Nonnegative Dynamics in Nonlocal Models Reaction Networks and Spatial Extensions

Theses of the PhD Dissertation

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1 Introduction

1.1 Nonnegative and kinetic systems

Nonnegative systems form an important subclass within dynamical systems, characterized by the property that the solution stays nonnegative for nonnegative initial values. Their theoretical development is motivated by applications in chemistry, biology, population and disease dynamics, where state variables in their original physical coordinates are naturally nonnegative [17].

Compartmental models describe the distribution and transport of entities (for example molecules, particles, vehicles, people, or information) among distinct storage compartments over time [17]. These compartments may represent physically separate subsystems, such as interconnected containers, or conceptual states, such as different stages of a disease in epidemiological models. Accordingly, the applicability of compartmental systems is rather wide including (bio)chemistry, pharmacokinetics, ecological, epidemiological and transportation modeling. Since the state variables in compartmental systems correspond to amounts, concentrations, or numbers of molecules, these models inherently belong to the nonnegative system class.

The fundamental properties of compartmental models have been extensively studied, particularly regarding observability, controllability, realizability, and identifiability [18]. Linear compartmental ODEs and their analytic solutions have been analyzed in kinetic contexts, while qualitative properties of general nonlinear compartmental models, including equilibrium structures and stability, are discussed in [19]. The strong descriptive power of compartmental models allows them to represent numerous complex dynamical phenomena [18]. Their associated directed graph structures (compartmental graphs) provide insights into dynamical properties [19].

An important related family of models is the class of chemical reaction networks (CRNs) or kinetic systems. CRNs are dynamical models formally represented by transformations (reactions) between abstract chemical complexes [20]. While originating in physical chemistry, CRNs have been mathematically generalized, broadening their applicability to non-chemical processes. The scope of reaction networks reaches far beyond the (bio)chemical application field, since they can be considered as general descriptors of nonlinear dynamics capable of producing complex dynamical phenomena such as multiple equilibria, nonlinear

oscillations, limit cycles, and even chaos [21]. Many compartmental models, such as those used in population dynamics or epidemiology, can naturally be represented in kinetic form, and other non-chemically motivated models can often be algorithmically transformed into reaction networks [22].

Chemical reaction network theory (CRNT) provides deep results on the relationship between network structure and qualitative dynamics [20]. A central problem in CRNT is persistence analysis, which is crucial for proving the global asymptotic stability of complex balanced networks in which, at equilibrium, the total rate of reactions entering each complex equals the total rate leaving it [23]. Stability in mass-action CRNs is typically analyzed using entropy-like logarithmic Lyapunov functions [24]. A major conjecture in CRNT, the "Global Attractor Conjecture," asserts that complex balanced kinetic systems are globally stable within the nonnegative orthant [25]. This was proven for networks with a single connected reaction graph component [23]. Related stability results for zero-deficiency networks extend beyond mass-action kinetics, allowing time-varying rate coefficients and generalized Lyapunov functions [26]. The stability analysis of ribosome flow models (RFMs) via CRN representation has also been identified as an important research direction [27, 28].

1.2 Conservation laws

Local conservation and balance laws have been widely applied in aerodynamics, Eulerian gas dynamics [29], traffic modeling [30], and ribosome flows [28]. Recently, nonlocality has been incorporated into these models to capture more realistic dynamics. A common approach is to define a nonlocal velocity using a spatial convolution, which has been applied to supply chain modeling [31] and traffic flows [32]. However, some nonlocal models fail to preserve monotonicity or violate the maximum principle. Alternative formulations using integral kernels have been explored to address these issues [33, 34]. Peridynamics and other spatial nonlocal models have also been developed [35]. A key advantage of nonlocal pair-interaction models is their reduction to local counterparts as the nonlocal horizon vanishes [36], which is not always true for other nonlocal models. Due to these advantages, nonlocal models are widely applied in peridynamics [37] and in the formulation of the nonlocal Allen-Cahn equation [38].

1.3 Quantum graphs

In recent decades differential operators on metric graphs, often called quantum graphs, have found a myriad of applications when describing quasi-one-dimensional phenomena in a broad range of fields, such as superconductivity in granular materials [39], classical wave propagation in wave guide networks [40], membrane potential of neurons [41], cell differentiation [42], and optimal control [43]. These applications can be seen, from a modelling point of view, as compartmental models, where the transitions are explicitly described by partial differential equations.

2 Aims and scope of the dissertation

Based on the above introduction, the aims of my doctoral research are as follows.

2.1 Nonlocal conservation laws

We study the semigroup theory of nonlocal conservation laws of the form

$$\begin{aligned} &\frac{\partial u}{\partial t} + \int_{\mathbb{R}^n} \sum_{i=1}^{k} \frac{\phi_i(u, \tau_{\beta_i(h)}u) - \phi_i(\tau_{-\beta_i(h)}u, u)}{\|\beta_i(h)\|_{\mathbb{R}^n}} \omega_i\big(\beta_i(h)\big)\,\mathrm{d}h = 0, \text{ in } \mathbb{R}^n \times \mathbb{R}_+; \\ &u(x,0) = u_0(x), \qquad\qquad x \in \mathbb{R}, \end{aligned} \tag{1}$$

where $\tau_{\pm h}u(x,t) = u(x \pm h, t)$ denote a spatial shift of the conserved quantity $u(x,t)$ and the flux functions $\phi_i : \mathbb{R} \times \mathbb{R} \mapsto \mathbb{R}$ are assumed to be increasing with respect to their first arguments and decreasing with respect to their second arguments, and to have the property $\phi_i(0,0) = 0$. The number $1 \leq k \leq n$ denotes the number of subinteractions and the functions $\beta_i : \mathbb{R}^n \mapsto \mathbb{R}^n$ are assumed to be of the form

$$\beta_i(h) = \sum_{j \in B_i} h_j e_j, \qquad h = (h_1, h_2, \ldots, h_n), \tag{2}$$

where the nonempty, pairwise disjoint sets $B_i \subset \{1, 2, \ldots, n\}$ are such that $\bigcup_{i=1}^{k} B_i = \{1, 2, \ldots, n\}$ and e_j denotes the jth unit vector in $\mathbb{R}^n$. The kernel functions $\omega_i \in \mathcal{L}^1(\mathbb{R}^n) \cap \mathcal{L}^\infty(\mathbb{R}^n)$ are assumed to be nonnegative with $\big\|\omega_i\big(\beta_i(.)\big)\big\|_{\mathcal{L}^1(\mathbb{R}^n)} = 1$. We further assume that the support of the kernel functions are finite and are either

1. symmetric around the origin, in which case we further assume that the kernels are even, or
2. contained in $\mathbb{R}^n_+$ such that the closure contains the origin.

Our goal was to prove the well-posedness of the multidimensional nonlocal pair-interaction via semigroup theory. While well-posedness in one-dimension was proved in [44] with a different method, the existence of an underlying operator semigroup is an important advancement, as well as the generalization to multiple dimensions. The results are presented in Chapter 3 of the dissertation.

2.2 Dynamical analysis of generalized ribosome flows

Let us consider a one-dimensional version of the nonlocal flow (1). Nonlocality is formally introduced as a continuum average of the finite difference approximation weighted with a bounded and nonnegative nonlocal interaction kernel $\omega \in \mathcal{L}^1(\mathbb{R})$ supported on $(0, \delta)$ with $\delta > 0$ and $\|\omega\|_{\mathcal{L}^1(\mathbb{R})} = 1$, as follows:

$$\begin{aligned} &\frac{\partial \rho}{\partial t} + \int_0^\delta \frac{F(\rho, \tau_h \rho) - F(\tau_{-h}\rho, \rho)}{h} \omega(h)\, \mathrm{d}h = r - s; \\ &\rho(x, 0) = \rho_0(x), \end{aligned} \tag{3}$$

where $\rho : \mathbb{R} \times (0, T) \mapsto \overline{\mathbb{R}}_+$ is the conserved quantity at a given point and at a given time, $F : \mathbb{R} \times \mathbb{R} \mapsto \mathbb{R}$ is the flux function, $\tau_{\pm h}\rho(x, t) = \rho(x \pm h, t)$ denotes a spatial shift and $r, s : \mathbb{R} \times (0, t) \times \overline{\mathbb{R}}_+ \mapsto \overline{\mathbb{R}}_+$ are the source and sink terms, respectively.

After an appropriate spatial discretization with a finite volume method we obtain a formally kinetic system. Let N_i and S_i denote particles and available space slots for particles in the ith cell, respectively. Furthermore, let f_i and b_i denote the number of cells affected by the ith cell and the number of cells affecting the ith cell. Then the particle flow can be represented as transformations of complexes (that is, as reactions) as follows:

$$N_{i-j} + S_i \xrightarrow{k_{i-j,i}} N_i + S_{i-j} \qquad j = 1, 2, \ldots, b_i \tag{4}$$

$$N_i + S_{i+j} \xrightarrow{k_{i,i+j}} N_{i+j} + S_i \qquad j = 1, 2, \ldots, f_i \tag{5}$$

$$S_i \xrightarrow{k_{in,i}} N_i \tag{6}$$

$$N_i \xrightarrow{k_{out,i}} S_i. \tag{7}$$

Reaction (4) shows that during the particles' transition from the $(i-j)$th cell to the ith cell the available spaces increase in the $(i-j)$th cell and decrease in the ith cell, while the number of particles decrease in the $(i-j)$th cell and increase in the ith cell. Reaction (5) expresses the same transition from the ith cell to the $(i+j)$th cell. Finally, reactions (6) and (7) show the behaviour of in- and out-flows. Note that (4) and (5) are redundant when enumerating all reactions.

If $f_i = b_i = 1$ and we consider the flux function $F(u,v) = u(1-v)$ corresponding to mass action kinetics, then the above system is formally equivalent to ribosome flow models [27]. We further generalize the above system in three ways. First, we allow arbitrary interconnection structure, altough most of our results hold for strongly connected structures. Second, we allow a wide range of transition rate functions and we only impose assumptions in accordance with the physical constraints of the flux function of (3). Finally, we also consider time-varying transition rates. The persistence and stability results are presented in Chapter 4 of the dissertation.

2.3 Stability analysis of delayed complex balanced CRNs

A kinetic model contains N species denoted by $\mathcal{X} = \{X_1, X_2, \ldots, X_N\}$, and the corresponding species vector is given as $X = [X_1 \; X_2 \; \ldots \; X_N]^\top$. Species are transformed into each other through elementary reaction steps of the form

$$C_k \xrightarrow{\mathcal{K}_k} C_{k'}, \quad k = 1, 2, \ldots, M, \tag{8}$$

where $C_k = y_k^\top X$ and $C_{k'} = y_{k'}^\top X$ are the complexes with the stoichiometric coefficient vectors $y_k, y_{k'} \in \overline{\mathbb{Z}}_+^N$ for $k = 1, 2, \ldots, M$. The transformation shown in Eq. (8) means that during an elementary reaction step between the C_k reactant complex and $C_{k'}$ product complex $[y_k]_i$ molecules of species X_i are consumed, and $[y_{k'}]_i$ molecules of X_i are produced for $i = 1, 2, \ldots, N$. The reaction (8) is called an input (output) reaction of species X_i if $[y_{k'}]_i > 0$ ($[y_k]_i > 0$).

Let $x(t) \in \overline{\mathbb{R}}_+^N$ denote the state vector corresponding to X for any $t \geq 0$ (in a chemical context, the state x is the vector of concentrations of the species in X). Then the ODEs describing the evolution of x in

the kinetic system containing the reactions (8) are given by

$$\dot{x} = \sum_{k=1}^{M} \mathcal{K}_k(x)[y_{k'} - y_k], \quad x(0) \in \overline{\mathbb{R}}_+^N, \tag{9}$$

where $\mathcal{K}_k : \overline{\mathbb{R}}_+^N \longrightarrow \overline{\mathbb{R}}_+$ is the rate function corresponding to reaction step k, determining the velocity of the transformation [20]. We impose standard assumptions on the rate functions to ensure the local existence and uniqueness of solutions as well as the invariance of the nonnegative orthant for the dynamics in Eq. (9).

An important special case in the theory of CRNs is mass action kinetics when the rate function is given in the following monomial form

$$\mathcal{K}_k(x) = \kappa_k \prod_{i=1}^{N} x_i^{[y_k]_i}, \quad k = 1, 2, \ldots, M \tag{10}$$

where $k_i > 0$ for $i = 1, 2, \ldots, M$ are the reaction rate coefficients; that is, the dynamics of mass action kinetic systems can be given as

$$\dot{x}(t) = \sum_{k=1}^{M} \kappa_k x^{y_k}(t)\big(y_{k'} - y_k\big). \tag{11}$$

Stability of systems of the form (11) can be investigated through the entropy-like logarithmic Lyapunov function

$$V(x, \overline{x}) = \sum_{i=1}^{N} \left(x_i \log \frac{x_i}{\overline{x}_i} + \overline{x}_i - x_i \right), \tag{12}$$

where $\overline{x}$ is a positive equilibrium.

We aim to generalize certain stability results to include non-mass action cases like the Michaelis-Menten kinetics or general Hill-type kinetics, and discrete time delays, while still relying on a similar Lyapunov function(al). The main motivation behind introducing delays is, for example, to substitute not explicitly modeled subsystems or reaction cascades. In order to do so, we consider kinetic systems of the form

$$\dot{x}(t) = \sum_{k=1}^{M} \kappa_k \Big(\gamma^{y_k}\big(x(t - \tau_k)\big) y_{k'} - \gamma^{y_k}\big(x(t)\big) y_k \Big), \tag{13}$$

where $\tau_k \geq 0$ are discrete constant time delays and the function $\gamma : \overline{\mathbb{R}}_+^N \mapsto \overline{\mathbb{R}}_+^N$ is defined element-wise by the increasing functions $\gamma_i \in$

$C^1(\mathbb{R})$. This class of systems include a wide variety of interesing and relevant kinetics, while the product structure of $\gamma^{y_k}(x)$ allows us to rely on logarithmic identities in the calculations. In particular, the Michaelis-Menten kinetics can be given by $\gamma_i(s) = \frac{s}{c_i+s}$ for $c_i > 0$, and more general Hill kinetics can be given by $\gamma_i(s) = \frac{s^{n_i}}{c_i+s^{n_i}}$ for $c_i > 0$ and $n_i > 0$.

Our hypothesis is that asymptotic stability w.r.t. the positive stoichiometric compatibility classes can be derived, as in the mass action case. The results are presented in Chapter 2 of the dissertation.

2.4 PIDE model for gene regulatory networks

We consider a gene regulatory network consisting of n different genes, denoted by $G = \{DNA_1, DNA_2, \dots, DNA_n\}$, that express n proteins $X = \{X_1, X_2, \dots, X_n\}$ via the corresponding messenger RNAs $M = \{mRNA_1, mRNA_2, \dots, mRNA_n\}$. We follow the central dogma of molecular biology, which asserts that the gene instructions are transcribed into messenger RNAs, that are translated into proteins. The continuous number of mRNA molecules and proteins are denoted by $\boldsymbol{m}, \boldsymbol{x} \in \mathbb{R}^n$, respectively. The promoters corresponding to each gene are assumed to switch between active and inactive states, denoted by $DNA_{i,\text{on}}$ and $DNA_{i,\text{off}}$, respectively. The transition is controlled by the binding of proteins. Note that in general, the feedback mechanism may require the binding of multiple types of proteins besides the one expressed by the given gene. For the sake of generality, we assume that any protein can repress or activate any gene in the network. This mechanism is typically modelled by multivariate Hill functions.

With the above assumptions the probability density function (PDF) of the protein level, $p(t, \boldsymbol{x})$, can be modelled with the following PIDE:

$$\begin{aligned}\frac{\partial p(t,\boldsymbol{x})}{\partial t} &= \sum_{i=1}^{n} \frac{\partial}{\partial x_i}\left[\gamma_x^i(\boldsymbol{x}) x_i p(t,\boldsymbol{x})\right] \\ &\quad + \sum_{i=1}^{n} k_m^i \int_0^{x_i} \beta_i(x_i - y_i) c_i(\boldsymbol{y_i}) p(t, \boldsymbol{y_i}) \,\mathrm{d}y_i \,,\end{aligned} \tag{14}$$

where $\boldsymbol{y_i} = \boldsymbol{x} + (y_i - x_i)e_i$, the c_i functions are general Hill functions and the β_i functions have the following form:

$$\beta_i(x) = \frac{1}{b_i} \exp\left[-\frac{x_i}{b_i}\right] - \delta(x). \tag{15}$$

Here the terms corresponds to protein degradation and protein bursting, respectively.

After an appropriate spatial discretization with a finite volume method we obtain a formally kinetic system with a strongly connected structure. While the main motivation was an efficient simulation technique, the discretization turns out to be benefitial for qualitative analysis too. The results are presented in Chapter 5 of the dissertation.

2.5 Domain decomposition methods for elliptic problems on metric graphs

We consider a quantum graph; that is, a metric graph G equipped with an elliptic differential operator on each edge and certain standard vertex conditions. The graph consists of a finite set V of vertices and a finite set E of edges connecting pairs of vertices. We assume that the graph is simple and does not contain parallel edges or loops. Let $n = |\mathsf{V}|$ denote the number of vertices and $m = |\mathsf{E}|$ the number of edges. We assume that the graph is directed; that is, each edge has a specified (but otherwise arbitrary) orientation, and thus an origin and a terminal vertex. Each edge $\mathsf{e} \in \mathsf{E}$ is assigned a length $\ell_\mathsf{e} \in (0, \infty)$ and a local coordinate $x \in [0, \ell_\mathsf{e}]$.

A function u on a metric graph G can be defined as a vector of functions and we write $u = (u_\mathsf{e})_{\mathsf{e}\in\mathsf{E}}$, and consider it to be an element of a product function space, to be specified later. Let $u_\mathsf{e}(\mathsf{v})$ denote the value of u at $\mathsf{v} \in \mathsf{V}$ along the edge $\mathsf{e} \in \mathsf{E}$.

To define the vertex conditions, let us denote by E_v the set of edges incident to the vertex $\mathsf{v} \in \mathsf{V}$, and by $d_\mathsf{v} = |\mathsf{E}_\mathsf{v}|$ the degree of $\mathsf{v} \in \mathsf{V}$. We denote by $\mathrm{int}(\mathsf{G})$ the set of vertices with degree $d_\mathsf{v} > 1$ and by $\partial\mathsf{G}$ the set $\mathsf{V}\backslash\mathrm{int}(\mathsf{G})$. We seek solutions that are continuous on G and satisfy the Neumann-Kirchhoff (often called standard) condition, given as

$$\sum_{\mathsf{e}\in\mathsf{E}_\mathsf{v}} u'_\mathsf{e}(\mathsf{v}) = 0, \qquad \mathsf{v} \in \mathsf{V}, \tag{16}$$

where the derivatives are assumed to be taken in the directions away from the vertex. When there are (variable) diffusion coefficients or conductances present, represented by the function $c = (c_\mathsf{e})_{\mathsf{e}\in\mathsf{E}}$ defined on the graph, the Neumann-Kirchhoff condition is defined as

$$\sum_{\mathsf{e}\in\mathsf{E}_\mathsf{v}} c_\mathsf{e}(\mathsf{v}) u'_\mathsf{e}(\mathsf{v}) = 0, \qquad \mathsf{v} \in \mathsf{V}. \tag{17}$$

If $d_{\mathsf{v}} = 1$, then this reduces to the classical zero Neumann boundary condition.

In order to write the vertex conditions more compactly, let us define the vector of function values at $\mathsf{v} \in \mathsf{V}$ as

$$U(\mathsf{v}) = \big(u_e(\mathsf{v})\big)_{\mathsf{e}\in\mathsf{E}_{\mathsf{v}}} \in \mathbb{R}^{d_{\mathsf{v}}} \tag{18}$$

and the bi-diagonal matrix

$$I_{\mathsf{v}} = \begin{bmatrix} 1 & -1 & & \\ & \ddots & \ddots & \\ & & 1 & -1 \end{bmatrix} \in \mathbb{R}^{(d_{\mathsf{v}}-1)\times d_{\mathsf{v}}}. \tag{19}$$

Then $I_{\mathsf{v}}U(\mathsf{v}) = 0 \in \mathbb{R}^{d_{\mathsf{v}}-1}$ implies that the function values along the edges in E_{v} coincide at $\mathsf{v} \in \mathsf{V}$. Similarly, we define

$$U'(\mathsf{v}) = \big(u'_e(\mathsf{v})\big)_{\mathsf{e}\in\mathsf{E}_{\mathsf{v}}} \in \mathbb{R}^{d_{\mathsf{v}}}, \tag{20}$$

the vector of function derivative at $\mathsf{v} \in \mathsf{V}$ and the row vector

$$C(\mathsf{v})^\top = \Big(c_{\mathsf{e}_1}(\mathsf{v})\ c_{\mathsf{e}_2}(\mathsf{v})\ \dots\ c_{\mathsf{e}_{d_{\mathsf{v}}}}(\mathsf{v})\Big) \in \mathbb{R}^{1\times d_{\mathsf{v}}}. \tag{21}$$

Then $C(\mathsf{v})^\top U'(\mathsf{v}) = 0$ implies that the function u satisfies the Neumann-Kirchhoff conditions at $\mathsf{v} \in \mathsf{V}$.

Then a quantum graph can be formally written as

$$\begin{cases} -(c_{\mathsf{e}}u'_{\mathsf{e}})'(x) + p_{\mathsf{e}}(x)u_{\mathsf{e}}(x) = f_{\mathsf{e}}(x), & x \in (0,\ell_{\mathsf{e}}),\ \mathsf{e} \in \mathsf{E}, \quad (a) \\ 0 = I_{\mathsf{v}}U(\mathsf{v}), & \mathsf{v} \in \operatorname{int}(\mathsf{G}), \quad (b) \\ 0 = C(\mathsf{v})^\top U'(\mathsf{v}), & \mathsf{v} \in \mathsf{V}, \quad (c) \end{cases} \tag{22}$$

where the function $p = (p_{\mathsf{e}})_{\mathsf{e}\in\mathsf{E}}$ represents a potential.

We wish to approximate the solution of (22) in a finite element framework. In [45] a special finite element is assigned to the vertices that have a star shaped support on the neighbouring edges ensuring the continuity of solutions, and use standard finite elements on the edges. Then the authors prove usual error estimates and an upper bound for the Neumann-Kirchhoff residual of the discrete solution. However, the size of the corresponding stiffness matrix can grow quickly and it loses its banded (tridiagonal) nature compared to one-dimensional problems. Our goal is to design a nonoverlapping domain decomposition method to mitigate these problems. The results are presented in Chapter 6 of the dissertation.

3 New scientific results

Thesis I.

I have shown that a class of multidimensional nonlocal conservation laws are well-posed for a broad class of flux functions and initial data, using the theory of nonlinear operator semigroups. I have also shown that the unique mild solution satisfies a Kružkov-type nonlocal entropy inequality, along with several desirable qualitative properties.
The results are described in detail in Chapter 3.
Related publication: [7].

Thesis II.

I have proven new results regarding two important classes of kinetic dynamical systems.

Thesis II.a

I have introduced generalized ribosome flows (GRFs) by generalizing the graph structure and the transition rate functions of existing ribosome flow models in the literature. I have shown that GRFs can be interpreted as finite volume approximations of nonlocal conservation laws. I have proven that GRFs with a strongly connected compartmental structure are asymptotically stable relative to the level sets of the linear conserved quantity. I have proven that strongly connected GRFs with time-varying transition rates are persistent and input-to-state stable.
The results are described in detail in Chapter 4.
Related publications: [3, 4, 5, 6][13].

Thesis II.b

I have shown that delayed complex balanced reaction networks with non-mass action kinetics are quasi-thermostatic; that is, each positive stoichiometric compatibility class contains a unique equilibrium point. I have shown that delayed complex balanced reaction networks with non-mass action kinetics are quasi-thermodynamic; that is, each positive equi-

librium is asymptotically stable relative to its compatibility class.
The results are described in detail in Chapter 2.
Related publication: [11].

Thesis III.

I have proposed an efficient finite volume discretization of the multidimensional PIDE model of gene regulatory networks that result in a kinetic system. I have shown that the semidiscretized model has a unique steady-state, which is globally asymptotically stable. I have used the semidiscretized model to design novel population level exogenous controllers that can drive the expected value of the system to desired values.
The results are described in detail in Chapter 5.
Related publications: [8][14, 16].

Thesis IV.

I have developed a Neumann-Neumann type nonoverlapping domain decomposition method for elliptic problems on metric graphs. I have proven that the iteration converges to the finite element solution with a geometric rate that is independent of the mesh size, via the theory of abstract additive Schwarz methods.
The results are described in detail in Chapter 6.
Related publication: [10].

4 Future plans

The above results can serve as the base for several further research directions, including:

- The results of Chapter 2 can be used to investigate the stability of complex balanced systems with distributed delays. A major shortcoming of the model class is that a given species has a fixed reaction rate function associated with it. Thus, it is not possible, for example, that a species is involved in a reaction with mass-action kinetics and involved in an other reaction with Hill kinetics.

To our knowledge, this is not handled in the literature yet, thus it would be an important extension.

- The results of Chapter 4 can be used to investigate ribosome flow models with not strongly connected compartmental structure, or with discrete delays or distributed delays. Flows open to the environment can also be investigated and used to solve control problems motivated by real-world examples.

- The results of Chapter 5 can be used to implement the finite volume discretization for gene regulatory networks with more than two proteins. The discretization can also be used for model reduction and further control.

- The results of Chapter 6 can be used to implement the Neumann-Neumann iteration for decomposition where the domains are not edges. The theoretical results can be used to prove the convergence of overlapping decompositions. These iterations can be used to solve further problems, for example, the efficient generation of Gaussian Whittle-Matérn fields on metric graphs. The key problem there is white noise realization, since that requires the assembly of the mass matrix and its Cholesky decomposition. This could be mitigated with the lumped mass method, where a diagonal approximation of the mass matrix is used, in which case white noise generation can be performed domain-wise.

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