

Analytic computation of the integrated response in nonlinear reaction-diffusion systems

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Abstract—In this work we analytically derive the time-integral of a class of nonlinear reaction-diffusion systems commonly found in networks of biochemical reactions. This formula is inferred using the Laplacian Spectral Decomposition method, which approximates the solution of the Partial Differential Equations by a finite series capturing the most relevant dynamics. The time-integrals allow us to understand how signal transmission depends on initial and boundary conditions, spatial geometry and the turnover rates of some species.

I. INTRODUCTION

Cellular activity is regulated by an intricate network of biochemical reactions and transport phenomena that confers robustness to cellular functions in variable environments [1]. Membrane receptors are typically responsible of sensing extracellular informations cues, whereas signalling, transcriptional and metabolic networks transmit, process and execute cellular functions.

Since molecules diffuse in the intracellular matrix, the signal processing ability of a cell is encoded in time and space. Moreover, cells are highly compartmentalized environments, and a number of reactions can occur only in certain organelles or in specific locations, e.g. the TCA cycle in eukaryotes occurs in the mitochondria, and cell receptors are fixed in the membrane. Spatiotemporal dynamics are essential in a number of processes, including cellular signalling [2], pattern formation [3], morphogenesis [4], among others.

Spatiotemporal dynamics of biochemical interactions are typically described via reaction-diffusion equations [5], which are PDEs describing the rate of change of the species concentrations. Because chemical reaction kinetics can be highly nonlinear, the vast majority of reaction-diffusion PDEs are analytically intractable. Our main goal in this paper is to analytically compute the time-domain integral of the solutions of reaction-diffusion systems.

In engineered control systems, system norms (e.g. \mathcal{H}_2 or \mathcal{H}_∞) are compact descriptions of their input/output behaviour. In natural biochemical systems, however, the nonlinearities hinder the construction of such measures and therefore the signal transmission ability of a biochemical network

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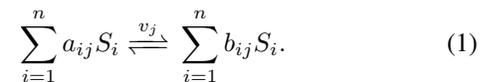
is typically difficult to characterize. A number of works have addressed this problem from different angles. For example, in [6] the authors computed the \mathcal{L}_2 norm of a class of signalling cascades, whereas several other works have quantified the time-domain integral of the species concentrations [7]–[10]. In particular, in [8] the authors used the time-integral to discover an input amplification phenomenon in the MAPK pathway, whereas in [10] it was used to quantify the signal transmission ability of the erythropoietin receptor. All these previous works focus on biochemical networks described by ODE models, and the effect of spatial dynamics has been generally overlooked.

We consider a general class of nonlinear reaction-diffusion models with inputs (§II) and use the Laplacian Spectral Decomposition (LSD, §III) to project its solutions onto a lower dimensional subspace. We use this model reduction technique to write the time-integral as a finite series. The main result of this paper is two-fold (§IV-B): firstly, we find conditions on the stoichiometry and diffusivity under which the series expansion of the time-integral of some species can be computed analytically. Secondly, we provide a closed form expression for the coefficients of the series expansion. For those species that satisfy the derived conditions, its time-integral can be explicitly computed in terms of the model parameters, initial conditions and the integral of the input. We illustrate our approach by means of an example that includes power-law binding kinetics (§V).

II. PROBLEM FORMULATION

A. Reaction-diffusion systems

A reaction network is composed of a group of species, whose chemical interaction is represented by



Here S_i is the i^{th} reactant or product for the j^{th} reaction, whereas v_j denotes the rate of this reaction. The symbols a_{ij} and b_{ij} denote the stoichiometric coefficients of the corresponding species. When a reaction is not reversible, we will just use a forward arrow to describe the species interaction. In addition, we will focus on biological systems that can be idealized as adiabatic and isothermal. This allows us to fully determine the state of the network exclusively from the species' concentration. This kind of systems can be thus modeled by

$$\dot{\mathbf{c}} = \mathbf{N}\mathbf{v}(\mathbf{c}) + \mathbf{B}\mathbf{u}. \quad (2)$$

Here, $\mathbf{c}(t) : \mathbb{R}_+ \rightarrow \mathbb{R}^n$ comprises the species concentrations in (1). The rate at which the reactants are becoming products compose the vector $\mathbf{v}(\mathbf{c}(t)) : \mathbb{R}_+ \rightarrow \mathbb{R}^m$. Besides synthesis and degradation rates (which are typically constant and linear, respectively), the reactions rates are typically nonlinear functions of the state $\mathbf{c}(t)$, which can be modelled by well-known principles such as the Mass Action Law, Michaelis-Menten kinetics, and Hill kinetics, for example. In turn, $\mathbf{u}(t) : \mathbb{R}_+ \rightarrow \mathbb{R}^q$ accounts the influx and efflux rate, resulting from the interaction of the reaction network with its surroundings. Accordingly, $\mathbf{B} \in \mathbb{R}^{n \times q}$ shows how this interaction affects the change rate of the species. The link from reaction rates to the actual concentration change is the stoichiometric matrix $\mathbf{N} \in \mathbb{R}^{n \times m}$, whose (i, j) element is defined as

$$N_{ij} = b_{ij} - a_{ij}.$$

When the diffusion of species in a spatial domain Ω is relevant, the second Fick's Law can be integrated into (2) as follows (see [5], for example)

$$\frac{\partial}{\partial t} \mathbf{c}(t, x) = \mathbf{D} \nabla_x^2 \mathbf{c}(t, x) + \mathbf{N} \mathbf{v}(\mathbf{c}) + \mathbf{B} \mathbf{u}(t, x), \quad (3)$$

where \mathbf{D} is a diagonal matrix that gathers the species diffusion constants. Note that in the spatiotemporal context, the concentrations depend on both space and time: $\mathbf{c}(t, x) : \mathbb{R}_+ \times \Omega \rightarrow \mathbb{R}^n$; in a similar way the domains of $\mathbf{v}(\mathbf{c}(t, x))$ and $\mathbf{u}(t, x)$ are extended. The initial and boundary conditions can be represented by the expressions

$$\begin{aligned} \mathbf{c}(0, x) &= \mathbf{c}_0(x) \quad \forall x \in \Omega \subset \mathbb{R} & (4) \\ m(t, \partial\Omega) &= p(t, \partial\Omega) \mathbf{c}(t, \partial\Omega) + q(t, \partial\Omega) \left. \frac{\partial \mathbf{c}(t, x)}{\partial \mathbf{n}} \right|_{x=\partial\Omega} & (5) \\ &\quad \forall t \in \mathbb{R}_+. \end{aligned}$$

Here \mathbf{n} is a the outward normal vector to the boundary of Ω , denoted as $\partial\Omega$. The expression in (5) is the generic form of the boundary conditions. In particular, when $q(t, \partial\Omega) = 0$ or $p(t, \partial\Omega) = 0$ it describes Dirichlet or Neumann boundary conditions, respectively.

B. Integrated response

We focus on quantifying the response of a reaction-diffusion system to initial conditions $\mathbf{c}(0, x)$ and a transient stimulus $\mathbf{u}(t, x)$ satisfying the boundary conditions in (5) and such that

$$\begin{aligned} \lim_{t \rightarrow \infty} \mathbf{u}(t, x) &= \mathbf{0}, \\ \int_0^\infty \mathbf{u}(t, x) dt &< \infty, \end{aligned}$$

where the symbol $<$ denotes element-wise inequality. Note that our results can also be obtained for the case of a persistent stimulus (i.e. $\lim_{t \rightarrow \infty} \mathbf{u}(t, x) = \bar{\mathbf{u}}$), but here we consider the simpler case $\bar{\mathbf{u}} = \mathbf{0}$. Furthermore, we assume that, once the effect of the stimulus $\mathbf{u}(t, x)$ has vanished, the network reaches a *unique exponentially stable* equilibrium point $\bar{\mathbf{c}}$ that satisfies

$$\frac{\partial}{\partial t} \bar{\mathbf{c}} - \nabla_x^2 \bar{\mathbf{c}} = \mathbf{N} \mathbf{v}(\bar{\mathbf{c}}) = \mathbf{0}.$$

Of note, the equilibrium point $\bar{\mathbf{c}}$ is independent of x . This equilibrium point is called the homogeneous steady state of the network [3].

One way of quantifying the overall response of the network is by computing its *integrated response*, which we define as

$$\mathbf{I}(x) = \int_0^\infty (\mathbf{c}(t, x) - \bar{\mathbf{c}}) dt. \quad (6)$$

Note that the exponential stability of the system guarantees that $\mathbf{I}(x)$ is finite. In the remainder of the paper, we will focus on the analytic computation of the integrated response for some species of a class of nonlinear reaction-diffusion networks.

III. LAPLACIAN SPECTRAL DECOMPOSITION

Solutions for the system (3) with boundary conditions (5) can be found in Hilbert spaces. We focus on Hilbert spaces equipped with an inner product of the form

$$\langle \mathbf{f}(x), \mathbf{g}(x) \rangle_\Omega = \int_\Omega \mathbf{g}^T(x) \mathbf{f}(x) dx,$$

where $\mathbf{f}(x)$ and $\mathbf{g}(x)$ are given functions over the spatial domain Ω . Moreover, this inner product induces a norm which endows this Hilbert space with the properties of a normed space [11].

In what follows we will assume that all the signals belong to the same Hilbert space, and hence they can be expressed in terms of a common basis $\{\phi_i(x)\}_{i=1}^\infty$ [11]. Let $\mathbf{c}(t, x)$ be an element of such a Hilbert space, then it can be expanded as

$$\mathbf{c}(t, x) = \sum_{i=1}^\infty \mathbf{w}_i(t) \phi_i(x), \quad (7)$$

where $\mathbf{w}_i(t) : \mathbb{R}_+ \rightarrow \mathbb{R}^n$ collects the so-called modes of $\phi_i(x)$. Note that in (7) we used a strict equality sign, which is a consequence of the completeness of the basis formed with the functions $\{\phi_i(x)\}_{i=1}^\infty$. We use the Laplacian Spectral Decomposition (LSD) method [12], where the set of functions $\{\phi_i(x)\}_{i=1}^\infty$ are invariant with respect to the Laplacian operator, i.e. they satisfy

$$\nabla_x^2 \phi_i(x) = -\lambda_i \phi_i(x). \quad (8)$$

Equation (8) must be solved with the appropriate boundary conditions (in our case equation (5)) to produce a complete set of orthonormal eigenfunctions $\{\phi_i(x)\}_{i=1}^\infty$, and their corresponding ordered positive eigenspectrum; that is to say $0 < \lambda_i < \lambda_j \quad \forall i < j < \infty$.

As shown in [13], [14] a field that obeys a quasi-linear parabolic PDE of the form (3) with locally Lipschitz continuous nonlinearities, is dissipative and $\lambda_n \rightarrow \infty$ exponentially fast as $n \rightarrow \infty$. The ordered structure of the eigenspectrum $\{\lambda_i\}_0^\infty$ defines a low-dimensional subspace spanned by $\{\phi_i(x)\}_0^p$ and illustrated in Figure 1, which approximate the original field, thus, guiding the selection of the subspace which captures most of the relevant dynamic features of the solution. From our experience in this class of systems, a

good approximation only requires a relatively low number of terms p . That is to say

$$\mathbf{c}(t, x) \approx \sum_{i=1}^p \mathbf{w}_i(t) \phi_i(x) := \mathbf{W}^T(t) \boldsymbol{\phi}(x), \quad (9)$$

here $\mathbf{W}^T(t) : \mathbb{R}_+ \rightarrow \mathbb{R}^{n \times p}$ and $\boldsymbol{\phi}(x) : \Omega \rightarrow \mathbb{R}^p$ is a vector whose i^{th} entry is $\phi_i(x)$. This truncation will lead to an approximation error that depends on the number of terms in the series expansion. Note however that, p can be arbitrarily large, and its choice depend on the required accuracy [13].

We also gather the eigenvalues $-\lambda_i$ in the diagonal matrix

$$\boldsymbol{\Lambda} = \text{diag} \{-\lambda_1, -\lambda_2, \dots, -\lambda_p\} \in \mathbb{R}^{p \times p}. \quad (10)$$

IV. COMPUTATION OF THE INTEGRATED RESPONSE

In this section we will present sufficient conditions on the network that allow for an accurate approximation of the integrated response.

A. Deviation coordinates

In general, the rate vector $\mathbf{v}(\mathbf{c})$ may contain species production rates, linear degradation rates, and nonlinear kinetics describing the interaction between two or more species. In what follows we reorder the elements in $\mathbf{v}(\mathbf{c})$ and \mathbf{c} , and express the original PDE model in deviation coordinates form the equilibrium, so as to make the linear and nonlinear terms explicit.

Consider a partition of the rate vector into r nonlinear rates and $(m-r)$ affine rates

$$\mathbf{v}(\mathbf{c}) = (\mathbf{v}_{\text{NL}}^T \quad \mathbf{v}_{\text{L}}^T)^T : \mathbb{R}_+ \rightarrow \mathbb{R}^{r+(m-r)}. \quad (11)$$

The partition in (11) induces the following partition in the stoichiometric matrix

$$\mathbf{N} = (\mathbf{N}_{\text{NL}} \quad \mathbf{N}_{\text{L}}) \in \mathbb{R}^{n \times (r+(m-r))}. \quad (12)$$

If we define new coordinates $\mathbf{e}(t, x) = \mathbf{c}(t, x) - \bar{\mathbf{c}}$, we can use a Taylor expansion of (3) around $\mathbf{c} = \bar{\mathbf{c}}$ to get

$$\frac{\partial}{\partial t} \mathbf{e}(t, x) = \mathbf{D} \nabla_x^2 \mathbf{e}(t, x) + \mathbf{N} \mathbf{J} \mathbf{e}(t, x) + \mathbf{N}_{\text{NL}} \mathbf{g}(\mathbf{e}) + \mathbf{B} \mathbf{u}(t, x), \quad (13)$$

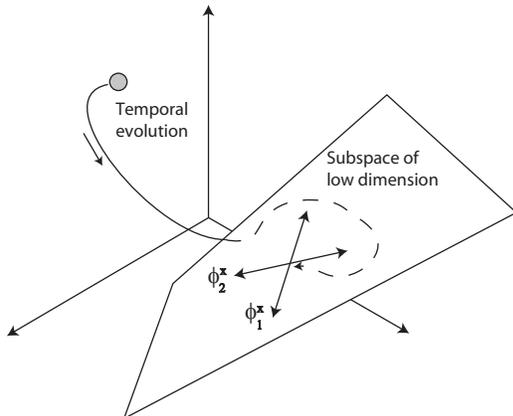


Fig. 1. Dynamic evolution of a dissipative process.

where

$$\mathbf{J} = \left. \frac{\partial}{\partial \mathbf{c}} \mathbf{v}(\mathbf{c}) \right|_{\mathbf{c}=\bar{\mathbf{c}}} \quad (14)$$

is the Jacobian of $\mathbf{v}(\mathbf{c})$ and the vector $\mathbf{g}(\mathbf{e})$ contains the 2nd and higher order derivatives of the entries of $\mathbf{v}_{\text{NL}}(\mathbf{e})$.

We further partition the species vector as

$$\mathbf{c}(t, x) = \begin{pmatrix} \mathbf{c}_{\text{NL}}(t, x) \\ \mathbf{c}_{\text{L}}(t, x) \end{pmatrix} : \mathbb{R}_+ \times \Omega \rightarrow \mathbb{R}^{k+(n-k)}. \quad (15)$$

The vector $\mathbf{c}_{\text{NL}}(t, x)$ is composed of the k species that are *exclusively* reactants or products of nonlinear reactions, whereas $\mathbf{c}_{\text{L}}(t, x)$ includes the rest of the species. Accordingly, the stoichiometric matrix, Jacobian, diffusion matrix, and input matrix in (3), and the deviation coordinate in (13), become

$$\mathbf{N} = \begin{pmatrix} \mathbf{N}_1 & \mathbf{N}_3 \\ \mathbf{N}_2 & \mathbf{N}_4 \end{pmatrix} \in \mathbb{R}^{(k+(n-k)) \times (r+(m-r))},$$

$$\mathbf{J} = \begin{pmatrix} \mathbf{J}_1 & \mathbf{J}_2 \\ \mathbf{J}_3 & \mathbf{J}_4 \end{pmatrix} \in \mathbb{R}^{(r+(m-r)) \times (k+(n-k))},$$

$$\mathbf{D} = \begin{pmatrix} \mathbf{D}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{D}_4 \end{pmatrix} \in \mathbb{R}^{(k+(n-k)) \times (k+(n-k))}, \quad (16a)$$

$$\mathbf{B} = \begin{pmatrix} \mathbf{B}_1 \\ \mathbf{B}_2 \end{pmatrix} \in \mathbb{R}^{(k+(n-k)) \times q}, \quad (16b)$$

$$\mathbf{e}(t, x) = \begin{pmatrix} \mathbf{e}_{\text{NL}}(t, x) \\ \mathbf{e}_{\text{L}}(t, x) \end{pmatrix} : \mathbb{R}_+ \times \Omega \rightarrow \mathbb{R}^{k+(n-k)}. \quad (16c)$$

As a consequence of the definition of $\mathbf{e}_{\text{L}}(t, x)$, we note that $\mathbf{J}_3 = \mathbf{N}_3^T = \mathbf{0}$, so the definitions for \mathbf{N} and \mathbf{J} above, reduce to

$$\mathbf{N} = \begin{pmatrix} \mathbf{N}_1 & \mathbf{0} \\ \mathbf{N}_2 & \mathbf{N}_4 \end{pmatrix}, \quad (17a)$$

$$\mathbf{J} = \begin{pmatrix} \mathbf{J}_1 & \mathbf{J}_2 \\ \mathbf{0} & \mathbf{J}_4 \end{pmatrix}. \quad (17b)$$

We also define

$$\mathbf{e}(t, x) \approx \sum_{i=1}^p \mathbf{w}_{\mathbf{e}_i}(t) \phi_i(x) := \mathbf{W}_{\mathbf{e}}^T(t) \boldsymbol{\phi}(x),$$

$$\mathbf{u}(t, x) \approx \sum_{i=1}^p \mathbf{w}_{\mathbf{u}_i}(t) \phi_i(x) := \mathbf{W}_{\mathbf{u}}^T(t) \boldsymbol{\phi}(x),$$

and we note that the modes $\mathbf{W}_{\mathbf{e}}^T(t)$ are partitioned following the order given in (16c)

$$\mathbf{W}_{\mathbf{e}}^T(t) = \begin{pmatrix} \mathbf{W}_{\text{NL}}^T(t) \\ \mathbf{W}_{\text{L}}^T(t) \end{pmatrix} : \mathbb{R}_+ \rightarrow \mathbb{R}^{(k+(n-k) \times p)}.$$

B. Computation of the integrated response

The next Proposition gives conditions under which the coefficients of the series expansion of $\int_0^\infty \mathbf{e}_{\text{L}}(t, x) dt$ can be computed analytically.

Proposition 4.1: Consider a reaction-diffusion system of the form given in (13), such that

$$\mathbf{D}_1 = \mathbf{0} \quad (18a)$$

$$r = k. \quad (18b)$$

Then, provided a sufficiently large p and that the inverse $(-\lambda_i \mathbf{D}_4 + \mathbf{N}_4 \mathbf{J}_4)^{-1}$ exists for $i = 1, 2, \dots, p$, the series expansion of the time integral of the species in $\mathbf{e}_L(t, x)$ can be approximated by

$$\int_0^\infty \mathbf{e}_L(t, x) dt \approx \sum_{i=1}^p (-\lambda_i \mathbf{D}_4 + \mathbf{N}_4 \mathbf{J}_4)^{-1} \mathbf{M} \left(\mathbf{w}_{e_i}(0) + \mathbf{B} \int_0^\infty \mathbf{w}_{u_i} dt \right) \phi_i(x), \quad (19)$$

where

$$\mathbf{M} = (\mathbf{N}_2 \mathbf{N}_1^{-1} \quad -\mathbf{I}_{n-k}), \quad (20)$$

and the basis $\{\phi_i\}_{i=1, \dots, p}$ satisfies the conditions in Section III.

Proof: Firstly, we define

$$\begin{aligned} \mathbf{A} &= \mathbf{N} \mathbf{J} \\ &= \begin{pmatrix} \mathbf{N}_1 \mathbf{J}_1 & \mathbf{N}_1 \mathbf{J}_2 \\ \mathbf{N}_2 \mathbf{J}_1 & \mathbf{N}_2 \mathbf{J}_2 + \mathbf{N}_4 \mathbf{J}_4 \end{pmatrix} \\ \mathbf{A} &:= \begin{pmatrix} \mathbf{A}_{11} & \mathbf{A}_{12} \\ \mathbf{A}_{21} & \mathbf{A}_{22} \end{pmatrix}. \end{aligned}$$

Moreover, we note that, since we deal with an exponentially stable system, $\mathbf{e}(\infty) = \mathbf{0}$. Hence integration in time of (13) yields

$$\begin{aligned} \mathbf{0} - \mathbf{e}_0(x) &= \mathbf{D} \nabla_x^2 \int_0^\infty \mathbf{e} dt + \mathbf{A} \int_0^\infty \mathbf{e} dt + \\ &+ \mathbf{N}_{\text{NL}} \int_0^\infty \mathbf{g}(\mathbf{e}) dt + \mathbf{B} \int_0^\infty \mathbf{u} dt. \end{aligned} \quad (21)$$

Considering the partition of the state $\mathbf{e}(t, x)$ in (15) and $\mathbf{D}_1 = \mathbf{0}$, the equation above becomes

$$\begin{aligned} -\mathbf{e}_{\text{NL}0}(x) &= \mathbf{A}_{11} \int_0^\infty \mathbf{e}_{\text{NL}} dt + \mathbf{A}_{12} \int_0^\infty \mathbf{e}_L dt + \\ &+ \mathbf{N}_1 \int_0^\infty \mathbf{g}(\mathbf{e}) dt + \mathbf{B}_1 \int_0^\infty \mathbf{u} dt, \end{aligned} \quad (22a)$$

$$\begin{aligned} -\mathbf{e}_{L0}(x) &= \mathbf{D}_4 \nabla_x^2 \int_0^\infty \mathbf{e}_L dt + \mathbf{A}_{21} \int_0^\infty \mathbf{e}_{\text{NL}} dt + \\ &+ \mathbf{A}_{22} \int_0^\infty \mathbf{e}_L dt + \mathbf{N}_2 \int_0^\infty \mathbf{g}(\mathbf{e}) dt + \\ &+ \mathbf{B}_2 \int_0^\infty \mathbf{u} dt. \end{aligned} \quad (22b)$$

Since $\mathbf{e}_{\text{NL}}(t, x)$, $\mathbf{e}_L(t, x)$ and $\mathbf{u}(t, x)$ belong to the same Hilbert space, we can represent them as a truncated series in terms of the common basis $\phi(x)$. Substituting these signals by its series representation and postmultiplying by $\phi^T(x)$,

the foregoing expressions become

$$\begin{aligned} & - \mathbf{W}_{\text{NL}}^T(0) \phi \phi^T = \\ & \mathbf{A}_{11} \int_0^\infty \mathbf{W}_{\text{NL}}^T dt \phi \phi^T + \mathbf{A}_{12} \int_0^\infty \mathbf{W}_L^T dt \phi \phi^T + \\ & + \mathbf{N}_1 \int_0^\infty \mathbf{g}(\mathbf{e}) dt \phi^T + \mathbf{B}_1 \int_0^\infty \mathbf{W}_u^T dt \phi \phi^T, \quad (23) \\ & - \mathbf{W}_L^T(0) \phi \phi^T = \\ & \mathbf{D}_4 \int_0^\infty \mathbf{W}_{\text{NL}}^T dt \Lambda \phi \phi^T + \mathbf{A}_{21} \int_0^\infty \mathbf{W}_{\text{NL}}^T dt \phi \phi^T + \\ & + \mathbf{A}_{22} \int_0^\infty \mathbf{W}_L^T dt \phi \phi^T + \mathbf{N}_2 \int_0^\infty \mathbf{g}(\mathbf{e}) dt \phi^T + \\ & + \mathbf{B}_2 \int_0^\infty \mathbf{W}_u^T dt \phi \phi^T, \end{aligned} \quad (24)$$

where the invariance w.r.t the Laplacian operator in (8) has been used. By noting that the orthonormality of the basis $\phi(x)$ implies $\int_\Omega \phi \phi^T dx = \mathbf{I}_p$, integration over Ω yields

$$\begin{aligned} -\mathbf{W}_{\text{NL}}^T(0) &= \mathbf{A}_{11} \int_0^\infty \mathbf{W}_{\text{NL}}^T dt + \mathbf{A}_{12} \int_0^\infty \mathbf{W}_L^T dt + \\ &+ \mathbf{N}_1 \mathbf{F} + \mathbf{B}_1 \int_0^\infty \mathbf{W}_u^T dt \end{aligned} \quad (25a)$$

$$\begin{aligned} -\mathbf{W}_L^T(0) &= \mathbf{D}_4 \int_0^\infty \mathbf{W}_L^T dt \Lambda + \mathbf{A}_{21} \int_0^\infty \mathbf{W}_{\text{NL}}^T dt + \\ &+ \mathbf{A}_{22} \int_0^\infty \mathbf{W}_L^T dt + \mathbf{N}_2 \mathbf{F} + \mathbf{B}_2 \int_0^\infty \mathbf{W}_u^T dt, \end{aligned} \quad (25b)$$

where we have defined $\mathbf{F} = \int_\Omega \int_0^\infty \mathbf{g}(\mathbf{e}) \phi^T(\mathbf{x}) dt dx$.

Given the stability of \mathbf{A} , we can ensure that its inverse exists and consequently \mathbf{A}_{11} is nonsingular. Therefore, we can solve (25a) for $\int_0^\infty \mathbf{W}_{\text{NL}}^T(t) dt$:

$$\begin{aligned} \int_0^\infty \mathbf{W}_{\text{NL}}^T(t) dt &= -\mathbf{A}_{11}^{-1} \left(\mathbf{W}_{\text{NL}}^T(0) + \mathbf{A}_{12} \int_0^\infty \mathbf{W}_L^T dt \right. \\ &\left. + \mathbf{N}_1 \mathbf{F} + \mathbf{B}_1 \int_0^\infty \mathbf{W}_u^T dt \right). \end{aligned} \quad (26)$$

Since $r = k$, $\mathbf{A}_{11}^{-1} = \mathbf{J}_1^{-1} \mathbf{N}_1^{-1}$ and the equation above becomes

$$\begin{aligned} \int_0^\infty \mathbf{W}_{\text{NL}}^T(t) dt &= -\mathbf{A}_{11}^{-1} \mathbf{W}_{\text{NL}}^T(0) - \\ &\mathbf{J}_1^{-1} \mathbf{J}_2 \int_0^\infty \mathbf{W}_L^T dt - \mathbf{J}_1^{-1} \mathbf{F} - \mathbf{A}_{11}^{-1} \mathbf{B}_1 \int_0^\infty \mathbf{W}_u^T dt. \end{aligned} \quad (27)$$

Substituting the Equation above in (25b) and simplifying, yields

$$\begin{aligned} \mathbf{0}_{n \times p} &= \mathbf{D}_4 \int_0^\infty \mathbf{W}_L^T dt \Lambda + \mathbf{N}_4 \mathbf{J}_4 \int_0^\infty \mathbf{W}_L^T dt \\ &- \mathbf{M} \left(\mathbf{W}_e^T(0) + \mathbf{B} \int_0^\infty \mathbf{W}_u^T dt \right), \end{aligned} \quad (28)$$

where \mathbf{M} is as in (20). We further consider the i^{th} column of the matrix expression above:

$$\mathbf{0}_{n \times 1} = (-\lambda_i \mathbf{D}_4 + \mathbf{N}_4 \mathbf{J}_4) \int_0^\infty \mathbf{w}_{\mathbf{L}i} dt - \mathbf{M} \left(\mathbf{w}_{\mathbf{e}i}(0) + \mathbf{B} \int_0^\infty \mathbf{w}_{\mathbf{u}i} dt \right), \quad (29)$$

solving for $\int_0^\infty \mathbf{w}_{\mathbf{L}i} dt$, leads to

$$\int_0^\infty \mathbf{w}_{\mathbf{L}i} dt = (-\lambda_i \mathbf{D}_4 + \mathbf{N}_4 \mathbf{J}_4)^{-1} \mathbf{M} \left(\mathbf{w}_{\mathbf{e}i}(0) + \mathbf{B} \int_0^\infty \mathbf{w}_{\mathbf{u}i} dt \right). \quad (30)$$

Multiplying each column by $\phi_i(x)$ and summing over all i (see Equation 9), gives the expression in (19). ■

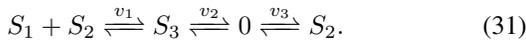
The result in Proposition 4.1 is two-fold. Firstly, it identifies a class of nonlinear networks for which the coefficients of the truncated series of the time-integral can be computed analytically. Secondly, it gives closed-form expressions for these coefficients in terms of the model parameters, initial conditions and the integral of the input.

V. CASE STUDY

In this section we illustrate our results with a simple reaction-diffusion network. The model describes two species forming a complex, which is also synthesized and degraded independently.

A. Model definition

Consider the network



We model the binding process by means of a power-law reaction rate and consider a synthesis and degradation for S_2 and S_3 . We assume that S_1 is a heavy molecule or that is attached to a fixed location and hence its diffusion is negligible. The reaction-diffusion model for this networks dynamics is

$$\begin{aligned} \frac{\partial}{\partial t} c_1 &= -k_{1f} c_1^{g_1} c_2^{g_2} + k_{1b} c_3, \\ \frac{\partial}{\partial t} c_2 &= d_2 \nabla_x^2 c_2 - k_{1f} c_1^{g_1} c_2^{g_2} + k_{1b} c_3 - k_{2f} c_2 + k_{2b}, \\ \frac{\partial}{\partial t} c_3 &= d_3 \nabla_x^2 c_3 + k_{1f} c_1^{g_1} c_2^{g_2} - k_{1b} c_3 - k_{3f} c_3 + k_{3b}. \end{aligned}$$

We consider the initial conditions

$$\begin{pmatrix} c_1(0, x) \\ c_2(0, x) \\ c_3(0, x) \end{pmatrix} = \begin{pmatrix} \bar{c}_1 \cos(\alpha \pi x) + \bar{c}_1 \\ \bar{c}_2 \\ \bar{c}_3 \end{pmatrix}, \quad \alpha \in \mathbb{N},$$

and homogeneous Neumann boundary conditions

$$\left. \frac{\partial \mathbf{c}(t, x)}{\partial \mathbf{n}} \right|_{x=\partial\Omega} = 0,$$

with $\Omega = [0, 1]$. This reaction network only has one homogeneous equilibrium point given by

$$\bar{\mathbf{c}} = \begin{pmatrix} \sqrt[2]{\frac{k_{1b} k_{3b}}{k_{1f} k_{3f}} \left(\frac{k_{2f}}{k_{2b}} \right)^{g_2}} \\ k_{2b}/k_{2f} \\ k_{3b}/k_{3f} \end{pmatrix}.$$

We partition the species vector as in (11) and (16). Let $\mathbf{c} = ([S_1] \mid [S_2] \mid [S_3])^T$ and $\mathbf{v}(\mathbf{c}) = (v_1 \mid v_2 \mid v_3)^T$ with

$$\mathbf{v}(\mathbf{c}) = (k_{1f} c_1^{g_1} c_2^{g_2} - k_{1b} c_3 \mid k_{2f} c_2 - k_{2b} \mid k_{3f} c_3 - k_{3b})^T. \quad (32)$$

The stoichiometric matrix, Jacobian, and diffusion matrix are

$$\mathbf{N} = \left(\begin{array}{c|cc} -1 & 0 & 0 \\ -1 & -1 & 0 \\ 1 & 0 & -1 \end{array} \right), \quad (33a)$$

$$\mathbf{J} = \left(\begin{array}{cc|cc} k_{1f} g_1 \bar{c}_1^{g_1-1} \bar{c}_2^{g_2} & & k_{1f} g_2 \bar{c}_1^{g_1} \bar{c}_2^{g_2-1} & -k_{1b} \\ 0 & & k_{2f} & 0 \\ 0 & & 0 & k_{3f} \end{array} \right), \quad (33b)$$

$$\mathbf{D} = \left(\begin{array}{c|cc} 0 & 0 & 0 \\ 0 & d_2 & 0 \\ 0 & 0 & d_3 \end{array} \right). \quad (33c)$$

B. Calculation of the integral

The species S_1 appears only in a nonlinear rate ($k = 1$), and the model contains $r = 1$ nonlinear reaction rates. Moreover, S_1 does not diffuse, and therefore the conditions in (18) in Proposition 4.1 are satisfied.

The functions

$$\begin{aligned} \phi_i(x) &= k_i \cos(\pi(i-1)x) \\ k_i &= \begin{cases} 1 & , i = 1 \\ \sqrt{2} & , i \neq 1 \end{cases} \end{aligned}$$

satisfy (8) and form an orthogonal basis for $\Omega = [0, 1]$ with homogeneous Neumann boundary conditions. The eigenvalues in (8) are

$$\lambda_i = [\pi(i-1)]^2 \quad \forall i = 1, 2, \dots, p.$$

In the deviation coordinates $\mathbf{e} = \mathbf{c} - \bar{\mathbf{c}}$, the initial conditions are

$$\begin{pmatrix} e_1(0, x) \\ e_2(0, x) \\ e_3(0, x) \end{pmatrix} = \begin{pmatrix} \bar{c}_1 \cos(\alpha \pi x) \\ 0 \\ 0 \end{pmatrix},$$

and hence, all the columns of the matrix $\mathbf{W}_{\mathbf{e}}^T(0)$ are zero, except the $(\alpha + 1)$ th column, which is

$$\mathbf{w}_{\mathbf{e}}(0)_{\alpha+1} = \begin{pmatrix} \bar{c}_1 \\ \sqrt{2} & 0 & 0 \end{pmatrix}^T.$$

From the expression above and the definitions in (33) and (20), the temporal integral of $\mathbf{e}_{\mathbf{L}}(t, x)$ is given by (19):

$$\int_0^\infty \mathbf{e}_{\mathbf{L}}(t, x) dt = \frac{\bar{c}_1}{\sqrt{2}} \begin{pmatrix} [(\alpha \pi)^2 d_2 + k_{2f}]^{-1} \\ [(\alpha \pi)^2 d_3 + k_{3f}]^{-1} \end{pmatrix} \cos(\alpha \pi x). \quad (34)$$

The left column of Figure 2 depicts the simulation of the reaction network in (31), whereas the right column shows the comparison of the numerical integration after simulation and the formula in (34). It is noteworthy that, despite having a complex dynamical behaviour, the expressions for the integrals in time of $e_2(t, x)$ and $e_3(t, x)$ are simple.

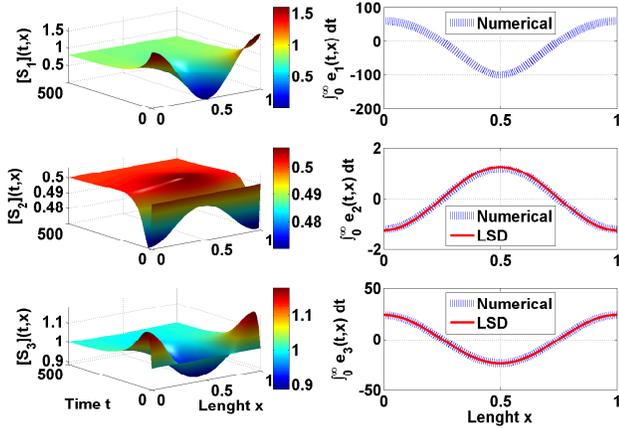


Fig. 2. Dynamics of the species in the case study and their integrals in time. The left column shows the spatiotemporal dynamics of the reactions in (31). The right column shows the comparison of the analytical calculation (Continuous line) and the numerical integration after simulation (Discontinuous line). The parameters used are $\{k_{1f}, k_{1b}, k_{2b}, k_{3f}, k_{3b}, k_{3f}, g_1, g_2\} = \{0.01, 0.005, 0.05, 0.025, 0.03, 0.03, 2, 0.35\}$, $\{d_2, d_3\} = \{0.015, 0.0001\}$, $\alpha = 2$.

VI. CONCLUSIONS AND OUTLOOK

In this paper we addressed the derivation of the time-integrals of species concentrations in reaction-diffusion systems. We define a class of systems where the species that appear *exclusively* on nonlinear reactions are equal to the number of nonlinear reactions and do not diffuse. Under these conditions we obtained an analytical formula for the integral in time of the rest of the species trajectories. We remark that we do not assume any prescribed functional form for the nonlinear reaction rates.

In order to obtain the formula, we exploited the Laplacian Spectral Decomposition method to find a finite set of ODEs associated to the original PDEs set, which allow us to find the integral of some species as an algebraic problem. The formula that describes the temporal integral of these species is expressed as a weighted series in terms of the elements

of the basis of the Hilbert space to which the trajectories of the reaction diffusion system belong.

Cases of interest include the interaction of species where some diffusive coefficients can be neglected due to their difference in molecular size or because they are bound to cellular membrane, such as the case of membrane receptors. Time-integrals of chemical species have been successfully used to quantify the signal transmission in diffusionless networks [8], [10], and therefore our work provides the initial step for such studies in systems where molecular diffusion is important. The extension of our results in terms the relationship between biophysical parameters, signal transmission and frequency response will be reported in an upcoming paper.

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