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ANALYTICAL SINGULAR VALUE DECOMPOSITION FOR A CLASS OF STOICHIOMETRY MATRICES*

JACQUELINE WENTZ†, JEFFREY C. CAMERON‡, AND DAVID M. BORTZ†

Abstract. We present the analytical singular value decomposition of the stoichiometry matrix for a spatially discrete reaction-diffusion system. The motivation for this work is to develop a matrix decomposition that can reveal hidden spatial flux patterns of chemical reactions. We consider a 1D domain with two subregions sharing a single common boundary. Each of the subregions is further partitioned into a finite number of compartments. Chemical reactions can occur within a compartment, whereas diffusion is represented as movement between adjacent compartments. Inspired by biology, we study both (1) the case where the reactions on each side of the boundary are different and only certain species diffuse across the boundary and (2) the case where reactions and diffusion are spatially homogeneous. We write the stoichiometry matrix for these two classes of systems using a Kronecker product formulation. For the first scenario, we apply linear perturbation theory to derive an approximate singular value decomposition in the limit as diffusion becomes much faster than reactions. For the second scenario, we derive an exact analytical singular value decomposition for all relative diffusion and reaction time scales. By writing the stoichiometry matrix using Kronecker products, we show that the singular vectors and values can also be written concisely using Kronecker products. Ultimately, we find that the singular value decomposition of the reaction-diffusion stoichiometry matrix depends on the singular value decompositions of smaller matrices. These smaller matrices represent modified versions of the reaction-only stoichiometry matrices and the analytically known diffusion-only stoichiometry matrix. Lastly, we present the singular value decomposition of the model for the Calvin cycle in cyanobacteria and demonstrate the accuracy of our formulation. The MATLAB code, available at www.github.com/MathBioCU/ReacDiffStoicSVD, provides routines for efficiently calculating the SVD for a given reaction network on a 1D spatial domain.

Key words. stoichiometry matrix, singular value decomposition, flux balance analysis

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1. Introduction.

In stoichiometric network analysis the mass balance equation for a reaction-only system is written as follows:

$$\frac{dw}{dt} = S_r f, \tag{1.1}$$

where w is a species concentration vector, S_r is the stoichiometry matrix, and f is a vector of reaction fluxes [2]. We use the subscript r to refer to a stoichiometry matrix that only describes reactive processes. Although the flux vector f is a function of the species concentration, the formulation given by (1.1) avoids assumptions about the form of the kinetic equations that relate the fluxes to the species concentration (e.g., mass-action [14] or Michaelis–Menten kinetics [5]). The stoichiometry matrix contains information about the species involved in each reaction. As a simple example, consider the following set of reactions:

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†Department of Applied Mathematics, University of Colorado Boulder, Boulder, CO 80309 USA (jacqueline.wentz@colorado.edu, dmbortz@colorado.edu).

‡Department of Biochemistry and Renewable and Sustainable Energy Institute, University of Colorado, Boulder, CO 80309-0526 USA (Jeffrey.c.cameron@colorado.edu).

$$\emptyset \longrightarrow \mathrm{A}, \qquad \mathrm{A} \longrightarrow \mathrm{B}, \qquad \mathrm{B} \longrightarrow \emptyset. \tag{1.2}$$

Here, species A is produced and transitions into species B, and species B decays. The stoichiometry matrix for this example system is

$$S_r = \begin{bmatrix} 1 & -1 & 0 \\ 0 & 1 & -1 \end{bmatrix}. \tag{1.3}$$

The first row of S_r corresponds to species A, and the second row corresponds to species B. Each of the three columns corresponds to the three reactions, respectively.

The analysis of S_r provides information on structural properties of the system without requiring kinetic information. In particular, the singular value decomposition (SVD) of S_r provides information on systemic properties, including decoupled eigenreactions (i.e., linear combinations of species that are moved by linear combinations of fluxes), conservation relations, and fluxes that can exist in the system under steady-state conditions [11]. This type of analysis can be used to determine hidden relationships in a network and to compare biochemical properties among different organisms [4, 10].

Here, our goal is to derive the SVD of a stoichiometry matrix that, in addition to the reactions, includes information on the spatial properties of a system. This approach allows a researcher to discover hidden *spatial* flux patterns of chemical reactions. These flux patterns provide information on how spatial features impact both dynamical and steady-state properties of the system. We will refer to the stoichiometry matrix of the full spatial system as the *reaction-diffusion (RD) stoichiometry matrix*.

To derive the RD stoichiometry matrix, we begin with a standard RD PDE with a vector of chemical species u and reactions described by the vector-valued function g:

$$u_t = \Delta u + g(u)\,. \tag{1.4}$$

We then rewrite this system to fit within the framework of (1.1):

$$\begin{aligned} u_t &= \quad (\nabla\bullet)(\nabla u) + S_r f \\ &= \begin{bmatrix}(\nabla\bullet) & S_r\end{bmatrix} \begin{bmatrix}\nabla u \\ f\end{bmatrix}, \end{aligned} \tag{1.5}$$

where the ∇u is a vector of *spatial* fluxes and $g(u) = S_r f$. Since we are only considering a 1D spatial domain, the $(\nabla\bullet)$ operation will be discretized to a first order finite-difference approximation. As we are not interested in the continuum limit, we set the spatial stepsize to be unity. An example *spatial* stoichiometry matrix S_d (i.e., a diffusion-only stoichiometry matrix), with three discrete spatial compartments for a single chemical species and homogeneous Neumann boundary conditions, is thus

$$(\nabla\bullet) \approx S_d = \begin{bmatrix} 0 & -1 & 0 & 0 \\ 0 & 1 & -1 & 0 \\ 0 & 0 & 1 & 0 \end{bmatrix}. \tag{1.6}$$

Analogously to S_r, each row in S_d corresponds to the species in each of the three compartments. The first and last column of S_d correspond to species movement across the boundary of the domain and, for this example, contain only zeros due to the homogenous Neumann boundary conditions. The middle columns represent the

movement of the species between adjacent compartments. Note that other boundary conditions may be considered by modifying the first and/or last column of S_d.

We next define the RD stoichiometry matrix for a 1D spatially discrete system where reactions and diffusion are spatially homogeneous (i.e., the reactions in each spatial compartment are the same, diffusion is allowed freely across the domain, and all species share the same diffusive properties). We write the RD stoichiometry matrix using the reaction-only and diffusion-only stoichiometry matrices, i.e., S_r and S_d, respectively. The reaction-only stoichiometry matrix is as described in (1.3), and the diffusion-only stoichiometry matrix is as described in (1.6). By itself, (1.6) represents the diffusive movement of a single species. However, by considering the Kronecker product of (1.6) with the identity matrix, we can represent the diffusive movement of an arbitrary number of species.

More specifically, suppose the RD system has n spatial compartments and m species that freely diffuse through space; the stoichiometry matrix S is

$$S = \begin{bmatrix} \gamma S_r \otimes I_n & I_m \otimes S_d \end{bmatrix}, \tag{1.7}$$

where $\otimes$ represents the Kronecker product [8], $\gamma > 0$ describes the relative rate of reactions to diffusion, and I_a is the identity matrix of size a. Here, the $S_r \otimes I_n$ block represents the reactions occurring in each compartment, whereas the $I_m \otimes S_d$ block represents diffusive movement. The Kronecker product has previously been used to compactly represent diffusion for the spatially discrete RD ODE system [1, 3], and we previously developed criteria to guarantee that a version of this ODE system is bounded for all time [15]. Here, we instead use (1.7) to study the spatially discrete system in the context of stoichiometric network analysis. We write both the reactive and diffusive terms using a Kronecker product formulation as this will simplify the SVD derivation.

In this paper we will consider a more general form of (1.7) where, in addition to diffusion, there is a spatial barrier in the system that divides the 1D domain into two subregions. We consider this class of systems because it allows our results to be applied to study, for example, the effect of metabolic compartmentalization within a cell. We will use concepts from linear perturbation theory [6] to derive the approximate SVD in the limit as diffusion becomes much faster than reactions. We additionally consider the special case where diffusion of all species is allowed freely throughout the domain, i.e., where the stoichiometry matrix can be written as given by (1.7). We show that for this scenario the SVD becomes exact for all values of γ. The derived SVDs for the system with and without a spatial barrier depend on the SVDs of smaller matrices, such as the reaction-only stoichiometry matrix.

To help provide structure and guide our argument, in section 2 we chose to present the main result first (see Theorems 2.1 and 2.2). We then provide a more complete set of definitions and notation in section 3. This includes a complete description of the system as well as definitions of matrices whose SVDs are used to write the main result. In section 4 we provide preliminary results that will be helpful for proving Theorem 2.1. In section 5 we provide the complete proofs of Theorems 2.1 and 2.2. Finally, in section 6 we provide some intuition for the SVD equations and discuss potential applications of this work.

2. System description and statement of main result. Here we provide a brief description of the system and state the main result. For a thorough description of the notation and definitions used, see section 3.

We consider a 1D, spatially discrete, RD system that is divided into two subregions. A subset of the species is allowed to diffuse between the two subregions, and we allow for different sets of reactions to occur in each region. We will consider three boundary conditions: no input/output fluxes, input/output fluxes at one boundary point, and input/output fluxes at both boundary points. As an example, biologically this system description might represent a radially symmetric cell, where the two subregions are the cytoplasm and the nucleus.

The stoichiometry matrix for this class of systems can be written as

$$S := \begin{bmatrix} \gamma \begin{bmatrix} I_{n_1} \otimes S_{r_1} & 0 \\ 0 & I_{n_2} \otimes S_{r_2} \end{bmatrix} & S_d \otimes D_+ + (S_d - H) \otimes D_- \end{bmatrix}, \tag{2.1}$$

where the first column block represents reactive processes and the second represents diffusive processes. Here, S_{r_1} and S_{r_2} represent the reaction-only stoichiometry matrices for each of the two subregions, $S_d \otimes D_+$ describes the diffusion of species that move across the entire domain (i.e., species that can cross the barrier between the two subregions), and $(S_d - H) \otimes D_-$ describes the diffusion of species that stay within a single subregion. The H matrix is constructed so that $S_d - H$ has a barrier of zero diffusion at a location internal to the domain; see (3.2). The parameter $\gamma > 0$ represents the relative rate of reactions compared with diffusion.

In this section we present the SVD of the stoichiometry matrix given by (2.1) in the limit as diffusion becomes much faster than reactions, i.e., as $\gamma \to 0$. Briefly, the main result depends on the SVD of smaller reaction-only and diffusion-only systems. This includes matrices that only involve reactive processes, which will be written using variations of S_r (e.g., S_{r_1}, S_{r_2}), and matrices that only involve diffusive processes, which will be written using variations of S_d (e.g., S_{d_1}, S_{d_2}).

Our general notation for writing down the SVD of $S_\bullet \in \mathbb{R}^{s_1 \times s_2}$ will be as follows:

$$S_\bullet = U_\bullet \Sigma_\bullet V_\bullet^T = \begin{bmatrix} \hat{U}_\bullet & \check{U}_\bullet \end{bmatrix} \begin{bmatrix} \hat{\Sigma}_\bullet & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \hat{V}_\bullet & \check{V}_\bullet \end{bmatrix}^T. \tag{2.2}$$

We will refer to the rank of $S_\bullet$ as $q_\bullet$ and the size of the nullspace as $\check{q}_\bullet$. In some cases the singular vectors will be divided into two components (e.g., $U_d = [U_{d,a}; U_{d,b}]$). With this SVD notation in mind, we next state the main result of the paper. Although the complete definitions and notations are not given until section 3, it is possible to immediately see that the SVD depends only on SVDs of variations of stoichiometry matrices for the reaction-only and diffusion-only systems.

THEOREM 2.1. *As $\gamma \to 0$ the unsorted SVD of S, as given by* (2.1)*, is*

$$S = U \Sigma V^T = \begin{bmatrix} \hat{U} & \check{U} \end{bmatrix} \begin{bmatrix} \hat{\Sigma} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \hat{V} & \check{V} \end{bmatrix}^T, \tag{2.3}$$

where the singular vectors that have nonzero singular values are given by six components, $\hat{U}_i$, $\hat{V}_i$, such that

$$S = \sum_{i \in \hat{\mathcal{J}}} \hat{U}_{1,j} \hat{\Sigma}_{1,j} \hat{V}_{1,j}^T + \sum_{i=2}^{6} \hat{U}_i \hat{\Sigma}_i \hat{V}_i^T, \tag{2.4}$$

where

$$\hat{U}_{1,j} = u_d^{(j)} \otimes I_m^{\mathcal{M}_+} U_{\bar{r}_+,j}, \qquad \hat{V}_{1,j} = \begin{bmatrix} \frac{\gamma}{|u_{d,s_1}^{(j)}|} u_{d,s_1}^{(j)} \otimes V_{\bar{r}_+,j,s_1} \Sigma_{\bar{r}_+,j}^T \\ \frac{\gamma}{|u_{d,s_2}^{(j)}|} u_{d,s_2}^{(j)} \otimes V_{\bar{r}_+,j,s_2} \Sigma_{\bar{r}_+,j}^T \\ \hline v_d^{(j)} \sigma_d^{(j)} \otimes I_m^{\mathcal{M}_+} U_{\bar{r}_+,j} \end{bmatrix} \hat{\Sigma}_{1,j}^{-1},$$

$$\hat{U}_2 = \begin{bmatrix} U_{d_1}^{\hat{\mathcal{J}}_1} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-} U_{r_1,-}, \qquad \hat{V}_2 = \begin{bmatrix} \gamma U_{d_1}^{\hat{\mathcal{J}}_1} \otimes V_{r_1,-} \Sigma_{r_1,-}^T \\ 0 \\ \hline (V_{d_1} \Sigma_{d_1})^{\hat{\mathcal{J}}_1} \otimes I_m^{\mathcal{M}_-} U_{r_1,-} \\ 0 \end{bmatrix} \hat{\Sigma}_2^{-1},$$

$$\hat{U}_3 = \begin{bmatrix} U_{d_1}^{n_1 \setminus (\mathcal{J}_1^C \cup \hat{\mathcal{J}}_1)} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-} \hat{U}_{r_1,-}, \qquad \hat{V}_3 = \begin{bmatrix} \gamma U_{d_1}^{n_1 \setminus (\mathcal{J}_1^C \cup \hat{\mathcal{J}}_1)} \otimes \hat{V}_{r_1,-} \hat{\Sigma}_{r_1,-}^T \\ 0 \\ \hline 0 \end{bmatrix} \hat{\Sigma}_3^{-1},$$

$$\hat{U}_4 = \begin{bmatrix} 0 \\ U_{d_2}^{\hat{\mathcal{J}}_2} \end{bmatrix} \otimes I_m^{\mathcal{M}_-} U_{r_2,-}, \qquad \hat{V}_4 = \begin{bmatrix} 0 \\ \gamma U_{d_2}^{\hat{\mathcal{J}}_2} \otimes V_{r_2,-} \Sigma_{r_2,-}^T \\ \hline 0 \\ (V_{d_2} \Sigma_{d_2})^{\hat{\mathcal{J}}_2} \otimes I_m^{\mathcal{M}_-} U_{r_2,-} \end{bmatrix} \hat{\Sigma}_4^{-1},$$

$$\hat{U}_5 = \begin{bmatrix} \frac{1}{C_1} U_{d,s_1}^{\hat{\mathcal{J}}^C} \otimes U_{\bar{r},m_1} \\ \frac{1}{C_2} U_{d,s_2}^{\hat{\mathcal{J}}^C} \otimes U_{\bar{r},m_2} \end{bmatrix}, \qquad \hat{V}_5 = \begin{bmatrix} \frac{\gamma}{C_1} U_{d,s_1}^{\hat{\mathcal{J}}^C} \otimes \begin{bmatrix} \hat{V}_{\bar{r},s_1} \hat{\Sigma}_{\bar{r}} & 0 \end{bmatrix} \\ \frac{\gamma}{C_2} U_{d,s_2}^{\hat{\mathcal{J}}^C} \otimes \begin{bmatrix} \hat{V}_{\bar{r},s_2} \hat{\Sigma}_{\bar{r}} & 0 \end{bmatrix} \\ \hline \frac{1}{C_1} V_{d,s_1}^{\hat{\mathcal{J}}^C} \Sigma_d^{\hat{\mathcal{J}}^C} \otimes U_{\bar{r},m_1} \\ \frac{1}{C_2} V_{d,s_2}^{\hat{\mathcal{J}}^C} \Sigma_d^{\hat{\mathcal{J}}^C} \otimes U_{\bar{r},m_2} \end{bmatrix} \hat{\Sigma}_5^{-1},$$

$$\hat{U}_6 = \begin{bmatrix} \frac{1}{C_1} \breve{U}_{d,s_1} \otimes \hat{U}_{\bar{r},m_1} \\ \frac{1}{C_2} \breve{U}_{d,s_2} \otimes \hat{U}_{\bar{r},m_2} \end{bmatrix}, \qquad \hat{V}_6 = \begin{bmatrix} \frac{\gamma}{C_1} \breve{U}_{d,s_1} \otimes \hat{V}_{\bar{r},s_1} \hat{\Sigma}_{\bar{r}} \\ \frac{\gamma}{C_2} \breve{U}_{d,s_2} \otimes \hat{V}_{\bar{r},s_2} \hat{\Sigma}_{\bar{r}} \\ \hline 0 \end{bmatrix} \hat{\Sigma}_6^{-1},$$

and

$$\hat{\Sigma}_{1,j}^2 = \left(\sigma_d^{(j)}\right)^2 I_{m_+} + \gamma^2 \left(\Sigma_{\bar{r}_+,j}^2\right)_{m_+}, \quad \hat{\Sigma}_2^2 = (\hat{\Sigma}_{d_1}^2)^{\hat{\mathcal{J}}_1} \oplus \gamma^2 \left(\hat{\Sigma}_{r_1,-}^2\right)_{m_-},$$
$$\hat{\Sigma}_3^2 = (\Sigma_{d_1}^2)^{n_1 \setminus (\mathcal{J}_1^C \cup \hat{\mathcal{J}}_1)} \oplus \gamma^2 \hat{\Sigma}_{r_1,-}^2, \qquad \hat{\Sigma}_4^2 = (\Sigma_{d_2}^2)^{\hat{\mathcal{J}}_2} \oplus \gamma^2 \left(\hat{\Sigma}_{r_2,-}^2\right)_{m_-},$$
$$\hat{\Sigma}_5^2 = (\hat{\Sigma}_d^2)^{\hat{\mathcal{J}}^C} \oplus \gamma^2 \left(\hat{\Sigma}_{\bar{r}}^2\right)_{q_{\bar{r}} + \breve{q}_{\bar{r}}}, \qquad \hat{\Sigma}_6^2 = I_{n-q_d} \otimes \gamma^2 \hat{\Sigma}_{\bar{r}}^2.$$

A basis for the left nullspace of S is

$$\breve{U} = \begin{bmatrix} \breve{U}_1 & \breve{U}_2 \end{bmatrix}, \tag{2.5}$$

where

$$\breve{U}_1 = \begin{bmatrix} U_{d_1}^{n_1 \setminus (\mathcal{J}_1^C \cup \hat{\mathcal{J}}_1)} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-} \breve{U}_{r_1,-}, \qquad \breve{U}_2 = \begin{bmatrix} \frac{1}{C_1} \breve{U}_{d,s_1} \otimes \breve{U}_{\bar{r},s_1} \\ \frac{1}{C_2} \breve{U}_{d,s_2} \otimes \breve{U}_{\bar{r},s_2} \end{bmatrix},$$

and a basis for the (right) nullspace of S is

$$\breve{V} = \begin{bmatrix} \breve{V}_1 & \breve{V}_2 & \breve{V}_3 & \breve{V}_4 & \breve{V}_5 \end{bmatrix}, \tag{2.6}$$

where

(2.7)

$$\breve{V}_1 = \begin{bmatrix} U_{d_1}^{n_1\setminus(\mathcal{J}_1^C\cup\hat{\mathcal{J}}_1)} \otimes \breve{V}_{r_1,-} \\ \hdashline 0 \end{bmatrix}, \quad \breve{V}_2 = \begin{bmatrix} \hat{U}_{d_1}\hat{\Sigma}_{d_1} \otimes V_{r_1} \\ \hdashline -\gamma \hat{V}_{d_1} \otimes U_{r_1}\Sigma_{r_1} \end{bmatrix} \left(\hat{\Sigma}_{d_1}^2 \oplus \gamma^2 \left(\hat{\Sigma}_{r_1}^2\right)_{p_1}\right)^{-\frac{1}{2}},$$

$$\breve{V}_3 = \begin{bmatrix} \frac{1}{C_1}\breve{U}_{d,s_1} \otimes \breve{V}_{\bar{r},s_1} \\ \frac{1}{C_2}\breve{U}_{d,s_2} \otimes \breve{V}_{\bar{r},s_2} \\ \hdashline 0 \end{bmatrix}, \qquad \breve{V}_4 = \begin{bmatrix} 0 \\ \hat{U}_{d_2}\hat{\Sigma}_{d_2} \otimes V_{r_2} \\ \hdashline 0 \\ -\gamma \hat{V}_{d_2} \otimes U_{r_2}\Sigma_{r_2} \end{bmatrix} \left(\hat{\Sigma}_{d_2}^2 \oplus \gamma^2 \left(\hat{\Sigma}_{r_2}^2\right)_{p_2}\right)^{-\frac{1}{2}},$$

$$\breve{V}_5 = \begin{bmatrix} 0 & 0 \\ \hdashline \breve{V}_d \otimes I_m^{\mathcal{M}_+} & I_{n+1}^{\mathcal{B}} \otimes I_m^{\mathcal{M}_-} \end{bmatrix}.$$

Note that the horizontal dashed lines used in the definition of the right singular vectors separate the vectors into components that correspond to the reactive fluxes (above dashed line) and diffusive fluxes (below dashed line). The proof of this theorem is given in section 5.

We have defined the SVD in Theorem 2.1 to be applicable for all three boundary conditions. Note that $\hat{U}_6$, $\hat{V}_6$, $\breve{U}_2$, and $\breve{V}_3$ are only nonempty for homogeneous Neumann boundary conditions (i.e., no input/output fluxes) and $\hat{U}_3$, $\hat{V}_3$, $\breve{U}_1$, and $\breve{V}_1$ are only nonempty when there is an input/output flux at a single boundary point.

The results given in Theorem 2.1 are simplified significantly when we consider systems that only have one region and spatially homogeneous reactions.[1] For such systems the stoichiometry matrix is simplified to

$$S = \begin{bmatrix} \gamma I_n \otimes S_r & S_d \otimes I_m \end{bmatrix}, \tag{2.8}$$

and the SVD is given by the following theorem.

THEOREM 2.2. *The SVD of the stoichiometry matrix S, as given by* (2.8)*, is*

$$S = U\Sigma V^T = \begin{bmatrix} \hat{U} & \breve{U} \end{bmatrix} \begin{bmatrix} \hat{\Sigma} & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \hat{V} & \breve{V} \end{bmatrix}^T, \tag{2.9}$$

where

$$\begin{aligned}
\hat{U} &= \begin{bmatrix} \hat{U}_d \otimes \hat{U}_r & \hat{U}_d \otimes \breve{U}_r & \breve{U}_d \otimes \hat{U}_r \end{bmatrix}, \\
\breve{U} &= \breve{U}_d \otimes \breve{U}_r, \\
\hat{V} &= \begin{bmatrix} \gamma\left(\hat{U}_d \otimes \hat{V}_r\hat{\Sigma}_r\right)\tilde{\Sigma}^{-1} & 0 & \breve{U}_d \otimes \hat{V}_r \\ \left(\hat{V}_d\hat{\Sigma}_d \otimes \hat{U}_r\right)\tilde{\Sigma}^{-1} & \hat{V}_d \otimes \breve{U}_r & 0 \end{bmatrix}, \\
\breve{V} &= \begin{bmatrix} \left(\hat{U}_d\hat{\Sigma}_d \otimes \hat{V}_r\right)\tilde{\Sigma}^{-1} & \hat{U}_d \otimes \breve{V}_r & 0 \\ -\gamma\left(\hat{V}_d \otimes \hat{U}_r\hat{\Sigma}_r\right)\tilde{\Sigma}^{-1} & 0 & \breve{V}_d \otimes U_r \end{bmatrix},
\end{aligned}$$

[1]Note that by *spatially homogeneous*, we simply mean that the same reactions can happen in every compartment of the domain and species can diffuse freely from any compartment to any other compartment.

$$\hat{\Sigma} = \begin{bmatrix} \tilde{\Sigma} & & \\ & \hat{\Sigma}_d \otimes I_{m-q_r} & \\ & & \gamma I_{n-q_d} \otimes \hat{\Sigma}_r \end{bmatrix},$$

$$\tilde{\Sigma}^2 = \hat{\Sigma}_d^2 \oplus \left(\gamma \hat{\Sigma}_r\right)^2.$$

3. Notation and definitions. Here we present notation and matrix definitions that are used to state and prove the main result. In section 3.1, we provide basic notation for referring to matrices. In section 3.2, we present definitions used to define the discrete RD system. In section 3.3 we define sets of indices that will be used for defining the SVD. In section 3.4, we define the set of *stoichiometry-like matrices* that are required for writing the SVD of the RD system. In section 3.5, we provide notation that, in addition to (2.2), will be used to define the SVD of relevant matrices. Table 1 summarizes the notational definitions presented in this section.

3.1. Matrix notation. Matrices will be defined using uppercase letters (e.g., A), and sets of indices will be defined using calligraphic fonts (e.g., $\mathcal{B}$). We will use $A^{\mathcal{B}}$ to represent the columns of A whose indices are in the set $\mathcal{B}$. If we refer to one column of a matrix (i.e., a column vector), we will typically use the lowercase letter and a superscript to refer to this column (i.e., the ith column of A will be written as $a^{(i)}$). One exception to these rules will be for any diagonal matrix of singular values $\Sigma_\bullet$ and variations of this matrix. In this case, $\Sigma_\bullet^{\mathcal{B}}$ will represent a square diagonal matrix containing the singular values whose indices are in $\mathcal{B}$. Additionally $(\Sigma_\bullet)_n$ will represent the matrix Σ padded by zeros to make it size $n \times n$. The ith diagonal element of $\Sigma_\bullet$ will be written as $\sigma_\bullet^{(i)}$.

Throughout the paper, we will use I_a to denote the identity matrix of size $a \times a$. We will also use 0 to represent a matrix of zeros. For notational simplicity we omit

TABLE 1
Description of constants, index sets, and stoichiometry/stoichiometry-like matrices used to define the SVD of the RD stoichiometry matrix.

Symbol	Size (if matrix)	Definition
n		Total number of spatial compartments
n_1		Number of spatial compartments in subregion 1
n_2		Number of spatial compartments in subregion 2
m		Total number of species
p_1		Number of reactions in subregion 1
p_2		Number of reactions in subregion 2
C_1, C_2		Constants dependent on the boundary conditions
$\mathcal{M}_+$		Index set for species that diffuse across barrier
$\mathcal{M}_-$		Index set for species that do not diffuse across barrier
$\mathcal{B}$		Index set that depends on boundary conditions
$\mathcal{J}, \mathcal{J}_i$		Index sets of singular values that only occur in Σ_d, Σ_{d_i}
$\hat{\mathcal{J}}, \hat{\mathcal{J}}_i$		Index sets of singular values that only occur in $\hat{\Sigma}_d$, $\hat{\Sigma}_{d_i}$
S_d	$n \times n+1$	Diffusion-only stoichiometry matrix for full domain
S_{d_1}	$n_1 \times n_1+1$	Diffusion-only stoichiometry matrix for subregion 1
S_{d_2}	$n_2 \times n_2+1$	Diffusion-only stoichiometry matrix for subregion 2
S_{r_1}	$m \times p_1$	Reaction-only stoichiometry matrix for subregion 1
S_{r_2}	$m \times p_2$	Reaction-only stoichiometry matrix for subregion 2
$S_{r_i,+}$	$m_+ \times p_i$	Rows of S_{r_i} for species that diffuse between subregions
$S_{r_i,-}$	$m_- \times p_i$	Rows of S_{r_i} for species that do not diffuse between subregions
$S_{\bar{r}}$	$2m \times p_1 + p_2$	Block matrix dependent on S_{r_1} and S_{r_2}; see (3.10).
$S_{\bar{r}_+,j}$	$m_+ \times p_1 + p_2$	Block matrix dependent on $S_{r_1,+}$, $S_{r_2,+}$, and $u_d^{(j)}$; see (3.14).

the size of each zero matrix but note that it can be deduced from the notation. We will use $\otimes$ to represent the Kronecker product[2] and $\oplus$ to represent the Kronecker sum.[3]

3.2. Discrete RD systems. We consider the discrete reaction-diffusion system on a 1D domain $[0, n]$ that is partitioned into n equal-sized spatial compartments. Let m denote the number of species (e.g., proteins or metabolites) in the system and p denote the number of reactions. We will allow for three different boundary conditions: homogeneous Neumann (no flux at both ends), mixed (homogeneous Neumann at $x = 0$ and open at $x = n$), and open (flux allowed at both ends). Note that both the reactive and diffusive fluxes can be either positive or negative. We define a positive diffusive flux as moving in the positive x direction. We will assume that all the species in the system diffuse at the same rate.

Within the domain there is a single barrier across which only a subset of species can diffuse. The barrier divides the system into two subregions where different reactions occur. Let $S_{r_1} \in \mathbb{R}^{m\times p_1}$ and $S_{r_2} \in \mathbb{R}^{m\times p_2}$ represent the stoichiometry matrices for the two subregions (i.e., p_1 reactions occur in the first subregion, and p_2 reactions occur in the second). Note that the same reaction can occur in both regions.

We will let $n_1 \in \{1, \dots, n-1\}$ denote the number of compartments in the first subregion and $n_2 = n - n_1$ denote the number of compartments in the second subregion. Within this system, there are three diffusive processes: diffusion across the entire domain, within the first subregion, and within the second subregion. We define diffusion-only stoichiometry matrices for these three processes using $S_d \in \mathbb{R}^{n\times n+1}$, $S_{d_1} \in \mathbb{R}^{n_1\times n_1+1}$, and $S_{d_2} \in \mathbb{R}^{n_2\times n_2+1}$, respectively. For diffusion across the entire domain, we have that

$$S_d := \begin{bmatrix} b_1 & -1 & 0 & & & \\ & 1 & -1 & & & \\ & & \ddots & \ddots & & \\ & & & 1 & -1 & \\ & & & 0 & 1 & -b_2 \end{bmatrix}, \tag{3.1}$$

where the values in the first and last column depend on the boundary conditions. Specifically, $b_1 = 0$, $b_2 = 0$ implies zero flux boundary conditions; $b_1 = 0$, $b_2 = 1$ implies mixed boundary conditions; and $b_1 = 1$, $b_2 = 1$ implies open boundary conditions. The diffusion-only stoichiometry matrices S_{d_1} and S_{d_2} are defined similarly. However, for S_{d_1} the value of b_2 is replaced by zero, and for S_{d_2} the value of b_1 is replaced by zero. The n rows of S_d corresponds to the species in each of the n compartments, and the $n + 1$ columns corresponds to the flux across each of the $n - 1$ interior edges as well as the two boundaries at either end of the domain. Using the matrix

[2]The Kronecker product of $A \in \mathbb{R}^{m\times n}$ and $B \in \mathbb{R}^{p\times r}$ is a $mp + nr$ block matrix, where

$$A \otimes B = \begin{bmatrix} A_{11}B & \cdots & A_{1n}B \\ \vdots & \ddots & \vdots \\ A_{m1}B & \cdots & A_{mn}B \end{bmatrix}.$$

[3]The Kronecker sum is given by $A \oplus B = A \otimes I_b + I_a \otimes B$, where A is an $a \times a$ matrix and B is a $b \times b$ matrix.

$$(H)_{i,j} := \begin{cases} -1 & i = n_1, \quad j = n_1 + 1, \\ 1 & i = n_1 + 1, \quad j = n_1 + 1 \\ 0 & \text{otherwise,} \end{cases} \tag{3.2}$$

we can relate S_d with S_{d_1} and S_{d_2} as follows:

$$\begin{bmatrix} S_{d_1}^{(1:n_1)} & 0 & 0 \\ 0 & 0 & S_{d_2}^{(2:n_2+1)} \end{bmatrix} = S_d - H. \tag{3.3}$$

Next, we provide definitions used to identify the species that can and cannot diffuse between the two subregions. When defining parameters (e.g., sets, matrices), a subscripted + or − will imply a relationship with the set of species that can (+) or cannot (−) diffuse across the barrier. The set $\mathcal{M}_+$ will contain indices for species that can diffuse across the barrier, whereas the set $\mathcal{M}_-$ will contain indices for species that cannot diffuse across the barrier. Additionally, let $m_+ = |\mathcal{M}_+|$ and $m_- = |\mathcal{M}_-|$, where $m_+ + m_- = m$. Using these sets we define the diagonal matrices $D_+, D_- \in \mathbb{R}^{m\times m}$, where

$$(D_+)_{i,j} := \begin{cases} 1 & i \in \mathcal{M}_+, \\ 0 & \text{otherwise,} \end{cases} \qquad (D_-)_{i,j} := \begin{cases} 1 & i \in \mathcal{M}_-, \\ 0 & \text{otherwise.} \end{cases}$$

Note that $D_- + D_+ = I_m$.

We can now write the equation for the spatially discrete RD stoichiometry matrix given by (2.1). For convenience we rewrite this equation below:

$$S := \left[\gamma \begin{bmatrix} I_{n_1} \otimes S_{r_1} & 0 \\ 0 & I_{n_2} \otimes S_{r_2} \end{bmatrix} \quad S_d \otimes D_+ + (S_d - H) \otimes D_- \right]. \tag{3.4}$$

The parameter $\gamma \geq 0$ represents the relative rate of the reactions compared with the rate of diffusion (i.e., if $\gamma \gg 1$ the reactions are much faster than diffusion, and, if $\gamma \ll 1$, the reactions are much slower than diffusion). The first $n_1 p_1 + n_2 p_2$ columns of S correspond to the reactions occurring in each compartment. The final $(n+1)m$ columns correspond to the diffusion of species into or out of the domain as well as between adjacent compartments.

3.3. Additional spatially dependent parameters. Here we define the constants C_1, C_2, the set $\mathcal{B}$, and sets denoted by variations of $\mathcal{J}$. These parameters are only dependent on the spatial properties of the system (e.g., compartment number and boundary conditions) and are therefore unaffected if reactive properties (e.g., reaction number and stoichiometry) change.

The constants C_1 and C_2 depend on the boundary conditions and compartment numbers. We have that

$$C_1 := \left(\frac{2n_1 + b_1}{2n + b_1 + b_2} \right)^{1/2}, \qquad C_2 := \left(\frac{2n_2 + b_2}{2n + b_1 + b_2} \right)^{1/2}. \tag{3.5}$$

We will show in Lemma 4.1 that these constants relate the singular vectors for S_d, S_{d_1}, and S_{d_2} to one another.

Next, the set $\mathcal{B}$ is defined to contain indices that correspond to the columns of S_d that are zero as well as the index of the column of S_d that corresponds to the flux between the two subregions. Specifically,

$$\mathcal{B} := \begin{cases} \{1, n_1+1, n+1\} & \text{zero flux,} \\ \{1, n_1+1\} & \text{mixed,} \\ \{n_1+1\} & \text{open.} \end{cases} \tag{3.6}$$

This set will be used to help define the nullspace of the RD stoichiometry matrix.

Finally, we define the index sets of singular values for the diffusion-only stoichiometry matrices,

$$\begin{aligned} \mathcal{J} &:= \{j \mid \sigma_d^{(j)} \in \operatorname{diag}(\Sigma_d) \text{ and } \sigma_d^{(j)} \notin \operatorname{diag}(\Sigma_{d_1})\}, \quad \mathcal{J}^C := \{1,\dots,n\} \setminus \mathcal{J}, \\ \mathcal{J}_1 &:= \{j \mid \sigma_{d_1}^{(j)} \in \operatorname{diag}(\Sigma_{d_1}) \text{ and } \sigma_{d_1}^{(j)} \notin \operatorname{diag}(\Sigma_d)\}, \quad \mathcal{J}_1^C := \{1,\dots,n_1\} \setminus \mathcal{J}_1, \\ \mathcal{J}_2 &:= \{j \mid \sigma_{d_2}^{(j)} \in \operatorname{diag}(\Sigma_{d_2}) \text{ and } \sigma_{d_2}^{(j)} \notin \operatorname{diag}(\Sigma_d)\}, \quad \mathcal{J}_2^C := \{1,\dots,n_2\} \setminus \mathcal{J}_2, \end{aligned} \tag{3.7}$$

and the analogous index sets for only nonzero singular values,

$$\begin{aligned} \hat{\mathcal{J}} &:= \{j \in \mathcal{J} \mid \sigma_d^{(j)} \neq 0\}, \quad \hat{\mathcal{J}}^C := \{1,\dots,q_d\} \setminus \hat{\mathcal{J}}, \\ \hat{\mathcal{J}}_1 &:= \{j \in \mathcal{J}_1 \mid \sigma_{d_1}^{(j)} \neq 0\}, \quad \hat{\mathcal{J}}_1^C := \{1,\dots,q_{d_1}\} \setminus \hat{\mathcal{J}}_1, \\ \hat{\mathcal{J}}_2 &:= \{j \in \mathcal{J}_2 \mid \sigma_{d_2}^{(j)} \neq 0\}, \quad \hat{\mathcal{J}}_2^C := \{1,\dots,q_{d_2}\} \setminus \hat{\mathcal{J}}_2. \end{aligned} \tag{3.8}$$

We will use these sets to define how singular values repeat in the system when $\gamma = 0$. Understanding this property is a key step in proving Theorem 2.1.

3.4. Additional reaction-dependent stoichiometry-like matrices. We refer to modified versions of the reaction-only stoichiometry matrices as *stoichiometry-like matrices*. In this section we will define the $4 + |\hat{\mathcal{J}}|$ stoichiometry-like matrices that are necessary for writing the SVD. These matrices are given as $S_{r_1,-}$, $S_{r_2,-}$, $S_{\bar{r}}$, and $S_{\bar{r}_+,j}$ for $j \in \hat{\mathcal{J}}$.

The matrices $S_{r_1,-}$ and $S_{r_2,-}$ will represent subsetted versions of S_{r_1} and S_{r_2}, respectively, that only contain rows for species that cannot diffuse across the boundary. Specifically,

$$\begin{aligned} S_{r_1,+} &:= (S_{r_1})_{\mathcal{M}_+}, \quad S_{r_1,-} := (S_{r_1})_{\mathcal{M}_-}, \\ S_{r_2,+} &:= (S_{r_2})_{\mathcal{M}_+}, \quad S_{r_2,-} := (S_{r_2})_{\mathcal{M}_-}, \end{aligned} \tag{3.9}$$

where $(A)_{\mathcal{B}}$ represents the rows of A that are in the index set $\mathcal{B}$.

Next, we define a stoichiometry-like matrix that represents a merger of the two reaction-only stoichiometry matrices:

$$S_{\bar{r}} := \begin{bmatrix} C_1^2 I_m^{\mathcal{M}_+} S_{r_1,+} + I_m^{\mathcal{M}_-} S_{r_1,-} & C_1 C_2 I_m^{\mathcal{M}_+} S_{r_2,+} \\ C_1 C_2 I_m^{\mathcal{M}_+} S_{r_1,+} & C_2^2 I_m^{\mathcal{M}_+} S_{r_2,+} + I_m^{\mathcal{M}_-} S_{r_2,-} \end{bmatrix}. \tag{3.10}$$

To prove Theorem 2.1, we will need to consider the eigendecomposition of

$$B := S_{\bar{r}} S_{\bar{r}}^T. \tag{3.11}$$

It can be shown that

$$B = \begin{bmatrix} B_2 + C_1^2(B_1 + B_4 + B_4^T) & C_1 C_2 (B_1 + B_5 + B_4^T) \\ C_1 C_2 (B_1 + B_4 + B_5^T) & B_3 + C_2^2 (B_1 + B_5 + B_5^T) \end{bmatrix} \tag{3.12}$$

and

$$
\begin{aligned}
B_1 &:= D_+ \left(C_1^2 S_{r_1} S_{r_1}^T + C_2^2 S_{r_2} S_{r_2}^T\right) D_+, \\
B_2 &:= D_- \left(S_{r_1} S_{r_1}^T\right) D_-, \\
B_3 &:= D_- \left(S_{r_2} S_{r_2}^T\right) D_-, \\
B_4 &:= D_+ \left(S_{r_1} S_{r_1}^T\right) D_-, \\
B_5 &:= D_+ \left(S_{r_2} S_{r_2}^T\right) D_-.
\end{aligned} \tag{3.13}
$$

To obtain this equation, we use that $I_m^{\mathcal{M}_+} S_{r_1,+} = D_+ S_{r_1}$ and similar identities.

Finally, for $j \in \hat{\mathcal{J}}$, define

$$
S_{\bar{r}_+,j} := \begin{bmatrix} |u_{d,s_1}^{(j)}| S_{r_1,+} & |u_{d,s_2}^{(j)}| S_{r_2,+} \end{bmatrix}. \tag{3.14}
$$

Note that $S_{\bar{r}_+,j}$ for $j \in \hat{\mathcal{J}}$ are the only stoichiometry-like matrices that depend on the spatial properties of the system.

3.5. Additional SVD notation for stoichiometry-like and the diffusion-only stoichiometry matrices. Generally, (2.2) will be used to write the SVDs of the stoichiometry and stoichiometry-like matrices. However, there are a few additional notational notes and one exception that will be discussed in this section.

First, the exception to this notational format will be for the left singular vectors of $S_{\bar{r}}$. Specifically, when considering the left nullspace of $S_{\bar{r}}$, we will exclude the space spanned by the following set of vectors:

$$
\breve{U}_{\bar{r},ex} := \begin{bmatrix} C_2 I_m^{\mathcal{M}_+} \\ -C_1 I_m^{\mathcal{M}_+} \end{bmatrix}. \tag{3.15}
$$

We define $\breve{U}_{\bar{r}} := \text{span}(\text{null}(S^T, \breve{U}_{\bar{r},ex}))$ and $U_{\bar{r}} := \begin{bmatrix} \hat{U}_{\bar{r}} & \breve{U}_{\bar{r}} \end{bmatrix}$. The reason for this will become clear in the proof to Theorem 2.1.

In some instances, we divide a given singular vector into two components. We will use a subscripted s_1 or s_2 to refer to portions of the singular vectors that correspond to processes that occur in the first or second subregion, respectively. Additionally, we wil use the subscript m_1 and m_2 to represent singular vectors that are divided into two subvectors of size m. More specifically, for the singular vectors of S_d, we have that

$$
u_d = \begin{bmatrix} u_{d,s_1} \\ u_{d,s_2} \end{bmatrix}, \qquad v_d = \begin{bmatrix} v_{d,s_1} \\ v_{d,s_2} \end{bmatrix}, \tag{3.16}
$$

where $u_{d,s_1} \in \mathbb{R}^{n_1}$, $u_{d,s_2} \in \mathbb{R}^{n_2}$, $v_{d,s_1} \in \mathbb{R}^{n_1}$, and $v_{d,s_2} \in \mathbb{R}^{n_2+1}$. For the singular vectors of $S_{\bar{r}}$ and the right singular vectors of $S_{\bar{r}_+,j}$, we define

$$
u_{\bar{r}} = \begin{bmatrix} u_{\bar{r},m_1} \\ u_{\bar{r},m_2} \end{bmatrix}, \quad v_{\bar{r}} = \begin{bmatrix} v_{\bar{r},s_1} \\ v_{\bar{r},s_2} \end{bmatrix}, \quad v_{\bar{r}_+,j} = \begin{bmatrix} v_{\bar{r}_+,j,s_1} \\ v_{\bar{r}_+,j,s_2} \end{bmatrix}, \tag{3.17}
$$

where $u_{\bar{r},m_1}, u_{\bar{r},m_2} \in \mathbb{R}^m$, $v_{\bar{r},s_1} \in \mathbb{R}^{p_1}$, $v_{\bar{r},s_2} \in \mathbb{R}^{p_2}$, $v_{\bar{r}_+,j,s_1} \in \mathbb{R}^{p_1}$, and $v_{\bar{r}_+,j,s_2} \in \mathbb{R}^{p_2}$. We will use the same notation to divide an entire set of right or left singular vectors into components. As an example, we have that

$$
U_d = \begin{bmatrix} U_{d,s_1} \\ U_{d,s_2} \end{bmatrix}, \quad \hat{U}_d = \begin{bmatrix} \hat{U}_{d,s_1} \\ \hat{U}_{d,s_2} \end{bmatrix}, \quad \breve{U}_d = \begin{bmatrix} \breve{U}_{d,s_1} \\ \breve{U}_{d,s_2} \end{bmatrix}. \tag{3.18}
$$

When considering the SVD of the diffusion-only stoichiometry matrices S_d, S_{d_1}, and S_{d_2}, the singular vectors and values can be written explicitly and depend on the specific boundary conditions (see Appendix B). The rank of S_d, given by q_d, also depends on the boundary conditions where

$$q_d = n - 1 + b_2$$

and b_2 is as given in (3.1). This implies that the left nullspace, spanned by $\breve{U}_d$, is empty for both mixed and open boundary conditions.

4. Preliminary lemmas. In this section, we will provide preliminary lemmas that will be used to prove the main result.

First we consider the SVD of the diffusion-only stoichiometry matrices. In the following lemma we prove that, if a given singular value repeats across $\hat{\Sigma}_d$, $\hat{\Sigma}_{d_1}$, and $\hat{\Sigma}_{d_2}$, then it must be in all of these matrices. That is, a singular value will occur in either one or all three matrices.

LEMMA 4.1. *Consider a system with zero flux, mixed, or open boundary conditions and the singular values defined in the matrices $\hat{\Sigma}_d$, $\hat{\Sigma}_{d_1}$, and $\hat{\Sigma}_{d_2}$. If a singular value is in two of these matrices, then it is in all three.*

For singular values that are in all three matrices, the corresponding singular vectors are related as follows:

$$u_d^{(j)} = \begin{bmatrix} C_1 u_{d_1}^{(j_1)} \\ (-1)^{n_1 - j_1} C_2 u_{d_2}^{(j_2)} \end{bmatrix}, \tag{4.1}$$

$$v_d^{(j)} = \begin{bmatrix} C_1 \left(v_{d_1}^{(j_1)} \right)_{1:n_1} \\ (-1)^{n_1 - j_1} C_2 v_{d_2}^{(j_2)} \end{bmatrix}, \tag{4.2}$$

where j, j_1, and j_2 are such that $\sigma_d^{(j)} = \sigma_{d_1}^{(j_1)} = \sigma_{d_2}^{(j_2)}$ and $(v_{d_1}^{(j_1)})_{1:n_1}$ represents the first n_1 entrees of $v_{d_1}^{(j_1)}$. Additionally, the indices j, j_1, and j_2 satisfy $j_1 = C_1^2 j$, $j_2 = C_2^2 j$, and $j = j_1 + j_2$.

The proof of this claim is given in Appendix D.

We next derive formulas for the dimensions of the four fundamental subspaces of S, as given by (2.1). This allows us to verify that the SVD has the correct number of singular vectors in each space.

LEMMA 4.2. *The rank of S, as given by* (2.1)*, is*

$$q = \begin{cases} (n-2)m + m_+ + q_{\bar{r}} & \textit{zero flux}, \\ (n-1)m + m_+ + q_{r_1,-} & \textit{mixed}, \\ nm & \textit{open}. \end{cases} \tag{4.3}$$

The dimension of the nullspace is

$$\breve{q} = \begin{cases} (n_1 - 1)p_1 + (n_2 - 1)p_2 + 3m - m_+ + \breve{q}_{\bar{r}} & \textit{zero flux}, \\ (n_1 - 1)p_1 + n_2 p_2 + 2m - m_+ + \breve{q}_{r_1,-} & \textit{mixed}, \\ n_1 p_1 + n_2 p_2 + m & \textit{open}, \end{cases} \tag{4.4}$$

and the dimension of the left nullspace is

$$\breve{q}_\ell = \begin{cases} m + m_- - q_{\bar{r}} & \textit{zero flux}, \\ m_- - q_{r_1,-} & \textit{mixed}, \\ 0 & \textit{open}. \end{cases} \tag{4.5}$$

Here we are using the rank and nullspace size of $S_{r_1,-}$ and $S_{\bar{r}}$ defined in (3.9) and (3.10). We omit the proof of this claim but note that it involves a sequence of row and column operations on S.

5. SVD derivation. In this section, we present the proofs for Theorems 2.1 and 2.2. Recall in Theorem 2.1 we provide the approximate SVD for a system with a barrier, whereas in Theorem 2.2 we consider a system without a barrier and derive an exact SVD for all relative diffusion/reaction time scales. We will also provide an alternative basis for the nullspace of the system with a barrier (Proposition 5.4).

To prove Theorem 2.1, we will apply concepts from linear perturbation theory and derive the SVD in the limit as diffusion becomes much faster than reactions. Specifically, we first consider the system at $\gamma = 0$ and derive a set of left singular vectors and singular values (i.e., the eigenvectors and eigenvalues of SS^T when $\gamma = 0$). Because this system necessarily has repeating eigenvalues, the associated eigenvectors are not unique and are not necessarily continuous with respect to γ. However, we can apply results from Lemma 4.1 to find the unique orthonormal eigenprojection associated with each eigenvalue. Using these eigenprojections and perturbation theory results, we find the basis of eigenvectors that the system converges to continuously as $\gamma \to 0$. For a review of the necessary concepts from perturbation theory that are used in the proof, see Appendix A.

To prove Theorem 2.2, we show directly that the given equations are equivalent to the SVD. We also show that the SVD given by Theorem 2.2 is a simplified version of the SVD given by Theorem 2.1 (see Corollary 5.5).

5.1. The perturbed and unperturbed systems. The left singular vectors of S are given by the solutions to the following eigenvalue problem:

$$\begin{aligned} &SS^T u_i \\ &= \left(\gamma^2 \begin{bmatrix} I_{n_1} \otimes S_{r_1} S_{r_1}^T & 0 \\ 0 & I_{n_2} \otimes S_{r_2} S_{r_2}^T \end{bmatrix} + S_d S_d^T \otimes D_+ + \left(S_d S_d^T - HH^T \right) \otimes D_- \right) u_i \\ &= \lambda_i u_i. \end{aligned}$$

We will consider solutions to this eigenvalue problem in the limit as diffusion becomes much faster than reactions (i.e., $\gamma \to 0$). To consider this in the context of perturbation theory, we rewrite the eigenvalue problem as follows:

$$T(\gamma) u_i(\gamma) = (T + \gamma^2 T^{(1)}) u_i(\gamma) = \lambda_i(\gamma) u_i(\gamma), \tag{5.1}$$

where now we are explicitly including the dependency of u_i and λ_i on γ. The unperturbed matrix is

$$T := S_d S_d^T \otimes D_+ + \left(S_d S_d^T - HH^T \right) \otimes D_-, \tag{5.2}$$

and the perturbation matrix is

$$T^{(1)} := \begin{bmatrix} I_{n_1} \otimes S_{r_1} S_{r_1}^T & 0 \\ 0 & I_{n_2} \otimes S_{r_2} S_{r_2}^T. \end{bmatrix}. \tag{5.3}$$

Given appropriate choices for the eigenvectors $u_i(\gamma)$, the eigenvectors and eigenvalues will be continuous functions of γ in the neighborhood of $\gamma = 0$.

5.2. The eigenvalues and eigenprojections of the unperturbed system. In this section we provide an orthonormal eigendecomposition for the unperturbed matrix T (Lemma 5.1). We then use this eigendecomposition along with the results from Lemma 4.1 to find the unique orthonormal eigenprojections associated with each eigenvalue (Lemma 5.2).

LEMMA 5.1. *An orthonormal eigendecomposition of T is given as*

$$T = Q_T \Lambda_T Q_T^T = \begin{bmatrix} \hat{Q}_T & \breve{Q}_T \end{bmatrix} \begin{bmatrix} \hat{\Lambda}_T & 0 \\ 0 & 0 \end{bmatrix} \begin{bmatrix} \hat{Q}_T & \breve{Q}_T \end{bmatrix}^T, \tag{5.4}$$

where $\hat{\Lambda}_T$ contains the nonzero eigenvalues of T and

$$\hat{Q}_T = \begin{bmatrix} \hat{Q}_{T,1} & \hat{Q}_{T,2} & \hat{Q}_{T,3} \end{bmatrix}, \tag{5.5}$$

$$\breve{Q}_T = \begin{bmatrix} \breve{Q}_{T,1} & \breve{Q}_{T,2} & \breve{Q}_{T,3} \end{bmatrix}, \tag{5.6}$$

$$\hat{\Lambda}_T = \begin{bmatrix} \hat{\Lambda}_{T,1} & & \\ & \hat{\Lambda}_{T,2} & \\ & & \hat{\Lambda}_{T,3} \end{bmatrix}, \tag{5.7}$$

where

$$\hat{Q}_{T,1} = \hat{U}_d \otimes I_m^{\mathcal{M}_+}, \qquad \hat{Q}_{T,2} = \begin{bmatrix} \hat{U}_{d_1} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-}, \qquad \hat{Q}_{T,3} = \begin{bmatrix} 0 \\ \hat{U}_{d_2} \end{bmatrix} \otimes I_m^{\mathcal{M}_-}, \tag{5.8}$$

$$\breve{Q}_{T,1} = \breve{U}_d \otimes I_m^{\mathcal{M}_+}, \qquad \breve{Q}_{T,2} = \begin{bmatrix} \breve{U}_{d_1} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-}, \qquad \breve{Q}_{T,3} = \begin{bmatrix} 0 \\ \breve{U}_{d_2} \end{bmatrix} \otimes I_m^{\mathcal{M}_-}, \tag{5.9}$$

$$\hat{\Lambda}_{T,1} = \hat{\Sigma}_d^2 \otimes I_{m_+}, \qquad \hat{\Lambda}_{T,2} = \hat{\Sigma}_{d_1}^2 \otimes I_{m_-}, \qquad \hat{\Lambda}_{T,3} = \hat{\Sigma}_{d_2}^2 \otimes I_{m_-}. \tag{5.10}$$

The proof of this lemma is given in Appendix D. From (5.10) it is immediately clear that T has repeating eigenvalues. This implies that the eigenvectors in the matrices given by (5.8) and (5.9) are not unique and, therefore, likely not the eigenvectors the system converges to as $\gamma \to 0$.

Lemma 4.1 and (5.10) imply that eigenvalues of T repeat either m_+, m_-, or $m + m_-$ times. Using this result and the set definitions defined in (3.7), we next identify each unique eigenvalue and find the associated orthonormal eigenprojection.

LEMMA 5.2. *The unique eigenvalues of T are contained in the following three sets:*

$$\left(\sigma_d^{(j)}\right)^2 \text{ for } j = 1, \ldots, n, \quad \left(\sigma_{d_1}^{(j)}\right)^2 \text{ for } j \in \mathcal{J}_1, \quad \left(\sigma_{d_2}^{(j)}\right)^2 \text{ for } j \in \mathcal{J}_2. \tag{5.11}$$

The corresponding unique orthonormal projections are, respectively,

$$P_j = u_d^{(j)} (u_d^{(j)})^T \otimes D_+, \qquad j \in \mathcal{J}, \tag{5.12}$$

$$P_j = u_d^{(j)} (u_d^{(j)})^T \otimes D_+ + \begin{bmatrix} u_{d_1}^{(j_1)} (u_{d_1}^{(j_1)})^T & 0 \\ 0 & u_{d_2}^{(j_2)} (u_{d_2}^{(j_2)})^T \end{bmatrix} \otimes D_-, \quad j \in \mathcal{J}^C, \tag{5.13}$$

$$P_{n_1,j} = \begin{bmatrix} u_{d_1}^{(j)}(u_{d_1}^{(j)})^T & 0 \\ 0 & 0 \end{bmatrix} \otimes D_-, \qquad j \in \mathcal{J}_1, \tag{5.14}$$

$$P_{n_2,j} = \begin{bmatrix} 0 & 0 \\ 0 & u_{d_2}^{(j)}(u_{d_2}^{(j)})^T \end{bmatrix} \otimes D_-, \qquad j \in \mathcal{J}_2, \tag{5.15}$$

where j_1 and j_2 are such that $\sigma_d^{(j)} = \sigma_{d_1}^{(j_1)} = \sigma_{d_2}^{(j_2)}$.

Proof. From Lemma 5.1, we see that every eigenvalue of T is contained in the sets defined by (5.11), and from Lemma 4.1 it follows that a given eigenvalue is only contained in one of the sets. Therefore, (5.11) contains the unique eigenvalues of T.

To find the orthonormal eigenprojection associated with each eigenvalue we will use the eigenvectors as defined in Lemma 5.1. Specifically, using the eigenvectors given by (5.8) and (5.9), we can use (A.4) in Appendix A to obtain the unique orthonormal eigenprojection.

For $j \in \mathcal{J}$ the m_+ eigenvectors associated with $(\sigma_d^{(j)})^2$ are the columns of $u_d^{(j)} \otimes I_m^{\mathcal{M}_+}$ (see Lemma 5.1). Therefore, the associated eigenprojection is

$$\begin{aligned} P_j &= \sum_{i \in \mathcal{M}_+} \left(u_d^{(j)} \otimes I_m^{(i)}\right)\left(u_d^{(j)} \otimes I_m^{(i)}\right)^T \\ &= \sum_{i \in \mathcal{M}_+} u_d^{(j)}(u_d^{(j)})^T \otimes I_m^{(i)}(I_m)_i \\ &= u_d^{(j)}(u_d^{(j)})^T \otimes D_+. \end{aligned} \tag{5.16}$$

For $j \in \mathcal{J}^C$, there are $m+m_-$ eigenvectors associated with $(\sigma_d^{(j)})^2$. These eigenvectors are given by the columns of the following three matrices:

$$u_d^{(j)} \otimes I_m^{\mathcal{M}_+}, \qquad \begin{bmatrix} u_{d_1}^{(j_1)} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-}, \qquad \begin{bmatrix} 0 \\ u_{d_2}^{(j_2)} \end{bmatrix} \otimes I_m^{\mathcal{M}_-},$$

where j_1 and j_2 are as given by Lemma 4.1. Using the same logic as shown in (5.16), we have that the eigenprojection can be written as

$$P_j = u_d^{(j)}(u_d^{(j)})^T \otimes D_+ + \begin{bmatrix} u_{d_1}^{(j_1)}(u_{d_1}^{(j_1)})^T & 0 \\ 0 & 0 \end{bmatrix} \otimes D_- + \begin{bmatrix} 0 & 0 \\ 0 & u_{d_2}^{(j_2)}(u_{d_2}^{(j_2)})^T \end{bmatrix} \otimes D_-. \tag{5.17}$$

Applying analogous logic for $(\sigma_{d_1}^{(j)})^2$ for $j \in \mathcal{J}_1$ and $(\sigma_{d_2}^{(j)})^2$ for $j \in \mathcal{J}_2$ leads to the eigenprojections $P_{n_1,j}$ and $P_{n_2,j}$, respectively, as written in the claim. ∎

5.3. The approximate left singular vectors of S. We next use the eigenprojections given in Lemma 5.2 to derive the left singular vectors (i.e., eigenvectors of T) that the system converges to continuously as $\gamma \to 0$. This provides an approximate orthonormal basis for the column space and left nullspace of S as $\gamma \to 0$.

PROPOSITION 5.3. *A complete set of left singular vectors of S and corresponding singular values is given by the columns/diagonal elements of the following matrices:*

$$U_{1,j} = u_d^{(j)} \otimes I_m^{\mathcal{M}_+} U_{\bar{r}_+,j}, \qquad \Sigma_{1,j}^2 = \left(\sigma_d^{(j)}\right)^2 I_{m_+} + \gamma^2 \left(\hat{\Sigma}_{\bar{r}_+,j}^2\right)_{m_+}, \quad j \in \mathcal{J},$$

$$U_2 = \begin{bmatrix} U_{d_1}^{\mathcal{J}_1} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-} U_{r_1,-}, \qquad \Sigma_2^2 = (\Sigma_{d_1}^2)^{\mathcal{J}_1} \oplus \gamma^2 \left(\hat{\Sigma}_{r_1,-}^2\right)_{m_-},$$

$$U_3 = \begin{bmatrix} 0 \\ U_{d_2}^{\hat{\mathcal{J}}_2} \end{bmatrix} \otimes I_m^{\mathcal{M}_-} U_{r_2,-}, \qquad \Sigma_3^2 = (\Sigma_{d_2}^2)^{\hat{\mathcal{J}}_2} \oplus \gamma^2 \left(\hat{\Sigma}_{r_2,-}^2\right)_{m_-},$$

$$U_4 = \begin{bmatrix} \frac{1}{C_1} U_{d,s_1}^{\mathcal{J}^C} \otimes U_{\bar{r},m_1} \\ \frac{1}{C_2} U_{d,s_2}^{\mathcal{J}^C} \otimes U_{\bar{r},m_2} \end{bmatrix}, \qquad \Sigma_4^2 = (\Sigma_d^2)^{\mathcal{J}^C} \oplus \gamma^2 \left(\hat{\Sigma}_{\bar{r}}^2\right)_{q_{\bar{r}}+\breve{q}_{\bar{r}}}.$$

Unlike Theorem 2.1, we are not identifying which singular vectors correspond to nonzero verse zero singular values. This is because the definitions provided in Proposition 5.3 allow for a direct comparison with the eigenprojections given by Lemma 5.2. However, Proposition 5.3 immediately gives the left singular vectors in Theorem 2.1. To see this, note that

$$\begin{aligned} \hat{U}_{1,j} &= U_{1,j}, \\ \begin{bmatrix} \hat{U}_2 & \hat{U}_3 & \breve{U}_1 \end{bmatrix} &= U_2 P_1, \\ \hat{U}_4 &= U_3, \\ \begin{bmatrix} \hat{U}_5 & \hat{U}_6 & \breve{U}_2 \end{bmatrix} &= U_4 P_2, \end{aligned}$$

where the matrices on the left of the equality represent those defined in Theorem 2.1 and the matrices on the right represent those defined in Proposition 5.3. The permutation matrices P_1 and P_2 are required to ensure the columns are in the correct order for comparison. Note that the singular values are related analogously.

Proof of Proposition 5.3. We will prove this result by considering the eigenprojections of T defined in Lemma 5.2. For each eigenprojection we calculate $\tilde{T}^{(1)}$, given by (A.7), and its eigendecomposition. We will write

$$\tilde{T}_\bullet^{(1)} = P_\bullet T^{(1)} P_\bullet, \tag{5.18}$$

where $\bullet$ depends on the eigenvalue/eigenprojection we are considering and $T^{(1)}$ is given by (5.3). In the limit as $\gamma \to 0$, the eigenvectors of (5.18) in the range of $P_\bullet$ are equivalent to the left singular vectors. Additionally, the eigenvalues of (5.18) are used to find linear approximations of the singular values as shown by (A.8).

First for $j \in \mathcal{J}$, consider the eigenprojection given by (5.12). We have that

$$\tilde{T}_j^{(1)} = P_j T^{(1)} P_j. \tag{5.19}$$

To find the eigendecomposition of (5.19), we apply Property C.1 given in Appendix C to show that

$$\begin{aligned} \tilde{T}_j^{(1)} &= u_d^{(j)} (u_d^{(j)})^T \otimes D_+ \left(|u_{d,\mathcal{N}_1}^{(j)}|^2 S_{r_1} S_{r_1}^T + |u_{d,\mathcal{N}_2}^{(j)}|^2 S_{r_2} S_{r_2}^T \right) D_+ \\ &= u_d^{(j)} (u_d^{(j)})^T \otimes I_m^{\mathcal{M}_+} S_{\bar{r}_+,j} S_{\bar{r}_+,j}^T I_{m,\mathcal{M}_+}, \end{aligned}$$

where we recall that $S_{\bar{r}_+,j}$ is given by (3.14). The eigenvectors of $\tilde{T}_j^{(1)}$ in the range of P_j are the columns of

$$\hat{U}_{1,j} = u_d^{(j)} \otimes I_m^{\mathcal{M}_+} U_{\bar{r}_+,j}, \tag{5.20}$$

and the corresponding eigenvalues are contained in $(\Sigma_{\bar{r}_+,j}^2)_{m_+}$. Using (A.8) this leads to the following linear approximation of the singular values:

$$\hat{\Sigma}_{1,j} = \sqrt{\left(\sigma_d^{(j)}\right)^2 I_{m_+} + \gamma^2 \left(\Sigma_{\bar{r}_+,j}^2\right)_{m_+}}. \tag{5.21}$$

Similarly, consider the eigenprojections given by (5.14) and (5.15). Using (5.18) and Property C.2 given in Appendix C, we have that

$$\tilde{T}^{(1)}_{n_1,j} = \begin{bmatrix} u^{(j)}_{d_1}(u^{(j)}_{d_1})^T & 0 \\ 0 & 0 \end{bmatrix} \otimes D_- \left(S_{r_1} S_{r_1}^T\right) D_- \tag{5.22}$$

and

$$\tilde{T}^{(1)}_{n_2,j} = \begin{bmatrix} 0 & 0 \\ 0 & u^{(j)}_{d_2}(u^{(j)}_{d_2})^T \end{bmatrix} \otimes D_- \left(S_{r_2} S_{r_2}^T\right) D_-. \tag{5.23}$$

The eigenvectors of $\tilde{T}^{(1)}_{n_1,j}$ and $\tilde{T}^{(1)}_{n_2,j}$ that are in the range of $P_{n_1,j}$ and $P_{n_2,j}$ are

$$U_{n_1,j} = \begin{bmatrix} u^{(j)}_{d_1} \\ 0 \end{bmatrix} \otimes I_m^{\mathcal{M}_-} U_{r_1,-} \quad \text{and} \quad U_{n_2,j} = \begin{bmatrix} 0 \\ u^{(j)}_{d_2} \end{bmatrix} \otimes I_m^{\mathcal{M}_-} U_{r_2,-}, \tag{5.24}$$

and the corresponding eigenvalues are $\Sigma^2_{r_1,-}$ and $\Sigma^2_{r_2,-}$, respectively. Recall the definition of $S_{r_i,-}$ is given by (3.9). Again, using (A.8) this leads to the singular values given by Σ_2 and Σ_3.

Finally, suppose $j \in \mathcal{J}^C$, and consider the eigenprojection P_j given by (5.13). Let j_1 and j_2 be as given by Lemma 4.1. For notational simplicity we will make the following substitutions:

$$\begin{aligned} u &= u^{(j)}_d, \\ u_1 &= u^{(j_1)}_{d_1}, \\ u_2 &= u^{(j_2)}_{d_2}, \\ \alpha &= (-1)^{n_1 - j_1}. \end{aligned}$$

We will also use the matrices B_i for $i = 1, \ldots, 5$ given by (3.13). Using Properties C.1 and C.2 given in Appendix C, the eigenvector relationship given by (4.1) in Lemma 4.1, and (5.18), we have that

$$\begin{aligned} \tilde{T}^{(1)}_j = {} & uu^T \otimes B_1 + \begin{bmatrix} u_1 u_1^T & 0 \\ 0 & 0 \end{bmatrix} \otimes B_2 + \begin{bmatrix} 0 & 0 \\ 0 & u_2 u_2^T \end{bmatrix} \otimes B_3 \\ & + \begin{bmatrix} C_1^2 u_1 u_1^T & 0 \\ \alpha C_1 C_2 u_2 u_1^T & 0 \end{bmatrix} \otimes B_4 + \begin{bmatrix} 0 & \alpha C_1 C_2 u_1 u_2^T \\ 0 & C_2^2 u_2 u_2^T \end{bmatrix} \otimes B_5 \\ & + \begin{bmatrix} C_1^2 u_1 u_1^T & \alpha C_1 C_2 u_1 u_2^T \\ 0 & 0 \end{bmatrix} \otimes B_4^T + \begin{bmatrix} 0 & 0 \\ \alpha C_1 C_2 u_2 u_1^T & C_2^2 u_2 u_2^T \end{bmatrix} \otimes B_5^T. \end{aligned}$$

To obtain the eigendecomposition of $\tilde{T}^{(1)}_j$ for $j \in \mathcal{J}^C$, we will suppose that the eigenvectors take the form

$$v = \begin{bmatrix} u_1 \otimes v_1 \\ \alpha u_2 \otimes v_2 \end{bmatrix} \tag{5.25}$$

and derive the values of $v_1, v_2 \in \mathbb{R}^{m \times 1}$.

We have that

$$\tilde{T}_j^{(1)} v = \begin{bmatrix} u_1 \otimes (C_1^2 B_1 v_1 + C_1 C_2 B_1 v_2) \\ \alpha u_2 \otimes (C_1 C_2 B_1 v_1 + C_2^2 B_1 v_2) \end{bmatrix} + \begin{bmatrix} u_1 \otimes B_2 v_1 \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ \alpha u_2 \otimes B_3 v_2 \end{bmatrix} + \begin{bmatrix} u_1 \otimes C_1^2 B_4 v_1 \\ \alpha u_2 \otimes C_1 C_2 B_4 v_1 \end{bmatrix} + \begin{bmatrix} u_1 \otimes C_1 C_2 B_5 v_2 \\ \alpha u_2 \otimes C_2^2 B_5 v_2 \end{bmatrix} + \begin{bmatrix} u_1 \otimes B_4^T (C_1^2 v_1 + C_2^2 v_2) \\ 0 \end{bmatrix} + \begin{bmatrix} 0 \\ \alpha u_2 \otimes B_5^T (C_1^2 v_1 + C_2^2 v_2) \end{bmatrix} = \lambda \begin{bmatrix} u_1 \otimes v_1 \\ \alpha u_2 \otimes v_2 \end{bmatrix}, \tag{5.26}$$

where we are using Property C.3 to calculate $(uu^T \otimes B_1)v$. Therefore, for v to be an eigenvector of $\tilde{T}_j^{(1)}$ the following smaller eigenvalue problem must hold:

$$B \begin{bmatrix} v_1 \\ v_2 \end{bmatrix} = \lambda \begin{bmatrix} v_1 \\ v_2 \end{bmatrix},$$

where B is given by (3.12). This implies that $[v_1; v_2]$ is equal to a left singular vector of $S_{\bar{r}}$, given by (3.10). Note that since $[v_1; v_2]$ is a unit vector, v is also a unit vector and, thus, properly normalized.

Only some of the singular vectors of $S_{\bar{r}}$ result in eigenvectors v that are in the range of P_j. Specifically, note the singular vectors contained in the columns of $\breve{U}_{\bar{r},ex}$ (see (3.15)) result in eigenvectors that are not in the range of P_j. To see this, note that when $[v_1, v_2] = \breve{U}_{\bar{r},ex}$,

$$\begin{aligned} P_j v &= \left(uu^T \otimes D_+ + \begin{bmatrix} u_1 u_1^T & 0 \\ 0 & u_2 u_2^T \end{bmatrix} \otimes D_- \right) \begin{bmatrix} u_1 \otimes C_2 I_m^{\mathcal{M}^+} \\ \alpha u_2 \otimes -C_1 I_m^{\mathcal{M}^+} \end{bmatrix} \\ &= \begin{bmatrix} C_1^2 u_1 \otimes C_2 I_m^{\mathcal{M}^+} - C_1 C_2 u_1 \otimes C_1 I_m^{\mathcal{M}^+} \\ \alpha C_1 C_2 u_2 \otimes C_2 I_m^{\mathcal{M}^+} - \alpha C_2^2 u_2 \otimes C_1 I_m^{\mathcal{M}^+} \end{bmatrix} \\ &= 0. \end{aligned}$$

Coupled with the left singular vector relationship given by (4.1), this completes our derivation of the singular vectors contained in U_4. Using (A.8), we obtain the singular values given by Σ_4. ∎

5.4. Right singular vectors. Next we will approximate the right singular vectors of the system in the limit as $\gamma \to 0$. To derive the right singular vectors that represent a basis for the row space, we use the following equation and the results from Proposition 5.3. For $i = 1, \ldots, 5$,

$$\hat{V}_i = S^T \hat{U}_i \hat{\Sigma}_i^{-1}. \tag{5.27}$$

Note that the equations for $\hat{U}_i$ and $\hat{\Sigma}_i$ are given by Theorem 2.1; however, their derivation is found in the proof to Proposition 5.3. Using this equation, we obtain the set of right singular vectors given by Theorem 2.1.

To complete the proof of Theorem 2.1, it remains to show that $\breve{V}$ defines a orthonormal basis for the nullspace that the system approaches as $\gamma \to 0$. The complete proof of this is given in Appendix D. Note that an alternative asymptotic nullspace can be found. The nullspace given by Theorem 2.1 has the property that it is orthogonal for small values of γ and $S\breve{V} \to 0$ as $\gamma \to 0$. It is possible to instead find a basis such that $S\breve{V} = 0$ for small values of γ and the basis approaches being orthogonal in the limit as $\gamma \to 0$. The following lemma provides the equations for this alternative basis.

PROPOSITION 5.4. *The column vectors in the following matrices span the nullspace of S as given by* (2.1)*, and this basis is orthogonal in the limit as $\gamma \to 0$:*

$$\breve{V} = \begin{bmatrix} \breve{V}_1 & \breve{V}_2 & \breve{V}_3 & \breve{V}_4 & \breve{V}_5 \end{bmatrix}, \tag{5.28}$$

where

$$\begin{aligned}
\breve{V}_1 &= \begin{bmatrix} U_{d_1}^{n\setminus(\mathcal{J}^C\cup\hat{\mathcal{J}}_1)} \otimes \breve{V}_{r_1,-} \\ \hline 0 \\ \hline -\gamma w_1 \otimes S_{r_1}\breve{V}_{r_1,-} \end{bmatrix} (I_{\breve{q}_{d_1}\breve{q}_{r_1,-}} + \gamma^2 W_1)^{-\frac{1}{2}}, \\
\breve{V}_2 &= \begin{bmatrix} \hat{U}_{d_1}\hat{\Sigma}_{d_1} \otimes V_{r_1} \\ \hline 0 \\ \hline -\gamma \hat{V}_{d_1} \otimes U_{r_1}\Sigma_{r_1} \\ 0 \end{bmatrix} \left(\hat{\Sigma}_{d_1}^2 \oplus \gamma^2 \left(\hat{\Sigma}_{r_1}^2\right)_{p_1}\right)^{-\frac{1}{2}}, \\
\breve{V}_3 &= \begin{bmatrix} \frac{1}{C_1}\breve{U}_{d,s_1} \otimes \breve{V}_{\bar{r},s_1} \\ \hline \frac{1}{C_2}\breve{U}_{d,s_2} \otimes \breve{V}_{\bar{r},s_2} \\ \hline -\gamma w_2 \otimes S_{r_1}\breve{V}_{\bar{r},s_1} \end{bmatrix} (I_{\breve{q}_d\breve{q}_{\bar{r}}} + \gamma^2 W_2)^{-\frac{1}{2}}, \\
\breve{V}_4 &= \begin{bmatrix} 0 \\ \hline \hat{U}_{d_2}\hat{\Sigma}_{d_2} \otimes V_{r_2} \\ \hline 0 \\ -\gamma \hat{V}_{d_2} \otimes U_{r_2}\Sigma_{r_2} \end{bmatrix} \left(\hat{\Sigma}_{d_2}^2 \oplus \gamma^2 \left(\hat{\Sigma}_{r_2}^2\right)_{p_2}\right)^{-\frac{1}{2}}, \\
\breve{V}_5 &= \begin{bmatrix} 0 & 0 \\ \hline \breve{V}_d \otimes I_m^{\mathcal{M}_+} & I_{n+1}^{\mathcal{B}} \otimes I_m^{\mathcal{M}_-} \end{bmatrix},
\end{aligned} \tag{5.29}$$

where

$$w_1 = \hat{V}_d\hat{\Sigma}_d^{-1}\hat{U}_d^T \begin{bmatrix} U_{d_1}^{n\setminus(\mathcal{J}^C\cup\hat{\mathcal{J}}_1)} \\ 0 \end{bmatrix}, \qquad (W_1)_{ii} = w_2^T w_2 \left(S_{r_1}\breve{V}_{r_1,-}^{(i)}\right)^T S_{r_1}\breve{V}_{r_1,-}^{(i)},$$

and

$$w_2 = \frac{n}{n_2 + \sqrt{n_1 n_2}}\hat{V}_d\hat{\Sigma}_d^{-1}\hat{U}_d^T \begin{bmatrix} \frac{1}{C_1}\breve{U}_{d,s_1} \\ -\frac{1}{C_2}\breve{U}_{d,s_2} \end{bmatrix}, \quad (W_2)_{ii} = w_1^T w_1 \left(S_{r_1}\breve{V}_{\bar{r},s_1}^{(i)}\right)^T S_{r_1}\breve{V}_{\bar{r},s_1}^{(i)}.$$

Notice that only $\breve{V}_1$ and $\breve{V}_3$ have changed when compared to Theorem 2.1.

5.5. SVD for systems with spatially homogeneous reactions and diffusion. In the previous section we presented the approximate SVD for a system with a spatial barrier. Here, we will consider a specific scenario where there is no barrier and the reactions are the same across the domain. In terms of the previous notation, this is equivalent to setting $m_+ = m$, $m_- = 0$, and $S_{r_1} = S_{r_2}$. Under these conditions, we will show that the SVD reduces to a simplified form (Corollaries 5.5 and 5.6) and becomes exact for all values of γ, i.e., prove Theorem 2.2. Below we set $S_r = S_{r_1}$ and refer to the SVD of S_r using the notation given in (2.2).

First note that under these conditions the SVDs of the stoichiometry-like matrices are simplified. We have that the SVD of $S_{\bar{r}_+,j}$ is

$$U_{\bar{r}_+,j} = U_r, \qquad V_{\bar{r}_+,j} = \begin{bmatrix} |u_{d,s_1}^{(j)}|V_r \\ |u_{d,s_2}^{(j)}|V_r \end{bmatrix}, \qquad \hat{\Sigma}_{\bar{r}_+,j} = \hat{\Sigma}_r \tag{5.30}$$

and the SVD of $S_{\bar{r}}$ is

$$U_{\bar{r}} = \begin{bmatrix} C_1 U_r \\ C_2 U_r \end{bmatrix}, \qquad V_{\bar{r}} = \begin{bmatrix} C_1 V_r \\ C_2 V_r \end{bmatrix}, \qquad \hat{\Sigma}_{\bar{r}} = \hat{\Sigma}_r. \tag{5.31}$$

This result is shown by considering the equations for $S_{\bar{r}}$ and $S_{\bar{r}_+,j}$ as given by (3.10) and (3.14), respectively. Using (5.30) and (5.31), we next show that the SVD given by Theorem 2.1 reduces to a simplified form.

COROLLARY 5.5. *The left singular vectors given by Theorem* 2.1 *reduce to the columns of the matrix*

$$U = U_d \otimes U_r, \tag{5.32}$$

and the singular values reduce to the diagonal of

$$\Sigma = \Sigma_d \otimes \Sigma_r. \tag{5.33}$$

Proof. To prove this corollary we will examine the SVD for a system with a barrier. Specifically, we consider the left singular vectors and values as written in Proposition 5.3. We will show that these vectors and values reduce to the singular vectors and values given in the corollary statement

First, note that U_2 and U_3 are empty matrices since $\mathcal{M}_-$ is an empty set. For $U_{1,j}$, $j \in \mathcal{J}$, using that $I_m^{\mathcal{M}_+} = I_m$ and the SVD given by (5.30) we have that,

$$\hat{U}_{1,j} = u_d^{(j)} \otimes U_r, \qquad \Sigma_{1,j}^2 = \left(\sigma_d^{(j)}\right)^2 I_m + \gamma^2 \Sigma_r^2. \tag{5.34}$$

For U_4 using the SVD given by (5.31) and that $q_{\bar{r}} = q_r$ and $\breve{q}_{\bar{r}} = m - q_r$, we have that

$$U_4 = U_d^{\mathcal{J}^C} \otimes U_r, \qquad \Sigma_4 = (\Sigma_d^2)^{\mathcal{J}^C} \oplus \gamma^2 \left(\hat{\Sigma}_r^2\right)_m. \tag{5.35}$$

Putting these results together we obtain the set of left singular vectors and singular values given by the corollary statement. ∎

COROLLARY 5.6. *The right singular vectors of* S *given by Theorem* 2.1 *reduce to the following for the simplified system:*

$$\hat{V} = \begin{bmatrix} \gamma\left(\hat{U}_d \otimes \hat{V}_r \hat{\Sigma}_r\right)\tilde{\Sigma}^{-1} & 0 & \breve{U}_d \otimes \hat{V}_r \\ \left(\hat{V}_d \hat{\Sigma}_d \otimes \hat{U}_r\right)\tilde{\Sigma}^{-1} & \hat{V}_d \otimes \breve{U}_r & 0 \end{bmatrix}, \tag{5.36}$$

$$\breve{V} = \begin{bmatrix} \left(\hat{U}_d \hat{\Sigma}_d \otimes \hat{V}_r\right)\tilde{\Sigma}^{-1} & \hat{U}_d \otimes \breve{V}_r & 0 \\ -\gamma\left(\hat{V}_d \otimes \hat{U}_r \hat{\Sigma}_r\right)\tilde{\Sigma}^{-1} & 0 & \breve{V}_d \otimes U_r \end{bmatrix}. \tag{5.37}$$

Proof. For the right singular vectors we will use the equations as given in Theorem 2.1. We will show the proof for $\breve{V}$ and note that the proof for $\breve{V}$ follows analogously. Note that $\hat{V}_2$, $\hat{V}_3$, and $\hat{V}_4$ are empty.

For $\hat{V}_{1,j}$, using the SVD given by (5.30), we have that

$$\hat{V}_{1,j} = \begin{bmatrix} \frac{\gamma}{|u^{(j)}_{d,s_1}|} u^{(j)}_{d,s_1} \otimes V_{\bar{r}_+,j,s_1} \Sigma^T_{\bar{r}_+,j} \\ \frac{\gamma}{|u^{(j)}_{d,s_2}|} u^{(j)}_{d,s_2} \otimes V_{\bar{r}_+,j,s_2} \Sigma^T_{+,j} \\ \hline v^{(j)}_d \sigma^{(j)}_d \otimes I^{\mathcal{M}_+}_m U_{\bar{r}_+,j} \end{bmatrix} \hat{\Sigma}^{-1}_{1,j} \tag{5.38}$$

$$= \begin{bmatrix} \gamma u^{(j)}_d \otimes V_r \Sigma^T_r \\ \hline v^{(j)}_d \sigma^{(j)}_d \otimes U_r \end{bmatrix} \left(\left(\sigma^{(j)}_d \right)^2 I_m + \gamma^2 \left(\Sigma^2_r \right)_m \right)^{-1/2}. \tag{5.39}$$

For $\hat{V}_5$ and $\hat{V}_6$, using the SVD given by (5.31), we have that

$$\hat{V}_5 = \begin{bmatrix} \frac{\gamma}{C_1} U^{\hat{\mathcal{J}}^C}_{d,s_1} \otimes \begin{bmatrix} \hat{V}_{\bar{r},s_1} \hat{\Sigma}_{\bar{r}} & 0 \end{bmatrix} \\ \frac{\gamma}{C_2} U^{\hat{\mathcal{J}}^C}_{d,s_2} \otimes \begin{bmatrix} \hat{V}_{\bar{r},s_2} \hat{\Sigma}_{\bar{r}} & 0 \end{bmatrix} \\ \hline \frac{1}{C_1} V^{\hat{\mathcal{J}}^C}_{d,s_1} \Sigma^{\hat{\mathcal{J}}^C}_d \otimes U_{\bar{r},m_1} \\ \frac{1}{C_2} V^{\hat{\mathcal{J}}^C}_{d,s_2} \Sigma^{\hat{\mathcal{J}}^C}_d \otimes U_{\bar{r},m_2} \end{bmatrix} \hat{\Sigma}^{-1}_5$$

$$= \begin{bmatrix} \gamma U^{\hat{\mathcal{J}}^C}_d \otimes V_r \Sigma_r \\ \hline V^{\hat{\mathcal{J}}^C}_d \Sigma^{\hat{\mathcal{J}}^C}_d \otimes U_r \end{bmatrix} \left((\hat{\Sigma}^2_d)^{\hat{\mathcal{J}}^C} \oplus \gamma^2 \left(\hat{\Sigma}^2_r \right)_m \right)^{-1/2},$$

$$\hat{V}_6 = \begin{bmatrix} \frac{\gamma}{C_1} \breve{U}_{d,s_1} \otimes \hat{V}_{\bar{r},s_1} \hat{\Sigma}_{\bar{r}} \\ \frac{\gamma}{C_2} \breve{U}_{d,s_2} \otimes \hat{V}_{\bar{r},s_2} \hat{\Sigma}_{\bar{r}} \\ \hline 0 \end{bmatrix} \hat{\Sigma}^{-1}_6$$

$$= \begin{bmatrix} \gamma \breve{U}_d \otimes \hat{V}_r \hat{\Sigma}_r \\ \hline 0 \end{bmatrix} \left(I_{n-q_d} \otimes \gamma^2 \hat{\Sigma}^2_r \right)^{-1/2}$$

$$= \begin{bmatrix} \gamma \breve{U}_d \otimes \hat{V}_r \\ \hline 0 \end{bmatrix}.$$

Putting this together and rearranging columns we obtain the equation for $\hat{V}$ given in the corollary statement. ∎

Finally, we will prove the main result that the SVD of the simplified S is valid for all values of γ.

Proof of Theorem 2.2. To show that (2.9) is the SVD of S as given by (2.8), it suffices to show that U and V are orthogonal matrices and $S = \hat{U}\hat{\Sigma}\hat{V}^T$.

We first show that U and V are orthogonal matrices. Recall that $U \in \mathbb{R}^{nm \times nm}$, where $U = U_d \otimes U_r$. We have that

$$(U_d \otimes U_r)^T (U_d \otimes U_r) = U^T_d U_d \otimes U^T_r U_r = I_{nm}. \tag{5.40}$$

It follows that U is orthogonal.

For V, we have that

$$\begin{aligned}\hat{V}^T\hat{V} &= \begin{bmatrix} \gamma\tilde{\Sigma}^{-1}\left(\hat{U}_d^T\otimes\hat{\Sigma}_r\hat{V}_r^T\right) & \tilde{\Sigma}^{-1}\left(\hat{\Sigma}_d\hat{V}_d^T\otimes\hat{U}_r^T\right) \\ 0 & \hat{V}_d^T\otimes\breve{U}_r^T \\ \breve{U}_d^T\otimes\hat{V}_r^T & 0 \end{bmatrix} \begin{bmatrix} \gamma\left(\hat{U}_d\otimes\hat{V}_r\hat{\Sigma}_r\right)\tilde{\Sigma}^{-1} & 0 & \breve{U}_d\otimes\hat{V}_r \\ \left(\hat{V}_d\hat{\Sigma}_d\otimes\hat{U}_r\right)\tilde{\Sigma}^{-1} & \hat{V}_d\otimes\breve{U}_r & 0 \end{bmatrix} \\ &= \begin{bmatrix} \gamma^2\tilde{\Sigma}^{-1}\left(\hat{U}_d^T\hat{U}_d\otimes\hat{\Sigma}_r^2+\hat{\Sigma}_d^2\otimes\hat{U}_r^T\hat{U}_r\right)\tilde{\Sigma}^{-1} & 0 & 0 \\ 0 & \hat{V}_d^T\hat{V}_d\otimes\breve{U}_r^T\breve{U}_r & 0 \\ 0 & 0 & \breve{U}_d^T\breve{U}_d\otimes\hat{V}_r^T\hat{V}_r \end{bmatrix} \\ &= I,\end{aligned}$$

where we recall that $\tilde{\Sigma}^2 = \hat{\Sigma}_d^2 \oplus (\gamma\hat{\Sigma}_r)^2$. It can similarly be shown that $\hat{V}^T\breve{V} = 0$, $\breve{V}\hat{V}^T = 0$, and $\breve{V}^T\breve{V} = I$.

Next, we will show that $S = \hat{U}\hat{\Sigma}\hat{V}^T$:

$$\begin{aligned}\hat{U}\hat{\Sigma}\hat{V}^T &= \begin{bmatrix}\hat{U}_d\otimes\hat{U}_r & \hat{U}_d\otimes\breve{U}_r & \breve{U}_d\otimes\hat{U}_r\end{bmatrix} \begin{bmatrix} \gamma\left(\hat{U}_d^T\otimes\hat{\Sigma}_r\hat{V}_r^T\right) & \left(\hat{\Sigma}_d\hat{V}_d^T\otimes\hat{U}_r^T\right) \\ 0 & \hat{\Sigma}_d\hat{V}_d^T\otimes\breve{U}_r^T \\ \gamma\breve{U}_d^T\otimes\hat{\Sigma}_r\hat{V}_r^T & 0 \end{bmatrix} \\ &= \begin{bmatrix}\gamma(\hat{U}_d\hat{U}_d^T+\breve{U}_d\breve{U}_d^T)\otimes S_r & S_d\otimes(\hat{U}_r\hat{U}_r^T+\breve{U}_r\breve{U}_r^T)\end{bmatrix} \\ &= \begin{bmatrix}\gamma U_dU_d^T\otimes S_r & S_d\otimes U_rU_r^T\end{bmatrix} \\ &= \begin{bmatrix}\gamma I_n\otimes S_r & S_d\otimes I_m\end{bmatrix}.\end{aligned}$$

Therefore, Theorem 2.1 gives the SVD of S at all values of γ. ∎

5.6. Example SVD of the model for the Calvin cycle in cyanobacteria including error analysis. In this section we present an error analysis for the approximate SVD of an example stoichiometry matrix. We demonstrate numerically that the approximate SVD presented in Theorem 2.1 converges to the true SVD in the limit as $\gamma \to 0$.[4] We will consider a simplified set of equations that describes part of the Calvin cycle in cyanobacteria. Specifically, cyanobacteria have cellular compartments called carboxysomes that serve to concentrate carbon within the cell [12]. Compartmentalization of the enzymes Rubisco and carbonic anhydrase increases the amount of carbon fixation while minimizing the competing oxygenase reaction and flux towards photorespiration. This is an example of the type of system that could, in the future, be investigated more thoroughly with the approach presented here.

We consider a system with $n = 8$ compartments, where $n_1 = 2$ and $n_2 = 6$. The first subregion in the domain represents the carboxysome, and the second region represents the cytoplasm. We will consider the scenario of mixed boundary conditions where fluxes are allowed only into the right side of the domain (i.e., into the cytoplasm region). Biologically, this scenario could represent a radially symmetric region in the cell centered on a carboxysome. The species in this system, as ordered in the stoichiometry matrix, are bicarbonate (HCO_3^-), ribulose 1,5-bisphosphate (RuBP), carbon dioxide (CO_2), 3-phosphoglycerate (3 PGA), oxygen (O_2), and 2-phosphoglycolate (2 PG). The reactions are given as

$$\begin{aligned} &\text{(R1)} \quad \mathrm{RuBP} + \mathrm{CO_2} \longrightarrow 2\,(3\,\mathrm{PGA}) && \text{(carbon fixation)},\\ &\text{(R2)} \quad \mathrm{RuBP} + \mathrm{O_2} \longrightarrow 3\,\mathrm{PGA} + 2\,\mathrm{PG} && \text{(oxygenation)},\\ &\text{(R3)} \quad \mathrm{CO_2} \rightleftharpoons \mathrm{HCO_3^-}. \end{aligned} \tag{5.41}$$

[4] MATLAB code available at www.github.com/MathBioCU/ReacDiffStoicSVD.

It is known that O_2 and CO_2 cannot diffuse into the carboxysome [7, 9]. Therefore we set $\mathcal{M}_- = \{3, 5\}$ and $\mathcal{M}_+ = \{1, 2, 4, 6\}$.

Given that O_2 is not present in the carboxysome, we know that only (R1) and (R3) occur in the first subregion. This leads to the following reaction-only stoichiometry matrices in the first and second region, respectively,

$$S_{r_1} = \begin{bmatrix} 0 & -1 \\ -1 & 0 \\ -1 & 1 \\ 2 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix} \qquad S_{r_2} = \begin{bmatrix} 0 & 0 & -1 \\ -1 & -1 & 0 \\ -1 & 0 & 1 \\ 2 & 1 & 0 \\ 0 & -1 & 0 \\ 0 & 1 & 0 \end{bmatrix}. \tag{5.42}$$

Using the defined parameters, we applied the equations in Theorem 2.1 at multiple values of γ and compared the results to the numerical SVD in MATLAB (Figure 1). At each value of γ, we find the maximum norm error for the singular vectors and values, as given by

$$\begin{aligned} \sigma_{err} &= \max_i |\sigma^{(i)} - \sigma^{(i)}_{num}|, \\ u_{err} &= \max_i \|u^{(i)} - u^{(i)}_{num}\|_2, \\ v_{err} &= \max_i \|v^{(i)} - v^{(i)}_{num}\|_2, \end{aligned} \tag{5.43}$$

where the *num* subscript refers to values found numerically in MATLAB. As expected we find that the error approaches zero as $\gamma \to 0$. In this comparison the singular vectors/values are sorted by the magnitude of the singular value. Singular values between the numerical and approximate SVD (and hence singular vectors) are paired by finding those that are closest to each other in size. Note that in the error analysis in Figure 1, we only consider the nonzero singular values and corresponding singular vectors. Similar results are observed for the right and left nullspace (e.g., $S\check{V} \to 0$ as $\gamma \to 0$).

Although a thorough analysis of the biological implications of the SVD is beyond the scope of this work, for demonstration purposes we plot four of the left singular

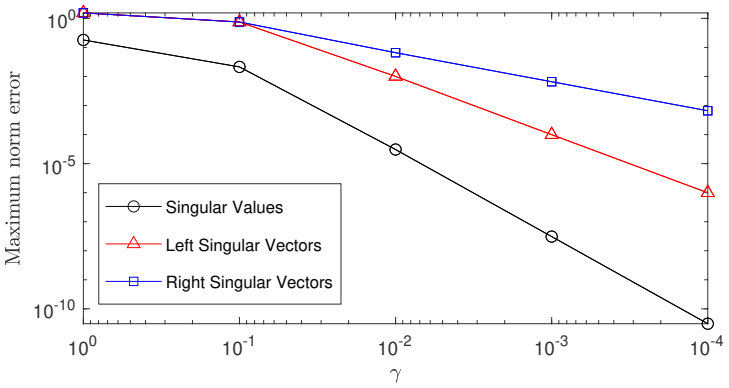

FIG. 1. *Error of approximate SVD decreases as* $\gamma \to 0$. *The error is measured based on the maximum norm error of the singular vactors and vectors; i.e., see* (5.43).

vectors for the cyanobacteria system (Figure 2). These four vectors correspond to the four largest singular values, implying they have a large structural significance. Recall the left singular vectors represent the species that are moved within a given eigenreaction. In this example we see that 3PGA, 2PG, and RuBP are decoupled from HCO_3^-. Although this is an intuitive result for this small-scale system, since HCO_3^- is not directly connected via reactions to 3PGA, 2PG, and RUBP, it shows the type of connections that our approach can illuminate for larger, more complex, systems. We additionally see that the magnitude of species moved, within these eigenreactions, is less within the carboxysome (i.e., the two spatial compartments on the left) compared with the cytoplasm (i.e., the six spatial compartments on the right). Indeed, a researcher could compare these flux magnitudes in systems with and without a barrier in order to determine how the barrier is influencing reaction fluxes.

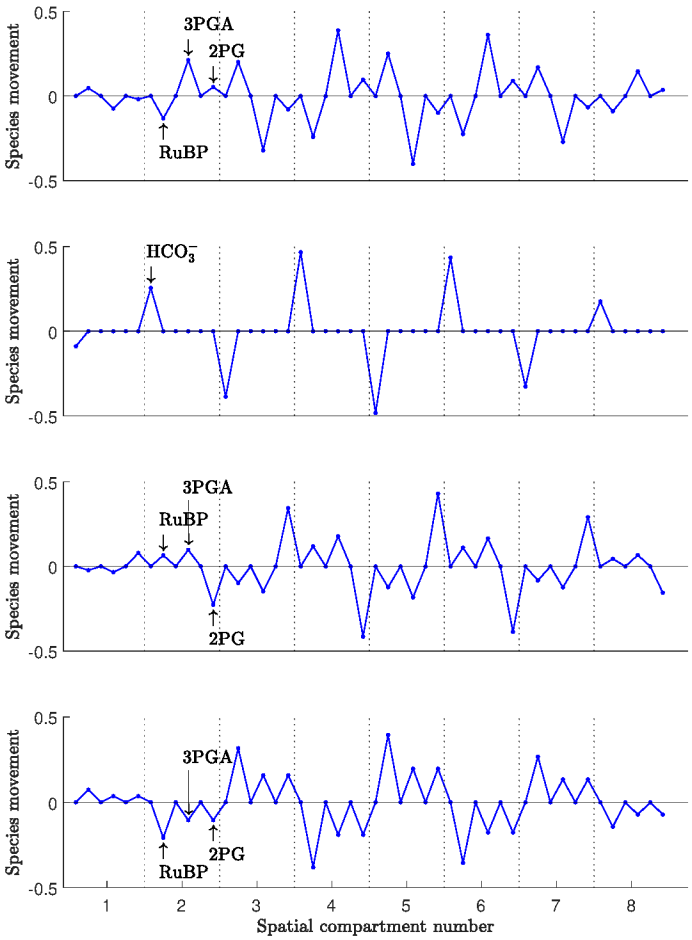

FIG. 2. *Example left singular vectors for cyanobacteria system. Each point corresponds to a species in the system, and the dotted lines represent delineations between compartment boundaries. The species with nonzero contribution to the left singular vectors are labeled and are the same across the* 8 *compartments.*

6. Discussion. In this paper we derived the approximate SVD of the stoichiometry matrix for a 1D discrete RD system partitioned into two subregions. Between these two subregions only certain species are allowed to diffuse. We additionally presented the exact SVD in the scenario where diffusion is allowed freely throughout the domain. This work provides a powerful tool for revealing hidden spatial fluxes and can be applied and expanded upon to examine a variety of RD scenarios. For example, we conjecture that in more complex scenarios (e.g., species-dependent boundary conditions) a Kronecker product formulation can still be used to write the SVD. Additionally, the formulas given by Theorems 2.1 and 2.2 allow for future analysis investigating the effects of spatial properties in multicompartmentalized systems.

Computationally, the results of Theorems 2.1 and 2.2 allow for the efficient estimation of the SVD of the RD stoichiometry matrix. Importantly, the approximate SVD is fully determined by the SVDs of smaller matrices. Analytical SVDs are only needed for relatively small matrices, i.e., matrices where the number of rows/columns is independent of the number of spatial compartments. For example, consider a system with m species, p reactions, and either n or $2n$ compartments. The diffusion-only stoichiometry matrices for this system are known analytically. The other matrices that the SVD depends on have dimensions proportional to m and/or p. Notably the total number of required smaller matrix decompositions will increase linearly with the number of compartments.

6.1. Intuition for SVD results. The approximate SVD for a system with a barrier provides intuition for how the system's structure influences dynamical and steady-state properties. As written in Theorem 2.1, we have partitioned the singular vectors into multiple sets, which we will refer to as *eigenreaction sets*. For example, the singular vectors in $\hat{U}_{1,j}$ and $\hat{V}_{1,j}$ and the singular values in $\hat{\Sigma}_{1,j}$ for $j \in \mathcal{J}$ represent the first eigenreaction set. Recall that the SVD defines eigenreactions, which represent decoupled linear combinations of species that are moved by linear combinations of fluxes, e.g.,

$$\frac{d}{dt}\left(u^{(i)}\right)^T w = \sigma_i \left(v^{(i)}\right)^T f, \tag{6.1}$$

where w is the species concentration vector and f is the vector of fluxes; e.g., see (1.1).

Each eigenreaction set describes the movement of species with similar diffusive properties. The first eigenreaction set describes the movement of species that are able to diffuse across the barrier. Note that the left singular vectors shown in Figure 2 come from eigenreactions in this first set. We see that the contributing species to these eigenreactions are those that can diffuse across the barrier. Additionally, we see a spatial dependency in the species movement defined by these eigenrections. The second, third, and fourth eigenreaction sets all describe the movement of species that are unable to diffuse across the barrier. The second eigenreaction set includes both reactive and diffusive movement in the first subregion, the third eigenreaction set describes only reactive movement in the first subregion, and, finally, the fourth eigenreaction set describes reactive and diffusive movement in the second subregion. Recall that the third eigenreaction set is only nonempty for mixed boundary conditions.

The fifth and sixth eigenreaction sets are unique in that they describe the movement of all species in the system. This movement is coupled due to the repeating singular values in the diffusion-only stoichiometry matrices (i.e., S_d, S_{d_1}, and S_{d_2}). This demonstrates that even in the regime where diffusion is much faster than reactions, there is still a coupling between species with different diffusive processes.

The basis for the nullspace of S is also partition into multiple sets, given by Theorem 2.1 (i.e., $\check{V}_i$ for $i = 1, \ldots, 5$). We will refer to these as *steady-state flux sets*, since they represent fluxes that can exist under steady-state conditions. The first and third steady-state flux sets include only reactive fluxes in the first subregion and throughout the domain, respectively. Note that the first steady-state flux set is only nonempty for mixed boundary conditions, whereas the third steady-state flux set is only nonempty for zero flux boundary conditions. The second and fourth steady-state flux sets represent reactive and diffusive flux combinations in the first subregion and second subregion, respectively. Finally the fifth steady-state flux set represents fluxes that are in the nullspace of S due to their infeasibility. That is, for a given dynamical system, these fluxes will never contribute since they define fluxes across barriers/boundaries that are not allowed.

6.2. Conclusion and future work. To find the SVD of the RD stoichiometry matrix, we first used linear perturbation theory to calculate the left singular vectors and values. We then used the resulting vectors and values to find the right singular vectors. An alternative approach would be to instead derive the right singular vectors directly using perturbation theory. Although this approach may provide additional insight into the system properties, it is slightly more complex as it involves additional terms in the expansions used in the perturbation analysis. Therefore, this analysis is the topic of future research.

The key assumption used to derive the approximate SVD is that diffusion is much faster than the reactions. Whether this is a valid assumption depends on the specific biological system under consideration. Indeed, the relative time scales of diffusion and reactions in biological systems can very greatly and are a complex topic [13]. A similar approach, as presented in this paper, could be applied to derive the approximate SVD in a system where reactions occur much faster than diffusion. That is, we would instead consider the perturbation problem in the limit as the diffusive term of (5.1) goes to zero. Rigorously showing whether the approach applied here could work in this alternative case is a topic of future research.

Our motivation in deriving the approximate SVD in terms of reduced systems is to gain insight into how including spatial barriers and diffusion impacts a biological system. The SVD for the reaction-only system has provided valuable insight in comparing genome-scale metabolic networks [4] and finding connections between biochemical processes [10]. In this paper we demonstrated our approach on a simplified cyanobacteria system; however, our goal is to ultimately apply these methods to larger, more complex, chemical reaction networks. By analyzing the resulting eigenreactions, we can explore how spatial properties influence reaction fluxes as well as interconnect species movement. By including spatial parameters, the work presented here provides tools that researchers can apply to reveal the hidden spatial fluxes that describe how reactive processes are coupled across space.

Appendix A. Background on linear perturbation theory.

Here, we present background information on concepts from linear perturbation theory that is used to derive the approximate SVD of the stoichiometry matrix for the RD system with a barrier. We refer the reader to [6] for a more thorough description of this material. Our discussion here focuses on symmetric matrices. This allows us to assume that the eigenvalues are semisimple and, therefore, the eigennilpotents (denoted with a D and as defined in [6]) vanish.

Consider the following matrix:

$$T(x) = T + xT^{(1)}, \tag{A.1}$$

where $T \in \mathbb{R}^{n\times n}$ and $T^{(1)} \in \mathbb{R}^{n\times n}$ are symmetric matrices and $x \geq 0$. We will refer to T as the unperturbed matrix and to $T^{(1)}$ as the perturbation matrix.

Our goal is to find an approximate eigendecomposition of $T(x)$ at small x. Consider the following eigenvalue problem:

$$T(x)u_i(x) = \lambda_i(x)u_i(x). \tag{A.2}$$

Additionally, $\lambda_i(x)$ is a continuous function of x (see Theorem 2.3 from [6, Chapter 2, section 2.3]), implying that as $x \to 0$ the eigenvalues of $T(x)$ are equal to the eigenvalues of T. However, the same statement does not hold for the eigenvectors. That is, suppose there exists $j \neq i$ such that $\lambda_j(0) = \lambda_i(0)$, but for arbitrarily small $x > 0$ $\lambda_k(x) \neq \lambda_i(x)$ for all $k \neq i$. In this scenario, the eigenvector that corresponds to $\lambda_i(x)$ is unique, but the eigenvector that corresponds to $\lambda_i(0)$ is not. Our task is to find the "correct" set of eigenvectors such that $u_i(x)$ converges to $u_i(0)$ as $x \to 0$.

More generally, let λ be an eigenvalue of T with multiplicity m, and denote the m eigenvalues such that $\lambda_k(0) = \lambda$ as the λ-group. Without loss of generality, suppose this is the first m eigenvalues. Let $(u_k)_{i=1}^m$ represent a set of orthogonal eigenvectors that solve the eigenvalue problem $Tu_k(0) = \lambda u_k(0)$. Let

$$P = \sum_{k=1}^{m} u_k u_k^T \tag{A.3}$$

be the unique orthogonal eigenprojection associated with λ (i.e., $P^2 = P$ and $TP = \lambda P$). We will additionally consider the sum of projections at small x for the entire λ-group:

$$P(x) = \sum_{k=1}^{m} u_k(x)u_k(x)^T. \tag{A.4}$$

Since, in practice, it is difficult to find $u_k(x)$, we can instead write $P(x)$ using a contour integral of the resolvent. That is, let the resolvent of $T(x)$ at the point η be given as

$$R(\zeta, x) = (T(x) - \eta I)^{-1}, \tag{A.5}$$

and let Γ be a closed positively oriented curve in the resolvent set that encloses λ and no other eigenvalues of T. The projection

$$P(x) = -\frac{1}{2\pi i}\int_{\Gamma} R(\zeta, x)d\zeta \tag{A.6}$$

is equal to the sum of the eigenprojections for eigenvalues of $T(x)$ that lie inside Γ (see [6, Chapter 2, section 1.4]).

To find the eigendecomposition of $T(x)$ at small x, we will instead consider the equivalent eigenvalue problem for

$$\tilde{T}^{(1)}(x) = \frac{1}{x}(T(x) - \lambda I)P(x) \tag{A.7}$$

as $x \to 0$. To see that these eigenvalue problems are equivalent, first note that since the eigenvalues $\lambda_k(x)$ are continuously differentiable in a neighborhood of $x = 0$ (see

Theorem 2.3 from [6, Chapter 2, section 2.3]), we can write the power series expansion of $\lambda_k(x)$ as

$$\lambda_k(x) = \lambda + x\lambda_k^{(1)} + \mathcal{O}(x^2). \tag{A.8}$$

Then, using (A.8) and $P(x)u_k(x) = u_k(x)$ for $k = 1, \ldots, m$ we obtain

$$\begin{aligned} T(x)u_k(x) &= \lambda_k(x)u_k(x), \\ T(x)P(x)u_k(x) &= (\lambda + x\lambda_k^{(1)} + \mathcal{O}(x^2))u_k(x), \\ (T(x) - \lambda I)P(x)u_k(x) &= (x\lambda_k^{(1)} + \mathcal{O}(x^2))u_k(x), \\ \frac{1}{x}(T(x) - \lambda I)P(x)u_k(x) &= (\lambda_k^{(1)} + \mathcal{O}(x))u_k(x). \end{aligned}$$

Therefore, the eigenvectors of $T(x)$ are equal to the eigenvectors of $\tilde{T}^{(1)}(x)$, and the associated eigenvalues of $T(x)$ can be written as

$$\lambda_k(x) = \lambda + x\lambda_{1,k} + \mathcal{O}(x^2), \tag{A.9}$$

where $\lambda_{1,k} = \lambda_k^{(1)} + \mathcal{O}(x)$ is the eigenvalue of $\tilde{T}^{(1)}(x)$ associated with eigenvector $u_k(x)$.

Next, we can use power series expansions to show that

$$\tilde{T}^{(1)}(x) = \tilde{T}^{(1)} + \mathcal{O}(x). \tag{A.10}$$

First, note the resolvent can be written as

$$R(\zeta, x) = R(\zeta) - xR(\zeta)T^{(1)}R(\zeta) + \mathcal{O}(x^2), \tag{A.11}$$

where $R(\zeta) = R(\zeta, 0)$ (see Chapter 2, section 1.3 of [6] for derivation). Using (A.11), we can write the sum of eigenprojections for the λ-group as

$$P(x) = P + xP^{(1)} + \mathcal{O}(x^2), \quad \text{where} \quad P^{(1)} = -\frac{1}{2\pi i}\int_\Gamma R(\zeta)T^{(1)}R(\zeta)d\zeta. \tag{A.12}$$

Using (A.5), (A.6), (A.11), and $(T - \lambda I)P = 0$ we have that

$$\begin{aligned} (T(x) - \lambda I)P(x) &= -\frac{1}{2\pi i}(T(x) - \lambda I)\int_\Gamma R(\zeta, x)d\zeta \\ &= -\frac{1}{2\pi i}\int_\Gamma (T(x) - \lambda I)(T(x) - \eta I)^{-1}d\zeta \\ &= -\frac{1}{2\pi i}\int_\Gamma I + (\zeta - \lambda)R(\zeta, x)d\zeta \\ &= -\frac{1}{2\pi i}\int_\Gamma (\zeta - \lambda)(R(\zeta) - xR(\zeta)T^{(1)}R(\zeta))d\zeta + \mathcal{O}(x^2) \\ &= (T - \lambda I)P + \frac{1}{2\pi i}\int_\Gamma (\zeta - \lambda)(xR(\zeta)T^{(1)}R(\zeta))d\zeta + \mathcal{O}(x^2) \\ &= x\tilde{T}^{(1)} + \mathcal{O}(x^2), \end{aligned} \tag{A.13}$$

where

$$\tilde{T}^{(1)} = \frac{1}{2\pi i}\int_\Gamma R(\zeta)T^{(1)}R(\zeta)(\zeta - \lambda)d\zeta. \tag{A.14}$$

We can evaluate this integral by substituting $R(\zeta)$ by its Laurent expansion at $\zeta = \lambda$, i.e.,

$$R(\zeta) = \sum_{n=-1}^{\infty} (\zeta - \lambda)^n S^{(n+1)}, \tag{A.15}$$

where

$$S^{(0)} = -P, \quad S^{(n)} = S^n, \tag{A.16}$$

where $S = S(\lambda)$ is the value at $\zeta = \lambda$ of the reduced resolvent of T. Using the Cauchy residue theorem,

$$\begin{aligned}
\tilde{T}^{(1)} &= \frac{1}{2\pi i} \int_\Gamma (\zeta - \lambda) \left(\sum_{n=-1}^{\infty} (\zeta - \lambda)^n S^{(n+1)} \right) T^{(1)} \left(\sum_{n=-1}^{\infty} (\zeta - \lambda)^n S^{(n+1)} \right) d\zeta \\
&= \frac{1}{2\pi i} \int_\Gamma (\zeta - \lambda) \left((\zeta - \lambda)^{-1} S^{(0)} \right) T^{(1)} \left((\zeta - \lambda)^{-1} S^{(0)} \right) d\zeta \\
&= \frac{1}{2\pi i} \int_\Gamma (\zeta - \lambda)^{-1} P T^{(1)} P \, d\zeta \\
&= P T^{(1)} P.
\end{aligned} \tag{A.17}$$

Notice that terms with $(\zeta - \lambda)^n$ where $n > 0$ in the integral vanish since there is no singularity.

Putting these results together, if λ is an eigenvalue of $T(0)$ that repeats m times, then at small x the associated eigenvalues and eigenvectors of $T(x)$ can be approximated, for $k = 1, \ldots, m$, as

$$u_k(x) = \tilde{u}_k(x), \tag{A.18}$$

$$\lambda_k(x) = \lambda + x\tilde{\lambda}_k, \tag{A.19}$$

where $\tilde{u}_k(x)$ are the eigenvectors of $\tilde{T}^{(1)}$ that are in the range of P and $\tilde{\lambda}_k$ are the corresponding eigenvalues of $\tilde{T}^{(1)}$.

Appendix B. SVD of S_d.

In this section we provide the explicit SVD of the diffusion-only stoichiometry matrix, S_d, as given by (3.1). We will consider a system with n compartments but note that by replacing n with n_1 or n_2 this notation can be used to define the SVD of the diffusion-only stoichiometry matrices for the two subregions, S_{d_1} and S_{d_2}.

In the main manuscript we present three possible boundary conditions: zero flux, mixed, and open. We will additionally include formulas for what we call *mixed-alt* boundary conditions, which can be thought of as the opposite of mixed boundary conditions (i.e., where input/output flux is allowed at $x = 0$ but not at $x = n$). We include this additional boundary condition because it is used to describe the first subregion in a system with a barrier and Dirichlet boundary conditions.

The SVD will depend on the following constants for $j = 1, \ldots, n$:

$$a_{n,j} = \frac{\pi(n - j)}{2n}, \tag{B.1}$$

$$b_{n,j} = \frac{\pi(n - j + 1/2)}{2n + 1}, \tag{B.2}$$

$$c_{n,j} = \frac{\pi(n - j + 1)}{2(n + 1)}. \tag{B.3}$$

Next we define the left singular vectors that correspond to the column space and left nullspace. For the left singular vectors in the column space, the ith element of the jth left singular vector is, for $i = 1, \ldots, n$ and $j = 1, \ldots, q_d$,

$$\left(u_d^{(j)}\right)_i = \begin{cases} \sqrt{\frac{2}{n}} \cos\left(2a_{n,j}(i - 1/2)\right) & \text{zero flux,} \\ \sqrt{\frac{2}{n+1/2}} \cos\left(2b_{n,j}(i - 1/2)\right) & \text{mixed,} \\ \sqrt{\frac{2}{n+1/2}} \sin\left(2b_{n,j} i\right) & \text{mixed-alt,} \\ \sqrt{\frac{2}{n+1}} \sin\left(2c_{n,j} i\right) & \text{open.} \end{cases} \tag{B.4}$$

The left nullspace is only nonempty for zero flux boundary conditions, and we have that

$$\left(u_d^{(n)}\right)_i = \frac{1}{\sqrt{n}}. \tag{B.5}$$

For the right singular vectors, the ith element of the jth right singular vector associated with nonzero singular values is, for $i = 1, \ldots, n+1$ and $j = 1, \ldots, q_d$,

$$\left(v_d^{(j)}\right)_i = \begin{cases} -\sqrt{\frac{2}{n}} \sin\left(2a_{n,j}(i - 1)\right) & \text{zero flux,} \\ -\sqrt{\frac{2}{n+1/2}} \sin\left(2b_{n,j}(i - 1)\right) & \text{mixed,} \\ \sqrt{\frac{2}{n+1/2}} \cos\left(2b_{n,j}(i - 1/2)\right) & \text{mixed-alt,} \\ \sqrt{\frac{2}{n+1}} \cos\left(2c_{n,j}(i - 1/2)\right) & \text{open.} \end{cases} \tag{B.6}$$

For the right singular vectors in the nullspace of S_d, for zero flux boundary conditions, we have that

$$v_d^{(n)} = e_1, \qquad v_d^{(n+1)} = e_{n+1}, \tag{B.7}$$

where e_i represents the vector with zeros and a one at the ith index. For mixed, mixed-alt, and open boundary conditions, we have

$$v_d^{(n+1)} = \begin{cases} e_1 & \text{mixed,} \\ e_{n+1} & \text{mixed-alt,} \\ \mathbf{1}\sqrt{\frac{1}{n+1}} & \text{open,} \end{cases} \tag{B.8}$$

where $\mathbf{1}$ is a vector of ones.

Finally, the jth singular value, for each of the boundary conditions, is

$$\sigma_d^{(j)} = \begin{cases} 2\sin\left(a_{n,j}\right) & \text{zero flux,} \\ 2\sin\left(b_{n,j}\right) & \text{mixed and mixed-alt,} \\ 2\sin\left(c_{n,j}\right) & \text{open.} \end{cases} \tag{B.9}$$

Appendix C. Kronecker product formulas.

In this section we provide some Kronecker product relations that are needed to prove Theorem 2.1. We omit the proof of these properties but note that they can be shown through a series of algebraic manipulations.

PROPERTY C.1. *Let* $u \in \mathbb{R}^{n\times 1}$ *be related to* $u_1 \in \mathbb{R}^{n_1\times 1}$ *and* $u_2 \in \mathbb{R}^{n_2\times 2}$ *such that*

$$u = \begin{bmatrix} u_1 \\ u_2 \end{bmatrix}. \tag{C.1}$$

Let A_1, A_2, B_1, B_2 *be square matrices of the same size. Then*

(C.2)
$$\left(uu^T \otimes A_1\right) \begin{bmatrix} I_{n_1} \otimes B_1 & 0 \\ 0 & I_{n_2} \otimes B_2 \end{bmatrix} \left(uu^T \otimes A_2\right) = uu^T \otimes A_1 \left(|u_1|^2 B_1 + |u_2|^2 B_2\right) A_2.$$

PROPERTY C.2. *Suppose* u_1 *and* u_2 *are unit vectors and* $a_i \in \mathbb{R}$ *for* $i = 1, \ldots, 8$. *Let* A_1, A_2, B_1, B_2 *be square matrices of the same size. Then*

(C.3)
$$\left(\begin{bmatrix} a_1u_1u_1^T & a_2u_1u_2^T \\ a_3u_2u_1^T & a_4u_2u_2^T \end{bmatrix} \otimes A_1\right) \begin{bmatrix} I_{n_1} \otimes B_1 & 0 \\ 0 & I_{n_2} \otimes B_2 \end{bmatrix} \left(\begin{bmatrix} a_5u_1u_1^T & a_6u_1u_2^T \\ a_7u_2u_1^T & a_8u_2u_2^T \end{bmatrix} \otimes A_2\right)$$
$$= \begin{cases} \begin{bmatrix} a_5u_1u_1^T & a_6u_1u_2^T \\ 0 & 0 \end{bmatrix} \otimes A_1 \left(a_1B_1\right) A_2 & \text{if } a_2, a_3, a_4 = 0, \\ \begin{bmatrix} 0 & 0 \\ a_7u_2u_1^T & a_8u_2u_2^T \end{bmatrix} \otimes A_1 \left(a_4B_2\right) A_2 & \text{if } a_1, a_2, a_3 = 0, \\ \begin{bmatrix} a_1u_1u_1^T & 0 \\ a_3u_2u_1^T & 0 \end{bmatrix} \otimes A_1 \left(a_5B_1\right) A_2 & \text{if } a_6, a_7, a_8 = 0, \\ \begin{bmatrix} 0 & a_2u_1u_2^T \\ 0 & a_4u_2u_2^T \end{bmatrix} \otimes A_1 \left(a_8B_2\right) A_2 & \text{if } a_5, a_6, a_7 = 0. \end{cases}$$

PROPERTY C.3. *Suppose that* u_1 *and* u_2 *are unit column vectors and* $a_i \in \mathbb{R}$ *for* $i = 1, \ldots, 6$ *such that*

$$a_1 = \frac{a_3a_5}{a_6} \quad \text{and} \quad a_4 = \frac{a_2a_6}{a_5}. \tag{C.4}$$

Let $A_1 \in \mathbb{R}^{m\times n}$ *and* $v_1, v_2 \in \mathbb{R}^{m\times 1}$. *We then have that*

$$\begin{bmatrix} a_1u_1u_1^T \otimes A_1 & a_2u_1u_2^T \otimes A_1 \\ a_3u_2u_1^T \otimes A_1 & a_4u_2u_2^T \otimes A_1 \end{bmatrix} \begin{bmatrix} a_5u_1 \otimes v_1 \\ a_6u_2 \otimes v_2 \end{bmatrix} = \begin{bmatrix} a_5u_1 \\ a_6u_2 \end{bmatrix} \otimes A_1 \left(a_1v_1 + a_4v_2\right). \tag{C.5}$$

Appendix D. Proofs.

This section contains supplemental proofs for the results presented in section 4 and 5. We first provide the proof of Lemma 4.1, which provides a relationship for the eigenvalues and eigenvectors of S_d, S_{d_1}, and S_{d_2}.

Proof of Lemma 4.1. We will consider the three possible boundary conditions independently.

Case 1: Homogeneous Neumann boundary conditions. In this scenario, both subregions have homogeneous Neumann boundary conditions. Suppose that, for $j \in \{1, 2, \ldots, n\}$, there exists $j_1 \in \{1, 2, \ldots, n_1\}$ such that

$$\begin{aligned} a_{n,j} = \frac{\pi(n-j)}{2n} = \frac{\pi(n_1 - j_1)}{2n_1} = a_{n_1,j_1} \\ \implies j_1 = \frac{n_1 j}{n} = C_1^2 j. \end{aligned} \tag{D.1}$$

From (B.9) this implies that $\sigma_{d_1}^{(j_1)} = \sigma^{(j)}$. Let $j_2 = j - j_1 = C_2^2 j$, and note that by definition $j_2 \in \{1, \dots, n_2\}$. Additionally, $\sigma_{d_2}^{(j_2)} = \sigma^{(j)}$ since

$$a_{n,j} = \frac{\pi(n-j)}{2n} = \frac{\pi(n_2 - C_2^2 j)}{2n_2} = \frac{\pi(n_2 - j_2)}{2n_2} = a_{n_2,j_2}. \tag{D.2}$$

Next we will prove (4.1) and (4.2). In what follows let $\ell = i - n_1$. For $i = 1, \dots, n_1$, (D.1) and (D.2) imply that

$$\left(u_d^{(j)}\right)_i = \sqrt{\frac{2}{n}} \cos\left(2a_{n,j}(i - 1/2)\right) = \sqrt{\frac{2}{n}} \cos\left(2a_{n_1,j_1}(i - 1/2)\right) = C_1 \left(u_{d_1}^{(j)}\right)_i,$$
$$\left(v_d^{(j)}\right)_i = \sqrt{\frac{2}{n}} \sin\left(2a_{n,j}(i - 1)\right) = \sqrt{\frac{2}{n}} \sin\left(2a_{n_1,j_1}(i - 1)\right) = C_1 \left(v_{d_1}^{(j_1)}\right)_i.$$

For $i = n_1 + 1, \dots, n$, (D.1) and (D.2) imply that

$$\begin{aligned}
\left(u_d^{(j)}\right)_{n_1+\ell} &= \sqrt{\frac{2}{n}} \cos\left(2a_{n,j}\left(n_1 + \ell - \frac{1}{2}\right)\right) \\
&= \sqrt{\frac{2}{n}} \cos\left(\frac{2\pi(n_1 - j_1)n_1}{2n_1} + 2a_{n,j}\left(\ell - \frac{1}{2}\right)\right) \\
&= (-1)^{n_1 - j_1} \sqrt{\frac{2}{n}} \cos\left(2a_{n_2,j_2}\left(\ell - \frac{1}{2}\right)\right) \\
&= (-1)^{n_1 - j_1} C_2 \left(u_{d_2}^{(j_2)}\right)_\ell
\end{aligned}$$

and

$$\begin{aligned}
\left(v_d^{(j)}\right)_{n_1+\ell} &= \sqrt{\frac{2}{n}} \sin\left(2a_{n,j}(n_1 + \ell - 1)\right) \\
&= \sqrt{\frac{2}{n}} \sin\left(\frac{2\pi(n_1 - j_1)n_1}{2n_1} + 2a_{n,j}(\ell - 1)\right) \\
&= (-1)^{n_1 - j_1} \sqrt{\frac{2}{n}} \sin\left(2a_{n_2,j_2}(\ell - 1)\right) \\
&= (-1)^{n_1 - j_1} C_2 \left(v_{d_2}^{(j_2)}\right)_\ell.
\end{aligned}$$

Case 2: Mixed boundary conditions. In this scenario, the first subregion with n_1 compartments has homogeneous Neumann boundary conditions, and the second subregion with n_2 compartment has mixed boundary conditions. For $j \in \{1, \dots, n\}$ suppose there exists a $j_1 \in \{1, \dots, n_1\}$ such that

$$\begin{aligned}
b_{n,j} = \frac{\pi(n - j + 1/2)}{2n + 1} &= \frac{\pi(n_1 - j_1)}{2n_1} = a_{n_1,j_1} \\
\implies j_1 &= \frac{2n_1 j}{2n + 1} = C_1^2 j.
\end{aligned} \tag{D.3}$$

From (B.9) this implies that $\sigma_{d_1}^{(j_1)} = \sigma^{(j)}$. Let $j_2 = j - j_1 = C_2^2 j$, and note by definition that $j_2 \in \{1, \dots, n_2\}$. Additionally, $\sigma_{d_2}^{(j_2)} = \sigma^{(j)}$, since

$$
\begin{aligned}
b_{n,j} &= \frac{\pi(n-j+1/2)}{2n+1} \\
&= \frac{\pi(n_2+1/2-C_2^2 j)}{2n_2+1} \\
&= \frac{\pi(n_2-j_2+1/2)}{2n_2+1} = b_{n_2,j_2}.
\end{aligned} \tag{D.4}
$$

Next we will prove (4.1) and (4.2). For $i = 1, \ldots, n_1$, (D.3) implies that

$$
\begin{aligned}
\left(u_d^{(j)}\right)_i &= \sqrt{\frac{2}{n+1/2}} \cos\left(2b_{n,j}(i-1/2)\right) \\
&= \sqrt{\frac{2}{n+1/2}} \cos\left(2a_{n_1,j_1}(i-1/2)\right) = C_1 \left(u_{d,n_1}^{(j_1)}\right)_i, \\
\left(v_d^{(j)}\right)_i &= \sqrt{\frac{2}{n+1/2}} \sin\left(2b_{n,j}(i-1)\right) \\
&= \sqrt{\frac{2}{n+1/2}} \sin\left(2a_{n_1,j_1}(i-1)\right) = C_1 \left(v_{d_1}^{(j_1)}\right)_i.
\end{aligned}
$$

For $i = n_1+1, \ldots, n$, (D.3) and (D.4) imply that

$$
\begin{aligned}
\left(u_d^{(j)}\right)_{n_1+\ell} &= \sqrt{\frac{2}{n+1/2}} \cos\left(2b_{n,j}(n_1+\ell-1/2)\right) \\
&= \sqrt{\frac{2}{n+1/2}} \cos\left(\frac{2\pi(n_1-j_1)n_1}{2n_1} + 2b_{n,j}(\ell-1/2)\right) \\
&= (-1)^{n_1-j_1} \sqrt{\frac{2}{n+1/2}} \cos\left(2b_{n_2,j_2}(i-1/2)\right) \\
&= (-1)^{n_1-j_1} C_2 \left(u_{d_2}^{(j_1)}\right)_\ell
\end{aligned}
$$

and

$$
\begin{aligned}
\left(v_d^{(j)}\right)_{n_1+\ell} &= \sqrt{\frac{2}{n+1/2}} \sin\left(2b_{n,j}(n_1+\ell-1)\right) \\
&= \sqrt{\frac{2}{n+1/2}} \sin\left(\frac{2\pi(n_1-j_1)n_1}{n_1} + 2b_{n,j}(\ell-1\right) \\
&= (-1)^{n_1-j_1} \sqrt{\frac{2}{n+1/2}} \sin\left(2b_{n_2,j_2}(i-1)\right) \\
&= (-1)^{n_1-j_1} C_2 \left(v_{d_2}^{(j_1)}\right)_\ell.
\end{aligned}
$$

Case 3: Open boundary conditions. In this case, the first subregion with n_1 compartments has mixed-alt boundary conditions (i.e., flux is only allowed at $x = 0$), and the second subregion with n_2 compartments has mixed boundary

conditions. For $j \in \{1, \dots, n\}$ suppose there exists a $j_1 \in \{1, \dots, n_1\}$ such that

$$\begin{aligned} c_{n,j} &= \frac{\pi(n-j+1)}{2(n+1)} = \frac{\pi(n_1 - j_1 + 1/2)}{2n_1+1} = b_{n_1,j_1} \\ &\implies j_1 = \frac{j(2n_1+1)}{2(n+1)} = C_1^2 j. \end{aligned} \tag{D.5}$$

From (B.9) this implies that $\sigma_{d_1}^{(j_1)} = \sigma^{(j)}$. Let $j_2 = j - j_1 = C_2^2 j$, and note by definition that $j_2 \in \{1, \dots, n_2\}$. Additionally, $\sigma_{d_2}^{(j_2)} = \sigma^{(j)}$, since

$$\begin{aligned} c_{n,j} &= \frac{\pi(n-j+1)}{2(n+1)} \\ &= \frac{\pi(2n_2 + 1 - 2C_2^2 j)}{2(2n_2+1)} \\ &= \frac{\pi(n_2 - j_2 + 1/2)}{2n_2+1} = b_{n_2,j_2}. \end{aligned} \tag{D.6}$$

Next we will prove (4.1) and (4.2). For $i = 1, \dots, n_1$, (D.5) implies that

$$\begin{aligned} \left(u_d^{(j)}\right)_i &= \sqrt{\frac{2}{n+1}} \sin\left(2ic_{n,j}\right) \\ &= \sqrt{\frac{2}{n+1}} \sin\left(2ib_{n_1,j_1}\right) = C_1 \left(u_{d_1}^{(j_1)}\right)_i, \\ \left(v_d^{(j)}\right)_i &= \sqrt{\frac{2}{n+1}} \cos\left(2c_{n,j}(i-1/2)\right) \\ &= \sqrt{\frac{2}{n+1}} \sin\left(2b_{n_1,j_1}(i-1/2)\right) = C_1 \left(v_{d_1}^{(j_1)}\right)_i. \end{aligned}$$

For $i = n_1 + 1, \dots, n$, (D.5) and (D.6) imply that

$$\begin{aligned} \left(u_d^{(j)}\right)_{n_1+\ell} &= \sqrt{\frac{2}{n+1}} \sin\left(2c_{n,j}(n_1+\ell)\right) \\ &= \sqrt{\frac{2}{n+1}} \sin\left(2c_{n,j}(n_1+1/2) + 2c_{n,j}(\ell - 1/2)\right) \\ &= \sqrt{\frac{2}{n+1}} \sin\left(\frac{2\pi(n_1 - j_1 + 1/2)(n_1+1/2)}{2n_1+1} + 2c_{n,j}(\ell-1/2)\right) \\ &= (-1)^{n_1-j_1} \sqrt{\frac{2}{n+1}} \cos\left(2b_{n_2,j_2}(\ell-1/2)\right) \\ &= (-1)^{n_1-j_1} C_2 \left(u_{d_2}^{(j_2)}\right)_\ell \end{aligned}$$

and

$$\begin{aligned} \left(v_d^{(j)}\right)_{n_1+\ell} &= \sqrt{\frac{2}{n+1}} \cos\left(2c_{n,j}(n_1+\ell-1/2)\right) \\ &= \sqrt{\frac{2}{n+1}} \cos\left(2c_{n,j}(n_1+1/2) + 2c_{n,j}(\ell-1)\right) \end{aligned}$$

$$= \sqrt{\frac{2}{n+1}} \cos\left(\frac{2\pi(n_1 - j_1 + 1/2)(n_1 + 1/2)}{2n_1+1} + 2c_{n,j}(\ell-1)\right)$$
$$= -(-1)^{n_1-j_1}\sqrt{\frac{2}{n+1}} \sin\left(2b_{n_2,j_2}(\ell-1)\right)$$
$$= (-1)^{n_1-j_1} C_2 \left(v_{d_2}^{(j_2)}\right)_\ell,$$

which completes the proof. ∎

Next, we prove Lemma 5.1, which provides an eigendecomposition of SS^T when $\gamma = 0$; recall S is given by (2.1). This is equivalent to the nonunique eigendecomposition of the unperturbed matrix T, given by (5.2).

Proof of Lemma 5.1. First note that $T \in \mathbb{R}^{nm\times nm}$ and, as needed, the number of eigenvectors defined is $nm_+ + n_1m_- + n_2m_- = nm$.

We will show that the matrices $\hat{Q}_{T,1}$, $\hat{Q}_{T,2}$, and $\hat{Q}_{T,3}$ contain eigenvectors of T and that $\hat{\Sigma}_{Q_{T,1}}$, $\hat{\Sigma}_{Q_{T,2}}$, and $\hat{\Sigma}_{Q_{T,3}}$ contain the corresponding nonzero eigenvalues. First, considering $\hat{Q}_{T,1}$, we have that

$$T\hat{Q}_{T,1} = \left(S_dS_d^T \otimes D_+ + \left(S_dS_d^T - HH^T\right)\otimes D_-\right)\left(\hat{U}_d \otimes I_m^{\mathcal{M}_+}\right)$$
$$= S_dS_d^T\hat{U}_d \otimes I_m^{\mathcal{M}_+} = \hat{U}_d\hat{\Sigma}_d^2 \otimes I_m^{\mathcal{M}_+} = \hat{Q}_{T,1}\left(\hat{\Sigma}_d^2 \otimes I_{m_+}\right).$$

Next for $\hat{Q}_{T,2}$, we have that

$$T\hat{Q}_{T,2} = \left(S_dS_d^T \otimes D_+ + \left(S_dS_d^T - HH^T\right)\otimes D_-\right)\left(\begin{bmatrix}\hat{U}_{d_1}\\ 0\end{bmatrix} \otimes I_m^{\mathcal{M}_-}\right)$$
$$= \left(S_dS_d^T - HH^T\right)\begin{bmatrix}\hat{U}_{d_1}\\ 0\end{bmatrix} \otimes I_m^{\mathcal{M}_-} = \begin{bmatrix}\hat{U}_{d_1}\\ 0\end{bmatrix}\hat{\Sigma}_{d_1}^2 \otimes I_m^{\mathcal{M}_-} = \hat{Q}_{T,2}\left(\hat{\Sigma}_{d_1}^2 \otimes I_{m_-}\right).$$

Finally, for $\hat{Q}_{T,3}$ we have that

$$T\hat{Q}_{T,3} = \left(S_dS_d^T \otimes D_+ + \left(S_dS_d^T - HH^T\right)\otimes D_-\right)\left(\begin{bmatrix}0\\ \hat{U}_{d_2}\end{bmatrix} \otimes I_m^{\mathcal{M}_-}\right)$$
$$= \left(S_dS_d^T - HH^T\right)\begin{bmatrix}0\\ \hat{U}_{d_2}\end{bmatrix} \otimes I_m^{\mathcal{M}_-} = \hat{Q}_{T,3}\left(\hat{\Sigma}_{d_2}^2 \otimes I_{m_-}\right).$$

It can analogously be shown that $\breve{Q}_{T,1}$, $\breve{Q}_{T,2}$, and $\breve{Q}_{T,3}$ represent the nullspace of T. We leave it as an exercise to show that the eigenvectors and nullspace basis vectors are orthogonal. ∎

Next, we will show that Theorem 2.1 provides an approximate basis for the nullspace of S (i.e., $\breve{V}$), where the basis is orthogonal at small gamma and satisfies $S\breve{V} = 0$ in the limit as γ goes to zero. We will also provide the proof to Proposition 5.4, which gives an exact basis for the nullspace of S that is orthogonal in the limit as $\gamma \to 0$.

Proof of Theorem 2.1 (nullspace). The dimension of the nullspace of S is given by Lemma 4.2. Notice that this dimension matches the number of columns in $\breve{V}$ as defined in Theorem 2.1. Specifically, for the five matrices that compose $\breve{V}$, i.e., $\breve{V}_i$ for $i = 1, \ldots, 5$ the number of columns is

$$\breve{q}_1 = \begin{cases} \breve{q}_{r_1,-} & \text{mixed,} \\ 0 & \text{otherwise,} \end{cases}$$

$$\breve{q}_2 = q_{d_1} p,$$

$$\breve{q}_3 = \begin{cases} \breve{q}_{\bar{r}} & \text{Neumann,} \\ 0 & \text{otherwise,} \end{cases}$$

$$\breve{q}_4 = q_{d_2} p,$$

$$\breve{q}_5 = \begin{cases} 3m - m_+ & \text{Neumann,} \\ 2m - m_+ & \text{mixed,} \\ m & \text{open,} \end{cases}$$

and by inspection we see that the number of columns is equivalent to the value of $\breve{q}$ given by Lemma 4.2.

We leave it as an exercise to show that all the vectors defined in these matrices are orthonormal.

To show that the vectors are in the nullspace of S, write S as follows:

$$S = \begin{bmatrix} \gamma I_{n_1} \otimes S_{r_1} & 0 & S_{d,s_1} \otimes D_+ + \begin{bmatrix} S_{d_1} & 0 \end{bmatrix} \otimes D_- \\ 0 & \gamma I_{n_2} \otimes S_{r_2} & S_{d,s_2} \otimes D_+ + \begin{bmatrix} 0 & S_{d_2} \end{bmatrix} \otimes D_- \end{bmatrix},$$

where S_{d,s_1} represents the first n_1 rows of S_d and S_{d,s_2} represents the last n_2 rows of S_d. Suppose a vector in the nullspace can be written as

$$v = \begin{bmatrix} v_1 \otimes v_2 \\ v_3 \otimes v_4 \\ v_5 \otimes v_6 \end{bmatrix} \Sigma,$$

where Σ is a diagonal matrix. Multiplying S by v, we obtain the following two equations that must be satisfied:

$$\gamma v_1 \otimes S_{r_1} v_2 + S_{d,s_1} v_5 \otimes D_+ v_6 + \begin{bmatrix} S_{d_1} & 0 \end{bmatrix} v_5 \otimes D_- v_6 = 0, \tag{D.7}$$

$$\gamma v_3 \otimes S_{r_2} v_4 + S_{d,s_2} v_5 \otimes D_+ v_6 + \begin{bmatrix} 0 & S_{d_2} \end{bmatrix} v_5 \otimes D_- v_6 = 0. \tag{D.8}$$

It is straightforward to show that the vectors given by the claim satisfy these equations in the limit as $\gamma \to 0$. In fact, for $\breve{V}_2$, $\breve{V}_4$, and $\breve{V}_6$ the equations are satisfied at small gamma. Below we will show the logic for $\breve{V}_2$. We leave it as an exercise to verify these results for $\breve{V}_4$ and $\breve{V}_6$. Additionally, it is trivial to show that as $\gamma \to 0$, $\breve{V}_1$ and $\breve{V}_3$ satisfy the condtions since, in this case, $v_5, v_6 = 0$.

For $\breve{V}_2$ we have that

$$v_1 = \hat{U}_{d_1} \hat{\Sigma}_{d_1}, \quad v_2 = V_{r_1}, \quad v_5 = \begin{bmatrix} -\gamma \hat{V}_{d_1} \\ 0 \end{bmatrix}, \quad v_6 = U_{r_1} \Sigma_{r_1},$$

and $v_3, v_4 = 0$. The first condition, i.e., (D.7), is satisfied since

$$\begin{aligned} \gamma \hat{U}_{d_1} \hat{\Sigma}_{d_1} \otimes S_{r_1} V_{r_1} + S_{d,s_1} \begin{bmatrix} -\gamma \hat{V}_{d_1} \\ 0 \end{bmatrix} \otimes D_+ U_{r_1} \Sigma_{r_1} + \begin{bmatrix} S_{d_1} & 0 \end{bmatrix} \begin{bmatrix} -\gamma \hat{V}_{d_1} \\ 0 \end{bmatrix} \otimes D_- U_{r_1} \Sigma_{r_1} \\ = \gamma \hat{U}_{d_1} \hat{\Sigma}_{d_1} \otimes U_{r_1} \Sigma_{r_1} - \gamma \hat{U}_{d_1} \hat{\Sigma}_{d_1} \otimes D_+ U_{r_1} \Sigma_{r_1} - \gamma \hat{U}_{d_1} \hat{\Sigma}_{d_1} \otimes D_- U_{r_1} \Sigma_{r_1} \\ = 0. \end{aligned}$$

Additionally, $\breve{V}_2$ satisfies (D.8) since

$$S_{d,s_2}\begin{bmatrix}-\gamma\hat{V}_{d_1}\\0\end{bmatrix}\otimes D_+U_{r_1}\Sigma_{r_1}+\begin{bmatrix}0 & S_{d_2}\end{bmatrix}\begin{bmatrix}-\gamma\hat{V}_{d_1}\\0\end{bmatrix}\otimes D_-U_{r_1}\Sigma_{r_1}$$
$$=0.$$

∎

Proof of Proposition 5.4. The proof to this proposition closely follows the proof given for the nullspace presented in Theorem 2.1. In addition to the logic of this proof we need to show that the basis vectors that differ (i.e., those in $\breve{V}_1$ and $\breve{V}_3$) satisfy the two conditions given in (D.7) and (D.8) at small values of γ. We will show the logic for $\breve{V}_3$ and leave it as an exercise to show that $\breve{V}_1$ satisfies the conditions.

For $\breve{V}_3$, when considering the conditions given by (D.7) and (D.8), we have that

$$v_1=\frac{1}{C_1}\breve{U}_{d,s_1}\quad v_2=\breve{V}_{\bar{r},s_1},\quad v_3=\frac{1}{C_2}\breve{U}_{d,s_2},$$
$$v_4=\breve{V}_{\bar{r},s_2},\qquad v_5=\gamma w_1,\quad v_6=S_{r_1}\breve{V}_{\bar{r},s_1}.$$

Note that, by definition of $S_{\bar{r}}$ (see (3.10)), the following equations must be satisfied:

$$\begin{aligned}C_1S_{r_1,+}\breve{V}_{\bar{r},s_1}&=-C_2S_{r_2,+}\breve{V}_{\bar{r},s_2},\\ S_{r_1,-}\breve{V}_{\bar{r},s_1}&=0,\\ S_{r_2,-}\breve{V}_{\bar{r},s_2}&=0.\end{aligned}\tag{D.9}$$

From these relations we have that $D_-S_{r_1}\breve{V}_{\bar{r},s_1}=0$ and $S_{r_1}\breve{V}_{\bar{r},s_1}=D_+S_{r_1}\breve{V}_{\bar{r},s_1}$. It follows that $\breve{V}_3$ satisfies (D.7) since

$$\begin{aligned}&\frac{\gamma}{C_1}\breve{U}_{d,s_1}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}-\gamma S_{d,s_1}w_1\otimes D_+S_{r_1}\breve{V}_{\bar{r},s_1}-\gamma\begin{bmatrix}S_{d_1} & 0\end{bmatrix}w_1\otimes D_-S_{r_1}\breve{V}_{\bar{r},s_1}\\ &=\frac{\gamma}{C_1}\breve{U}_{d,s_1}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}-\gamma\frac{n}{n_2+\sqrt{n_1n_2}}S_{d,s_1}\hat{V}_d\hat{\Sigma}_d^{-1}\hat{U}_d^T\begin{bmatrix}\frac{1}{C_1}\breve{U}_{d,s_1}\\-\frac{1}{C_2}\breve{U}_{d,s_2}\end{bmatrix}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}\\ &=\frac{\gamma}{C_1}\breve{U}_{d,s_1}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}-\gamma\frac{n}{n_2+\sqrt{n_1n_2}}\hat{U}_{d,s_1}\hat{U}_d^T\begin{bmatrix}\frac{1}{C_1}\breve{U}_{d,s_1}\\-\frac{1}{C_2}\breve{U}_{d,s_2}\end{bmatrix}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}\\ &=\frac{\gamma}{C_1}\breve{U}_{d,s_1}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}-\frac{\gamma}{C_1}\frac{n_2+\sqrt{n_1n_2}}{n_2+\sqrt{n_1n_2}}\breve{U}_{d,s_1}\otimes S_{r_1}\breve{V}_{\bar{r},s_1}\\ &=0.\end{aligned}$$

Here, we are using the fact that $\breve{U}_d=\frac{1}{\sqrt{n}}\mathbf{1}$ is a constant vector and

$$\begin{aligned}&\breve{U}_d\breve{U}_d^T+\hat{U}_d\hat{U}_d^T=I\\ &\implies \hat{U}_{d,s_1}\hat{U}_{d,s_1}^T=I-\breve{U}_{d,s_1}\breve{U}_{d,s_1}^T\\ &\implies \hat{U}_{d,s_1}\hat{U}_{d,s_2}^T=-\breve{U}_{d,s_1}\breve{U}_{d,s_2}^T;\end{aligned}\tag{D.10}$$

therefore,

$$\begin{aligned}\hat{U}_{d,s_1}\hat{U}_d^T\begin{bmatrix}\frac{1}{C_1}\breve{U}_{d,s_1}\\-\frac{1}{C_2}\breve{U}_{d,s_2}\end{bmatrix}&=\frac{1}{\sqrt{n}}\begin{bmatrix}\hat{U}_{d,s_1}\hat{U}_{d,s_1}^T & \hat{U}_{d,s_1}\hat{U}_{d,s_2}^T\end{bmatrix}\begin{bmatrix}\frac{1}{C_1}\mathbf{1}\\-\frac{1}{C_2}\mathbf{1}\end{bmatrix}\\ &=\frac{1}{\sqrt{n}}(\frac{1}{C_1}(I-\breve{U}_{d,s_1}\breve{U}_{d,s_1}^T)+\frac{1}{C_2}\breve{U}_{d,s_1}\breve{U}_{d,s_2}^T)\mathbf{1}\\ &=\frac{1}{\sqrt{n}}\left(\frac{1}{C_1}(I-a^2\mathbf{1}_{n_1\times n_1})\mathbf{1}_{n_1}+a^2\frac{1}{C_2}\mathbf{1}_{n_1\times n_2}\mathbf{1}_{n_2}\right)\end{aligned}\tag{D.11}$$

$$= \frac{1}{\sqrt{n}}\left(\frac{1}{C_1}(1-n_1/n)+\frac{1}{nC_2}n_2\right)\mathbf{1}_{n_1}$$
$$= \left(\frac{1}{C_1}(1-n_1/n)+\frac{1}{nC_2}n_2\right)\breve{U}_{d,s_1}.$$

Using that, for Neumann boundary conditions, $C_1 = \sqrt{n_1/n}$ and $C_2 = \sqrt{n_2/n}$, we have that

$$\begin{aligned}\hat{U}_{d,s_1}\hat{U}_d^T\begin{bmatrix}\frac{1}{C_1}\breve{U}_{d,s_1}\\ -\frac{1}{C_2}\breve{U}_{d,s_2}\end{bmatrix} &= \left(\sqrt{\frac{n}{n_1}}(1-n_1/n)+\sqrt{\frac{1}{nn_2}}n_2\right)\breve{U}_{d,s_1}\\ &= \left(\sqrt{\frac{n}{n_1}}(1-n_1/n)+\sqrt{\frac{n_2}{n}}\right)\breve{U}_{d,s_1}\\ &= \left(\frac{n_2+\sqrt{n_1n_2}}{\sqrt{n_1n}}\right)\breve{U}_{d,s_1}\\ &= \frac{1}{C_1}\left(\frac{n_2+\sqrt{n_1n_2}}{n}\right)\breve{U}_{d,s_1}.\end{aligned}$$

The equalities given by (D.9) also imply that $S_{r_1}\breve{V}_{\bar{r},s_2} = -\frac{C_2}{C_1}S_{r_2}\breve{V}_{\bar{r},s_2}$. Using this, we have that $\breve{V}_3$ satisfies (D.8) since

$$\begin{aligned}&\frac{\gamma}{D_2}\breve{U}_{d,s_2}\otimes S_{r_2}\breve{V}_{\bar{r},s_2} - \gamma\frac{n}{n_2+\sqrt{n_1n_2}}S_{d,s_2}\hat{V}_d\hat{\Sigma}_d^{-1}\hat{U}_d^T\begin{bmatrix}\frac{1}{C_1}\breve{U}_{d,s_1}\\ -\frac{1}{C_2}\breve{U}_{d,s_2}\end{bmatrix}\otimes D_+S_{r_1}\breve{V}_{\bar{r},s_1}\\ &\quad= \frac{\gamma}{C_2}\breve{U}_{d,s_2}\otimes S_{r_2}\breve{V}_{\bar{r},s_2} - \frac{\gamma}{C_2}\frac{n_1+\sqrt{n_1n_2}}{n_2+\sqrt{n_1n_2}}\frac{C_2}{C_1}\breve{U}_{d,s_2}\otimes S_{r_2}\breve{V}_{\bar{r},s_2}\\ &\quad= 0,\end{aligned}$$

where, similar to the result for the first condition,

$$\hat{U}_{d,s_2}\hat{U}_d^T\begin{bmatrix}\frac{1}{C_1}\breve{U}_{d,s_1}\\ -\frac{1}{C_2}\breve{U}_{d,s_2}\end{bmatrix} = \frac{1}{C_2}\left(\frac{n_1+\sqrt{n_1n_2}}{n}\right)\breve{U}_{d,s_1}$$

and $C_2/C_1 = \sqrt{n_2/n_1}$. We leave it as an exercise to show that all the vectors defined in the columns of $\breve{V}$ are linearly independent and that, in the limit as $\gamma \to 0$, they become orthogonal. ∎

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