = \sqrt{k_{p+}} N_{C,\infty}$,

$$\begin{aligned} \left(\sqrt{k_+}\,\overline{N_S}\,\overline{N_E} - \sqrt{k_-}\,\overline{N_C}\right)^2 &= k_- N_{C,\infty}^2((1+\mu_S)(1+\mu_E)-(1+\mu_C))^2, \\ \left(\sqrt{k_{p-}}\,\overline{N_P}\,\overline{N_E} - \sqrt{k_{p+}}\,\overline{N_C}\right)^2 &= k_{p+} N_{C,\infty}^2((1+\mu_P)(1+\mu_E)-(1+\mu_C))^2. \end{aligned} \tag{47}$$

Hence, (44) follows from

$$\begin{aligned} \sum_i N_{i,\infty}^2 \mu_i^2 + \sum_i \overline{\delta_i^2} \leq \left(C_3 - C_4(\sqrt{k_+}K_1 + \sqrt{k_{p-}}K_2)\right) \sum_i \overline{\delta_i^2} \\ + C_4 K_3 (\underbrace{((1+\mu_S)(1+\mu_E)-(1+\mu_C))^2}_{=I_1} + \underbrace{((1+\mu_P)(1+\mu_E)-(1+\mu_C))^2}_{=I_2}) \end{aligned} \tag{48}$$

where $K_3 = \min\{\sqrt{k_-}, \sqrt{k_{p+}}\} N_{C,\infty}^2$.

It remains to prove (48). The basic idea is to explore all possible combinations of values of $(\mu_E, \mu_C, \mu_S, \mu_P)$ introduced in (45) subject to the conservation law (39). It follows from (39) that, for example, the case when $\mu_E > 0$ and $\mu_C > 0$ cannot happen at the same time since, otherwise, by using (10) and the Jensen inequality $\overline{N_i^2} \geq \overline{N_i}^2$ we obtain

$$M_1 = \overline{N_E^2} + \overline{N_C^2} \geq \overline{N_E}^2 + \overline{N_C}^2 > N_{E,\infty}^2 + N_{C,\infty}^2 = M_1,$$

which is a contradiction. Analogously, we can exclude the case when $\mu_S > 0$, $\mu_C > 0$ and $\mu_P > 0$ hold at the same time. For all the other admissible cases, see Table 1, we show by using elementary inequalities for real numbers and (39) that

$$\sum_{i\in\mathscr{K}} N_{i,\infty}^2 \mu_i^2 \leq \alpha \sum_{i\in\mathscr{K}} \overline{\delta_i^2} \quad \text{and} \quad I_1 + I_2 \geq \beta \sum_{i\in\mathscr{L}} N_{i,\infty}^2 \mu_i^2 - \gamma \sum_{i\in\mathscr{L}} \overline{\delta_i^2}$$

for two not necessarily distinct sets of indices $\mathscr{K}, \mathscr{L} \subset \{S,E,C,P\}$ such that $\mathscr{K} \cup \mathscr{L} = \{S,E,C,P\}$, and positive constants $\alpha$, $\beta$ and $\gamma$. The constants $C_3$ and $C_4$ in (48) are deduced from $\alpha$, $\beta$ and $\gamma$. Since the rest of the proof is rather simple but technical, we have placed it to Appendix B. □

We can finally prove the exponential convergence of the solution $\mathbf{n}(t)$ of (4)-(6) to the equilibrium $\mathbf{n}_\infty$ given by (12).

Table 1: Eleven quadruples of possible relations among $\mu_i$, $i \in \{S,E,C,P\}$, which are allowed by the conservation laws (61) and (62). In the table "$+$" means that $\mu_i > 0$ and "$-$" that $-1 \le \mu_i \le 0$. Each quadruple is denoted by a Roman numeral from I to XI.

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $\mu_E$ | $-$ | | | | $+$ | | | | $-$ | | |
| $\mu_C$ | $-$ | | | | $-$ | | | | $+$ | | |
| $\mu_S$ | $-$ | $-$ | $+$ | $+$ | $-$ | $-$ | $+$ | $+$ | $-$ | $-$ | $+$ |
| $\mu_P$ | $-$ | $+$ | $-$ | $+$ | $-$ | $+$ | $-$ | $+$ | $-$ | $+$ | $-$ |
| | (I) | (II) | (III) | (IV) | (V) | (VI) | (VII) | (VIII) | (IX) | (X) | (XI) |

*Proof. (of Theorem 1.1)* We deduce from (19) that

$$D(\mathbf{n}) = -\frac{\mathrm{d}}{\mathrm{d}t}E(\mathbf{n}) = -\frac{\mathrm{d}}{\mathrm{d}t}E(\mathbf{n}|\mathbf{n}_\infty)$$

and from the EEDI (33) that

$$\frac{\mathrm{d}}{\mathrm{d}t}E(\mathbf{n}|\mathbf{n}_\infty) \le -C_1 E(\mathbf{n}|\mathbf{n}_\infty).$$

Then the Gronwall inequality yields

$$E(\mathbf{n}|\mathbf{n}_\infty) \le E(\mathbf{n}(0,x)|\mathbf{n}_\infty)e^{-C_1 t}, \tag{49}$$

that is the exponential convergence in the relative entropy as $t \to \infty$. On the other hand, the CKP inequality (29) applied on the *l.h.s.* of (49) implies that

$$\begin{aligned} E(\mathbf{n}|\mathbf{n}_\infty) \ge & \frac{1}{2M_2}\|n_S - n_{S,\infty}\|^2_{L^1(\Omega)} + \frac{1}{M_1+M_2}\|n_C - n_{C,\infty}\|^2_{L^1(\Omega)} \\ & + \frac{1}{2M_1}\|n_E - n_{E,\infty}\|^2_{L^1(\Omega)} + \frac{1}{2M_2}\|n_P - n_{P,\infty}\|^2_{L^1(\Omega)} \end{aligned} \tag{50}$$

due to (27) and the conservation laws (7) and (8). Thus, with $C_1$ found in Lemma 3.5 and

$$C_2 = E(\mathbf{n}(0,x)|\mathbf{n}_\infty)/\min\{1/2M_1, 1/2M_2, 1/(M_1+M_2)\}$$

we obtain (9). □

# 4 Discussion

The mathematical treatment of the enzyme reactions (1) and (3) usually relies on using ODEs. There are significant assumptions leading to an ODE formalism: elimination of molecular noise, assuming volumes and temperature to be constant, and considering spatial structure to be insignificant [30], p. 16.

In this paper we have extended an ODE model for the reversible enzyme reaction (3), which is derived from the mass action kinetics, by taking spatial structure of, for example, a test tube or a living cell, into account. Hence we proposed to study the reaction-diffusion model (4)-(6) in an open, bounded and connected domain subject to homogeneous Neumann boundary condition. In particular, we focused on the asymptotic behaviour of the solution of (4)-(6). We showed that the solution converges exponentially fast to the unique constant steady state assuming that the initial concentrations of the species are nonzero. The same would be true if there was an enzyme (either free or bound to the intermediate complex) and either a substrate or a product present initially in the system.

The method we used is the entropy method that is based on the functional inequality (33) between the entropy of the system and the associated entropy dissipation. In contrast, it seems that the entropy method cannot be applied to the reaction-diffusion system for the irreversible enzyme reaction (1) (i.e., system (4)-(6) with $k_{p-} = 0$). The kinetics can still be seen in this case, nevertheless, there is no entropy such as (14) for this "irreversible" system.

Moreover, the studied reaction-diffusion model (4)-(6) is still rather simple as, for example, we assume that the diffusivities of the four species are all positive constants. As it often happens in living cells that enzymes are confined to subcellular compartments, it would be interesting to see how the entropy method would have to be shaped in the case when one or more species were immobilised, especially since the diffusion terms play a role in the derivation of the entropy-entropy dissipation inequality. The global-in-time existence of solutions of the reaction-diffusion systems for some reversible chemical reactions with one or more diffusivities equal to zero was studied in [14].

We conclude the article by a few remarks on a spatial version of the Michaelis-Menten kinetics that is omitted from the present article. Without any rigorous derivation and without any validity of its use, the Michaelis-Menten equation (2) in the presence of diffusion was considered in [31]. In particular, the author studied the asymptotic behaviour and stability of the steady state solution of the scalar equation

$$\frac{\partial n_S}{\partial t} - \operatorname{div}(D(x)\nabla n_S) = -k_{p+}\frac{e_0 n_S}{K_m + n_S} \tag{51}$$

on a bounded domain in $\mathbb{R}^d$ for $d \geq 1$ subject to Robin boundary condition. By a suitable construction of upper and lower solution, it was proved that the equation (51) possesses a unique nonnegative equilibrium that is exponentially asymptotically stable. Another problem considered in [31] involved two equations for the concentration of a substrate $n_S$ and an enzyme $n_E = [E]$,

$$\begin{cases} \dfrac{\partial n_S}{\partial t} - \operatorname{div}(D(x)\nabla n_S) = -k_+ n_S n_E + k_-(e_0 - n_E), \\ \qquad\qquad\qquad\qquad \dfrac{\partial n_E}{\partial t} = -k_+ n_S n_E + (k_- + k_{p+})(e_0 - n_E), \end{cases} \tag{52}$$

with Robin boundary condition for $n_S$ and suitably smooth initial data for both species. A threshold result on the stability and instability of steady state solutions of (52) was explicitly given. In both models (51) and (52) enzymes were found immobilised in space.

The reaction-diffusion models described above as well as other models for both irreversible (1) and reversible (3) enzyme reactions either with or without the Michaelis-Menten kinetics but always including an immobilised enzyme were studied in [22]. The validity of the Michaelis-Menten equation (2) by means of numerical analysis of the dynamical behaviour of a reaction-diffusion system for (1) with the immobilised enzyme was given in [28]. A QSSA was also applied to a more realistic enzymatic reaction where some of the enzyme is inactivated by reaction with the substrate, the so-called suicide substrate system, in which the substrate diffuses freely over the region containing the immobilised enzyme [25, 7].

The validity of the Michaelis-Menten equation (2) in a spatial reaction-diffusion framework for (1) including a mobile enzyme $E$ and intermediate complex $C$ was studied in [21] in one spatial dimension by comparing different relations between the time scales of reactions and diffusion. In particular, combinations of enzyme kinetics with large, moderate and slow diffusivities were discussed in [21]. It was shown that the Michaelis-Menten kinetics applies as soon as the concentrations of the species become homogeneous in space in the first two cases of the large and moderate diffusion. For slow diffusion, the reaction kinetics dominates so that at every point in space, the reaction proceeds exactly as in the kinetics problem at these points without any strong influence from the other points. After the substrate was used up and all of the complex decayed into product and enzyme at every point, the enzyme profile becomes homogenised due to diffusion.

Another QSSA approach for a reaction-diffusion system modelling the reaction

$$A+B \underset{k_{1-}}{\overset{k_{1+}}{\rightleftharpoons}} C \underset{k_{2-}}{\overset{k_{2+}}{\rightleftharpoons}} P+Q,$$

with the diffusing species in a bounded domain and with a highly reactive intermediate complex $C$ (the limit $k_{1-}+k_{2+}\to\infty$) was analysed in [3].

# Appendix A. Duality principle

We recall a duality principle [33, 34] which is used to show $L^2(\log L)^2$ and $L^2$ bounds, respectively, for the solution of the system (4)-(6). Note that a more general result is proved in [33], Chap. 6, than presented here.

**Lemma 4.1** (Duality principle)**.** *Let $0<T<\infty$ and $\Omega$ be a bounded, open and regular (e.g., $C^2$) subset of $\mathbb{R}^d$. Consider a nonnegative weak solution $u$ of the problem*

$$\begin{cases} \partial_t u - \Delta(Au) \le 0, \\ \nabla(Au)\cdot \nu = 0, \quad \forall t\in I,\ x\in\partial\Omega, \\ u(0,x) = u_0(x), \end{cases} \tag{53}$$

*where we assume that $0<A_1\le A=A(t,x)\le A_2<\infty$ is smooth, $A_1$ and $A_2$ are strictly positive constants, $u_0\in L^2(\Omega)$ and $\int u_0\ge 0$. Then,*

$$\|u\|_{L^2(Q_T)} \le C\|u_0\|_{L^2(\Omega)} \tag{54}$$

*where $C=C(\Omega,A_1,A_2,T)$.*

*Proof.* Let us consider an adjoint problem: find a nonnegative function $v\in C(I;L^2(\Omega))$ which is regular in the sense that $\partial_t v, \Delta v\in L^2(Q_T)$ and satisfies

$$\begin{cases} -\partial_t v - A\Delta v = F, \\ \nabla v\cdot \nu = 0, \quad \forall t\in I,\ x\in\partial\Omega, \\ v(T,x) = 0, \end{cases} \tag{55}$$

for $F = F(t,x) \in L^2(Q_T)$ nonnegative. The existence of such $v$ follows from the classical results on parabolic equations [24].

By combining equations for $u$ and $v$, we can readily check that

$$-\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega uv \geq \int_\Omega uF$$

which, by using $v(T) = 0$, yields

$$\int_{Q_T} uF \leq \int_\Omega u_0 v_0. \tag{56}$$

By multiplying equation for $v$ in (55) by $-\Delta v$, integrating per partes and using the Young inequality, we obtain

$$-\frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega |\nabla v|^2 + \int_\Omega A(\Delta v)^2 = -\int_\Omega F\Delta v \leq \int_\Omega \frac{F^2}{2A} + \frac{A}{2}(\Delta v)^2,$$

i.e.

$$-\frac{\mathrm{d}}{\mathrm{d}t}\int_\Omega |\nabla v|^2 + \int_\Omega A(\Delta v)^2 \leq \int_\Omega \frac{F^2}{A}.$$

Integrating this over $[0,T]$ and using $v(T) = 0$ gives

$$\int_\Omega |\nabla v_0|^2 + \int_{Q_T} A(\Delta v)^2 \leq \int_{Q_T} \frac{F^2}{A}.$$

Thus we obtain the a-priori bounds

$$\|\nabla v_0\|_{L^2(\Omega,\mathbb{R}^d)} \leq \left\|\frac{F}{\sqrt{A}}\right\|_{L^2(Q_T)} \quad \text{and} \quad \|\sqrt{A}\Delta v\|_{L^2(\Omega)} \leq \left\|\frac{F}{\sqrt{A}}\right\|_{L^2(Q_T)}. \tag{57}$$

From the equation for $v$ we can write (again, by integrating this equation over $\Omega$ and $[0,T]$ and using $v(T) = 0$)

$$\int_\Omega v_0 = \int_{Q_T} A\Delta v + F.$$

Hence,

$$\begin{aligned}\int_\Omega v_0 = \int_{Q_T} \sqrt{A}\left(\sqrt{A}\Delta v + \frac{F}{\sqrt{A}}\right) &\leq \|\sqrt{A}\|_{L^2(Q_T)} \left\|\sqrt{A}\Delta v + \frac{F}{\sqrt{A}}\right\|_{L^2(Q_T)} \\ &\leq 2\|\sqrt{A}\|_{L^2(Q_T)} \left\|\frac{F}{\sqrt{A}}\right\|_{L^2(Q_T)},\end{aligned} \tag{58}$$

which follows from the Hölder inequality and (57).

To conclude the proof, let us return to (56) and write

$$\begin{aligned}0 \leq \int_{Q_T} uF \leq \int_\Omega u_0 v_0 &= \int_\Omega u_0(v_0 - \overline{v_0}) + u_0\overline{v_0} \\ &\leq \|u_0\|_{L^2(\Omega)}\|v_0 - \overline{v_0}\|_{L^2(\Omega)} + \int_\Omega \overline{u_0} v_0 \\ &\leq C(\Omega)\|u_0\|_{L^2(\Omega)}\|\nabla v_0\|_{L^2(\Omega,\mathbb{R}^d)} + \overline{u_0}\int_\Omega v_0,\end{aligned}$$

where we have used the Hölder and Poincaré-Wirtinger inequalities, respectively. Recall that $\overline{v} = \frac{1}{|\Omega|}\int_\Omega v\,\mathrm{d}x$. The norm of the gradient $v_0$ can be estimated by (57) and the last remaining integral by (58) so that we obtain

$$\int_{Q_T} uF \leq \Big(C(\Omega)\|u_0\|_{L^2(\Omega)} + 2\overline{u_0}\|\sqrt{A}\|_{L^2(Q_T)}\Big)\left\|\frac{F}{\sqrt{A}}\right\|_{L^2(Q_T)}, \tag{59}$$

which holds true for any $F \in L^2(Q_T)$. Thus, for $F = Au$ we can finally write

$$\|\sqrt{A}u\|_{L^2(Q_T)} \leq C(\Omega)\|u_0\|_{L^2(\Omega)} + 2\overline{u_0}\|\sqrt{A}\|_{L^2(Q_T)} \tag{60}$$

and deduce (54) by using the boundedness of $A$, i.e. $A_1 \leq A(t,x) \leq A_2$. □

We remark that, by construction, $A(t,x)$ in (23) is not smooth but $L^\infty$ only. We refer to [5] for the corresponding existence and regularity result for the adjoint problem (55).

# Appendix B. Inequality (48)

In this section we give a full proof of the inequality (48). We recall that all the summations below go for $i \in \{S,E,C,P\}$, i.e., $\sum = \sum_{i\in\{S,E,C,P\}}$.

We start by noting that that the conservation law (39), reflecting the ansatz (40) and the substitution (45), namely

$$N_{E,\infty}^2 + N_{C,\infty}^2 = N_{E,\infty}^2(1+\mu_E)^2 + \overline{\delta_E^2} + N_{C,\infty}^2(1+\mu_C)^2 + \overline{\delta_C^2}, \tag{61}$$

$$\begin{aligned} N_{S,\infty}^2 + N_{C,\infty}^2 + N_{P,\infty}^2 = N_{S,\infty}^2(1+\mu_S)^2 + \overline{\delta_S^2} + N_{C,\infty}^2(1+\mu_C)^2 + \overline{\delta_C^2} \\ + N_{P,\infty}^2(1+\mu_P)^2 + \overline{\delta_P^2}, \end{aligned} \tag{62}$$

possesses restrictions on the signs of $\mu_i$'s. In particular, we remark that

i) $\forall i \in \{S,E,C,P\}$, $-1 \leq \mu_i \leq \mu_{i,max}$ where $\mu_{i,max}$ depends on $\mathbf{n}_\infty$;

ii) the conservation law (61) excludes the case when $\mu_E > 0$ and $\mu_C > 0$, since in this case $\overline{N_E} > N_{E,\infty}$ and $\overline{N_C} > N_{C,\infty}$ and we deduce from (39), (61) and the Jensen inequality $\overline{N_i^2} \geq \overline{N_i}^2$, that

$$M_1 = \overline{N_E^2} + \overline{N_C^2} \geq \overline{N_E}^2 + \overline{N_C}^2 > N_{E,\infty}^2 + N_{C,\infty}^2 = M_1,$$

which is a contradiction;

iii) analogously, the conservation law (62) excludes the case when $\mu_S > 0$, $\mu_C > 0$ and $\mu_P > 0$;

iv) for $-1 \leq \mu_E, \mu_C \leq 0$, the conservation law (61) implies $N_{E,\infty}^2\mu_E^2 + N_{C,\infty}^2\mu_C^2 \leq \sum \overline{\delta_i^2}$, since for any $s \in [-1,0]$ we have $-1 \leq s \leq -s^2 \leq 0$ and we can deduce from (61) that

$$\begin{aligned} 0 = N_{E,\infty}^2(2\mu_E + \mu_E^2) + N_{C,\infty}^2(2\mu_C + \mu_C^2) + \overline{\delta_C^2} + \overline{\delta_E^2} \\ \leq -N_{E,\infty}^2\mu_E^2 - N_{C,\infty}^2\mu_C^2 + \sum \overline{\delta_i^2}; \end{aligned}$$

v) analogously, for $-1 \leq \mu_S, \mu_C, \mu_P \leq 0$, the conservation law (62) implies that $N_{S,\infty}^2 \mu_S^2 + N_{C,\infty}^2 \mu_C^2 + N_{P,\infty}^2 \mu_P^2 \leq \sum \overline{\delta_i^2}$.

To find explicitly $C_3$ and $C_4$ in (48), we have to consider all possible configurations of $\mu_i$'s in (48), that is all possible quadruples $(\mu_E, \mu_C, \mu_S, \mu_P)$ depending on their signs. The remarks (ii) and (iii) reduce the total number of quadruples by five and the remaining 11 quadruples are shown in Table 1.

Ad (I). The remarks (iv) and (v) imply that $\sum N_{i,\infty}^2 \mu_i^2 \leq 2 \sum \overline{\delta_i^2}$ and, therefore, (48) is satisfied for $C_3 = 3$ and $C_4 = 0$.

Ad (II) and (III). We prove (48) for $-1 \leq \mu_E, \mu_C \leq 0$ and $\mu_S$ and $\mu_P$ having opposite signs. Firstly, let us remark that (61) implies that

$$N_{E,\infty}^2 = N_{E,\infty}^2 (1+\mu_E)^2 + N_{C,\infty}^2 (2\mu_C + \mu_C^2) + \overline{\delta_E^2} + \overline{\delta_C^2},$$

i.e.,

$$\begin{aligned} (1+\mu_E)^2 &= 1 - \frac{N_{C,\infty}^2}{N_{E,\infty}^2}(2\mu_C + \mu_C^2) - \frac{1}{N_{E,\infty}^2}(\overline{\delta_E^2} + \overline{\delta_C^2}) \\ &\geq 1 - \frac{1}{N_{E,\infty}^2} \sum \overline{\delta_i^2} \end{aligned} \tag{63}$$

since for $-1 \leq \mu_C \leq 0$ there is $-1 \leq 2\mu_C + \mu_C^2 \leq 0$. Then, by using an elementary inequality $a^2 + b^2 \geq (a-b)^2/2$ we obtain that

$$I_1 + I_2 = ((1+\mu_S)(1+\mu_E) - (1+\mu_C))^2 + ((1+\mu_P)(1+\mu_E) - (1+\mu_C))^2$$

satisfies

$$\begin{aligned} I_1 + I_2 &\geq \frac{1}{2}(\mu_S - \mu_P)^2 (1+\mu_E)^2 \\ &\geq \frac{1}{2} K_4 (N_{S,\infty}^2 \mu_S^2 + N_{P,\infty}^2 \mu_P^2) - K_5 \sum \overline{\delta_i^2} \end{aligned} \tag{64}$$

where we have used (63) and the fact that $\mu_S$ and $\mu_P$ have opposite signs and are bounded above by $\mu_{S,max}$ and $\mu_{P,max}$ (by the remark (i)). In (64), $K_4 = \min\left\{1/N_{S,\infty}^2, 1/N_{P,\infty}^2\right\}$ is sufficient, nevertheless, we will take

$$K_4 = \min_{i \in \{S,E,C,P\}} \left\{ \frac{1}{N_{i,\infty}^2} \right\} \quad \text{and} \quad K_5 = \frac{1}{N_{E,\infty}^2}(\mu_{S,max}^2 + \mu_{P,max}^2), \tag{65}$$

since $K_4$ in (65) will appear several times elsewhere. We deduce from (64) and the remark (iv) that

$$\sum N_{i,\infty}^2 \mu_i^2 + \sum \overline{\delta_i^2} \leq 2\left(1 + \frac{K_5}{K_4}\right) \sum \overline{\delta_i^2} + \frac{2}{K_4}(I_1 + I_2), \tag{66}$$

and we see that (48) is satisfied for

$$C_4 = \frac{2}{K_3 K_4} \quad \text{and} \quad C_3 = 2\left(1 + \frac{K_5}{K_4}\right) + C_4\left(\sqrt{k_+} K_1 + \sqrt{k_{p-}} K_2\right),$$

when (48) is compared with the *r.h.s.* of (66).

Ad (IV) Assume $-1 \le \mu_E, \mu_C \le 0$ and $\mu_S, \mu_P > 0$. A combination of (61) and (62) gives

$$\begin{aligned} N_{E,\infty}^2 - N_{S,\infty}^2 - N_{P,\infty}^2 &= \overline{N_E}^2 + \overline{\delta_E^2} - \overline{N_S}^2 - \overline{\delta_S^2} - \overline{N_P}^2 - \overline{\delta_P^2} \\ &\le N_{E,\infty}^2 - \overline{N_S}^2 - \overline{N_P}^2 + \overline{\delta_E^2} - \overline{\delta_S^2} - \overline{\delta_P^2}, \end{aligned} \tag{67}$$

since $\overline{N_E}^2 \le N_{E,\infty}^2$ for $-1 \le \mu_E \le 0$, where $\overline{N_E}^2 = N_{E,\infty}^2 (1+\mu_E)^2$. We deduce from (67) that

$$-N_{S,\infty}^2 - N_{P,\infty}^2 \le -N_{S,\infty}^2 (1+\mu_S)^2 - N_{P,\infty}^2 (1+\mu_P)^2 + \overline{\delta_E^2} - \overline{\delta_S^2} - \overline{\delta_P^2}$$

and

$$N_{S,\infty}^2 (2\mu_S + \mu_S^2) + N_{P,\infty}^2 (2\mu_P + \mu_P^2) \le \overline{\delta_E^2} - \overline{\delta_S^2} - \overline{\delta_P^2} \le \sum \overline{\delta_i^2}.$$

Since $\mu_S, \mu_P > 0$, then $N_{S,\infty}^2 \mu_S^2 + N_{P,\infty}^2 \mu_P^2 \le \sum \overline{\delta_i^2}$. This estimate together with the remark (iv) yields $\sum N_{i,\infty}^2 \mu_i^2 \le 2 \sum \overline{\delta_i^2}$. Similarly as in the case (I), (48) is satisfied for $C_3 = 3$ and $C_4 = 0$.

Ad (V) Let us now consider the case when $-1 \le \mu_S, \mu_C, \mu_P \le 0$ and $\mu_E > 0$. As in the case (IV), a combination of (61) and (62) gives

$$\begin{aligned} N_{S,\infty}^2 + N_{P,\infty}^2 - N_{E,\infty}^2 &= \overline{N_S}^2 + \overline{\delta_S^2} + \overline{N_P}^2 + \overline{\delta_P^2} - \overline{N_E}^2 - \overline{\delta_E^2} \\ &\le N_{S,\infty}^2 + N_{P,\infty}^2 - \overline{N_E}^2 + \overline{\delta_S^2} + \overline{\delta_P^2} - \overline{\delta_E^2}, \end{aligned} \tag{68}$$

since, again, $\overline{N_i}^2 \le N_{i,\infty}^2$ for $-1 \le \mu_i \le 0$ and $i = S, P$. Hence, for $\mu_E > 0$ we deduce from (68) that $N_{E,\infty}^2 \mu_E^2 < \sum \overline{\delta_i^2}$, which with the remark (v) gives $\sum N_{i,\infty}^2 \mu_i^2 < 2 \sum \overline{\delta_i^2}$. Thus, (48) is satisfied for $C_3 = 3$ and $C_4 = 0$.

Ad (VI) and (VII). Assume that $\mu_E > 0$, $-1 \le \mu_C \le 0$ and $\mu_S$ and $\mu_P$ have opposite signs. Then using an elementary inequality $a^2 + b^2 \ge (a+b)^2/2$ we obtain

$$I_1 + I_2 \ge \frac{1}{2}(\mu_S - \mu_P)^2 (1+\mu_E)^2 > \frac{1}{2}(\mu_S - \mu_P)^2 \ge \frac{1}{2}(\mu_S^2 + \mu_P^2),$$

since $(1+\mu_E)^2 > 1$ and $\mu_S$ and $\mu_P$ have opposite signs. Further, it holds that $(1+\mu_k)(1+\mu_E) > (1+\mu_E)$ for $\mu_k$ being either $\mu_S > 0$ or $\mu_P > 0$ (one of them is positive). This implies $(1+\mu_k)(1+\mu_E) - (1+\mu_C) > \mu_E - \mu_C > 0$ and thus ($\mu_E$ and $\mu_C$ have opposite signs)

$$I_1 + I_2 > (\mu_E - \mu_C)^2 \ge \mu_E^2 + \mu_C^2.$$

Altogether, we obtain for both cases that $I_1 + I_2 > \sum \mu_i^2 / 4 \ge K_4/4 \sum N_{i,\infty}^2 \mu_i^2$ where $K_4$ is defined in (65). We deduce that (48) is satisfied for

$$C_4 = \frac{4}{K_3 K_4} \quad \text{and} \quad C_3 = 1 + C_4 \left( \sqrt{k_+} K_1 + \sqrt{k_{p-}} K_2 \right). \tag{69}$$

Ad (VIII). Assume that $\mu_E, \mu_S, \mu_P > 0$ and $-1 \leq \mu_C \leq 0$. Using the similar arguments as in the previous case, in particular, $(1+\mu_S)(1+\mu_E) > (1+\mu_S)$, $(1+\mu_S)(1+\mu_E) > (1+\mu_E)$, $(1+\mu_P)(1+\mu_E) > (1+\mu_P)$ and $(1+\mu_P)(1+\mu_E) > (1+\mu_E)$ and since $\mu_i - \mu_C > 0$ for each $i \in \{S, E, P\}$, we can write

$$\begin{aligned} I_1 + I_2 &= ((1+\mu_S)(1+\mu_E) - (1+\mu_C))^2 + ((1+\mu_P)(1+\mu_E) - (1+\mu_C))^2 \\ &\geq \frac{1}{2}(\mu_S - \mu_C)^2 + (\mu_E - \mu_C)^2 + \frac{1}{2}(\mu_P - \mu_C)^2 \geq \frac{1}{2}\sum \mu_i^2 \geq \frac{K_4}{2}\sum N_{i,\infty}^2 \mu_i^2. \end{aligned}$$

Hence, (48) is satisfied for $C_4 = 2/K_3K_4$ and $C_3$ defined in (69).

Ad (IX). The case when $-1 \leq \mu_E, \mu_S, \mu_P \leq 0$ and $\mu_C > 0$ is similar to the case (VIII). Now we observe that $\mu_C - \mu_i > 0$ for each $i \in \{S, E, P\}$ and that $(1+\mu_S)(1+\mu_E) \leq (1+\mu_S)$, $(1+\mu_S)(1+\mu_E) \leq (1+\mu_E)$, $(1+\mu_P)(1+\mu_E) \leq (1+\mu_P)$ and $(1+\mu_P)(1+\mu_E) \leq (1+\mu_E)$ which can be used to conclude $I_1 + I_2 \geq \sum \mu_i^2/2 \geq K_4/2 \sum N_{i,\infty}^2 \mu_i^2$. The constants $C_3$ and $C_4$ are the same as in the case (VIII).

Ad (X). Assume that $-1 \leq \mu_E \leq 0$, $\mu_C > 0$, $-1 \leq \mu_S \leq 0$ and $\mu_P > 0$. By the same argument as in (IX), we can write

$$I_1 + I_2 \geq I_1 \geq (\mu_C - \mu_E)^2 \geq \mu_C^2 + \mu_E^2. \tag{70}$$

Using the same elementary inequality as in (II) and (VI), we obtain

$$I_1 + I_2 \geq \frac{1}{2}(\mu_S - \mu_P)^2(1+\mu_E)^2, \tag{71}$$

where $-1 \leq \mu_E \leq 0$, thus we cannot proceed in the way as in the cases (VI) and (VII) nor in the cases (II) and (III), since $\mu_C$ is positive now. Nevertheless, we distinguish two subcases when $-1 < \eta \leq \mu_E \leq 0$ and $-1 \leq \mu_E < \eta$. For example, $\eta = -1/2$ works well, however, a more suitable constant $\eta$ could be possibly found. For $\eta = -1/2$ and $\eta \leq \mu_E \leq 0$ we obtain from (71) that

$$I_1 + I_2 \geq \frac{1}{8}(\mu_S - \mu_P)^2 \geq \frac{1}{8}(\mu_S^2 + \mu_P^2). \tag{72}$$

This with (70) implies that $I_1 + I_2 \geq \sum \mu_i^2/16 \geq K_4/16 \sum N_{i,\infty}^2 \mu_i^2$ and we conclude that (48) is satisfied for $C_4 = 16/K_3K_4$ and $C_3$ defined in (69).

For $\eta = -1/2$ and $-1 \leq \mu_E < \eta$ we obtain, by using an elementary inequality $(a-b)^2 \geq a^2/2 - b^2$, that

$$\begin{aligned} I_1 + I_2 \geq I_1 &= ((1+\mu_C) - (1+\mu_S)(1+\mu_E))^2 \\ &\geq \frac{1}{2}(1+\mu_C)^2 - (1+\mu_S)^2(1+\mu_E)^2 > \frac{1}{4}, \end{aligned} \tag{73}$$

since $(1+\mu_C)^2 > 1$ for $\mu_C > 0$ and $(1+\mu_S)^2(1+\mu_E)^2 < 1/4$ for $-1 \leq \mu_S \leq 0$ and $-1 \leq \mu_E < -1/2$. On the other hand, $\sum N_{i,\infty}^2 \mu_i^2 \leq \sum N_{i,\infty}^2 \mu_{i,\max}^2 =: K_6$ by the remark (i). We see that (48) is satisfied for $C_4 = K_6/4K_3$ and $C_3$ as in (69).

Ad (XI). Finally, assume that $-1 \le \mu_E \le 0$, $\mu_C > 0$, $\mu_S > 0$ and $-1 \le \mu_P \le 0$. This case is symmetric to the previous case (X), thus the same procedure can be applied again (it is sufficient to exchange superscripts $S$ and $P$ everywhere they appear in (X)) to deduce the constants $C_3$ and $C_4$ in (48). In particular, we take $C_4 = 16/K_3K_4$ for $-1/2 \le \mu_E \le 0$ and $C_4 = K_6/4K_3$ for $-1 \le \mu_E < -1/2$. In both subcases $C_3$ is as in (69).

From the eleven cases (I)-(XI), we need to take

$$C_4 = \frac{1}{K_3} \max\left\{\frac{16}{K_4}, \frac{K_6}{4}\right\} \tag{74}$$

and

$$C_3 = \max\left\{3, 2\left(1 + \frac{K_5}{K_4}\right)\right\} + C_4\left(\sqrt{k_+}K_1 + \sqrt{k_{p-}}K_2\right) \tag{75}$$

to find (48) true.

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