SCALING LIMITS OF SPATIAL COMPARTMENT MODELS FOR CHEMICAL REACTION NETWORKS

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We study the effects of fast spatial movement of molecules on the dynamics of chemical species in a spatially heterogeneous chemical reaction network using a compartment model. The reaction networks we consider are either single- or multi-scale. When reaction dynamics is on a single-scale, fast spatial movement has a simple effect of averaging reactions over the distribution of all the species. When reaction dynamics is on multiple scales, we show that spatial movement of molecules has different effects depending on whether the movement of each type of species is faster or slower than the effective reaction dynamics on this molecular type. We obtain results for both when the system is without and with conserved quantities, which are linear combinations of species evolving only on the slower time scale.

1. Introduction. When chemical species react, they are present in some (open or closed) system with a spatial dimension. Most models of chemical reaction systems describe the evolution of the concentration of chemical species and ignore both stochastic and spatial effects inherent in the system. This can be justified by law of large number results when both: the number of species across all molecular types is large, and when the movement of molecules within the system is much faster than the chemical reactions themselves. In applications where these assumptions hold, the system is spatially homogeneous, and the use of the deterministic law of mass action kinetics is approximately appropriate [Kurtz (1970)].

However, in biological cells, low numbers of certain key chemical species involved in the reaction systems result in appreciable noise in gene expression and many regulatory functions of the cell, and lead to cell–cell variability and different cell fate decisions [McAdams and Arkin (1997), Elowitz et al. (2002)]. In order to understand the key effects of intrinsic noise in chemical reaction networks on the overall dynamics, one needs to derive new approximations of stochastic models describing the evolution of molecular counts of chemical species. Furthermore, the cell is not a spatially homogeneous environment, and it has been repeatedly demonstrated that spatial concentration of certain molecules plays an important

role in many cellular processes [Howard and Rutenberg (2003), Takahashi, Tanase-Nicola and Ten Wolde (2010)]. Deterministic spatial models (reaction–diffusion PDEs) are insufficient for this purpose, since local fluctuations of small molecular counts can have propagative effects, even when the overall total number of molecules in the cell of the relevant species is high.

Numerical simulations of biochemical reactions are indispensable since the stochastic spatial dynamics of most systems of interest is analytically intractable. A number of different simulation methods have been developed for this purpose, ranging from exact methods (accounting for each stochastic event) to approximate methods (replacing exact stochastics for some aspects of the system with approximate statistical distributions); see, for example, Fange et al. (2010), Drawert et al. (2010), Jeschke, Ewald and Uhrmacher (2011). For effective computations, a mesoscopic form of the full stochastic spatial reaction model is necessary. These are compartment models in which a heterogeneous system is divided into homogeneous subsystems in each of which a set of chemical reactions are performed. Molecular species are distributed across compartments and their diffusion is modeled by moves between neighboring compartments [Burrage et al. (2011)].

An important mathematical feature of models of biochemical reactions lies in the essential multi-scale nature of the reaction processes. In some cases, all chemical species are present in a comparable amount and change their concentrations on the same temporal scale. We call this a *single-scale* reaction network. However, if at least one chemical species changes its abundance (relative to its abundance) on a much faster time scale, we call this a *multi-scale* reaction network. The fast change of the concentrations of some chemical species then has an impact on the dynamics of the slow species. When one adds spatial movement of species into the system, then the species with fast movement can have an averaging effect on the dynamics as well. The overall dynamics depends on how these two averaging factors interact, and subsequently determines the evolution of the slow species on the final time scale of interest.

In this paper, we analyze the effects of movement of molecules on the dynamics of the molecular counts of chemical species. We consider a finite number of compartments in which different reactions can happen, with species moving between compartments, and derive results for the evolution of the sum total of molecules in all compartments. We consider the following for chemical reactions within compartments: (i) single-scale chemical reactions, (ii) multi-scale chemical reactions without conserved quantities and (iii) multi-scale chemical reactions with conserved quantities. We focus on the derivation of simplified models obtained as limits of rescaled versions of the original model [in the spirit of Kang, Kurtz and Popovic (2014), Ball et al. (2006), Franz, Liebscher and Zeiser (2012)]. We stress that our results are for mesoscopic models of spatial systems, as opposed to models in which the number of compartments increases and the size of compartments shrinks [Blount (1994), Kouritzin and Long (2002), Kotelenez (1988)].

Our goal is to find reduced models that capture all relevant stochastic features of the original model, while focusing only on the quantities that are easy to measure (sum total of molecular numbers for each species) in the system. Our results for this reduced dynamics make stochastic simulations almost trivial, while at the same time differentiating (being able to detect) between different cases of system heterogeneity and between different relative time scales of species movement.

1.1. *Outline of results.* After introducing a model for chemical reactions in Section 2.1, we provide results in nonspatial systems which we need later for spatial results: asymptotics for a single-scale reaction network (Lemma 2.4), asymptotics for two-scale systems without (Lemma 2.7) and with conserved quantities on the fast time scale (Lemma 2.12), as well as extensions to three-scale systems (Lemma 2.10). Examples of each type of system are provided as well (Examples 2.5, 2.8, 2.13). In Section 3, we give results for spatial compartment models: for single-scale spatial systems (Theorem 3.7), for two-scale spatial systems (Theorem 3.13) in the absence of conserved quantities, and in the presence of conserved quantities (Theorem 3.23). We also place the earlier examples in a spatial setting (Examples 3.10, 3.19, 3.27). We conclude the paper with a discussion of possible implications and extensions.

REMARK 1.1 (Notation). For some Polish space E, we denote the set of continuous (bounded and continuous, continuous with compact support), real-valued functions by $\mathcal{C}(E)$ [$\mathcal{C}_b(E), \mathcal{C}_c(E)$]. In general, we write $\underline{x} := (x_k)_k$ for vectors and $\underline{\underline{x}} := (x_{ik})_{i,k}$ for matrices. In addition, $\underline{x}_{i\cdot}$ is the ith line and $\underline{x}_{\cdot k}$ is the kth column of $\underline{\underline{x}}$. We denote by $\mathcal{D}(I; E)$ the space of càdlàg functions $I \subseteq \mathbb{R} \to E$, which is equipped, as usual, with the Skorohod topology, metrized by the Skorohod metric, d_{Sk}. For sets $F, F' \subseteq E$, we write $F - F' := \{f \in F : f \notin F'\}$.

2. Chemical reactions in a single compartment. Before we present our main results on spatial systems in the next section, we provide basic results on reaction networks in a single compartment, which are special cases of theorems given in Kang and Kurtz (2013). Our results for the spatial case both rely on them and are proved using similar techniques.

We consider a set $\mathcal{I}$ of different chemical species, involved in $\mathcal{K}$ different reactions of the form

$$(2.1) \qquad\qquad (v_{ik})_{i \in \mathcal{I}} \to (v'_{ik})_{i \in \mathcal{I}}$$

with $\underline{\underline{v}} = (v_{ik})_{i \in \mathcal{I}, k \in \mathcal{K}}, \underline{\underline{v}}' = (v'_{ik})_{i \in \mathcal{I}, k \in \mathcal{K}} \in \mathbb{Z}_+^{\mathcal{I} \times \mathcal{K}}$ and $v_{ik} = l$ if l molecules of the chemical species i take part in reaction k and $v'_{ik} = l$ if reaction k produces l molecules of species i. In the chemical reaction literature, $\underline{\underline{\zeta}} = \underline{\underline{v}}' - \underline{\underline{v}}$ is called the *stoichiometric matrix* of the system, and $\sum_{i \in \mathcal{I}} v_{ik}$ the *order* of reaction k. In addition, we set $\underline{\zeta}_{\cdot k} := (\zeta_{ik})_{i \in \mathcal{I}}$.

2.1. *The Markov chain model and the rescaled system.*   Denoting by $X_i(t)$ the number of molecules of species i at time t, we assume that $(\underline{X}(t))_{t \geq 0}$ with $\underline{X}(t) = (X_i(t))_{i \in \mathcal{I}}$ is solution of

$$(2.2) \qquad X_i(t) = X_i(0) + \sum_{k \in \mathcal{K}} \zeta_{ik} Y_k \left(\int_0^t \Lambda_k^{CR}(\underline{X}(u)) \, du \right),$$

where the Y_k's are independent (rate 1) Poisson processes and $\Lambda_k^{CR}(\underline{X}(u))$ is the reaction rate of reaction k at time u, $k \in \mathcal{K}$. We will assume throughout the following.

ASSUMPTION 2.1 (Dynamics of unscaled single compartment reaction network).   The reaction network dynamics satisfies the following conditions:

  (i) The reaction rate $\underline{x} \mapsto \Lambda_k^{CR}(\underline{x})$ is a nonnegative locally Lipshitz, locally bounded function and $\Lambda_k^{CR} \neq 0$, $k \in \mathcal{K}$.
  (ii) Given $(Y_k)_{k \in \mathcal{K}}$, the time-change equation (2.2) has a unique solution.

The most important chemical reaction kinetics is given by mass action, that is,

$$(2.3) \qquad \Lambda_k^{CR}(\underline{x}) = \kappa_k' \prod_{i \in \mathcal{I}} v_{ik}! \binom{x_i}{v_{ik}}$$

for constants κ_k. In other words, the rate of reaction k is proportional to the number of possible combinations of reacting molecules. Solutions to (2.2) can be guaranteed by using, for example, Ethier and Kurtz (1986), Theorem 6.2.8; see also their Remark 6.2.9(b). Note, however, that Assumption 2.1(i) does not suffice to guarantee a global solution to (2.2), since it has to be certain—usually by imposing some growth condition—that the solution does not become infinite in finite time.

Chemical reaction networks in many applications involve chemical species with vastly differing numbers of molecules and reactions with rate constants that also vary over several orders of magnitude Ball et al. (2006), Examples. This wide variation in number and rate yield phenomena that evolve on very different time scales. Recognizing that the variation in time scales is due both to variation in species number and to variation in rate constants, we normalize species numbers and rate constants by powers of a parameter N which we assume to be large, and consider a sequence of models, parametrized by $N \in \mathbb{N}$. Rescaled versions of the original model, under certain assumptions, have a limit as $N \to \infty$. We will use stochastic equations of the form (2.2) driven by independent Poisson processes to show convergence, exploiting the law of large numbers and martingale properties of the Poisson processes. We rely heavily on the stochastic averaging methods that date back to Khasminskii, for which we follow the formalism in terms of martingale problems from Kurtz (1992).

We rescale the system as follows: consider the solution $(\underline{X}^N(t))_{t \geq 0}$ of (2.2) with the chemical reaction rates Λ_k^{CR} replaced by $\Lambda_k^{\mathrm{CR},N}$. For real-valued

$$(2.4) \qquad \underline{\alpha} = (\alpha_i)_{i \in \mathcal{I}}, \qquad \underline{\beta} = (\beta_k)_{k \in \mathcal{K}}, \qquad \gamma$$

with $\alpha_i \geq 0, i \in \mathcal{I}$, we denote the $(\underline{\alpha}, \underline{\beta}, \gamma)$-rescaled system by

$$(2.5) \quad V_i^N(t) := N^{-\alpha_i} X_i^N(N^\gamma t), \qquad \lambda_k^{\mathrm{CR},N}(\underline{v}) := N^{-\beta_k} \Lambda_k^{\mathrm{CR},N}((N^{\alpha_i} v_i)_{i \in \mathcal{I}}),$$

where $(\underline{\alpha}, \underline{\beta}, \gamma)$ is chosen so that: $V_i^N = \mathcal{O}(1), i \in \mathcal{I}$, for all time (a.s. does not go infinity in finite time, but also does not have a.s. zero limit for all time), and $\lambda_k^{\mathrm{CR},N} = \mathcal{O}(1), k \in \mathcal{K}$ (for all values of $\underline{v}$ when it is not equal to zero). We will restrict to the case $\gamma = 0$ which can always be achieved when considering $\beta_k' = \beta_k + \gamma, k \in \mathcal{K}$. From (2.2), we see that the $(\underline{\alpha}, \underline{\beta}, \gamma)$-rescaled system $\underline{V}^N := (\underline{V}^N(t))_{t \geq 0}$ is a solution to the system of stochastic equations

$$(2.6) \quad V_i^N(t) = V_i^N(0) + \sum_{k \in \mathcal{K}} N^{-\alpha_i} \zeta_{ik} Y_k \left(N^{\beta_k + \gamma} \int_0^t \lambda_k^{\mathrm{CR},N}(\underline{V}^N(u)) \, du \right),$$

which has a unique solution thanks to Assumption 2.1. In vector notation, we use the diagonal matrix $N^{-\underline{\alpha}}$ with ith diagonal entry $N^{-\alpha_i}$ and write

$$(2.7) \quad \underline{V}^N(t) = \underline{V}^N(0) + \sum_{k \in \mathcal{K}} N^{-\underline{\alpha}} \underline{\zeta}_{\cdot k} Y_k \left(N^{\beta_k + \gamma} \int_0^t \lambda_k^{\mathrm{CR},N}(\underline{V}^N(u)) \, du \right).$$

The reaction rates satisfy the following.

ASSUMPTION 2.2 (Dynamics of scaled single compartment reaction network). There exist locally Lipshitz functions $\lambda_k^{\mathrm{CR}} : \mathbb{R}_+^{\mathcal{I}} \to \mathbb{R}_+, k \in \mathcal{K}$ with

$$(2.8) \qquad N^{-\beta_k} \Lambda_k^{\mathrm{CR},N}((N^{\alpha_i} v_i)_{i \in \mathcal{I}}) \overset{N \to \infty}{\longrightarrow} \lambda_k^{\mathrm{CR}}(\underline{v})$$

uniformly on compacts. [Without loss of generality, we will assume that convergence in (2.8) is actually an identity; our results easily generalize by the assumed uniform convergence on compacts.]

In the special case of mass action kinetics (2.3), if $\alpha_i = 1$ for all $i \in \mathcal{I}$ and $\kappa_k = \kappa_k' N^{-(\sum_i v_{ik}) + 1}$ with $\beta_k = 1$ and some $\kappa_k' > 0$ for all $k \in \mathcal{K}$, then

$$N^{-\beta_k} \Lambda_k^{\mathrm{CR},N}((N^{\alpha_i} v_i)_{i \in \mathcal{I}}) \overset{N \to \infty}{\longrightarrow} \kappa_k' \prod_{i \in \mathcal{I}} v_i^{v_{ik}}.$$

The polynomial on the right-hand side is known in the literature for deterministic chemical reaction systems as the *mass action kinetic* rate.

2.2. *Single scale systems.* For $i \in \mathcal{I}$, the set of reactions which change the number of species i is

$$\mathcal{K}_i := \{k \in \mathcal{K} : \zeta_{ik} \neq 0\}$$

(a reaction of the form $A + B \to A + C$ does not change the number of species A). A chemical reaction network is a *single scale system* if $(\underline{\alpha}, \underline{\beta}, \gamma)$ from (2.4) satisfy

(2.9)
$$\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i, \qquad i \in \mathcal{I}.$$

For $i \in \mathcal{I}$, let $\mathcal{K}_i^* \subseteq \mathcal{K}_i$ be the set of reactions such that $\beta_k + \gamma = \alpha_i$, and let $\mathcal{K}^* = \bigcup_{i \in \mathcal{I}} \mathcal{K}_i^*$. Define $\underline{\underline{\zeta}}^*$ by

$$\zeta_{ik}^* = \lim_{N \to \infty} N^{-\alpha_i} N^{\beta_k + \gamma} \zeta_{ik}.$$

Then $\underline{\underline{\zeta}}^*$ is the matrix whose $i \in \mathcal{I}, k \in \mathcal{K}_i^*$ entries are ζ_{ik} and its $i \in \mathcal{I}, k \in \mathcal{K}_i - \mathcal{K}_i^*$ entries are zero. Let $\mathcal{I}_\circ$ be the subset of species with $\alpha_i = 0$, called the *discrete species*, and let $\mathcal{K}_\circ^* = \bigcup_{i \in \mathcal{I}_\circ} \mathcal{K}_i^*$, called the *slow reactions*. Let $\mathcal{I}_\bullet$ be the subset of species with $\alpha_i > 0$, called the *continuous species*, and let $\mathcal{K}_\bullet^* = \bigcup_{i \in \mathcal{I}_\bullet} \mathcal{K}_i^*$, called the *fast reactions*. Then $\mathcal{K}^* = \mathcal{K}_\circ^* \cup \mathcal{K}_\bullet^*$. Note that by definition $\mathcal{I}_\circ$ and $\mathcal{I}_\bullet$ are disjoint, and by definition of $\mathcal{K}_i^*$ (and as reaction rates come with a single scaling $N^{\beta_k + \gamma}$), $\mathcal{K}_\circ^*$ and $\mathcal{K}_\bullet^*$ are also disjoint. In the limit of the rescaled system, the species indexed by $\mathcal{I}_\circ$ are $\mathbb{Z}_+$-valued (hence the name discrete species), while the species indexed by $\mathcal{I}_\bullet$ are $\mathbb{R}_+$-valued (continuous species). See Table 1 for an overview of these definitions. We next assume the following.

TABLE 1
An overview of different sets and possibilities in the case $\gamma = 0$. The set $\mathcal{I}$ is split into discrete ($\mathcal{I}_\circ$) and continuous ($\mathcal{I}_\bullet$) chemical species, while the set $\mathcal{K}^*$ is split into slow ($\mathcal{K}_\circ^*$) and fast ($\mathcal{K}_\bullet^*$) reactions. The gray boxes give the reactions which still appear in the limit dynamics. A special feature of single-scale systems is that discrete species are exactly changed through slow reactions, and continuous species are changed by fast reactions. In particular, discrete species are not changed by fast reactions. This is different in multi-scale networks; see Table 2

	Slow reactions $k \in \mathcal{K}_\circ^*, \beta_k = 0$	Fast reactions $k \in \mathcal{K}_\bullet^*, \beta_k > 0$
Discrete species, $\alpha_i = 0, i \in \mathcal{I}_\circ$	$\zeta_{ik}^* \begin{cases} \neq 0, & k \in \mathcal{K}_i^*, \\ = 0, & \text{else} \end{cases}$	$\zeta_{ik} = \zeta_{ik}^* = 0$
Continuous species, $\alpha_i > 0, i \in \mathcal{I}_\bullet$	$\zeta_{ik} = 0$ or $\beta_k + \gamma - \alpha_i < 0$ $\implies \zeta_{ik}^* = 0$	$\zeta_{ik}^* \begin{cases} \neq 0, & k \in \mathcal{K}_i^*, \\ = 0, & \text{else} \end{cases}$

TABLE 2

As in the single-scale case, the set $\mathcal{I}$ is split into discrete and continuous chemical species. In addition, discrete and continuous species are either changed on the fast or slow time scale. (This means that $\mathcal{I}_\circ^f, \mathcal{I}_\bullet^f, \mathcal{I}_\circ^s, \mathcal{I}_\bullet^s$ are disjoint sets.) The set of reactions is split into several categories, which can overlap. Here, $k \in \mathcal{K}_\circ^f$ is a reaction which changes a discrete species on the fast time scale, etc. Note that such a reaction can as well change a continuous species on the slow time scale. The separation of fast and slow time scales is determined by (2.11) with $\varepsilon = 1$. As in Table 1, we mark the cells which finally determine the dynamics of the limiting object

Fast time scale $N\,dt$

	Reactions of discrete species on fast scale $k \in \mathcal{K}_\circ^f, \beta_k = 1$	Reactions of continuous species on fast scale $k \in \mathcal{K}_\bullet^f, \beta_k > 1$	Other reactions $k \in \mathcal{K} - \mathcal{K}_\circ^f - \mathcal{K}_\bullet^f$, $\beta_k \geq 0$
Discrete species, $\alpha_i = 0, i = \mathcal{I}_\circ^f$	$\zeta_{ik}^f \begin{cases} \neq 0, & k \in \mathcal{K}_i^f, \\ = 0, & \text{else} \end{cases}$	$\zeta_{ik} = \zeta_{ik}^f = 0$	$\zeta_{ik}^f = 0$
Continuous species, $\alpha_i > 0, i = \mathcal{I}_\bullet^f$	$\zeta_{ik} = 0$ or $\beta_k - \alpha_i - 1 < 0$ $\implies \zeta_{ik}^f = 0$	$\zeta_{ik}^f \begin{cases} \neq 0, & k \in \mathcal{K}_i^f, \\ = 0, & \text{else} \end{cases}$	$\zeta_{ik} = 0$ or $\beta_k - \alpha_i - 1 > 0$ $\implies \zeta_{ik}^f = 0$

Slow time scale dt

	Reactions of discrete species on slow scale $k \in \mathcal{K}_\circ^s, \beta_k = 0$	Reactions of continuous species on slow scale $k \in \mathcal{K}_\bullet^s, \beta_k > 0$
Discrete species, $\alpha_i = 0, i = \mathcal{I}_\circ^s$	$\zeta_{ik}^s \begin{cases} \neq 0, & k \in \mathcal{K}_i^s \\ = 0, & \text{else} \end{cases}$	$\zeta_{ik} = \zeta_{ik}^s = 0$
Continuous species, $\alpha_i > 0, i = \mathcal{I}_\bullet^s$	$\zeta_{ik} = 0$ or $\beta_k - \alpha_i < 0$ $\implies \zeta_{ik}^s = 0$	$\zeta_{ik}^s \begin{cases} \neq 0, & k \in \mathcal{K}_i^s, \\ = 0, & \text{else} \end{cases}$

ASSUMPTION 2.3 (Dynamics of the reaction network). For Poisson processes $(Y_k)_{k \in \mathcal{K}_\circ^*}$, the time-change equation

(2.10)
$$\underline{V}(t) = \underline{V}(0) + \sum_{k \in \mathcal{K}_\circ^*} \underline{\zeta}_{\cdot k}^* Y_k \left(\int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}(u))\,du \right)$$
$$+ \sum_{k \in \mathcal{K}_\bullet^*} \underline{\zeta}_{\cdot k}^* \int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}(u))\,du$$

has a unique solution $\underline{V} := (\underline{V}(t))_{t \geq 0}$.

Actually, the last display is shorthand notation for

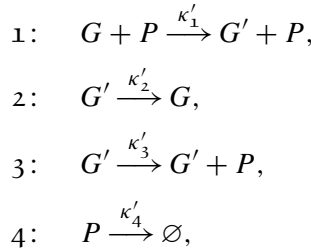$$V_i(t) = V_i(0) + \sum_{k \in \mathcal{K}_\circ^*} \zeta_{ik}^* Y_k \left(\int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}(u))\,du \right), \qquad i \in \mathcal{I}_\circ,$$

$$V_i(t) = V_i(0) + \sum_{k \in \mathcal{K}_\bullet^*} \zeta_{ik}^* \int_0^t \lambda_k^{CR}(\underline{V}(u)) \, du, \qquad i \in \mathcal{I}_\bullet.$$

LEMMA 2.4 (Convergence of single-scale reaction networks). *Let $\underline{V}^N$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to (2.6). Assume $(\underline{\alpha}, \underline{\beta}, \gamma)$ from (2.5) satisfy the single scale system assumptions (2.9), and Assumptions 2.2 and 2.3 for the rescaled reaction network are satisfied. Then, if $V^N(0) \Longrightarrow V(0)$, the process of rescaled amounts $\underline{V}^N$ converges weakly to the solution $\underline{V}$ of (2.10) in the Skorohod topology.*

The proof of Lemma 2.4 is an extension of the classical theorem for convergence of Markov chains to solutions of ODEs; see Kurtz (1970, 1981), or Ethier and Kurtz (1986). It is essentially shown in Kang and Kurtz (2013), Theorem 4.1. For other recent related results, see Franz, Liebscher and Zeiser (2012).

EXAMPLE 2.5 (Self-regulating gene). We give a simple example of a single-scale reaction network which leads to a piecewise deterministic solution [similar to Franz, Liebscher and Zeiser (2012), Section 5]. Consider a self-regulating gene modeled by the set of reactions

$$1: \quad G + P \xrightarrow{\kappa_1'} G' + P,$$

$$2: \quad G' \xrightarrow{\kappa_2'} G,$$

$$3: \quad G' \xrightarrow{\kappa_3'} G' + P,$$

$$4: \quad P \xrightarrow{\kappa_4'} \varnothing,$$

where G is the inactivated gene, G' is the activated gene (hence G, G' sums to 1 and is conserved by the reactions), and P is the protein expressed by the gene. Here, 1 describes activation of the gene by the protein, 2 is spontaneous deactivation of the gene, 3 is production of the protein by the activated gene and 4 is degradation of the protein. Let $\underline{x} = (x_G, x_{G'}, x_P) = (1 - x_{G'}, x_{G'}, x_P)$ and let the reaction rates be

$$\Lambda_1^{CR}(\underline{x}) = \kappa_1' x_G x_P = \kappa_1'(1 - x_{G'})x_P, \qquad \Lambda_2^{CR}(\underline{x}) = \kappa_2' x_{G'},$$
$$\Lambda_3^{CR}(\underline{x}) = \kappa_3' x_{G'}, \qquad \Lambda_4^{CR}(\underline{x}) = \kappa_4' x_P$$

with scaling $\alpha_G = \alpha_{G'} = 0, \alpha_P = 1$, that is, $\mathcal{I}_\circ = \{G, G'\}$ and $\mathcal{I}_\bullet = \{P\}$, as well as

$$\beta_1 = 0, \qquad \beta_2 = 0, \qquad \beta_3 = 1, \qquad \beta_4 = 1,$$
$$\kappa_1' = N^{-1}\kappa_1, \qquad \kappa_2' = \kappa_2, \qquad \kappa_3' = N\kappa_3, \qquad \kappa_4' = \kappa_4.$$

Then $v_G = x_G = 1 - v_{G'}$, $v_{G'} = x_{G'}$, $v_P = N^{-1}x_P$, and see (2.8),

$$\lambda_1^{CR}(\underline{v}) = \kappa_1 v_G v_P = \kappa_1(1 - v_{G'})v_P, \qquad \lambda_2^{CR}(\underline{v}) = \kappa_2 v_{G'},$$

$$\lambda_3^{CR}(\underline{v}) = \kappa_3 v_{G'}, \qquad \lambda_4^{CR}(\underline{v}) = \kappa_4 v_P.$$

Here, $\mathcal{K}_\circ^* = \mathcal{K}_G = \mathcal{K}_{G'} = \{1, 2\}$ and $\mathcal{K}_\bullet^* = \mathcal{K}_P = \{3, 4\}$. In this example, the matrices $\underline{\underline{\zeta}}$ and $\underline{\underline{\zeta}}^*$ are given by

$$\underline{\underline{\zeta}} = \underline{\underline{\zeta}}^* = \begin{matrix} G \\ G' \\ P \end{matrix} \begin{pmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}.$$

Moreover, according to Lemma 2.4, the limit $(\underline{V}(t))_{t \geq 0}$ of $(V^N(t))_{t \geq 0}$ solves

$$V_{G'}(t) = V_{G'}(0) + Y_1\left(\kappa_1 \int_0^t (1 - V_{G'}(u))V_P(u)\,du\right) - Y_2\left(\kappa_2 \int_0^t V_{G'}(u)\,du\right),$$

$$V_P(t) = V_P(0) + \kappa_3 \int_0^t V_{G'}(u)\,du - \kappa_4 \int_0^t V_P(u)\,du.$$

2.3. Multi-scale systems.

Two-scale systems. We say that the chemical network (2.1) is a two scale system if $(\underline{\alpha}, \underline{\beta}, \gamma)$ from (2.4) are such that: there is a partition of $\mathcal{I}$ into (disjoint) $\mathcal{I}^f$, called the *fast species*, and $\mathcal{I}^s$, called the *slow species*, such that, for some $\varepsilon > 0$,

(2.11)
$$\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i + \varepsilon, \qquad i \in \mathcal{I}^f,$$

$$\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i, \qquad i \in \mathcal{I}^s.$$

Without loss of generality, we assume that $\gamma = 0$, and that our choice of N is such that $\varepsilon = 1$ in (2.11), so the relative change of fast species happens at rate $\mathcal{O}(N)$ and the relative change of slow species happens at rate $\mathcal{O}(1)$.

We first consider what happens on the *faster time scale* $N\,dt$. For each $i \in \mathcal{I}^f$, let $\mathcal{K}_i^f \subseteq \mathcal{K}_i$ be the set of reactions with $\beta_k = \alpha_i + 1$. Define

(2.12)
$$\mathcal{K}^f = \{k \in \mathcal{K} : \exists i \in \mathcal{I}^f : k \in \mathcal{K}_i, \beta_k = \alpha_i + 1\},$$

and a matrix $\underline{\underline{\zeta}}^f$ with $|\mathcal{I}^f|$ rows and $|\mathcal{K}^f|$ columns defined by

(2.13)
$$\zeta_{ik}^f = \lim_{N \to \infty} N^{-(\alpha_i+1)} N^{\beta_k} \zeta_{ik}, \qquad i \in \mathcal{I}^f, k \in \mathcal{K}_i^f.$$

This matrix identifies a subnetwork of reactions and their effective change on the faster time scale $N\,dt$. Let $\mathcal{I}_\circ^f \subseteq \mathcal{I}^f$ be the subset of fast species for which $\alpha_i = 0$, and let $\mathcal{K}_\circ^f = \bigcup_{i \in \mathcal{I}_\circ^f} \mathcal{K}_i^f$ be the subset of reactions changing these fast discrete species on this time scale. Let $\mathcal{I}_\bullet^f \subseteq \mathcal{I}^f$ be the subset of fast species for which $\alpha_i >$

0, which are continuous species on the fast time scale, and let $\mathcal{K}_\bullet^f = \bigcup_{i \in \mathcal{I}_\bullet^f} \mathcal{K}_i^f$ be the subset of reactions changing continuous species on this time scale. Since $\mathcal{I}_\circ^f$ and $\mathcal{I}_\bullet^f$ are disjoint in $\mathcal{I}^f = \mathcal{I}_\circ^f \cup \mathcal{I}_\bullet^f$, and since β_k is unique for each reaction in $\mathcal{K}^f = \mathcal{K}_\circ^f \cup \mathcal{K}_\bullet^f$, it follows that $\mathcal{K}_\circ^f$ and $\mathcal{K}_\bullet^f$ are disjoint as well.

We next consider what happens on the *slower time scale dt*. For each $i \in \mathcal{I}^s$, let

(2.14)
$$\mathcal{K}^s = \{k \in \mathcal{K} : \exists i \in \mathcal{I}^s, \beta_k = \alpha_i\},$$

be the set of reactions such that $\beta_k = \alpha_i$, and $\underline{\underline{\zeta}}^s = (\zeta_{ik}^s)_{i \in \mathcal{I}^s, k \in \mathcal{K}^s}$ defined by

(2.15)
$$\zeta_{ik}^s = \lim_{N \to \infty} N^{-\alpha_i} N^{\beta_k} \zeta_{ik}, \qquad i \in \mathcal{I}^s, k \in \mathcal{K}_i^s.$$

This matrix identifies the subnetwork of reactions and their effective change on the slower time scale dt. Let $\mathcal{I}_\circ^s \subseteq \mathcal{I}^s$ be the subset of (discrete) slow species for which $\alpha_i = 0$, and $\mathcal{K}_\circ^s = \bigcup_{i \in \mathcal{I}_\circ^s} \mathcal{K}_i^s$ the subset of reactions changing discrete species on this time scale. Let $\mathcal{I}_\bullet^s \subseteq \mathcal{I}$ be the subset of (continuous) slow species for which $\alpha_i > 0$, and $\mathcal{K}_\bullet^s = \bigcup_{i \in \mathcal{I}_\bullet^s} \mathcal{K}_i^s$ the subset of reactions changing continuous species on this time scale. As before, $\mathcal{I}_\circ^s$ and $\mathcal{I}_\bullet^s$ being disjoint in $\mathcal{I}^s = \mathcal{I}_\circ^s \cup \mathcal{I}_\bullet^s$ implies that $\mathcal{K}_\circ^s$ and $\mathcal{K}_\bullet^s$ are disjoint in $\mathcal{K}^s = \mathcal{K}_\circ^s \cup \mathcal{K}_\bullet^s$ as well.

Note, however, that there is no reason for $\mathcal{K}^s$ to be disjoint from $\mathcal{K}^f$. In fact, there may be reactions in $\mathcal{K}^s$ with parameter β_k that make an effective change on the time scale dt in a slow species of high enough abundance $\alpha_i = \beta_k$, that also effectively change some fast species on the time scale $N\,dt$, that is, for some $j \in \mathcal{I}^f$ with $\beta_k = \alpha_j + 1$. The important factor for limiting results is that we identify contributions from reactions on each of the two scales independently, and make assumptions on their stability.

Our initial division of species into fast and slow may include some *conserved quantities*, that is, linear combinations of fast species that remain unchanged on the faster time scale $N\,dt$. Let $\mathcal{N}((\underline{\underline{\zeta}}^f)^{\mathrm{T}})$ be the null space of $(\underline{\underline{\zeta}}^f)^{\mathrm{T}}$. If its dimension is >0 it is formed by all the linear combinations of species conserved by the limiting fast subnetwork, meaning that they see no effective change on the time scale $N\,dt$. In spatial systems, the fast species are counts of species in a single compartment (which evolves due to both, movement and chemical reactions) while conserved quantities are the sum total of the coordinates in all compartments (which evolves only according to chemical reactions). For now—unless stated otherwise—we assume that the basis for the species is such that $\dim(\mathcal{N}((\underline{\underline{\zeta}}^f)^{\mathrm{T}})) = 0$.

Define the *fast process* $\underline{V}_f^N := (\underline{V}_f^N(t))_{t \geq 0}$ as $\underline{V}_f^N(t) := (V_i^N(t))_{i \in \mathcal{I}^f}$ and the *slow process* $\underline{V}_s^N := (\underline{V}_s^N(t))_{t \geq 0}$ as $\underline{V}_s^N(t) := (V_i^N(t))_{i \in \mathcal{I}^s}$. We give necessary assumptions on the dynamics of $\underline{V}_f^N$ on the time scale $N\,dt$ conditional on $\underline{V}_s^N(t) \equiv \underline{v}_s$ being constant, on the dynamics of $\underline{V}_s^N$, and on the overall behavior of $\underline{V}^N$ in order to obtain a proper limiting dynamics of slow species, $\underline{V}_s^N$.

ASSUMPTION 2.6 (Dynamics of a two-scale reaction network).   Recall λ_k^{CR} from (2.8). The two-scale reaction network (2.11) with effective change $\underline{\zeta}^f$ as in (2.13) on time scale $N\,dt$ and $\underline{\underline{\zeta}}^s$ as in (2.15) on time scale dt satisfies the following conditions:

(i) For each $\underline{v}_s \in \mathbb{R}_+^{|\mathcal{I}^s|}$ there exists a well-defined process $\underline{V}_{f|v_s}$, giving the dynamics of the fast species given the vector of slow species, that is, the solution of

$$
\underline{V}_{f|\underline{v}_s}(t) = \underline{V}_{f|\underline{v}_s}(0) + \sum_{k \in \mathcal{K}_\circ^f} \underline{\zeta}_{\cdot k}^f Y_k\left(\int_0^t \lambda_k^{CR}(\underline{V}_{f|\underline{v}_s}(u), \underline{v}_s)\,du\right)
$$

(2.16)

$$
+ \sum_{k \in \mathcal{K}_\bullet^f} \underline{\zeta}_{\cdot k}^f \int_0^t \lambda_k^{CR}(\underline{V}_{f|\underline{v}_s}(u), \underline{v}_s)\,du
$$

with a unique stationary probability measure $\mu_{\underline{v}_s}(d\underline{z})$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$, such that

(2.17) $\bar{\lambda}_k^{CR}(\underline{v}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \lambda_k^{CR}(\underline{z}, \underline{v}_s)\mu_{\underline{v}_s}(d\underline{z}) < \infty, \qquad k \in \mathcal{K}^s.$

(ii) There exists a well-defined process $\underline{V}_s$ that is the solution of

$$
\underline{V}_s(t) = \underline{V}_s(0) + \sum_{k \in \mathcal{K}_\circ^s} \underline{\zeta}_{\cdot k}^s Y_k\left(\int_0^t \bar{\lambda}_k^{CR}(\underline{V}_s(u))\,du\right)
$$

(2.18)

$$
+ \sum_{k \in \mathcal{K}_\bullet^s} \underline{\zeta}_{\cdot k}^s \int_0^t \bar{\lambda}_k^{CR}(\underline{V}_s(u))\,du
$$

with $\bar{\lambda}_k^{CR}$ given by (2.17).

(iii) There exists a locally bounded function $\psi : \mathbb{R}_+^{|\mathcal{I}|} \to \mathbb{R}$, $\psi \geq 1$ such that $\psi(x) \to \infty$ as $x \to \infty$, and

(iii-a) for each $t > 0$

$$
\sup_N \mathbb{E}\left[\int_0^t \psi(\underline{V}^N(u))\,du\right] < \infty;
$$

(iii-b) for all $k \in \mathcal{K}$

$$
\lim_{K \to \infty} \sup_{|x| > K} \frac{\lambda_k^{CR}(x)}{\psi(x)} = 0.
$$

LEMMA 2.7 (Convergence of two-scale reaction networks).   *Let $\underline{V}^N$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to* (2.6) [*or* (2.7)]. *Assume that* $(\underline{\alpha}, \underline{\beta}, \gamma = 0)$ *satisfy the two-scale system assumptions* (2.11) *for some* $\mathcal{I}^f, \mathcal{I}^s$ *and* $\varepsilon = 1$, *and the Assumptions* 2.6 *are*

satisfied. Then, if $\underline{V}_s^N(0) \overset{N \to \infty}{\Longrightarrow} \underline{V}_s(0)$, *the process of rescaled amounts of the slow species* $\underline{V}_s^N(\cdot)$ *converges weakly to the solution* $\underline{V}_s(\cdot)$ *of* (2.18) *with rates given by* (2.17) *in the Skorokhod topology.*

The proof of Lemma 2.7 is given in Kang and Kurtz (2013), Theorem 5.1.

EXAMPLE 2.8 (Production from a fluctuating source). We present here an example of a reaction network with two time scales with no conserved species on the fast time scale. In our example, two species A and B react and produce species C. Source B fluctuates as it is quickly transported into the system and degrades very fast. We have the set of reactions

$$1: \quad A + B \overset{\kappa_1'}{\longrightarrow} C, \qquad 2: \quad \varnothing \overset{\kappa_2'}{\longrightarrow} B, \qquad 3: \quad B \overset{\kappa_3'}{\longrightarrow} \varnothing.$$
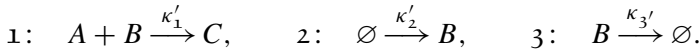
Here, the sum of the numbers of molecules A and C is constant (but both will turn out to be slow species), so we only need to consider the dynamics of the A molecules. We denote molecules numbers by x_A and x_B, respectively, set $\underline{x} = (x_A, x_B)$ and consider the reaction rates as given by mass action kinetics,

$$(2.19) \quad \Lambda_1^{CR}(\underline{x}) = \kappa_1' x_A x_B, \qquad \Lambda_2^{CR}(\underline{x}) = \kappa_2', \qquad \Lambda_3^{CR}(\underline{x}) = \kappa_3' x_B.$$

For the scaled system, we use $\alpha_A = \alpha_C = 1$, $\alpha_B = 0$. So, setting the rescaled species counts $v_A = N^{-1} x_A$, $v_B = x_B$ and

$$(2.20) \qquad \beta_1 = 0, \qquad \beta_2 = 1, \qquad \beta_3 = 1,$$

$$(2.21) \qquad \kappa_1 = \kappa_1', \qquad \kappa_2 = N^{-1} \kappa_2', \qquad \kappa_3 = N^{-1} \kappa_3',$$

we write

$$(2.22) \quad \lambda_1^{CR}(\underline{v}) = \kappa_1 v_A v_B, \qquad \lambda_2^{CR}(\underline{v}) = \kappa_2, \qquad \lambda_3^{CR}(\underline{v}) = \kappa_3 v_B.$$

Now, the process $\underline{V}^N = (V_A^N, V_B^N)$ is given by (2.6) as

$$V_A^N(t) = V_A^N(0) - N^{-1} Y_1 \left(N \int_0^t \kappa_1 V_A^N(u) V_B^N(u) \, du \right),$$

$$(2.23) \quad V_B^N(t) = V_B^N(0) - Y_1 \left(N \int_0^t \kappa_1 V_A^N(u) V_B^N(u) \, du \right) + Y_2(N \kappa_2 t)$$

$$- Y_3 \left(N \int_0^t \kappa_3 V_B^N(u) \, du \right).$$

From this representation, it should be clear that V_B is fast while V_A is a slow species. For $\gamma = 0$, $\varepsilon = 1$, we have $\mathcal{K}^s = \{1\}$, $\mathcal{K}^f = \{1, 2, 3\}$ (in particular $\mathcal{K}^s \cap \mathcal{K}^f \neq \varnothing$), $\mathcal{K}_A = \{1\}$, $\mathcal{K}_B = \{1, 2, 3\}$ and $\mathcal{I}_f = \mathcal{I}_f^\circ = \{B\}$, $\mathcal{I}_s = \mathcal{I}_s^\bullet = \{A\}$. The matrices describing the reaction dynamics on both scales are

$$\underline{\underline{\zeta}} = \begin{matrix} A \\ B \end{matrix} \begin{pmatrix} -1 & 0 & 0 \\ -1 & 1 & -1 \end{pmatrix}, \qquad \underline{\underline{\zeta}}^f = B \, (\,-1 \quad 1 \quad -1\,), \qquad \underline{\underline{\zeta}}^s = A \, (\,-1\,),$$

where the three columns in $\underline{\underline{\zeta}}$ and $\underline{\underline{\zeta}}^f$ give reactions 1, 2 and 3, and $\underline{\underline{\zeta}}^s$ is a 1×1-matrix since there is only one reaction where A is involved. Note that $\mathcal{N}((\underline{\underline{\zeta}}^f)^t) = \{0\}$, indicating that there are no conserved quantities on the fast time scale. In order to study the dynamics of the slow species, $\underline{V}_s := V_A$, we apply Lemma 2.7 and have to check Assumption 2.6. Here, for Poisson processes Y_1, Y_2 and Y_3, and fixed $\underline{V}_s = V_A = v_A$, from (2.16),

$$
\begin{aligned}
V_{B|v_A}(t) - V_{B|v_A}(0) &= -Y_1\left(\int_0^t \kappa_1 v_A V_{B|v_A}(u)\,du\right) + Y_2(\kappa_2 t) \\
&\quad - Y_3\left(\int_0^t \kappa_3 V_{B|v_A}(u)\,du\right) \\
&\overset{d}{=} Y_2(\kappa_2 t) - Y_{1+3}\left(\int_0^t (\kappa_1 v_A + \kappa_3) V_{B|v_A}(u)\,du\right)
\end{aligned}
$$

for some Poisson process Y_{1+3} which is independent of Y_2. Note that $V_{B|v_A}(\cdot)$ is a birth–death process with constant birth rate κ_2 and linear death rates, proportional to $\kappa_1 v_A + \kappa_3$. It is well known that in equilibrium, $V_{B|v_A} \overset{d}{=} X$ with

$$
X \sim \mathrm{Poi}\left(\frac{\kappa_2}{\kappa_3 + \kappa_1 v_A}\right),
$$

which gives the desired $\mu_{v_A}(dv_B)$. Hence, (2.17) gives

$$
\bar{\lambda}_1^{\mathrm{CR}}(v_A) = \mathbf{E}[\kappa_1 v_A X] = \frac{\kappa_1 \kappa_2 v_A}{\kappa_3 + \kappa_1 v_A}.
$$

Finally, Lemma 2.7 implies that in the limit $N \to \infty$, we obtain the dynamics

$$
V_A(t) = V_A(0) - \int_0^t \bar{\lambda}_1^{\mathrm{CR}}(\underline{V}_s(u))\,du = V_A(0) - \int_0^t \frac{\kappa_1 \kappa_2 V_A(u)}{\kappa_3 + \kappa_1 V_A(u)}\,du.
$$

Three time scales. Chemical reaction networks with more than two time scales also appear in the literature; see E, Liu and Vanden-Eijnden (2007) for a simulation algorithm for such systems. One example is the heat shock response in *Escherichia coli*, introduced by Srivastava, Peterson and Bentley (2001) and studied in detail by Kang (2012). Here, we state an extension of Lemma 2.7 to reaction networks with more than two time scales [see Kang, Kurtz and Popovic (2014)]. Namely, suppose that for some $\gamma \in \mathbb{R}$ the parameters $\underline{\alpha}, \underline{\beta}$ in (2.5) and (2.8) are such that: there is a partition of $\mathcal{I}$ into disjoint sets $\mathcal{I}^f, \mathcal{I}^m, \mathcal{I}^s$ such that, for some $\varepsilon_2 > \varepsilon_1 > 0$,

$$
\begin{aligned}
&\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i + \varepsilon_2, && i \in \mathcal{I}^f, \\
(2.24) \quad &\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i + \varepsilon_1, && i \in \mathcal{I}^m, \\
&\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i, && i \in \mathcal{I}^s.
\end{aligned}
$$

We will assume, as before, that $\gamma = 0$, and that our choice of N is such that $\varepsilon_2 = 1$ in (2.24), so the relative change of fastest species $\mathcal{I}^f$ happens at rate $\mathcal{O}(N)$, the relative change of the *middle species* $\mathcal{I}^m$ happens at rate $\mathcal{O}(N^{\varepsilon_1})$, $0 < \varepsilon_1 < 1$, and the relative change of slow species $\mathcal{I}^s$ happens at rate $\mathcal{O}(1)$.

Again, we need to consider what happens on each single time scale separately. In addition to earlier definitions, for each $i \in \mathcal{I}^m$ we let $\mathcal{K}_i^m \subseteq \mathcal{K}$ be the set of reactions with $\beta_k = \alpha_i + \varepsilon_1$, $\mathcal{K}^m = \bigcup_{i \in \mathcal{I}^m} \mathcal{K}_i^m$, and a matrix $\underline{\underline{\zeta}}^m$ with $|\mathcal{I}^m|$ rows and $|\mathcal{K}^m|$ columns defined by

$$(2.25) \qquad \zeta_{ik}^m = \lim_{N \to \infty} N^{-(\alpha_i + \varepsilon_1)} N^{\beta_k} \zeta_{ik}, \qquad i \in \mathcal{I}^m, k \in \mathcal{K}_i^m,$$

which identifies a subnetwork of reactions and their effective change on the middle time scale $N^{\varepsilon_1} dt$, and we let $\mathcal{I}_\circ^m \subset \mathcal{I}^m$ be the subset of middle species for which $\alpha_i = 0$, $\mathcal{I}_\bullet^m \subseteq \mathcal{I}^m$ be the subset of fast species for which $\alpha_i > 0$, and finally $\mathcal{K}_\circ^m = \bigcup_{i \in \mathcal{I}_\circ^m} \mathcal{K}_i^m$, and $\mathcal{K}_\bullet^m = \bigcup_{i \in \mathcal{I}_\bullet^m} \mathcal{K}_i^m$. We now need an additional set of assumptions on the dynamics of $\underline{V}_f^N$ on the time scale $N\, dt$ conditional on $(\underline{V}_m^N(t), \underline{V}_s^N(t)) = (\underline{v}_m, \underline{v}_s)$ being constant, and on the dynamics of $\underline{V}_m^N$ on the time scale $N^{\varepsilon_1} dt$ conditional on $\underline{V}_s^N(t) = \underline{v}_s$ being constant.

ASSUMPTION 2.9 (Dynamics of a three-scale reaction network). The three time scale reaction network (2.24) with effective change (2.13) on time scale $N\, dt$, (2.25) on time scale $N^{\varepsilon_1} dt$ and (2.15) on time scale dt satisfies the following conditions:

(i-a) For each $(\underline{v}_m, \underline{v}_s) \in \mathbb{R}_+^{|\mathcal{I}^m| + |\mathcal{I}^s|}$ there exists a well-defined process that is the solution of

$$\underline{V}_{f|(\underline{v}_m, \underline{v}_s)}(t) = \underline{V}_{f|(\underline{v}_m, \underline{v}_s)}(0) + \sum_{k \in \mathcal{K}_\circ^f} \underline{\zeta}_{\cdot k}^f Y_k\left(\int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}_{f|(\underline{v}_m, \underline{v}_s)}(u), \underline{v}_m, \underline{v}_s)\, du\right)$$

$$+ \sum_{k \in \mathcal{K}_\bullet^f} \underline{\zeta}_{\cdot k}^f \int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}_{f|(\underline{v}_m, \underline{v}_s)}(u), \underline{v}_m, \underline{v}_s)\, du$$

with a unique stationary probability measure $\mu_{(\underline{v}_m, \underline{v}_s)}(d\underline{z})$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$, such that

$$(2.26) \quad \tilde{\lambda}_k^{\mathrm{CR}}(\underline{v}_m, \underline{v}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \lambda_k^{\mathrm{CR}}(\underline{z}, \underline{v}_m, \underline{v}_s) \mu_{(\underline{v}_m, \underline{v}_s)}(d\underline{z}) < \infty, \qquad k \in \mathcal{K}^m.$$

(i-b) For each $\underline{v}_s \in \mathbb{R}_+^{|\mathcal{I}^s|}$ there exists a well-defined process that is the solution of

$$\underline{V}_{m|\underline{v}_s}(t) = \underline{V}_{m|\underline{v}_s}(0) + \sum_{k \in \mathcal{K}_\circ^m} \underline{\zeta}_{\cdot k}^m Y_k\left(\int_0^t \tilde{\lambda}_k^{\mathrm{CR}}(\underline{V}_{m|\underline{v}_s}(u), \underline{v}_s)\, du\right)$$

$$+ \sum_{k \in \mathcal{K}_\bullet^m} \underline{\zeta}_{\cdot k}^m \int_0^t \tilde{\lambda}_k^{\mathrm{CR}}(\underline{V}_{m|\underline{v}_s}(u), \underline{v}_s)\, du,$$

which has a unique stationary probability measure $\mu_{\underline{v}_s}(d\underline{v}_m)$ on $\mathbb{R}^{|\mathcal{I}^m|}$, such that

$$(2.27) \qquad \bar{\lambda}_k^{\text{CR}}(\underline{v}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^m|}} \tilde{\lambda}_k^{\text{CR}}(\underline{v}_m, \underline{v}_s)\mu_{\underline{v}_s}(d\underline{v}_m) < \infty, \qquad k \in \mathcal{K}^s.$$

(ii) There exists a well-defined process that is the solution of (2.18) with $\bar{\lambda}_k^{\text{CR}}$ given by (2.27).

(iii) see Assumption 2.6(iii).

The extension of Lemma 2.7 then becomes the following.

LEMMA 2.10 (Convergence of three-scale reaction networks). *Let $\underline{V}^N$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to* (2.6) [*or* (2.7)]. *Assume that* $(\underline{\alpha}, \underline{\beta}, \gamma = 0)$ *satisfy the three time scale system assumptions* (2.24) *for some* $\mathcal{I}^f, \mathcal{I}^m, \mathcal{I}^s$ *and* $0 < \varepsilon_1 < \varepsilon_2 = 1$, *and the Assumptions* 2.9 *are satisfied. Then, if* $\underline{V}^N(0) \stackrel{N\to\infty}{\Longrightarrow} \underline{V}(0)$, *the process of rescaled amounts of the slow species* $\underline{V}_s^N$ *converges weakly to the solution* $\underline{V}_s$ *of* (2.18) *with rates given by* (2.27) *in the Skorokhod topology.*

The proof of Lemma 2.10 is along the same lines as the proof of Lemma 2.7, this time applying the stochastic averaging twice; see Kang (2012) for the same approach.

Conserved quantities. We turn now to the problem of *conserved quantities.* Suppose we have a two-scale reaction network with $\dim(\mathcal{N}((\underline{\underline{\zeta}}^f)^{\text{T}})) =: n^f > 0$. Then there exist linearly independent $\mathbb{R}$-valued vectors $\underline{\theta}^{c_i} = (\theta_1^{c_i}, \ldots, \theta_{|\mathcal{I}^f|}^{c_i})$, $i = 1, \ldots, n^f$ such that $t \mapsto \langle \underline{\theta}^{c_i}, \underline{V}_{f|\underline{v}_s}(t) \rangle$ where $\underline{V}_{f|\underline{v}_s}$ from (2.16) is constant. In other words, the change of $\langle \underline{\theta}^{c_i}, \underline{V}_f^N(t) \rangle$ on the time scale $N\, dt$ goes to 0. We set $\Theta^f := (\underline{\theta}^{c_i})_{i=1,\ldots,n^f}$, that is,

$$(2.28) \qquad \mathcal{N}((\underline{\underline{\zeta}}^f)^{\text{T}}) = \text{span}(\Theta^f)$$

and note that the construction implies that $\underline{\theta}^{c_i}$ has a unique parameter α_i associated with it, which we denote by α_{c_i}, $i = 1, \ldots, |\Theta^f|$ (all the species in the support of $\underline{\theta}^{c_i}$ must have the same scaling parameter α_{c_i}, as any species with a greater value of the scaling parameter does not effectively contribute to the conservation law in the limit).

We assume that the effective changes for these combinations are on the time scale dt, that is, $\sup_{k\in\mathcal{K}:\langle\underline{\theta}^{c_i},\underline{\zeta}_{\cdot k}\rangle\neq 0} \beta_k \leq \alpha_{c_i}$. In other words, we exclude the possibility that they create a new time scale, or that they effectively remain constant as then we do not need to worry about their dynamics. This will be all we need for our main results on the compartment model of multi-scale reaction networks.

If they change on the time scale dt, we need to consider their behavior together with that of the slow species.

We let $\underline{V}_c^N = (V_{c_i}^N)_{i=1,\dots,|\Theta^f|}$ be the vector of rescaled conserved quantities. For each $i = 1, \dots, |\Theta^f|$, let $\mathcal{K}_{\underline{\theta}^{c_i}}$ be the set of slow reactions such that $\beta_k = \alpha_{c_i}$ and $\langle \underline{\theta}^{c_i}, \underline{\zeta}_{\cdot k} \rangle \neq 0$, and let $\mathcal{K}^c := \bigcup_{i=1}^{|\Theta^f|} \mathcal{K}_{\underline{\theta}^{c_i}}$. Note that $\mathcal{K}^c \cap \mathcal{K}^f = \varnothing$ by construction. Let $\underline{\underline{\zeta}}^c$ be the matrix with $|\Theta^f|$ rows and $|\mathcal{K}^c|$ columns defined by

$$(2.29) \qquad \underline{\underline{\zeta}}^c_{\underline{\theta}^{c_i} k} = \lim_{N \to \infty} N^{-\alpha_{c_i}} N^{\beta_k} \langle \underline{\theta}^{c_i}, \underline{\zeta}_{\cdot k} \rangle, \qquad i = 1, \dots, |\Theta^f|, k \in \mathcal{K}_i^c.$$

Let $\Theta_\circ^f \subseteq \Theta^f$ be the subset of conserved quantities for which $\alpha_{c_i} = 0$, $\mathcal{K}_\circ^c = \bigcup_{\underline{\theta}^{c_i} \in \Theta_\circ^f} \mathcal{K}_{\underline{\theta}^{c_i}}$. Let $\Theta_\bullet^f \subseteq \Theta^f$ be the subset of conserved quantities for which $\alpha_{c_i} > 0$, $\mathcal{K}_\bullet^c = \bigcup_{\underline{\theta}^{c_i} \in \Theta_\bullet^f} \mathcal{K}_{\underline{\theta}^{c_i}}$. As before, $\mathcal{K}_\circ^c$ and $\mathcal{K}_\bullet^c$ are disjoint.

We extend our results, under obvious modifications of our earlier assumptions below. Note that the dynamics of conserved quantities depends on that of the fast species in the same way as the dynamics of the slow species does.

ASSUMPTION 2.11 (Dynamics of a two-scale reaction network with conserved quantities). The two-scale reaction network (2.11) with effective change (2.13) on time scale $N\,dt$ and (2.15) and (2.29) on time scale dt satisfies the following conditions:

(i) For each $(\underline{v}_s; \underline{v}_c) \in \mathbb{R}_+^{|\mathcal{I}^s| + |\Theta^f|}$, $\underline{v}_c := (v_{c_i})_{i=1,\dots,|\Theta^f|}$, there exists a well-defined process that is the solution of

$$
\begin{aligned}
\underline{V}_{f|(\underline{v}_s; \underline{v}_c)}(t) = {}& \underline{V}_{f|(\underline{v}_s; \underline{v}_c)}(0) \\
& + \sum_{k \in \mathcal{K}_\circ^f} \underline{\zeta}_{\cdot k}^f Y_k \left(\int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}_{f|(\underline{v}_s; \underline{v}_c)}(u), \underline{v}_s)\, du \right) \\
& + \sum_{k \in \mathcal{K}_\bullet^f} \underline{\zeta}_{\cdot k}^f \int_0^t \lambda_k^{\mathrm{CR}}(\underline{V}_{f|(\underline{v}_s; \underline{v}_c)}(u), \underline{v}_s)\, du,
\end{aligned}
$$

which satisfies the constraints

$$(2.30) \qquad \langle \underline{\theta}^{c_i}, \underline{V}_{f|(\underline{v}_s; \underline{v}_c)} \rangle = v_{c_i}, \qquad \theta^{c_i} \in \Theta^f,$$

and which has a unique stationary probability measure $\mu_{(\underline{v}_s; \underline{v}_c)}(d\underline{z})$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$ [concentrated on the linear subspace such that (2.30) is satisfied], such that

$$(2.31) \quad \bar{\lambda}_k^{\mathrm{CR}}(\underline{v}_s, \underline{v}_c) = \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \lambda_k^{\mathrm{CR}}(\underline{z}, \underline{v}_s, \underline{v}_c) \mu_{(\underline{v}_s; \underline{v}_c)}(d\underline{z}) < \infty, \qquad k \in \mathcal{K}^s.$$

(ii) In addition to a well-defined solution of (2.18), there exists a well-defined process that is the solution of

$$
\underline{V}_c(t) = \underline{V}_c(0) + \sum_{k \in \mathcal{K}_\circ^c} \underline{\zeta}_{\cdot k}^c Y_k \left(\int_0^t \bar{\lambda}_k^{\mathrm{CR}}(\underline{V}_s(u), \underline{V}_c(u)) \, du \right)
$$

(2.32)

$$
+ \sum_{k \in \mathcal{K}_\bullet^c} \underline{\zeta}_{\cdot k}^c \int_0^t \bar{\lambda}_k^{\mathrm{CR}}(\underline{V}_s(u), \underline{V}_c(u)) \, du,
$$

that is,

$$
V_{c_i}(t) = V_{c_i}(0) + \sum_{k \in \mathcal{K}_\circ^c} \zeta_{\underline{\theta}^{c_i} k}^c Y_k \left(\int_0^t \bar{\lambda}_k^{\mathrm{CR}}(\underline{V}_s(u), \underline{V}_c(u)) \, du \right)
$$

(2.33)

$$
+ \sum_{k \in \mathcal{K}_\bullet^c} \zeta_{\underline{\theta}^{c_i} k}^c \int_0^t \bar{\lambda}_k^{\mathrm{CR}}(\underline{V}_s(u), \underline{V}_c(u)) \, du,
$$

where the rates in both (2.18) and (2.32), (2.33) are given by (2.31).

(iii) Same as in Assumptions 2.6.

The following Lemma 2.12 is again in Theorem 5.1 of Kang and Kurtz (2013).

LEMMA 2.12 (Convergence of two-scale reaction networks with conserved fast quantities). *Let $\underline{V}^N$ be the process of rescaled species amounts (2.6) for a two-scale reaction network, with $\underline{\alpha}, \underline{\beta}$ satisfying (2.11), $\gamma = 0, \varepsilon = 1$, and with conserved quantities $\Theta^f = (\underline{\theta}^{c_i})_{i=1,\dots,|\Theta^f|}$ [which is a basis of the null space of $((\zeta_{ik})_{i \in \mathcal{I}^f, k \in \mathcal{K}^f})^{\mathrm{T}}]$ whose effective change is on time scale dt, with Assumptions 2.11 satisfied. Then, if $\underline{V}^N(0) \overset{N \to \infty}{\Longrightarrow} \underline{V}(0)$, we have joint convergence of the process of rescaled amounts of the slow and conserved quantities $(\underline{V}_s^N(\cdot), \underline{V}_c^N(\cdot)) \overset{N \to \infty}{\Longrightarrow} (\underline{V}_s(\cdot), \underline{V}_c(\cdot))$ in the Skorohod topology, with $\underline{V}_s$ the solution of (2.18) and $\underline{V}_c$ the solution of (2.32) with rates given by (2.31).*

It is clear that the result on the limiting dynamics of the conserved quantities which change on the time scale dt holds even if we do not have any slow species on this time scale. We then only have the dynamics of conserved quantities following (2.33) with the rates $\bar{\lambda}_k^{\mathrm{CR}}$ obtained using the stationary probability measure for the fast species $\mu_{\underline{v}_c}(\cdot)$ which depends on the conserved quantities only. Analogously, it is possible that the dynamics of conserved species on time scale dt is trivial in which case we have the dynamics of slow quantities following (2.18) with $\underline{V}_c(u) = \underline{v}_c, u > 0$. Furthermore, if we have a reaction network on three scales, it is obvious how to write the analogous result for the conserved quantities on whichever slower time scale their dynamics is. Both of these situations appear in the dynamics of compartment reaction network models, and the above lemmas provide all the tools we need for our results on models with movement between compartments.

EXAMPLE 2.13 (Michaelis–Menten kinetics). One of the simplest multi-scale reaction systems with conserved quantities on the fast time scale leads to the well-known Michaelis–Menten kinetics. A substrate S is transformed into a product P with the help of an enzyme E via a complex ES formed by enzyme and substrate. The set of reactions is

$$1: \quad E + S \xrightarrow{\kappa'_1} ES,$$

(2.34)
$$-1: \quad ES \xrightarrow{\kappa'_{-1}} E + S,$$

$$2: \quad ES \xrightarrow{\kappa'_2} E + P.$$
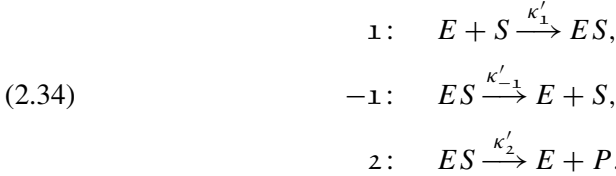
The sum of numbers of free and bound enzymes E, ES is a constant, which will be denoted m (also the sum of numbers S, ES, P molecules is a constant but S, P will be more abundant and they will not effectively contribute to a conserved quantity on the fast time scale). We denote molecules numbers by x_S, x_E, x_{ES} and x_P, let $\underline{x} = (x_S, x_E, x_{ES}, x_P)$ and let the reaction rates be given by mass action kinetics,

$$(2.35) \quad \Lambda_1^{\mathrm{CR}}(\underline{x}) = \kappa'_1 x_S x_E, \qquad \Lambda_{-1}^{\mathrm{CR}}(\underline{x}) = \kappa'_{-1} x_{ES}, \qquad \Lambda_2^{\mathrm{CR}}(\underline{x}) = \kappa'_2 x_{ES}.$$

For the scaled system, we use $\alpha_S = \alpha_P = 1, \alpha_E = \alpha_{ES} = 0$. Setting the rescaled species counts $v_S = N^{-1} x_S, v_E = x_E, v_{ES} = x_{ES}, v_P = N^{-1} x_P$, and

$$\beta_1 = 0, \qquad \beta_{-1} = 1, \qquad \beta_2 = 1,$$

(2.36)
$$\kappa_1 = \kappa'_1, \qquad \kappa_{-1} = N^{-1} \kappa'_{-1}, \qquad \kappa_2 = N^{-1} \kappa'_2,$$

we write

$$\lambda_1^{\mathrm{CR}}(\underline{v}) = \kappa_1 v_S v_E, \qquad \lambda_{-1}^{\mathrm{CR}}(\underline{v}) = \kappa_{-1} v_{ES}, \qquad \lambda_2^{\mathrm{CR}}(\underline{v}) = \kappa_2 v_{ES}.$$

Note that the rescaling gives that $V_S^N + V_P^N = O(1)$, such that we only need to describe V_S^N. The process $\underline{V}^N = (V_S^N, V_E^N, V_{ES}^N)$ is given by

$$V_S^N(t) = V_S^N(0) - N^{-1} Y_1 \left(N \int_0^t \kappa_1 V_S^N(u) V_E^N(u) \, du \right)$$
$$+ N^{-1} Y_{-1} \left(N \int_0^t \kappa_{-1} V_{ES}^N(u) \, du \right),$$

$$V_E^N(t) = V_E^N(0) - Y_1 \left(N \int_0^t \kappa_1 V_S^N(u) V_E^N(u) \, du \right) + Y_{-1} \left(N \int_0^t \kappa_{-1} V_{ES}^N(u) \, du \right)$$
$$+ Y_2 \left(N \int_0^t \kappa_2 V_{ES}^N(u) \, du \right),$$

$$V_{ES}^N(t) = V_{ES}^N(0) + Y_1 \left(N \int_0^t \kappa_1 V_S^N(u) V_E^N(u) \, du \right) - Y_{-1} \left(N \int_0^t \kappa_{-1} V_{ES}^N(u) \, du \right)$$
$$- Y_2 \left(N \int_0^t \kappa_2 V_{ES}^N(u) \, du \right).$$

From this, we see V_E, V_{ES} are fast while V_S, V_P are slow species. For $\gamma = 0$, $\varepsilon = 1$, we have $\mathcal{K}^f = \mathcal{K}^s = \{1, -1, 2\}$, $\mathcal{K}_S = \{1, -1\}$, $\mathcal{K}_E = \mathcal{K}_{ES} = \{1, -1, 2\}$, $\mathcal{K}_P = \{2\}$ and $\mathcal{I}_f = \mathcal{I}_f^\circ = \{E, ES\}$, $\mathcal{I}_s = \mathcal{I}_s^\bullet = \{S, P\}$. The matrices describing the reaction dynamics on both scales are

(2.37)
$$
\underline{\underline{\zeta}} = \begin{matrix} S \\ E \\ ES \\ P \end{matrix} \begin{pmatrix} -1 & 1 & 0 \\ -1 & 1 & 1 \\ 1 & -1 & -1 \\ 0 & 0 & 1 \end{pmatrix}, \qquad \underline{\underline{\zeta}}^f = \begin{matrix} E \\ ES \end{matrix} \begin{pmatrix} -1 & 1 & 1 \\ 1 & -1 & -1 \end{pmatrix},
$$
$$
\underline{\underline{\zeta}}^s = \begin{matrix} S \\ P \end{matrix} \begin{pmatrix} -1 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix},
$$

where the three columns give reactions $1, -1$ and 2. Note that $\mathcal{N}((\underline{\underline{\zeta}}^f)^t) = \text{span}((1, 1))$, indicating that $V_c := V_E + V_{ES}$ is constant (at least on the fast time scale). In order to study the dynamics of the slow species, $\underline{V}_s := (V_S, V_P)$, we have to check Assumption 2.11 and apply Lemma 2.12. Here, for Poisson processes Y_1 and Y_{-1}, and fixed $\underline{V}_s = (V_S, V_P) = (v_S, v_P) = \underline{v}_s$ and $V_c = V_E + V_{ES} =: m$, from (2.16),

$$
V_{E|(\underline{v}_s, v_c)}(t) - V_{E|(\underline{v}_s, v_c)}(0)
$$
$$
= -Y_1\left(\int_0^t \kappa_1 v_S V_E(u)\, du\right) + Y_{-1}\left(\int_0^t \kappa_{-1} V_{ES}(u)\, du\right)
$$
$$
+ Y_2\left(\int_0^t \kappa_2 V_{ES}(u)\, du\right)
$$
$$
\stackrel{d}{=} -Y_1\left(\int_0^t \kappa_1 v_S V_E(u)\, du\right) + Y_{-1+2}\left(\int_0^t (\kappa_{-1} + \kappa_2) V_{ES}(u)\, du\right),
$$
$$
V_{ES|(\underline{v}_s, v_c)}(t) - V_{ES|(\underline{v}_s, v_c)}(0)
$$
$$
= Y_1\left(\int_0^t \kappa_1 v_S V_E(u)\, du\right) + Y_{-1+2}\left(\int_0^t (\kappa_{-1} + \kappa_2) V_{ES}(u)\, du\right)
$$

for some Poisson process Y_{-1+2} which is independent of Y_1. Note that $(V_{E|(\underline{v}_s, v_c)}(\cdot), V_{ES|(\underline{v}_s, v_c)}(\cdot))$ behaves like an Ehrenfest urn with two compartments, where each E turns to ES at rate $\kappa_1 v_S$, and each ES turns to E at rate $(\kappa_{-1} + \kappa_2)$. It is well known that $(V_{E|(\underline{v}_s, v_c)}, V_{ES|(\underline{v}_s, v_c)}) \stackrel{d}{=} (X, m - X)$ has an equilibrium

$$
X \sim \text{Binom}\left(m, \frac{\kappa_{-1} + \kappa_2}{\kappa_{-1} + \kappa_2 + \kappa_1 v_S}\right),
$$

which gives the desired $\mu_{(\underline{v}_s, m)}(dv_E, dv_{ES})$ concentrated on $V_c = V_E + V_{ES} = m$. The conserved species V_c do not change even on the time scale dt (this will no longer be the case in a heterogeneous compartment model in the next section).

Hence, (2.31) gives

$$\bar{\lambda}_1(\underline{v}_s) = \mathbf{E}[\kappa_1 v_S X] = \kappa_1 v_S \frac{m(\kappa_{-1} + \kappa_2)}{\kappa_{-1} + \kappa_2 + \kappa_1 v_S},$$

$$\bar{\lambda}_{-1}(\underline{v}_s) = \mathbf{E}[\kappa_{-1}(m - X)] = \kappa_{-1} \frac{m\kappa_1 v_S}{\kappa_{-1} + \kappa_2 + \kappa_1 v_S},$$

$$\bar{\lambda}_2(\underline{v}_s) = \mathbf{E}[\kappa_2(m - X)] = \kappa_2 \frac{m\kappa_1 v_S}{\kappa_{-1} + \kappa_2 + \kappa_1 v_S}.$$

Lemma 2.12 implies that in the limit $N \to \infty$, we obtain the dynamics

$$
\begin{aligned}
(2.38) \quad V_S(t) &= V_S(0) - \int_0^t \bar{\lambda}_1(\underline{V}_s(u)) \, du + \int_0^t \bar{\lambda}_{-1}(\underline{V}_s(u)) \, du \\
&= V_S(0) - \int_0^t \frac{m\kappa_1\kappa_2 V_S(u)}{\kappa_{-1} + \kappa_2 + \kappa_1 V_S(u)} \, du,
\end{aligned}
$$

for V_S, which is the classical Michaelis–Menten kinetics.

3. Chemical reactions in multiple compartments.

We now assume that the chemical system is separated into a set of $\mathcal{D}$ *compartments*, and chemical species can migrate within these compartments. For species $i \in \mathcal{I}$, *movement* happens from compartment d' to d'' at rate $\Lambda^{\mathrm{M}}_{i,d',d''}$.

3.1. *The Markov chain model.* Denoting by $X_{id}(t)$ the number of molecules of species i in compartment d at time t, we assume that $(\underline{\underline{X}}(t))_{t \geq 0}$ with $\underline{\underline{X}}(t) = (X_{id}(t))_{i \in \mathcal{I}, d \in \mathcal{D}}$ is solution of

$$
\begin{aligned}
(3.1) \quad X_{id}(t) &= X_{id}(0) + \sum_{k \in \mathcal{K}} \zeta_{ik} Y_{kd}\left(\int_0^t \Lambda^{\mathrm{CR}}_{kd}(\underline{X}_{\cdot d}(u)) \, du \right) \\
&\quad + \sum_{d',d'' \in \mathcal{D}} (\delta_{d''}(d) - \delta_{d'}(d)) Y_{i,d',d''}\left(\int_0^t \Lambda^{\mathrm{M}}_{i,d',d''} X_{id'}(u) \, du \right),
\end{aligned}
$$

where $\delta_d(\cdot)$ is a Dirac delta function, $\underline{X}_{\cdot d} = (X_{id})_{i \in \mathcal{I}}$ and all the Y's are independent (rate 1) Poisson processes. We assume the following.

ASSUMPTION 3.1 (Dynamics of un-scaled multi-compartment reaction network). The reaction network dynamics satisfies the following conditions:

 (i) Same as Assumption 2.1(i) in each compartment and for all k there is at least one d with $\Lambda^{\mathrm{CR}}_{kd} \neq 0$.

 (ii) Given $(Y_{kd})_{k \in \mathcal{K}, d \in \mathcal{D}}$, and $(Y_{i,d',d''})_{i \in \mathcal{I}, d', d'' \in \mathcal{D}}$, the time change equation (3.1) has a unique solution.

For $X_i(t) := \sum_{d \in \mathcal{D}} X_{id}(t)$,

$$X_i(t) \stackrel{d}{=} X_i(0) + \sum_{k \in \mathcal{K}} \zeta_{ik} Y_k \left(\int_0^t \sum_{d \in \mathcal{D}} \Lambda_{kd}^{\mathrm{CR}}(\underline{X}_{\cdot d}(u)) \, du \right),$$

for some independent (rate 1) Poisson processes $(Y_k)_{k \in \mathcal{K}}$. However, since the rate $\sum_{d \in \mathcal{D}} \Lambda_{kd}^{\mathrm{CR}}(\underline{X}_{\cdot d}(s))$ depends on all entries in $\underline{X}(s)$, the process $((X_i(t))_{i \in \mathcal{I}})_{t \geq 0}$ is not in general Markov.

3.2. *The rescaled system.* Consider the solution of (3.1) with the chemical reaction rates $\Lambda_{kd}^{\mathrm{CR}}$ and movement rates $\Lambda_{i,d',d''}^{\mathrm{M}}$ replaced by $\Lambda_{kd}^{\mathrm{CR},N}$ and $\Lambda_{i,d',d''}^{\mathrm{M},N}$, respectively. For real-valued

$$\underline{\alpha} = (\alpha_i)_{i \in \mathcal{I}}, \qquad \underline{\beta} = (\beta_k)_{k \in \mathcal{K}}, \qquad \gamma, \qquad \underline{\eta} = (\eta_i)_{i \in \mathcal{I}},$$

with $\alpha_i \geq 0$, $i \in \mathcal{I}$, we denote the $(\underline{\alpha}, \underline{\beta}, \gamma, \underline{\eta})$-rescaled system by

$$V_{id}^N(t) := N^{-\alpha_i} X_{id}^N(N^\gamma t), \qquad i \in \mathcal{I}, d \in \mathcal{D},$$

$$\lambda_k^{\mathrm{CR},N}(\underline{v}) := N^{-\beta_k} \Lambda_k^{\mathrm{CR},N}((N^{\alpha_i} v_i)_{i \in \mathcal{I}}), \qquad k \in \mathcal{K},$$

$$\lambda_{i,d',d''}^{\mathrm{M},N}(\underline{v}) := N^{-\eta_i} \Lambda_{i,d',d''}^{\mathrm{M},N}((N^{\alpha_i} v_i)_{i \in \mathcal{I}}), \qquad i \in \mathcal{I}, d', d'' \in \mathcal{D},$$

where $\underline{\alpha}, \underline{\beta}, \gamma, \underline{\eta}$ is chosen so that $V_{id}^N = \mathcal{O}(1)$, $\lambda_k^{\mathrm{CR},N} = \mathcal{O}(1)$, $\lambda_{i,d',d''}^{\mathrm{M},N} = \mathcal{O}(1)$ (reactions of the same type and species of the same type are scaled by the same parameters in each compartment). Again, we will restrict to the case $\gamma = 0$.

ASSUMPTION 3.2 (Dynamics of scaled multiple compartment reaction network). In addition to Assumption 2.2 within each compartment, there exist $\lambda_{i,d',d''}^{\mathrm{M}}$, $i \in \mathcal{I}$, $d', d'' \in \mathcal{D}$ with

$$(3.2) \qquad\qquad N^{-\eta_i} \Lambda_{i,d',d''}^{\mathrm{M},N} \stackrel{N \to \infty}{\longrightarrow} \lambda_{i,d',d''}^{\mathrm{M}}.$$

Again, we will assume that this convergence is actually an identity.

The $(\underline{\alpha}, \underline{\beta}, \gamma, \underline{\eta})$-rescaled system $\underline{V}^N(t) = N^{-\underline{\alpha}} \underline{\underline{X}}(N^\gamma t)$ is the unique solution to the system of stochastic equations

$$V_{id}^N(t) = V_{id}^N(0) + \sum_{k \in \mathcal{K}} N^{-\alpha_i} \zeta_{ik} Y_{kd} \left(N^{\beta_k + \gamma} \int_0^t \lambda_{kd}^{\mathrm{CR}}(\underline{V}_{\cdot d}^N(u)) \, du \right)$$

$$(3.3)$$

$$+ \sum_{d',d'' \in \mathcal{D}} N^{-\alpha_i} (\delta_{d''}(d) - \delta_{d'}(d)) Y_{i,d',d''} \left(N^{\alpha_i + \eta_i + \gamma} \int_0^t \lambda_{i,d',d''}^{\mathrm{M}} V_{id'}^N(s) \right).$$

In addition, define

$$(3.4) \qquad\qquad \underline{S}^N = (S_i^N)_{i \in \mathcal{I}} \qquad \text{with } S_i^N := \sum_{d \in \mathcal{D}} V_{id}^N,$$

then S_i^N solves

$$(3.5) \quad S_i^N(t) = S_i^N(0) + \sum_{k \in \mathcal{K}} N^{-\alpha_i} \zeta_{ik} \sum_{d \in \mathcal{D}} Y_{kd}\left(N^{\beta_k + \gamma} \int_0^t \lambda_{kd}^{\mathrm{CR}}(\underline{V}_{\cdot d}^N(u)) \, du\right).$$

REMARK 3.3 (Heterogeneity of the reaction network).   Our set-up does not preclude the option that different compartments may have different reaction networks all together. We contain all possible reactions in the stoichiometric matrix $\underline{\underline{\zeta}}$, then setting individual compartment rates $\lambda_{kd}^{\mathrm{CR}}$ to zero in desired compartments can achieve this.

3.3. *Spatial single-scale systems.* We can now examine the effect of heterogeneity on the chemical reaction systems via compartmental models. We assume that (2.9) holds within every compartment. The sets $\mathcal{I}, \mathcal{I}_\circ, \mathcal{I}_\bullet$ and $\mathcal{K}, \mathcal{K}_\circ^*, \mathcal{K}_\bullet^*$ and $\underline{\underline{\zeta}}^*$ are used as in Section 2. We assume that movement of species is fast, $\eta_i > 0, i \in \mathcal{I}$ and it has a unique equilibrium.

ASSUMPTION 3.4 (Equilibrium for movement).   For each species $i \in \mathcal{I}$, the movement Markov chain, given through the jump rates $\lambda_{i,d',d''}^{\mathrm{M}}$ from d' to d'', has a unique stationary probability distribution denoted by $(\pi_i(d))_{d \in \mathcal{D}}$.

LEMMA 3.5 (Movement equilibrium).   *Let Assumption 3.4 hold.*

(1) *Let $i \in \mathcal{I}$ be such that $\alpha_i = 0$ (i.e., $i \in \mathcal{I}_\circ$). Consider the Markov chain of only the movement of molecules of species i, that is, the solution of*

$$V_{id}(t) = V_{id}(0) + \sum_{d',d'' \in \mathcal{D}} (\delta_{d''}(d) - \delta_{d'}(d)) Y_{i,d',d''}\left(\int_0^t \lambda_{i,d',d''}^{\mathrm{M}} V_{id'}(u) \, du\right)$$

started with $\sum_{d \in \mathcal{D}} V_{id}(0) = s_i$. Then, the unique equilibrium probability distribution of this Markov chain is given as the multinomial distribution with parameters $(s_i; (\pi_i(d))_{d \in \mathcal{D}})$.

(2) *Let $i \in \mathcal{I}$ be such that $\alpha_i > 0$ (i.e., $i \in \mathcal{I}_\bullet$). Consider the limiting deterministic process of only the movement of molecules of species i, that is, the solution of*

$$V_{id}(t) = V_{id}(0) + \sum_{d' \in \mathcal{D}} \int_0^t \left(\lambda_{i,d',d}^{\mathrm{M}} V_{id'}(u) - \lambda_{i,d,d'}^{\mathrm{M}} V_{id}(u)\right) du$$

started with $\sum_{d \in \mathcal{D}} V_{id}(0) = s_i$. Then the unique equilibrium of this process is given by $(s_i \pi_i(d))_{d \in \mathcal{D}}$.

We denote the equilibrium probability distribution of movement of all species, started in $(s_i)_{i \in \mathcal{I}}$ by $\mathbf{P}_{\underline{s}}$ and by $\mathbf{E}_{\underline{s}}$ the corresponding expectation operator. From the above, $\mathbf{P}_{\underline{s}}$ is a product of multinomial and point mass distributions.

PROOF. In (1), we have an Ehrehfest urn model with $|\mathcal{D}|$ boxes; due its reversibility it is easy to check we have the correct equilibrium. In (2), we have a deterministic system of $|\mathcal{D}|$ equations whose equilibrium is equally easy to obtain. □

We start with the simplest results for chemical reaction networks which are on a single scale, and describe the effect of mixing on the heterogeneous chemical reaction system.

ASSUMPTION 3.6 (Dynamics of the spatial single-scale reaction network). The spatial single-scale reaction network on time scale dt, where Assumption 3.4 holds, satisfies the following conditions:

(i) Given $(Y_k)_{k \in \mathcal{K}_\circ^*}$, the time change equation

(3.6)
$$\underline{S}(t) = \underline{S}(0) + \sum_{k \in \mathcal{K}_\circ^*} \underline{\zeta}_{\cdot k}^* Y_k \left(\int_0^t \bar{\lambda}_k^{CR}(\underline{S}(u)) \, du \right)$$
$$+ \sum_{k \in \mathcal{K}_\bullet^*} \underline{\zeta}_{\cdot k}^* \int_0^t \bar{\lambda}_k^{CR}(\underline{S}(u)) \, du$$

has a unique solution $\underline{S} := (\underline{S}(t))_{t \geq 0}$, where

(3.7)
$$\bar{\lambda}_k^{CR}(\underline{s}) := \mathbf{E}_{\underline{s}} \left[\sum_{d \in \mathcal{D}} \lambda_{kd}^{CR}(\underline{V}_{\cdot d}) \right].$$

(ii) Same as (iii) in Assumption 2.6 for all $d \in \mathcal{D}$.

THEOREM 3.7 (Heterogeneous single-scale system). *Let $\underline{\underline{V}}^N$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to (3.3). Assume that $(\underline{\alpha}, \underline{\beta}, \gamma = 0)$ satisfy single scale assumption (2.9) within compartments and $\eta_i = \eta > 0$, $i \in \mathcal{I}$. Let $\underline{S}^N(t) = (S_i^N(t))_{i \in \mathcal{I}}$ be $S_i^N(t) := \sum_{d \in \mathcal{D}} V_{id}^N(t)$, and suppose Assumptions 3.4 and 3.6 for the rescaled network hold. If $\underline{S}^N(0) \overset{N \to \infty}{\Longrightarrow} \underline{S}(0)$, then the process of rescaled sums $\underline{S}^N(\cdot)$ converges weakly to the unique solution $\underline{S}(\cdot)$ of (3.6) in the Skorohod topology.*

PROOF. In the heterogeneous reaction network, we have $|\mathcal{I}| \times |\mathcal{D}|$ species; one for each type and each compartment, with rescaled amounts V_{id}^N. Movement between compartments can be viewed as (at most) $|\mathcal{D}| \times |\mathcal{D}|$ first-order reactions involving only species of the same type $i \in \mathcal{I}$ in different compartments, with net change in compartment d of $(\delta_{d''}(d) - \delta_{d'}(d))_{(d',d'') \in \mathcal{D} \times \mathcal{D}}$ at rate $\{\Lambda_{i,d',d''}^M, d', d'' \in \mathcal{D}\}$. This set of reactions together with the original reactions within each compartment give an overall network in which all the species V_{id}^N with $(i, d) \in \mathcal{I} \times \mathcal{D}$ are fast, whose conserved quantities is a vector of sums over all the compartments for

each species type, which are given by $S_i^N := \sum_{d \in \mathcal{D}} V_{id}^N, i \in \mathcal{I}$. Since $\eta_i > 0, i \in \mathcal{I}$ the movement reactions change all the species amounts on the time scale $N^\eta \, dt$, and its effective changes on this time scale are still $(\delta_{d''}(d') - \delta_{d'}(d''))_{(d',d'') \in \mathcal{D} \times \mathcal{D}}$ while the original within compartment reactions effectively change only the conserved sum quantities on the time scale dt and its effective changes on this time scale are given by $\underline{\underline{\zeta}}^*$.

In order to apply Lemma 2.12, set $\varepsilon := \eta$ and we need to check Assumptions 2.11. In this special case, there are no slow species only fast species and conserved quantities. Condition (i) is simply the requirement that—in the limit $N \to \infty$—for fixed given vector of sums of species movement leads to a well-defined process on the species amounts in different compartments, which for each value of the vector of sums $\underline{s}$ has a unique stationary probability measure $\mathbf{P}_{\underline{s}}$, which is concentrated on $\sum_{d \in \mathcal{D}} v_{id} = s_i$. This is exactly implied by Lemma 3.5 under Assumption 3.4. Conditions (ii) and (iii) in Assumptions 2.11 is assumed in the statement of the theorem.

Let us consider the dynamics of the conserved quantities. Here, $\underline{\theta}^{c_i} = (1_{j=i})_{j \in \mathcal{I}, d \in \mathcal{D}}$ is the ith conserved quantity. On the time scale dt, the reaction dynamics of these conserved sums is a Markov chain whose effective change is given by the matrix $\underline{\underline{\zeta}}^c = \underline{\underline{\zeta}}^*$ with overall rate equal to a sum of the individual compartment rates.

Since the equilibrium for the movement dynamics $\mathbf{P}_{\underline{s}}$ is given by

(3.8)
$$
\begin{aligned}
\mathbf{P}_{\underline{s}}(d\underline{v}) = \prod_{i \in \mathcal{I}_\circ} & \binom{s_i}{v_{i1} \cdots v_{i|\mathcal{D}|}} \pi_i(1)^{v_{i1}} \cdots \pi_i(|\mathcal{D}|)^{v_{i|\mathcal{D}|}} \\
& \times \prod_{i \in \mathcal{I}_\bullet} \delta_{\pi_i(1)s_i}(dv_{i1}) \cdots \delta_{\pi_i(\mathcal{D})s_i}(dv_{i|\mathcal{D}|}),
\end{aligned}
$$

the averaged rates for reaction dynamics in each compartment under the equilibrium probability measure as considered in (3.7) are exactly of the form (2.31),

(3.9)
$$
\begin{aligned}
\bar{\lambda}_k^{\mathrm{CR}}(\underline{s}) = & \sum_{\underline{v}_1 : \sum_d v_{1d} = s_1} \cdots \sum_{\underline{v}_{|\mathcal{I}|} : \sum_d v_{|\mathcal{I}|d} = s_{|\mathcal{I}|}} \sum_{d \in \mathcal{D}} \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d}) \\
& \times \prod_{i \in \mathcal{I}_\circ} \binom{s_i}{v_{i1} \cdots v_{i|\mathcal{D}|}} \pi_i(1)^{v_{i1}} \cdots \pi_i(|\mathcal{D}|)^{v_{i|\mathcal{D}|}} \\
& \times \prod_{i \in \mathcal{I}_\bullet} \delta_{\pi_i(1)s_i}(v_{i1}) \cdots \delta_{\pi_i(|\mathcal{D}|)s_i}(v_{i|\mathcal{D}|}) \\
= & \sum_{d \in \mathcal{D}} \mathbf{E}_{\underline{s}}[\lambda_{kd}^{\mathrm{CR}}(\underline{V}_{\cdot d})].
\end{aligned}
$$
$\square$

COROLLARY 3.8 (Mass-action kinetics). *Let $\underline{\alpha}, \underline{\beta}, \underline{\gamma}, \underline{\eta}$ be as in Theorem 3.7. If the reaction rates are given by mass action kinetics for some $\kappa_{kd}, k \in \mathcal{K}, d \in \mathcal{D}$*

$$(3.10) \qquad \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{kd} \prod_{i \in \mathcal{I}_\circ} v_{ik}! \binom{v_{id}}{v_{ik}} \cdot \prod_{i \in \mathcal{I}_\bullet} v_{id}^{v_{ik}},$$

then the limit of $\underline{S}^N(\cdot)$ in the Skorohod topology is the solution of (3.6) with rates given by

$$\bar{\lambda}_k^{\mathrm{CR}}(\underline{s}) = \sum_{d \in \mathcal{D}} \kappa_{kd} \prod_{i \in \mathcal{I}_\circ} v_{ik}! \binom{s_i}{v_{ik}} \pi_i(d)^{v_{ik}} \cdot \prod_{i \in \mathcal{I}_\bullet} (\pi_i(d) s_i)^{v_{ik}}.$$

If $\alpha_i = 0$ for all $i \in \mathcal{I}$, the limit process for the sums is a Markov chain model for reaction networks with mass action kinetics (2.3) whose rate parameters are

$$(3.11) \qquad \bar{\kappa}_k = \sum_{d \in \mathcal{D}} \kappa_{kd} \prod_{i \in \mathcal{I}} \pi_i(d)^{v_{ik}}.$$

If $\alpha_i > 0$ for all $i \in \mathcal{I}$, the limit process for the sums is the deterministic solution to an ordinary differential equation

$$d\underline{S}(t) = \sum_{k \in \mathcal{K}} \underline{\zeta}_{\cdot k}^* \bar{\lambda}_k^{\mathrm{CR}}(\underline{S}(t)) \, dt$$

with mass action kinetics (2.3) whose rate parameters are (3.11).

REMARK 3.9 (Different time scales for the movement). From the point of view of the limit on time scale dt, the parameters for time scale of movement of different species types do not have to all be equal $\eta_i = \eta$; as long as $\eta_i > 0$ for all $i \in \mathcal{I}$, it is easy to show that the limit dynamics of $\underline{S}^N(\cdot)$ is as above.

PROOF OF COROLLARY 3.8. We plug (3.10) into (3.9). This gives

$$\bar{\lambda}_k^{\mathrm{CR}}(\underline{s}) = \sum_{\substack{\underline{x}_{1\cdot}: \sum_d x_{1d} = s_1 \\ \text{if } \alpha_1 = 0}} \cdots \sum_{\substack{\underline{x}_{|\mathcal{I}|\cdot}: \sum_d x_{|\mathcal{I}|d} = s_{|\mathcal{I}|} \\ \text{if } \alpha_{|\mathcal{I}|} = 0}} \sum_{d \in \mathcal{D}} \kappa_{kd}$$

$$\times \prod_{i \in \mathcal{I}_\circ} v_{ik}! \binom{x_{id}}{v_{ik}} \binom{s_i}{x_{i1} \cdots x_{i|\mathcal{D}|}} \pi_i(1)^{x_{i1}} \cdots \pi_i(|\mathcal{D}|)^{x_{i|\mathcal{D}|}}$$

$$\times \prod_{i \in \mathcal{I}_\bullet} (\pi_i(d) s_i)^{v_{ik}}$$

$$= \sum_{d \in \mathcal{D}} \kappa_{kd} \sum_{\substack{x_{1d} = 0, \dots, s_1 \\ \text{if } \alpha_1 = 0}} \cdots \sum_{\substack{x_{|\mathcal{I}|d} = 0, \dots, s_{|\mathcal{I}|} \\ \text{if } \alpha_{|\mathcal{I}|} = 0}}$$

$$\times \prod_{i \in \mathcal{I}_\circ} v_{ik}! \binom{s_i}{x_{id}} \binom{x_{id}}{v_{ik}} \pi_i(d)^{x_{id}} (1 - \pi_i(d))^{s_i - x_{id}} \cdot \prod_{i \in \mathcal{I}_\bullet} (\pi_i(d) s_i)^{v_{ik}}$$

$$= \sum_{d \in \mathcal{D}} \kappa_{kd} \prod_{i \in \mathcal{I}_\circ} \nu_{ik}! \binom{s_i}{\nu_{ik}} \pi_i(d)^{\nu_{ik}} \sum_{\substack{x_{1d}=0,\ldots,s_1 \\ \text{if } \alpha_1 = 0}} \cdots \sum_{\substack{x_{|\mathcal{I}|d}=0,\ldots,s_{|\mathcal{I}|} \\ \text{if } \alpha_{|\mathcal{I}|}=0}}$$

$$\times \prod_{i \in \mathcal{I}_\circ} \binom{s_i - \nu_{ik}}{x_{id} - \nu_{ik}} \pi_i(d)^{x_{id} - \nu_{ik}} \left(1 - \pi_i(d)\right)^{s_i - x_{id}} \cdot \prod_{i \in \mathcal{I}_\bullet} \left(\pi_i(d) s_i\right)^{\nu_{ik}}$$

$$= \sum_{d \in \mathcal{D}} \kappa_{kd} \prod_{i \in \mathcal{I}_\circ} \nu_{ik}! \binom{s_i}{\nu_{ik}} \pi_i(d)^{\nu_{ik}} \cdot \prod_{i \in \mathcal{I}_\bullet} \left(\pi_i(d) s_i\right)^{\nu_{ik}}.$$

When $\alpha_i = 0$ for all $i \in \mathcal{I}$ only the first sum in (3.6) exists, whereas when $\alpha_i > 0$ for all $i \in \mathcal{I}$ only the second sum in (3.6) exists. $\square$

EXAMPLE 3.10 (Self-regulating gene in multiple compartments). We place the reaction kinetics from Example 2.5 in a spatial multi-compartment setting. Let the dynamics initiate with $S_G(0) + S_{G'}(0) = 1$ active and inactive genes and $S_P(0) = s_P$ proteins in the whole space. If $\eta_G, \eta_{G'}, \eta_P > 0$, the movement is faster than any effective reaction dynamics, and the limiting dynamics of the rescaled sums in the whole system solves

$$S_{G'}(t) = S_{G'}(0) + Y_1 \left(\bar{\kappa}_1 \int_0^t \left(1 - S_{G'}(u)\right) S_P(u) \, du \right) - Y_2 \left(\bar{\kappa}_2 \int_0^t S_{G'}(u) \, du \right),$$

$$S_P(t) = S_P(0) + \bar{\kappa}_3 \int_0^t S_{G'}(u) \, du - \bar{\kappa}_4 \int_0^t S_P(u) \, du,$$

where $\bar{\kappa}_k$ are given by (3.11) and $\pi_G, \pi_{G'}, \pi_P$ are the equilibrium distributions of the movement of G, G' and P, respectively. Given the values of system sums $S_{G'}(t), S_P(t)$ the molecules of G', P will then be distributed in compartments according to

$$V_{G'd}(t) \sim \text{Multinom}\left(S_{G'}(t), \pi_{G'}(d)\right), \qquad V_{Pd}(t) \sim \delta_{S_P(t)\pi_P(d)}.$$

3.4. *Spatial multi-scale systems.* We next consider heterogeneous reaction networks on multiple time scales, with interplay between time scales on which the reaction network dynamics evolves and time scales on which the species move between compartments. We give results for chemical reactions on two time scales, extensions to more are obvious.

We stick to our notation from Section 2.3. In particular, we assume the reaction dynamics (within each compartment) has a separation of time scales (2.11) with $\varepsilon = 1, \gamma = 0$. We set $\mathcal{K}^f$ and $\mathcal{K}^s$ as in (2.12) and (2.14), respectively, and $\mathcal{I}^f$ and $\mathcal{I}^s$ for the sets of fast and slow species, if only chemical reactions within compartments are considered. The scaling parameters for movement of all fast species is $\eta_i = \eta_f$ for $i \in \mathcal{I}^f$ while for all slow species is $\eta_i = \eta_s, i \in \mathcal{I}^s$. We assume both $\eta_f, \eta_s > 0$. In order to assess the interplay of dynamics on different

time scales, we need to consider all possible orderings of $\varepsilon = 1$, η_f and η_s. In the sequel, we assume that η_f, $\eta_s \neq 1$ for simplicity. Moreover, the cases $\eta_s \leq \eta_f < 1$ and $\eta_f < \eta_s < 1$, as well as $1 < \eta_s \leq \eta_f$ and $1 < \eta_f < \eta_s$ lead to the same limiting behavior, because the movement processes occurring on the time scale $N^{\eta_f} \, dt$ and $N^{\eta_s} \, dt$ are independent (a movement of one species type on a time scale that is different from that of reactions depends only on its own molecular counts and is independent of other species types). Therefore, we are left with the four cases

(3.12)
$$\begin{array}{llll} (1) & 1 < \eta_s, \eta_f; & (2) & \eta_s < 1 < \eta_f; \\[4pt] (3) & \eta_f < 1 < \eta_s; & (4) & \eta_f, \eta_s < 1. \end{array}$$

As in the nonspatial situation, we also need to distinguish the cases when (i) there are no conserved quantities on the time scale of fast species [meaning that $\mathcal{N}((\underline{\underline{\zeta}}^f)^{\mathrm{T}})$ is the null space], and (ii) when some quantities are conserved [i.e., $\mathcal{N}((\underline{\underline{\zeta}}^f)^{\mathrm{T}}) = \mathrm{span}(\Theta^f)$, where $\Theta^f = (\underline{\theta}^{c_i})_{i=1,\ldots,n^f}$ is a linearly independent family of $\mathbb{R}^{|\mathcal{I}^f|}$-valued vectors]. In the latter case, the quantities $\langle \underline{\theta}^{c_i}, (V_{id}^N(\cdot))_{i \in \mathcal{I}^f} \rangle$ also change on the time scale $N^{\eta_f} \, dt$ for $d \in \mathcal{D}$ by movement of the fast species, but $\langle \underline{\theta}^{c_i}, (S_i^N(\cdot))_{i \in \mathcal{I}^f} \rangle$ is constant on the time scale $N^{\eta_f} \, dt$. We start with the case of $\mathcal{N}((\underline{\underline{\zeta}}^f)^{\mathrm{T}}) = $ null space.

No conserved quantities on the fast time scale. We need to consider different processes of possible effective reaction dynamics for fast species and their sums, conditional on knowing the values of the slow species. In each of the four cases above we need to consider different intermediate processes and assumptions on them. We write here, distinguishing fast and slow species, $\underline{\underline{v}} = (\underline{\underline{v}}_f, \underline{\underline{v}}_s)$ with $\underline{\underline{v}}_f = (v_{id})_{i \in \mathcal{I}^f, d \in \mathcal{D}}$, $\underline{\underline{v}}_s = (v_{id})_{i \in \mathcal{I}^s, d \in \mathcal{D}}$, as well as $\underline{s} = (\underline{s}_f, \underline{s}_s)$, $\underline{s}_f = (s_i)_{i \in \mathcal{I}^f}$, $\underline{s}_s = (s_i)_{i \in \mathcal{I}^s}$.

ASSUMPTION 3.11 (Dynamics of the spatial multi-scale reaction network). In each case (1)–(4), the spatial two-scale reaction network on time scale $N \, dt$, where Assumption 3.4 holds, satisfies the following conditions:

(i) (1) Given $(Y_k)_{k \in \mathcal{K}_o^f}$, the time-change equation of the dynamics of $\underline{S}_f$ given the value of $\underline{S}_s = \underline{s}_s$

(3.13)
$$\begin{aligned} \underline{S}_{f|\underline{s}_s}(t) = {} & \underline{S}_{f|\underline{s}_s}(0) + \sum_{k \in \mathcal{K}_o^f} \underline{\zeta}_{\cdot k}^f Y_k \left(\int_0^t \tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{S}_{f|\underline{s}_s}(u), \underline{s}_s) \, du \right) \\ & + \sum_{k \in \mathcal{K}_\bullet^f} \underline{\zeta}_{\cdot k}^f \int_0^t \tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{S}_{f|\underline{s}_s}(u), \underline{s}_s) \, du \end{aligned}$$

has a unique solution, where for all $\underline{s}_f, \underline{s}_s$

$$\tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_f, \underline{s}_s) = \int_{\substack{\mathbb{R}_+^{|\mathcal{I}^f| \times |\mathcal{D}|} \\ \times \mathbb{R}_+^{|\mathcal{I}^s| \times |\mathcal{D}|}}} \sum_{d \in \mathcal{D}} \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mathbf{P}_{(\underline{s}_f, \underline{s}_s)}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s)$$

(3.14)
$$< \infty,$$

where $\underline{v}_{\cdot d, f} = (v_{id})_{i \in \mathcal{I}^f}, \underline{v}_{\cdot d, s} = (v_{id})_{i \in \mathcal{I}^s}$, for $\mathbf{P}_{(\underline{s}_f, \underline{s}_s)}$ a product of multinomial and point mass probability distributions for both $\underline{\underline{v}}_f$ and $\underline{\underline{v}}_s$ defined in (3.8). In addition, $\underline{S}_{f|\underline{s}_s}(\cdot)$ has a unique stationary probability measure $\mu_{\underline{s}_s}(d\underline{s}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$.

(2) Given $(Y_k)_{k \in \mathcal{K}_\circ^f}$, the time-change equation of the dynamics of $\underline{S}_f$ given the value of $\underline{\underline{V}}_s = \underline{\underline{v}}_s$

$$\underline{S}_{f|\underline{\underline{v}}_s}(t) = \underline{S}_{f|\underline{\underline{v}}_s}(0) + \sum_{k \in \mathcal{K}_\circ^f} \underline{\zeta}_{\cdot k}^f Y_k \left(\int_0^t \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{S}_{f|\underline{\underline{v}}_s}(u), \underline{\underline{v}}_s) \, du \right)$$

(3.15)
$$+ \sum_{k \in \mathcal{K}_\bullet^f} \underline{\zeta}_{\cdot k}^f \int_0^t \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{S}_{f|\underline{\underline{v}}_s}(u), \underline{\underline{v}}_s) \, du$$

has a unique solution, where for all $\underline{s}_f, \underline{\underline{v}}_s$

$$(3.16) \quad \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_f, \underline{\underline{v}}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^f| \times |\mathcal{D}|}} \sum_{d \in \mathcal{D}} \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mathbf{P}_{\underline{s}_f}(d\underline{\underline{v}}_f) < \infty$$

for $\mathbf{P}_{\underline{s}_f}$ a product of multinomial and point mass probability distributions as in (3.8), where $\mathcal{I}$ is replaced by $\mathcal{I}^f$, $\underline{s}$ by $\underline{s}_f$ and $\underline{v}$ by $\underline{v}_f$. In addition, $\underline{S}_{f|\underline{\underline{v}}_s}(\cdot)$ has a unique stationary probability measure $\mu_{\underline{\underline{v}}_s}(d\underline{s}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$.

(3) Given $(Y_{kd})_{k \in \mathcal{K}_\circ^f, d \in \mathcal{D}}$, the time-change equation of the dynamics of $\underline{\underline{V}}_f$ given the value of $\underline{S}_s = \underline{s}_s$

$$\underline{V}_{\cdot d, f|\underline{s}_s}(t) = \underline{V}_{\cdot d, f|\underline{s}_s}(0) + \sum_{k \in \mathcal{K}_\circ^f} \underline{\zeta}_{\cdot k}^f Y_{kd} \left(\int_0^t \tilde{\lambda}_{kd}^{\mathrm{CR}(3)}(\underline{V}_{\cdot d, f|\underline{s}_s}(u), \underline{s}_s) \, du \right)$$

(3.17)
$$+ \sum_{k \in \mathcal{K}_\bullet^f} \zeta_{ik}^f \int_0^t \tilde{\lambda}_{kd}^{\mathrm{CR}(3)}(\underline{V}_{\cdot d, f|\underline{s}_s}(u), \underline{s}_s) \, du$$

has a unique solution, where for all $\underline{\underline{v}}_f, \underline{s}_s$

$$(3.18) \qquad \tilde{\lambda}_{kd}^{\mathrm{CR}(3)}(\underline{v}_{\cdot d, f}, \underline{s}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^s| \times |\mathcal{D}|}} \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s) < \infty$$

for $\mathbf{P}_{\underline{s}_s}$ a product of multinomial and point mass probability distributions as in (3.8), where $\mathcal{I}$ is replaced by $\mathcal{I}^s$, $\underline{s}$ by $\underline{s}_s$ and $\underline{v}$ by $\underline{v}_s$. In addition, $\underline{\underline{V}}_{f|\underline{s}_s}(\cdot) = $

$(V_{id,f|\underline{s}_s}(\cdot))_{i\in\mathcal{I}^f,d\in\mathcal{D}}$ has a unique stationary probability measure $\mu_{\underline{s}_s}(d\underline{v}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f|\times|\mathcal{D}|}$.

(4) Given $(Y_{kd})_{k\in\mathcal{K}_\circ^f,d\in\mathcal{D}}$, the time-change equation of the dynamics of $\underline{V}_f$ given the value of $\underline{V}_s = \underline{v}_s$

$$\underline{V}_{\cdot d,f|\underline{v}_s}(t) = \underline{V}_{\cdot d,f|\underline{v}_s}(0)$$

$$(3.19) \qquad\qquad + \sum_{k\in\mathcal{K}_\circ^f} \underline{\zeta}_{\cdot k}^f Y_{kd}\left(\int_0^t \tilde{\lambda}_{kd}^{\mathrm{CR}(4)}(\underline{V}_{\cdot d,f|\underline{v}_s}(u),\underline{v}_{\cdot d,s})\,du\right)$$

$$+ \sum_{k\in\mathcal{K}_\bullet^f} \zeta_{ik}^f \int_0^t \tilde{\lambda}_{kd}^{\mathrm{CR}(4)}(\underline{V}_{\cdot d,f|\underline{v}_s}(u),\underline{v}_{\cdot d,s})\,du$$

has a unique solution with unique stationary probability measure $\mu_{\underline{v}_s}(d\underline{v}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f|\times|\mathcal{D}|}$. Here, we set

$$(3.20) \qquad\qquad \tilde{\lambda}_{kd}^{\mathrm{CR}(4)} := \lambda_{kd}^{\mathrm{CR}}.$$

(ii) There exists a well-defined process $\underline{S}_s(\cdot)$ that is the unique solution of

$$\underline{S}_s(t) = \underline{S}_s(0) + \sum_{k\in\mathcal{K}_\circ^s} \underline{\zeta}_{\cdot k}^s Y_k\left(\int_0^t \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{S}_s(u))\,du\right)$$

$$(3.21) \qquad\qquad + \sum_{k\in\mathcal{K}_\bullet^s} \underline{\zeta}_{\cdot k}^s \int_0^t \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{S}_s(u))\,du,$$

where rates $(\bar{\lambda}_k^{\mathrm{CR}(\ell)})_{\ell=1,2,3,4}$ are given from $(\tilde{\lambda}_k^{\mathrm{CR}(\ell)})_{\ell=1,2,3,4}$ in each case as

$$\bar{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_f,\underline{s}_s)\mu_{\underline{s}_s}(d\underline{s}_f)$$

$$(3.22) \qquad = \sum_{d\in\mathcal{D}} \iint \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d,f},\underline{v}_{\cdot d,s})\mathbf{P}_{(\underline{s}_f,\underline{s}_s)}(d\underline{v}_f,d\underline{v}_s)\mu_{\underline{s}_s}(d\underline{s}_f) < \infty;$$

$$\bar{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^s|\times|\mathcal{D}|}} \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_f,\underline{v}_s)\mu_{\underline{v}_s}(d\underline{s}_f)\mathbf{P}_{\underline{s}_s}(d\underline{v}_s)$$

$$(3.23) \qquad = \sum_{d\in\mathcal{D}} \iiint \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d,f},\underline{v}_{\cdot d,s})\mathbf{P}_{\underline{s}_f}(d\underline{v}_f)\mu_{\underline{v}_s}(d\underline{s}_f)\mathbf{P}_{\underline{s}_s}(d\underline{v}_s) < \infty;$$

$$\bar{\lambda}_k^{\mathrm{CR}(3)}(\underline{s}_s) = \sum_{d\in\mathcal{D}} \int_{\mathbb{R}_+^{|\mathcal{I}^f|\times|\mathcal{D}|}} \tilde{\lambda}_{kd}^{\mathrm{CR}(3)}(\underline{v}_f,\underline{s}_s)\mu_{\underline{s}_s}(d\underline{v}_f)$$

$$(3.24) \qquad = \sum_{d\in\mathcal{D}} \iint \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d,f},\underline{v}_{\cdot d,s})\mathbf{P}_{\underline{s}_s}(d\underline{v}_s)\mu_{\underline{s}_s}(d\underline{v}_f) < \infty;$$

$$\bar{\lambda}_k^{\text{CR}(4)}(\underline{s}_s) = \sum_{d \in \mathcal{D}} \int_{\mathbb{R}_+^{|\mathcal{I}^s| \times |\mathcal{D}|}} \int_{\mathbb{R}_+^{|\mathcal{I}^f| \times |\mathcal{D}|}} \tilde{\lambda}_k^{\text{CR}(4)}(\underline{\underline{v}}_f, \underline{\underline{v}}_s) \mu_{\underline{v}_s}(d\underline{\underline{v}}_f) \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s)$$

$$(3.25)$$

$$= \sum_{d \in \mathcal{D}} \iint \lambda_{kd}^{\text{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mu_{\underline{v}_s}(d\underline{\underline{v}}_f) \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s) < \infty.$$

(iii) Same as (iii) in Assumption 2.6 in each compartment.

REMARK 3.12 (Equivalent formulation). For the dynamics under the above assumption, the following is immediate: In each case (1)–(4), the spatial two-scale reaction network on time scale dt, where Assumption 3.11 holds, satisfies the following condition: given $(Y_k)_{k \in \mathcal{K}_\circ^s}$, the time-change equation (3.21) has a unique solution, where for all $\underline{s}_s$

$$(3.26) \qquad \bar{\lambda}_k^{\text{CR}(\ell)}(\underline{s}_s) := \mathbf{E}_{\underline{s}_s}\left[\sum_{d \in \mathcal{D}} \lambda_{kd}^{\text{CR}}(\underline{V}_{\cdot d})\right] < \infty$$

and the distribution of $(V_{id})_{i \in \mathcal{I}, d \in \mathcal{D}}$ in (3.26) depends on the parameters η_s, η_f as follows:

$$(3.27) \quad (\ell) = (1) \quad \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s) = \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \mu_{\underline{s}_s}(d\underline{s}_f) \mathbf{P}_{(\underline{s}_f, \underline{s}_s)}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s),$$

$$(3.28) \quad (\ell) = (2) \quad \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s) \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \mu_{\underline{v}_s}(d\underline{s}_f) \mathbf{P}_{\underline{s}_f}(d\underline{\underline{v}}_f),$$

$$(3.29) \quad (\ell) = (3) \quad \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s) \mu_{\underline{s}_s}(d\underline{\underline{v}}_f),$$

$$(3.30) \quad (\ell) = (4) \quad \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s) \mu_{\underline{v}_s}(d\underline{\underline{v}}_f).$$

We can now state our results for the limiting behavior of $\underline{S}_f^N := (S_i^N, i \in \mathcal{I}^f)$ and $\underline{S}_s^N := (S_i^N, i \in \mathcal{I}^s)$ on the time scales $N\,dt$ and dt.

THEOREM 3.13 (Two-scale system without conserved fast quantities). *Let* $\underline{V}^N$ *be the vector process of rescaled species amounts for the reaction network which is the unique solution to* (3.3). *Assume that* $(\underline{\alpha}, \underline{\beta}, \gamma = 0)$ *satisfy two-scale system assumption* (2.11) *for some* $\mathcal{I}^f, \mathcal{I}^s$ *with* $\varepsilon = 1$ *and* $\mathcal{N}((\underline{\zeta}^f)^{\mathrm{T}}) = 0$ [*with* $\underline{\zeta}^f$ *from* (2.13)] *within compartments without conserved quantities on the fast time scale. In addition,* $\eta_i = \eta_f > 0$ *for all* $i \in \mathcal{I}^f$ *and* $\eta_i = \eta_s > 0$ *for all* $i \in \mathcal{I}^s$, *one of the cases* (1)–(4) *holds, and Assumption* 3.11 *holds. Then, if* $\underline{S}^N(0) \overset{N \to \infty}{\Longrightarrow} \underline{S}(0)$, *the rescaled sums of slow species* $\underline{S}_s^N(\cdot)$ *from* (3.4) *converges weakly to the unique solution* $\underline{S}_s(\cdot)$ *of* (3.21) *in the Skorohod topology.*

REMARK 3.14 (Interpretation). The rates in Theorem 3.13 have an intuitive interpretation. In order to compute $\mathbf{E}_{\underline{s}}[\lambda_{kd}^{\text{CR}}(\underline{V}_{\cdot d})]$, we have to know the distribution

of $\underline{V}$ given $\underline{S}_s$. Consider case (1) as an example: since movement of particles are the fastest reactions in the system, given the value of $\underline{S}_s = \underline{s}_s$, (i) $\underline{V}_s$ are distributed according to $\mathbf{P}_{\underline{s}_s}(d\underline{v}_s)$ from (3.8), and (ii) $\underline{S}_f$ is distributed according to the probability measure $\mu_{\underline{s}_s}(d\underline{s}_f)$ from Assumption 3.11(i)(1); then, given the value of $\underline{S}_f = \underline{s}_f$, the values of $\underline{V}_f$ are distributed according to $\mathbf{P}_{\underline{s}_f}(d\underline{v}_f)$ from (3.8). In case (3), fast reactions within compartments intertwine with movement between them: given the value of $\underline{S}_s = \underline{s}_s$, (i) $\underline{V}_s$ are again distributed according to $\mathbf{P}_{\underline{s}_s}$ from (3.8), but (ii) $\underline{V}_f$ are distributed according to $\mu_{\underline{s}_s}(d\underline{v}_f)$.

PROOF OF THEOREM 3.13. The proof relies on use of Lemmas 2.10 and 2.12. Let us first consider the case (1): $\eta_f, \eta_s > 1$. In this case on the two fastest time scales $N^{\eta_f} dt$ and $N^{\eta_s} dt$, we have movement of fast and slow species, respectively, whose sums are unchanged on any time scale faster than $N dt$. We view these two fastest time scales as one, since dynamics of movement of fast and slow species are in this case independent of each other and can be combined. Regarding all of the movement as a set of first-order reactions as in proof of Theorem 3.7, we have a three time scale dynamics: movement of all species is the fast process on time scales $N^{\eta_f} dt$, $N^{\eta_s} dt$, effective change of fast species is the medium process on time scale $N dt$, and effective change of slow species is the slow process on the time scale dt. The fast process of movement of all species has a stationary probability measure that is a product of multinomial and point mass probability distributions $\mathbf{P}_{(\underline{s}_f, \underline{s}_s)}$ from (3.8). Arguments from Lemma 2.12 imply that on the time scale $N dt$ all rates for the reaction network dynamics $\tilde{\lambda}_k^{\mathrm{CR}(1)}$ are sums over compartments of rates averaged with respect to $\mathbf{P}_{(\underline{s}_f, \underline{s}_s)}$ as in (3.14), and the medium process of the sums of fast species $\underline{S}_f$ has effective change given by $\underline{\underline{\zeta}}^f$. Condition (i)(1) of Assumption 3.11 ensures that on time scale $N dt$ the medium process $\underline{S}_f(\cdot)$ is well defined and has a unique stationary probability distribution $\mu_{\underline{s}_s}(d\underline{s}_f)$. Condition (ii) of Assumption 3.11 then ensures that, in addition to conditions (i-a) and (i-b), also condition (ii) in the assumptions for Lemma 2.10 is met, and consequently the limiting dynamics of the slow process $\underline{S}_s(\cdot)$ with effective change given by $\underline{\underline{\zeta}}^f$ is well defined and given by the solution of (3.21) with rates as in (3.22).

Next, consider the case (2): $\eta_f > 1, \eta_s < 1$. In this case we have a four time scale dynamics: movement of fast species is the fast process on time scale $N^{\eta_f} dt$, effective change of fast species is the medium-fast process on time scale $N dt$, movement of slow species is the medium-slow process on time scale $N^{\eta_s} dt$, and finally effective change of slow species is the slow process on time scale dt. The fast process on time scale $N^{\eta_f} dt$ of movement of all species has a stationary probability measure that is $\mathbf{P}_{\underline{s}_f}$ (3.8) (over $i \in \mathcal{I}^f$ only). Lemma 2.12 implies that on the next time scale $N dt$ rates $\tilde{\lambda}_k^{\mathrm{CR}(2)}$ are averaged with respect to $\mathbf{P}_{\underline{s}_f}$ as in (3.16), and the medium-fast process $\underline{S}_f$ has an effective change given by $\underline{\underline{\zeta}}^f$. We now have

that this process is well defined and has a unique stationary probability distribution $\mu_{\underline{v}_{\underline{s}_s}}(d\underline{s}_f)$. Furthermore, on the next time scale $N^{\eta_s} dt$ we only have the movement of slow species, which has a stationary probability measure that is $\mathbf{P}_{\underline{s}_s}$ from (3.8) (over $i \in \mathcal{I}^s$ only). Finally, the limiting dynamics of the slow process $\underline{S}_s(\cdot)$ on time scale dt, by an extension of Lemma 2.10 to four time scales, is well defined and given by the solution of (3.21) with rates as in (3.23).

Let us next consider the case (3): $\eta_f < 1, \eta_s > 1$. We again have a four time scale dynamics: movement of slow species is the fast process on time scale $N^{\eta_s} dt$, effective change of fast species is the medium-fast process on time scale $N dt$, movement of fast species is the medium-slow process on time scale $N^{\eta_f} dt$, and finally effective change of slow species is the slow process on time scale dt. Lemma 2.12 implies that on the medium-fast time scale $N dt$ rates $\tilde{\lambda}_{kd}^{\mathrm{CR}(3)}$ are averaged with respect to $\mathbf{P}_{\underline{s}_s}$ (3.8) (over $i \in \mathcal{I}^s$ only) as in (3.18), and the medium-fast process $\underline{V}_f$ has an effective change given by $\underline{\zeta}^f$ in each compartment $d \in \mathcal{D}$. This process is well defined and has a unique stationary probability distribution $\mu_{\underline{s}_s}(d\underline{v}_f)$. On the next time scale $N^{\eta_s} dt$ we only have the movement of slow species, which has a stationary probability measure that is $\mathbf{P}_{\underline{s}_f}$ (3.8) (over $i \in \mathcal{I}^f$ only). Finally, on time scale dt, Lemma 2.10 extended to four time-scales implies the limiting dynamics of the slow process $\underline{S}_s(\cdot)$ is well defined and given by the solution of (3.21) with rates as in (3.24).

Finally, we consider case (4): $\eta_f < 1, \eta_s < 1$. On the fast time scale $N dt$ in each compartment $d \in \mathcal{D}$, independently we have reaction dynamics of the fast species, with a unique equilibrium $\mu_{\underline{v}_s}(\underline{v}_f)$ that must be a product distribution over the different compartments. Similarly, to case (1) when all the movement is fastest, now all the movement is on the medium time scale, and the movement of all molecules (fast and slow) is independent and can be viewed as combined on one time scale with unique stationary probability distribution $\mathbf{P}_{(\underline{s}_f, \underline{s}_s)}$ (3.8) (over all $i \in \mathcal{I}$). This implies that on the slow time scale dt, the effective change of $\underline{S}_s$ is due to reaction dynamics with rates $\tilde{\lambda}_{kd}^{\mathrm{CR},4}(\underline{v}_f^N, \underline{v}_s^N)$ that have been averaged over $\mathbf{P}_{(\underline{s}_f, \underline{s}_s)}$, and is given by $\underline{\zeta}^s$. Lemma 2.10 implies that $\underline{S}_s(\cdot)$ is well defined and given by the solution of (3.21) with rates as in (3.25). □

If the movement of fast species is slower than fast reactions [i.e., we consider cases (3) or (4)], the equilibria for reactions is always attained before movement of fast species can change this equilibrium, as stated in the next corollary.

COROLLARY 3.15 (Irrelevance of movement of fast species). *In cases* (3) *or* (4) *of Theorem* 3.13, *the limiting dynamics of* $\underline{S}_s$ *is independent of* $\mathbf{P}_{\underline{s}_f}$.

PROOF. The assertion can be seen directly from (3.29) and (3.30), since the right-hand sides do not depend on $\mathbf{P}_{\underline{s}_f}$. □

If all slow species are continuous, the limiting dynamics for cases (1), (2) and (3), (4) are equal. The key to this observation is the following lemma.

LEMMA 3.16. *In the situation of Theorem* 3.13, *assume all slow species are continuous,* $\mathcal{I}_\circ^s = \varnothing$, *and let* $\underline{\underline{\pi s}}_s := (\pi_i(d)s_i)_{i \in \mathcal{I}^s, d \in \mathcal{D}}$.

 (i) *For stationary probability measures* $\mu_{\underline{s}_s}(d\underline{s}_f)$ *of* $\underline{S}_{f|\underline{s}_s}$ *from Assumption* 3.11(i)(1) *and* $\mu_{\underline{\underline{v}}_s}(d\underline{s}_f)$ *of* $\underline{S}_{f|\underline{\underline{v}}_s}$ *from* (i)(2), *we have*

$$\mu_{\underline{s}_s}(d\underline{s}_f) = \mu_{\underline{\underline{\pi s}}_s}(d\underline{s}_f).$$

(ii) *Likewise, for stationary probability measures* $\mu_{\underline{s}_s}(d\underline{\underline{v}}_f)$ *of* $\underline{\underline{V}}_{f|\underline{s}_s}$ *from* (i)(3) *and* $\mu_{\underline{\underline{v}}_s}(d\underline{\underline{v}}_f)$ *of* $\underline{\underline{V}}_{f|\underline{\underline{v}}_s}$ *from* (i)(4), *we have*

$$\mu_{\underline{s}_s}(d\underline{\underline{v}}_f) = \mu_{\underline{\underline{\pi s}}_s}(d\underline{\underline{v}}_f).$$

PROOF.   (i) It suffices to show that $\mu_{\underline{\underline{\pi s}}_s}$ is a stationary probability measure for the process $\underline{S}_{f|\underline{s}_s}(\cdot)$ from (3.13), since we assumed that this process has a unique stationary probability distribution. Note that, by independence of the movement of fast and slow species, for $k \in \mathcal{K}^f$,

$$\tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_f, \underline{s}_s) = \int \sum_{d \in \mathcal{D}} \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mathbf{P}_{(\underline{s}_f, \underline{s}_s)}(d\underline{\underline{v}}_f, d\underline{\underline{v}}_s)$$

$$= \int \sum_{d \in \mathcal{D}} \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mathbf{P}_{\underline{s}_f}(d\underline{\underline{v}}_f) \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s)$$

$$= \int \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_f, \underline{\underline{v}}_s) \mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s)$$

$$= \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_f, \underline{\underline{\pi s}}_s).$$

Since these rates are equal, the corresponding equilibrium distributions must be equal as well. In other words, the equilibrium distribution $\mu_{\underline{s}_s}(d\underline{s}_f)$ from Assumption 3.11(i)(1) must equal the equilibrium distribution $\mu_{\underline{\underline{\pi s}}_s}(d\underline{s}_f)$ from Assumption 3.11(i)(2). (ii) follows along similar lines.   □

COROLLARY 3.17. *Suppose in Theorem* 3.13 *all slow species are continuous,* $\mathcal{I}_\circ^s = \varnothing$. *Then, the dynamics of* (3.21) *is the same among the first two cases* (1) *and* (2), *and among the last two cases* (3) *and* (4).

PROOF.   Since $\mathbf{P}_{\underline{s}_s}(d\underline{\underline{v}}_s)$ is the delta-measure on $\underline{\underline{\pi s}}_s$, all assertions can be read directly from (3.27)–(3.30) together with Lemma 3.16.   □

We note that the case (1) (where all species move faster than the fast reactions occur) plays a special role under mass action kinetics.

COROLLARY 3.18 (Homogeneous mass action kinetics). *Suppose that in Theorem* 3.13 *the reaction rates are given by mass action kinetics with constants satisfying the homogeneity condition*

$$\kappa_k := |\mathcal{D}|\kappa_{kd} \prod_{i \in \mathcal{I}} \pi_i(d)^{\nu_{ik}}.$$

Then the dynamics of $\underline{S}_s$ in case (1) *is the same as for the system regarded as a single compartment.*

PROOF. For (1) from (3.14), we only need to calculate the average with respect to equilibrium of the movement dynamics for both slow and fast species. The same calculation as for mass action kinetics in Corollary 3.8 we get the first equality in

$$\tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_f, \underline{s}_s) = \sum_{d \in \mathcal{D}} \int \lambda_{kd}^{\mathrm{CR}}(\underline{v}_{\cdot d, f}, \underline{v}_{\cdot d, s}) \mathbf{P}_{(\underline{s}_f, \underline{s}_s)}(d\underline{v}_f, d\underline{v}_s)$$

$$= \sum_{d \in \mathcal{D}} \kappa_{kd} \prod_{i \in \mathcal{I}_\circ} \nu_{ik}! \binom{s_i}{\nu_{ik}} \pi_i(d)^{\nu_{ik}} \cdot \prod_{i \in \mathcal{I}_\bullet} (\pi_i(d)s_i)^{\nu_{ik}}$$

$$= \kappa_k \prod_{i \in \mathcal{I}_\circ} \nu_{ik}! \binom{s_i}{\nu_{ik}} \prod_{i \in \mathcal{I}_\bullet} s_i^{\nu_{ik}}.$$

Since the right-hand side gives the reaction rates for mass action kinetics within a single compartment, as given through $\underline{V}_{f|\underline{v}_s}$ from (2.16), the equilibrium $\mu_{\underline{v}_s}(d\underline{z})$ from Assumption 2.6(i) and $\mu_{\underline{s}_s}(d\underline{s}_f)$ from Assumption 3.11(i)(1) must be the same and the assertion follows. □

EXAMPLE 3.19 (Production from fluctuating source in multiple compartments). We consider reaction kinetics from Example 2.8 and extend it to a spatial multi-compartment setting. Recall that the chemical reaction network is given (within compartments) by the set of reactions

$$1: \quad A + B \xrightarrow{\kappa_{1d}'} C, \qquad 2: \quad \varnothing \xrightarrow{\kappa_{2d}'} B, \qquad 3: \quad B \xrightarrow{\kappa_{3d}'} \varnothing.$$
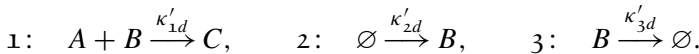
We consider $\Lambda_k^{\mathrm{CR}}(\underline{x})$ as in (2.19) with κ_k' replaced by κ_{kd}', $k \in \{1, 2, 3\}$. We have $\underline{x} = (\underline{x}_{\cdot d})_{d \in \mathcal{D}}$, $\underline{x}_{\cdot d} = (x_{Ad}, x_{Bd})$, and the dynamics are given by

$$\Lambda_{1d}^{\mathrm{CR}}(\underline{x}_{\cdot d}) = \kappa_{1d}' x_{Ad} x_{Bd}, \qquad \Lambda_{2d}^{\mathrm{CR}}(\underline{x}_{\cdot d}) = \kappa_{2d}', \qquad \Lambda_{3d}^{\mathrm{CR}}(\underline{x}_{\cdot d}) = \kappa_{3d}' x_{Bd}.$$

Movement of species is given as in (3.3). Scaling in each compartment is as in the nonspatial setting (2.20), (2.21) and (2.22), so rescaled species counts are

$$v_{Ad} = N^{-1} x_{Ad}, \qquad v_{Bd} = x_{Bd},$$

and rates are

$$\lambda_{1d}^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{1d} v_{Ad} v_{Bd}, \qquad \lambda_{2d}^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{2d}, \qquad \lambda_3^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{3d} v_{Bd}.$$

The process $\underline{V}^N = (V_{Ad}^N, V_{Bd}^N)$ is given as in (2.23) and additional movement terms. We set $\eta_s = \eta_A$ for movement of slow species and $\eta_f = \eta_B$ for movement of fast species. We assume (as in Assumption 3.4) that movement of species A, B have stationary probability distributions $(\pi_A(d))_{d \in \mathcal{D}}$ and $(\pi_B(d))_{d \in \mathcal{D}}$. We derive the dynamics of S_A as

$$S_A(t) = S_A(0) - \int_0^t \bar{\lambda}^{CR}(S_A(u)) \, du$$

for appropriate λ. Since the slow species A are continuous, we are in the regime of Corollary 3.17 and we distinguish the following two cases:

Dynamics in the cases $(1) + (2)$. We have

$$S_{B|s_A}(t) - S_{B|s_A}(0)$$

$$= -Y_1 \left(\int_0^t \int \sum_{d \in \mathcal{D}} \kappa_{1d} v_{Ad} v_{Bd} \mathbf{P}_{(s_A, S_{B|s_A}(u))}(d\underline{v}_A, d\underline{v}_B) \, du \right)$$

$$+ Y_2 \left(\sum_{d \in \mathcal{D}} \kappa_{2d} t \right) - Y_3 \left(\int_0^t \int \sum_{d \in \mathcal{D}} \kappa_{3d} v_{Bd} \mathbf{P}_{(s_A, S_{B|s_A}(u))}(d\underline{v}_A, d\underline{v}_B) \, du \right)$$

$$\overset{d}{=} -Y_{1+3} \left(\int_0^t \Big(\underbrace{\sum_{d \in \mathcal{D}} \kappa_{1d} \pi_A(d) \pi_B(d) \, s_A}_{=: \bar{\kappa}_1} + \underbrace{\sum_{d \in \mathcal{D}} \kappa_{3d} \pi_B(d)}_{=: \bar{\kappa}_3} \Big) S_{B|s_A}(u) \, du \right)$$

$$+ Y_2 \Big(\underbrace{\sum_{d \in \mathcal{D}} \kappa_{2d}}_{=: \bar{\kappa}_2} t \Big).$$

Hence, the equilibrium of the above process is as in Example 2.8 given by

$$X \sim \mu_{s_A}(ds_B) = \text{Pois} \left(\frac{\bar{\kappa}_2}{\bar{\kappa}_3 + \bar{\kappa}_1 s_A} \right).$$

We can now compute $\bar{\lambda}_1^{CR(1)+(2)}$ from (3.22) as

$$\bar{\lambda}_1^{CR(1)+(2)}(s_A) = -\int \sum_{d \in \mathcal{D}} \kappa_{1d} \pi_A(d) s_A \pi_B(d) s_B \mu_{s_A}(ds_B)$$

(3.31)

$$= -\sum_{d \in \mathcal{D}} \kappa_{1d} \pi_A(d) s_A \pi_B(d) \frac{\bar{\kappa}_2}{\bar{\kappa}_3 + \bar{\kappa}_1 s_A} = -\frac{\bar{\kappa}_1 \bar{\kappa}_2 s_A}{\bar{\kappa}_3 + \bar{\kappa}_1 s_A}.$$

Dynamics in the cases $(3) + (4)$. We have in each compartment $d \in \mathcal{D}$

$$V_{Bd|s_A}(t) - V_{Bd|s_A}(0)$$

$$= -Y_1 \left(\int_0^t \int \kappa_{1d} v_{Ad} V_{Bd|s_A}(u) \mathbf{P}_{s_A}(d\underline{v}_{A_d}) \, du \right) + Y_2(\kappa_{2d} t)$$

$$- Y_3 \left(\int_0^t \int \kappa_{3d} V_{B_d|s_A}(u) \mathbf{P}_{s_A}(d\underline{v}_{A_d}) \, du \right)$$

$$\stackrel{d}{=} -Y_{1+3} \left(\int_0^t (\kappa_{1d} \pi_A(d) s_A + \kappa_{3d}) V_{B_d|s_A}(u) \, du \right) + Y_2(\kappa_{2d} t).$$

Hence, the equilibrium of the above process is

$$X \sim \mu_{s_A}(dv_{B_d}) = \mathrm{Pois}\left(\frac{\kappa_{2d}}{\kappa_{3d} + \kappa_{1d} \pi_A(d) s_A} \right)$$

and for $\bar{\lambda}_1^{\mathrm{CR}(3)+(4)}$ from (3.24) we have

(3.32)
$$\bar{\lambda}_1^{\mathrm{CR}(3)+(4)}(s_A) = - \sum_{d \in \mathcal{D}} \int \kappa_{1d} v_{Ad} v_{Bd} \mu_{s_A}(dv_{B_d}) \mathbf{P}_{s_A}(dv_{A_d})$$

$$= - \sum_{d \in \mathcal{D}} \frac{\kappa_{1d} \kappa_{2d} \pi_A(d) s_A}{\kappa_{3d} + \kappa_{1d} \pi_A(d) s_A}.$$

Note that we are in the regime of Corollary 3.15, which shows that $\bar{\lambda}_1^{\mathrm{CR}(3)+(4)}$ is independent of π_B.

Comparison of dynamics in cases (1) + (2) *and* (3) + (4). Let us compare the case (1) + (2), when the turnover rate of A is given by (3.31), and (3) + (4), when the rate is given by (3.32). First note that even when the network is spatially homogeneous (the chemical constants satisfy assumption in Corollary 3.18) there is a marked difference between the dynamics of cases (1) + (2) (as in single compartment case) and cases (3) + (4) depending on the movement equilibria π_A and π_B. However, if we additionally suppose the slow species A are equidistributed $\pi_A(d) = 1/|\mathcal{D}|$ then all four cases have the same dynamics.

Conserved quantities on the fast time scale. Now, we include *conserved quantities* in our two-scale system in multiple compartments, that is, we have a two-scale reaction network with $\dim(\mathcal{N}((\underline{\underline{\zeta}}^f)^{\mathrm{T}})) =: n^f > 0$. We will use the same notation as in Section 2.3. In particular, $\Theta^f := (\underline{\theta}^{c_j})_{j=1,\dots,n^f}$ are linearly independent vectors which span the null space of $(\underline{\underline{\zeta}}^f)^{\mathrm{T}}$. Every $\underline{\theta}^{c_j}$ has a unique parameter α_i associated with it, $j = 1, \dots, |\Theta^f| = n^f$. Here, $\Theta_\circ^f$ is the subset of conserved quantities for which $\alpha_{c_j} = 0$, and $\Theta_\bullet^f$ is the subset of conserved quantities for which $\alpha_{c_j} > 0$. Conservation means that $t \mapsto \langle \underline{\theta}^{c_j}, \underline{S}_{f|\underline{s}_s}(t) \rangle$ with $\underline{S}_{f|\underline{s}_s}$ from (3.13) is constant, $j = 1, \dots, |\Theta^f|$. We let $S_{c_j}^N = \langle \underline{\theta}^{c_j}, \underline{S}_f^N \rangle$ and $\underline{S}_c^N = (S_{c_j}^N)_{i=1,\dots,|\Theta^f|}$ be the vector of rescaled conserved quantities. Again, $\mathcal{K}_{\underline{\theta}^{c_j}}$ is the set of reactions such that $\beta_k = \alpha_{c_j}$ and $\langle \underline{\theta}^{c_j}, \underline{\zeta}_{\cdot k} \rangle \neq 0$, and let $\mathcal{K}^c := \bigcup_{j=1}^{|\Theta^f|} \mathcal{K}_{\underline{\theta}^{c_i}}$, $\mathcal{K}_\circ^c := \bigcup_{j=1}^{|\Theta_\circ^f|} \mathcal{K}_{\underline{\theta}^{c_j}}$ and $\mathcal{K}_\bullet^c := \bigcup_{j=1}^{|\Theta_\bullet^f|} \mathcal{K}_{\underline{\theta}^{c_j}}$. We still let $\underline{\underline{\zeta}}^c$ be the matrix defined by (2.29).

Again, we consider the four cases as given in (3.12). In addition, we assume that $\langle \underline{\theta}^{c_j}, \underline{S}^N \rangle$ changes on the time scale dt. We write here, distinguishing fast species, conserved quantities and slow species, $\underline{v} = (\underline{v}_f, \underline{v}_c, \underline{v}_s)$ with $\underline{v}_f = (v_{id})_{i \in \mathcal{I}^f, d \in \mathcal{D}}$, $\underline{v}_c = (\langle \underline{\theta}^{c_j}, \underline{v}_{\cdot d, f} \rangle)_{j=1,\dots,|\Theta^f|, d \in \mathcal{D}}$, $\underline{v}_s = (v_{id})_{i \in \mathcal{I}^s, d \in \mathcal{D}}$, as well as $\underline{s} = (\underline{s}_f, \underline{s}_c, \underline{s}_s)$, $\underline{s}_f = (s_i)_{i \in \mathcal{I}^f}$, $\underline{s}_c = (\langle \underline{\theta}^{c_j}, \underline{s}_f \rangle)_{j=1,\dots,|\Theta^f|}$, and $\underline{s}_s = (s_i)_{i \in \mathcal{I}^s}$.

REMARK 3.20 (Conserved quantities as new species). In light of the previous results, one would guess that conserved quantities on the fast time scale can be handled as if they are new chemical species, evolving on the slow time scale. However, an important distinction between slow species and conserved quantities does exist: movement of conserved quantities occurs on the time scale $N^{\eta_f} dt$ rather than on the time scale $N^{\eta_s} dt$, on which it occurs for the slow species. This implies *an important distinction between slow species and conserved quantities occurs in cases* (2) *and* (3); the averaging measures over the intermediate time scales treat conserved and slow species differently.

Although what follows resembles our previous results, in order to be able to use them, we do have to state the assumptions and results for systems with conserved species explicitly. We omit all the proofs as they follow analogous steps to those for systems without conserved species.

ASSUMPTION 3.21 (Dynamics of the spatial multi-scale reaction network with conserved quantities). In each case (1)–(4), the spatial two-scale reaction network on time scale $N dt$, where Assumption 3.4 holds, satisfies the following conditions:

(i) (1) Given $(Y_k)_{k \in \mathcal{K}_\circ^f}$, the time-change equation of the dynamics of $\underline{S}_f$ given the values of $\underline{S}_s = \underline{s}_s$ and $\underline{S}_c = \underline{s}_c$, denoted $(\underline{S}_{f|(\underline{s}_s, \underline{s}_c)}(t))_{t \geq 0}$, given by (3.13) with $\underline{S}_{f|\underline{s}_s}$ replaced by $\underline{S}_{f|(\underline{s}_s, \underline{s}_c)}$, has a unique solution, where $\tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_f, \underline{s}_s)$ is given by (3.14). In addition, $\underline{S}_{f|(\underline{s}_s, \underline{s}_c)}(\cdot)$ has a unique stationary probability measure $\mu_{(\underline{s}_s, \underline{s}_c)}(d\underline{s}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$ with $\langle \underline{\theta}^{c_j}, \underline{s}_f \rangle = s_{c_j}$, $\mu_{(\underline{s}_s, \underline{s}_c)}$-almost surely, $j = 1, \dots, |\Theta^f|$.

(2) Given $(Y_k)_{k \in \mathcal{K}_\circ^f}$, the time-change equation of the dynamics of $\underline{S}_f$ given the value of $\underline{V}_s = \underline{v}_s$ and $\underline{S}_c = \underline{s}_c$, denoted $(\underline{S}_{f|(\underline{v}_s, \underline{s}_c)}(t))_{t \geq 0}$, given by (3.15) with $\underline{S}_{f|\underline{v}_s}$ replaced by $\underline{S}_{f|(\underline{v}_s, \underline{s}_c)}$, has a unique solution, where $\tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_f, \underline{v}_s)$ is given by (3.16). In addition, $\underline{S}_{f|(\underline{v}_s, \underline{s}_c)}(\cdot)$ has a unique stationary probability measure $\mu_{(\underline{v}_s, \underline{s}_c)}(d\underline{s}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f|}$ with $\langle \underline{\theta}^{c_j}, \underline{s}_f \rangle = s_{c_j}$, $\mu_{(\underline{v}_s, \underline{s}_c)}$-almost surely, $j = 1, \dots, |\Theta^f|$.

(3) Given $(Y_{kd})_{k \in \mathcal{K}_\circ^f, d \in \mathcal{D}}$, the time-change equation of the dynamics of $\underline{V}_f$ given the values of $\underline{S}_s = \underline{s}_s$ and $\underline{V}_c = \underline{v}_c$, denoted by $(\underline{V}_{f|(\underline{s}_s, \underline{v}_c)}(t))_{t \geq 0}$, given

by (3.17) with $\underline{V}_{\cdot d, f|\underline{s}_s}$ replaced by $\underline{V}_{\cdot d, f|(\underline{s}_s, \underline{v}_c)}$, has a unique solution, where $\tilde{\lambda}_{kd}^{\mathrm{CR}(3)}(\underline{\underline{v}}_f, \underline{s}_s)$ is given by (3.18). In addition, $\underline{V}_{f|(\underline{s}_s, \underline{v}_c)}(\cdot)$ has a unique stationary probability measure $\mu_{(\underline{s}_s, \underline{v}_c)}(d\underline{\underline{v}}_f)$ on $\mathbb{R}_+^{|\mathcal{I}^f| \times |\mathcal{D}|}$ with $\langle \underline{\theta}^{c_j}, \underline{\underline{v}}_f \rangle = \underline{v}_{c_j}$, $\mu_{(\underline{s}_s, \underline{v}_c)}$-almost surely, $j = 1, \ldots, |\Theta^f|$.

Moreover, given $\underline{s}_s$ and $\underline{s}_c$, the movement dynamics of $\underline{\underline{V}}_{c|(\underline{s}_s, \underline{s}_c)}$ is a unique solution $\underline{\underline{V}}_{c|(\underline{s}_s, \underline{s}_c)}(\cdot) = (\underline{V}_{\cdot d, c|(\underline{s}_s, \underline{s}_c)})_{d \in \mathcal{D}}$ of the time-change equations

$$\langle \underline{\theta}^{c_j}, \underline{V}_{\cdot d, f} \rangle_{|(\underline{s}_s, \underline{s}_c)}(t) - \langle \underline{\theta}^{c_j}, \underline{V}_{\cdot d, f} \rangle_{|(\underline{s}_s, \underline{s}_c)}(0)$$
$$= \sum_{i \in \mathcal{I}_\circ^f} \theta_i^{c_j} \sum_{d', d'' \in \mathcal{D}} (\delta_{d''}(d) - \delta_{d'}(d))$$
$$\times Y_{i, d', d''} \left(\int_0^t \lambda_{i, d', d''}^{\mathrm{M}} \int v_{id'} \mu_{(\underline{s}_s, \underline{\underline{V}}_{c|(\underline{s}_s, \underline{s}_c)}(u))}(d\underline{\underline{v}}_f) \, du \right),$$
(3.33) $\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \theta^{c_j} \in \Theta_\circ^f,$
$$\langle \underline{\theta}^{c_j}, \underline{V}_{\cdot d, f} \rangle_{|(\underline{s}_s, \underline{s}_c)}(t) - \langle \underline{\theta}^{c_j}, \underline{V}_{\cdot d, f} \rangle_{|(\underline{s}_s, \underline{s}_c)}(0)$$
$$= \sum_{i \in \mathcal{I}_\bullet^f} \theta_i^{c_j} \sum_{d' \in \mathcal{D}} \int_0^t \int (\lambda_{i, d', d}^{\mathrm{M}} v_{id'} - \lambda_{i, d, d'}^{\mathrm{M}} v_{id})$$
$$\times \mu_{(\underline{s}_s, \underline{\underline{V}}_{c|(\underline{s}_s, \underline{s}_c)}(u))}(d\underline{\underline{v}}_f) \, du, \qquad \theta^{c_j} \in \Theta_\bullet^f,$$

with an equilibrium probability distribution of movement $\mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{\underline{v}}_c)$ with $\sum_{d \in \mathcal{D}} \underline{v}_{\cdot d, c} = \underline{s}_c$, $\mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{\underline{v}}_c)$-almost surely.

(4) Given $(Y_{kd})_{k \in \mathcal{K}_c^f, d \in \mathcal{D}}$, the time-change equation of the dynamics of $\underline{\underline{V}}_f$ given the values of $\underline{V}_s = \underline{v}_s$ and $\underline{V}_c = \underline{v}_c$, denoted by $(\underline{V}_{f|(\underline{v}_s, \underline{v}_c)}(t))_{t \geq 0}$, given by (3.19) with $\underline{V}_{\cdot d, f|\underline{v}_s}$ replaced by $\underline{V}_{\cdot d, f|(\underline{v}_s, \underline{v}_c)}$, has a unique solution, where $\tilde{\lambda}_{kd}^{\mathrm{CR}(4)}(\underline{\underline{v}}_f, \underline{v}_s)$ is given by (3.20). In addition, $\underline{V}_{c|(\underline{v}_s, \underline{v}_c)}$ has a unique stationary probability measure $\mu_{(\underline{v}_s, \underline{v}_c)}(d\underline{\underline{v}}_f)$ with $\langle \underline{\theta}^{c_j}, \underline{\underline{v}}_f \rangle = \underline{v}_{c_j}$, $\mu_{(\underline{v}_s, \underline{v}_c)}$-almost surely, $j = 1, \ldots, |\Theta^f|$.

Moreover, given $\underline{v}_s$ and $\underline{s}_c$, the movement dynamics of $\underline{\underline{V}}_{c|(\underline{v}_s, \underline{s}_c)}$ is a unique solution $\underline{\underline{V}}_{c|(\underline{v}_s, \underline{s}_c)} = (\underline{V}_{\cdot d, c|(\underline{v}_s, \underline{s}_c)})_{d \in \mathcal{D}}$ of the time-change equations (3.33) with $\underline{\underline{V}}_{c|(\underline{s}_s, \underline{s}_c)}$ replaced by $\underline{\underline{V}}_{c|(\underline{v}_s, \underline{s}_c)}$ with an equilibrium probability distribution of movement $\mathbf{P}_{(\underline{v}_s, \underline{s}_c)}(d\underline{\underline{v}}_c)$ with $\sum_{d \in \mathcal{D}} \underline{v}_{\cdot d, c} = \underline{s}_c$, $\mathbf{P}_{(\underline{v}_s, \underline{s}_c)}$-almost surely.

(ii) From $\{\tilde{\lambda}_k^{\mathrm{CR}(\ell)}\}_{\ell = 1, 2, 3, 4}$, we set in each case

$$(3.34) \quad \bar{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_s, \underline{s}_c) = \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \tilde{\lambda}_k^{\mathrm{CR}(1)}(\underline{s}_f, \underline{s}_s) \mu_{(\underline{s}_s, \underline{s}_c)}(d\underline{s}_f);$$

$$(3.35) \quad \bar{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_s, \underline{s}_c) = \int_{\mathbb{R}_+^{|\mathcal{I}^s| \times |\mathcal{D}|}} \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \tilde{\lambda}_k^{\mathrm{CR}(2)}(\underline{s}_f, \underline{v}_s) \mu_{(\underline{v}_s, \underline{s}_c)}(d\underline{s}_f) \mathbf{P}_{\underline{s}_s}(d\underline{v}_s);$$

$$\bar{\lambda}_k^{\mathrm{CR}(3)}(\underline{s}_s, \underline{s}_c) = \int_{\mathbb{R}_+^{|\Theta^f| \times |\mathcal{D}|}} \int_{\mathbb{R}_+^{|\mathcal{I}^f| \times |\mathcal{D}|}} \tilde{\lambda}_k^{\mathrm{CR}(3)}(\underline{v}_f, \underline{s}_s) \mu_{(\underline{s}_s, \underline{v}_c)}(d\underline{v}_f)$$

$$(3.36) \qquad\qquad\qquad\qquad\qquad\qquad\qquad \times \mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{v}_c);$$

$$\bar{\lambda}_k^{\mathrm{CR}(4)}(\underline{s}_s, \underline{s}_c) = \int_{\mathbb{R}_+^{|\mathcal{I}^s| \times |\mathcal{D}|}} \int_{\mathbb{R}_+^{|\Theta^f| \times |\mathcal{D}|}} \int_{\mathbb{R}_+^{|\mathcal{I}^f| \times |\mathcal{D}|}} \tilde{\lambda}_k^{\mathrm{CR}(4)}(\underline{v}_f, \underline{v}_s) \mu_{(\underline{v}_s, \underline{v}_c)}(d\underline{v}_f)$$

$$(3.37) \qquad\qquad\qquad\qquad\qquad\qquad\qquad \times \mathbf{P}_{(\underline{v}_s, \underline{s}_c)}(d\underline{v}_c) \mathbf{P}_{\underline{s}_s}(d\underline{v}_s).$$

For $j = 1, 2, 3, 4$, there exists a well-defined process $(\underline{S}_s(\cdot), \underline{S}_c(\cdot))$ that is the unique solution of

$$(3.38) \quad \begin{aligned} \underline{S}_s(t) &= \underline{S}_s(0) + \sum_{k \in \mathcal{K}_\circ^s} \underline{\zeta}_{\cdot k}^s Y_k \left(\int_0^t \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{S}_s(u), \underline{S}_c(u))\, du \right) \\ &\quad + \sum_{k \in \mathcal{K}_\bullet^s} \underline{\zeta}_{\cdot k}^s \int_0^t \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{S}_s(u), \underline{S}_c(\cdot))\, du, \end{aligned}$$

and for $j = 1, \ldots, |\Theta^f|$,

$$(3.39) \quad \begin{aligned} S_{c_j}(t) &= S_{c_j}(0) \\ &\quad + \sum_{k \in \mathcal{K}_\circ^c} \sum_{i \in \mathcal{I}^f} \theta_{c_j}^i \underline{\zeta}_{ik}^s Y_k \left(\int_0^t \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{S}_s(u), \underline{S}_c(u))\, du \right) \\ &\quad + \sum_{k \in \mathcal{K}_\bullet^c} \sum_{i \in \mathcal{I}^f} \theta_{c_j}^i \underline{\zeta}_{ik}^s \int_0^t \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{S}_s(u), \underline{S}_c(u))\, du. \end{aligned}$$

(iii) Same as (iii) in Assumption 2.6 in each compartment.

REMARK 3.22 (Equivalent formulation). For the dynamics under the above assumption, the following is immediate: In each case (1)–(4), the spatial two-scale reaction network on time scale dt, where Assumption 3.21 holds, satisfies the following condition: given $(Y_k)_{k \in \mathcal{K}_\circ^s \cup \mathcal{K}_\circ^c}$, the time change equations (3.38) and (3.39) have a unique solution, with

$$(3.40) \qquad \bar{\lambda}_k^{\mathrm{CR}(\ell)}(\underline{s}_s) := \mathbf{E}_{(\underline{s}_s, \underline{s}_c)} \left[\sum_{d \in \mathcal{D}} \lambda_{kd}^{\mathrm{CR}}(\underline{V}_{\cdot d}) \right] < \infty.$$

The distribution of $(V_{id})_{i \in \mathcal{I}, d \in \mathcal{D}}$ in (3.40) depends on the parameters η_s, η_f as follows:

$$(1) \qquad \mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{v}_f, d\underline{v}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{v}_s) \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \mathbf{P}_{\underline{s}_f}(d\underline{v}_f) \mu_{(\underline{s}_s, \underline{s}_c)}(d\underline{s}_f),$$

$$(2) \qquad \mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{v}_f, d\underline{v}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{v}_s) \int_{\mathbb{R}_+^{|\mathcal{I}^f|}} \mathbf{P}_{\underline{s}_f}(d\underline{v}_f) \mu_{(\underline{v}_s, \underline{s}_c)}(d\underline{s}_f),$$

$$(3) \qquad \mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{v}_f, d\underline{v}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{v}_s) \int_{\mathbb{R}_+^{|\Theta_f| \times |\mathcal{D}|}} \mu_{(\underline{s}_s, \underline{v}_c)}(d\underline{v}_f) \mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{v}_c),$$

$$(4) \qquad \mathbf{P}_{(\underline{s}_s, \underline{s}_c)}(d\underline{v}_f, d\underline{v}_s) = \mathbf{P}_{\underline{s}_s}(d\underline{v}_s) \int_{\mathbb{R}_+^{|\Theta_f| \times |\mathcal{D}|}} \mu_{(\underline{v}_s, \underline{v}_c)}(d\underline{v}_f) \mathbf{P}_{(\underline{v}_s, \underline{s}_c)}(d\underline{v}_c).$$

THEOREM 3.23 (Heterogeneous two-scale system with conserved fast quantities). *Let $\underline{V}^N$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to (3.3). Assume that $(\underline{\alpha}, \underline{\beta}, \gamma = 0)$ satisfy two-scale system assumptions (2.11) for some $\mathcal{I}^f, \mathcal{I}^s$ with $\varepsilon = 1$ and $\mathcal{N}((\underline{\zeta}^f)^{\mathrm{T}}) = \mathrm{span}(\Theta^f)$ [with $\underline{\zeta}^f$ from (2.13) and Θ^f from (2.28)] within compartments with conserved quantities $(\theta^{c_j})_{i=1,\ldots,|\Theta^f|}$ on the fast time scale. In addition, $\eta_i = \eta_f > 0$, $i \in \mathcal{I}^f$, $\eta_i = \eta_s > 0$, $i \in \mathcal{I}^s$, one of the cases (1)–(4) holds and Assumption 3.21 holds. Then, if $(\underline{S}_s^N(0), \underline{S}_c^N(0)) \overset{N \to \infty}{\Longrightarrow} (\underline{S}_s(0), \underline{S}_c(0))$, we have joint convergence of the process of rescaled amounts of slow and conserved quantities $(\underline{S}_s^N(\cdot), \underline{S}_c^N(\cdot))$ to $(\underline{S}_s(\cdot), \underline{S}_c(\cdot))$ in the Skorohod topology, with $\underline{S}_s$ the solution of (3.38) and $\underline{S}_c$ the solution of (3.39) with rates given by (3.34)–(3.37).*

Results analogous to Corollary 3.15 stating the irrelevance of the movement of fast species in cases (3) and (4) does not carry over to the case with conserved quantities, since on the time scale $N^{\eta_f} dt$ conserved quantities are still preserved and their movement equilibria affects the end result.

LEMMA 3.24. *In the situation of Theorem 3.23, assume $\mathcal{I}_\circ^s = \varnothing$, that is, all slow species are continuous, and let $\underline{\underline{\pi s}}_s := (\pi_i(d)s_i)_{i \in \mathcal{I}^s, d \in \mathcal{D}}$.*

(i) *For stationary probability measures $\mu_{(\underline{s}_s, \underline{s}_c)}(d\underline{s}_f)$ of $\underline{S}_{f|(\underline{s}_s, \underline{s}_c)}$ from Assumption 3.21(i)(1) and $\mu_{(\underline{v}_s, \underline{s}_c)}(d\underline{s}_f)$ of $\underline{S}_{f|(\underline{v}_s, \underline{s}_c)}$ from (i)(2), we have*

$$\mu_{(\underline{s}_s, \underline{s}_c)}(d\underline{s}_f) = \mu_{(\underline{\underline{\pi s}}_s, \underline{s}_c)}(d\underline{s}_f).$$

(ii) *Likewise, for stationary probability measures $\mu_{(\underline{s}_s, \underline{v}_c)}(d\underline{v}_f)$ of $\underline{V}_{f|(\underline{s}_s, \underline{v}_c)}$ from (i)(3) and $\mu_{(\underline{v}_s, \underline{v}_c)}(d\underline{v}_f)$ of $\underline{V}_{f|(\underline{v}_s, \underline{v}_c)}$ from (i)(4), we have*

$$\mu_{(\underline{s}_s, \underline{v}_c)}(d\underline{v}_f) = \mu_{(\underline{\underline{\pi s}}_s, \underline{v}_c)}(d\underline{v}_f).$$

COROLLARY 3.25. *Suppose in Theorem 3.23 all slow species are continuous, $\mathcal{I}_\circ^s = \varnothing$. Then dynamics of (3.38) is the same in cases (1), (2) and also in cases (3), (4).*

COROLLARY 3.26 (Homogeneous mass action kinetics). *Corollary* 3.18 *carries over to the same situation as in Theorem* 3.23.

EXAMPLE 3.27 (Michaelis–Menten kinetics in multiple compartments). We place Michaelis–Menten reaction kinetics from Example 2.13 in a spatial multi-compartment setting. The chemical reaction network is given (within compartments) by the set of reactions from (2.34), with κ'_k replaced by κ'_{kd} in compartment d. We have $\underline{x} = (\underline{x}_{\cdot d})_{d\in\mathcal{D}}$, $\underline{x}_{\cdot d} = (x_{Sd}, x_{Ed}, x_{ESd}, x_{Pd})$, and the dynamics in each compartment d is given by rates (2.35) with κ'_k replaced by κ'_{kd}. Movement of species is given as in (3.3). Again, we set $\alpha_S = \alpha_P = 1, \alpha_E = \alpha_{ES} = 0$, and $\kappa_{1d} = \kappa'_{1d}$, $\kappa_{-1d} = N^{-1}\kappa'_{-1d}$ and $\kappa_{2d} = N^{-1}\kappa'_{2d}$ as in (2.37) so, setting the rescaled species counts

$$v_{Sd} = N^{-1}x_{Sd}, \qquad v_{Ed} = x_{Ed}, \qquad v_{ESd} = x_{ESd}, \qquad v_{Pd} = N^{-1}x_{Pd},$$

and $\beta_1 = 1, \beta_{-1} = 1, \beta_2 = 1$ as in (2.36). We write

$$\lambda_{1d}^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{1d}v_{Sd}v_{Ed}, \qquad \lambda_{-1d}^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{-1d}v_{ESd}, \qquad \lambda_{2d}^{\mathrm{CR}}(\underline{v}_{\cdot d}) = \kappa_{2d}v_{ESd}.$$

The process $\underline{V}^N = (V_{Sd}^N, V_{Ed}^N, V_{ESd}^N, V_{Pd}^N)$ is given as in Example (2.13) plus additional movement terms. We set $\eta_s = \eta_S = \eta_P$ for movement of slow species and $\eta_f = \eta_E = \eta_{ES}$ for movement of fast species. We assume (as in Assumption 3.4) that movement of species i has a stationary probability distribution $(\pi_i(d))_{d\in\mathcal{D}}$. We have $\mathcal{I}^f = \mathcal{I}_\circ^f = \{E, ES\}$ and $\mathcal{I}^s = \mathcal{I}_\bullet^s = \{S, P\}$ and $\mathcal{K}^f = \mathcal{K}^s = \{1, -1, 2\}$, $\mathcal{K}_S = \{1, -1\}, \mathcal{K}_E = \mathcal{K}_{ES} = \mathcal{K}$ and $\underline{\underline{\zeta}}, \underline{\underline{\zeta}}^f, \underline{\underline{\zeta}}^s$ as in (2.37). For conserved quantities within compartments, we set $V_{Cd} := \overline{V}_{Ed} + V_{ESd}$ and note that while movement changes the values of V_{Cd} the overall sum $S_C = \sum_{d\in\mathcal{D}} V_{Cd} := m$ is a conserved quantity for all times, and thus, the dynamics of S_C is trivial.

We derive the dynamics of S_S (as in Example 2.13, $S_S + S_P$ is a conserved quantity on the slow time scale). We have from (3.21) that

$$S_S(t) = S_S(0) - \int_0^t \bar{\lambda}^{\mathrm{CR}}(S_S(u))\,du$$

for appropriate $\bar{\lambda}$. Since all slow species are continuous, we are in the regime of Corollary 3.25 and we only need to distinguish the following two cases:

Dynamics in cases (1) + (2). From (3.13) with $\underline{S}_{f|\underline{s}_s}$ replaced by $\underline{S}_{f|(\underline{s}_s, \underline{s}_c)}$, we have

$$\begin{aligned}
S_{E|s_S}&(t) - S_{E|s_S}(0) \\
&= -Y_1\left(\int_0^t \int \sum_{d\in\mathcal{D}} \kappa_{1d}v_{Sd}v_{Ed}\mathbf{P}_{(s_S, S_{E|s_S}(u))}(d\underline{v}_S, d\underline{v}_E)\,du\right) \\
&\quad + Y_{-1+2}\left(\int_0^t \int \sum_{d\in\mathcal{D}} (\kappa_{-1d} + \kappa_{2d})v_{ESd}\mathbf{P}_{(m-S_{E|s_S}(u))}(d\underline{v}_{ES})\,du\right)
\end{aligned}$$

$$= -Y_1\left(\int_0^t \underbrace{\left(\sum_{d\in\mathcal{D}} \kappa_{1d}\pi_S(d)\pi_E(d)\right)}_{=:\bar{\kappa}_1} s_S S_{E|s_S}(u)\,du\right)$$

$$+ Y_{-1+2}\left(\int_0^t \underbrace{\left(\sum_{d\in\mathcal{D}}(\kappa_{-1d}+\kappa_{2d})\pi_{ES}(d)\right)}_{=:\bar{\kappa}_{-1}+\bar{\kappa}_2}(m - S_{E|s_S}(u))\,du\right).$$

Hence, the equilibrium of the above process is as in Example 2.13 given by $X \sim \mu_{(s_S,m)}(ds_E)$ where

$$X \sim \text{Binom}\left(m, \frac{\bar{\kappa}_{-1}+\bar{\kappa}_2}{\bar{\kappa}_{-1}+\bar{\kappa}_2+\bar{\kappa}_1 s_S}\right)$$

and $S_{ES|s_S}$ has equilibrium $m - X$. We next compute $\bar{\lambda}^{\text{CR}(1)+(2)}$ from (3.34) as

$$\bar{\lambda}^{\text{CR}(1)+(2)}(s_S) = \bar{\lambda}_1^{\text{CR}(1)+(2)}(s_S) - \bar{\lambda}_{-1}^{\text{CR}(1)+(2)}(s_S)$$

$$= \sum_{d\in\mathcal{D}}\int \left(\kappa_{1d}\pi_S(d)\pi_E(d)s_S s_E\right.$$

$$\left. - \kappa_{-1d}\pi_{ES}(d)(m - s_E)\right)\mu_{(s_S,m)}(ds_E)$$

$$= \sum_{d\in\mathcal{D}}\kappa_{1d}\pi_S(d)\pi_E(d)s_S m \frac{\bar{\kappa}_{-1}+\bar{\kappa}_2}{\bar{\kappa}_{-1}+\bar{\kappa}_2+\bar{\kappa}_1 s_S}$$

$$- \kappa_{-1d}\pi_{ES}(d)m \frac{\bar{\kappa}_1 s_S}{\bar{\kappa}_{-1}+\bar{\kappa}_2+\bar{\kappa}_1 s_S}$$

$$= \frac{m\bar{\kappa}_1\bar{\kappa}_2 s_S}{\bar{\kappa}_{-1}+\bar{\kappa}_2+\bar{\kappa}_1 s_S}.$$

Comparing this with (2.38), we see that in cases $(1)+(2)$ Michaelis–Menten kinetics in multiple compartments equals the same kinetics in a single compartment, when κ_i is exchanged by $\bar{\kappa}_i$, $i = -1, 1, 2$; compare also with Corollary 3.25.

Dynamics in cases $(3)+(4)$. For simplicity, we assume that $\lambda_{d,d'}^{\text{M}} := \lambda_{E,d,d'}^{\text{M}} = \lambda_{ES,d,d'}^{\text{M}}$, that is, movement of E and ES is the same, and hence $\pi_E(d) = \pi_{ES}(d), d \in \mathcal{D}$ [we will use this property for deriving $\mathbf{P}_{(s_S,m)}(d\underline{v}_C)$ and $\mathbf{P}_{(v_S,m)}(d\underline{v}_C)$ below]. We will treat the cases (3) and (4) separately and show the result of Corollary 3.25 which states that these two cases lead to the same limiting dynamics.

(3) From Assumption 3.21(i)(3), for $\underline{v}_C$ with $\sum_{d\in\mathcal{D}} v_{Cd} = m$, we have

$$V_{Ed|(s_S,\underline{v}_C)}(t) - V_{Ed|(s_S,\underline{v}_C)}(0)$$

$$= -Y_{1d}\left(\int_0^t \int \kappa_{1d}V_{Ed|(s_S,\underline{v}_C)}(u)v_{Sd}\mathbf{P}_{s_S}(dv_{Sd})\,du\right)$$

$$+ Y_{(-1+2)d}\left(\int_0^t (\kappa_{-1d} + \kappa_{2d})(v_{Cd} - V_{Ed|(s_S,\underline{v}_C)}(u))\,du\right)$$

$$= -Y_{1d}\left(\int_0^t \kappa_{1d}V_{Ed|(s_S,\underline{v}_C)}(u)s_S\pi_S(d)\,du\right)$$

$$+ Y_{(-1+2)d}\left(\int_0^t (\kappa_{-1d} + \kappa_{2d})(v_{Cd} - V_{Ed|(s_S,\underline{v}_C)}(u))\,du\right).$$

Hence, the equilibrium of $V_{Ed|(s_S,\underline{v}_C)}$ is as in Example 2.13 given by

$$X_d \sim \mu_{(v_{Sd},v_{Cd})}(ds_{Ed}) = \text{Binom}\left(v_{Cd}, \frac{\kappa_{-1d} + \kappa_{2d}}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}s_S\pi_S(d)}\right)(s_{Ed})$$

and $V_{ESd|(s_S,\underline{v}_C)}$ has equilibrium $v_{Cd} - X_d$. We compute $\bar{\lambda}^{CR(3)}$ from (3.36) as

$$\bar{\lambda}^{CR(3)}(s_S) = \bar{\lambda}_1^{CR(3)}(s_S) - \bar{\lambda}_{-1}^{CR(3)}(s_S)$$

$$= \sum_{d\in\mathcal{D}} \int \kappa_{1d}v_{Ed}s_S\pi_S(d)$$

$$- \kappa_{-1d}(v_{Cd} - v_{Ed})\mu_{(v_{Sd},v_{Cd})}(dv_{Ed})\mathbf{P}_{(s_S,m)}(dv_{Cd})$$

$$= \sum_{d\in\mathcal{D}} \int \left(\kappa_{1d}v_{Cd}\frac{\kappa_{-1d} + \kappa_{2d}}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}s_S\pi_S(d)}s_S\pi_S(d)\right.$$

$$\left. - \kappa_{-1d}v_{Cd}\frac{\kappa_{1d}s_S\pi_S(d)}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}s_S\pi_S(d)}\right)\mathbf{P}_{(s_S,m)}(dv_{Cd})$$

$$= \sum_{d\in\mathcal{D}} \int \frac{v_{Cd}\kappa_{1d}\kappa_{2d}s_S\pi_S(d)}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}s_S\pi_S(d)}\mathbf{P}_{(s_S,m)}(dv_{Cd}).$$

Consider the equilibrium $\mathbf{P}_{(s_S,m)}(dv_{Cd})$ of movement dynamics for conserved species $V_{Cd} = V_{Ed} + V_{ESd}$. Since we assume the same migration dynamics for E and ES, the equilibrium $\mathbf{P}_{(\underline{s}_S,m)}(d\underline{v}_C)$ is given by a multinomial distribution with parameters m, $(\pi_E(d))_{d\in\mathcal{D}}$ and $\int v_{Cd}\mathbf{P}_{(s_S,m)}(dv_{Cd}) = m\pi_E(d)$, $d\in\mathcal{D}$.

For (4), the overall rate $\bar{\lambda}^{CR(4)}$ from (3.37) has the same form as $\bar{\lambda}^{CR(3)}$ except that $\mathbf{P}_{(s_S,m)}(dv_{Cd})$ is replaced by $\mathbf{P}_{(v_{Sd},m)}(dv_{Cd})$. We first derive the equilibrium probability distribution $\mu_{(v_{Sd},v_{Cd})}(dv_{Ed})$ as above. Here, we find that $s_S\pi_S(d)$ is replaced by v_{Sd}, leading to

$$X_d \sim \mu_{(v_{Sd},v_{Cd})}(dv_{Ed}) = \text{Binom}\left(v_{Cd}, \frac{\kappa_{-1d} + \kappa_{2d}}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}v_{Sd}}\right)(v_{Ed}).$$

The conserved quantities $V_{Cd}(\cdot)$ follow the same dynamics as in case (3) except that $s_S\pi_S(d)$ is replaced by v_{Sd} and, therefore, $\mathbf{P}_{(\underline{v}_S,m)}(d\underline{v}_C)$ is a multinomial distribution with parameters m, $(\pi_E(d))_{d\in\mathcal{D}}$ as in case (3). Hence, in the equation for

the rates we have $\int v_{Cd}\mathbf{P}_{(v_{Sd},m)}(dv_{Cd}) = m\pi_E(d)$, $d \in \mathcal{D}$, and the limiting dynamics in cases (3) and (4) is given by

$$\bar{\lambda}^{CR(3)+(4)}(s_S) = \sum_{d \in \mathcal{D}} \frac{m\pi_E(d)\kappa_{1d}\kappa_{2d}s_S\pi_S(d)}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}s_S\pi_S(d)}.$$

Although we have seen that the dynamics for cases $(1)+(2)$, as well as for $(3)+(4)$ is the same, in general they are quite different from each other, unless some very special relationships between the chemical constants and movement equilibria in different compartments are assumed. See the results in Pfaffelhuber and Popovic (2014) on notions of dynamical homogeneity that allow one to make some interesting conclusions.

4. Discussion. *Specific features and extensions of spatial chemical reaction models.*

(a) *Heterogeneous reaction and migration rates.* The reaction rates Λ_{kd}^{CR} in general depend on the compartment d. For the same reason, the outflow of species i from compartment d', $\sum_{d'' \in \mathcal{D}} \Lambda_{i,d',d''}^{M}$ might depend on i and d'. Moreover, it is possible that $\Lambda_{kd}^{CR}(\underline{x}_{\cdot d})$ is zero for some compartments, that is, our model is flexible enough to restrict some reactions to a subset of compartments. Analogously, movement of certain species types can be restricted to only a subset of compartments, that is, $\Lambda_{i,d,d'}^{M}$ can also be set to zero for some i, d, d'. The only thing which is required is that every reaction k happens within at least one compartment.

(b) *Geometry of space.* The geometry of the spatial system has not been explicitly relevant for our results. The reason is that movement dynamics is assumed to happen at a different time scale (either faster or slower) than the effective reaction dynamics of either the slow or fast species. This implies that only the equilibrium of the movement is relevant for any dynamics occurring on the respectively slower scale.

(c) *Chemical conformations.* Our model can be extended in order to model different chemical conformations of chemical species instead of spatial compartments. For this, let $\mathcal{D}_i$ be the set of possible conformations of species i. Then any molecule of species i performs a Markov chain on $\mathcal{D}_i$ due to changes in conformation. Moreover, in this case for each type of reaction k its reaction rate $\Lambda_{k,\underline{d},\underline{d}'}^{CR}$ might then depend on all conformations of reacting and produced molecules $\underline{d} = (d_i)_{i \in \mathcal{I}}$ and $\underline{d}' = (d_i')_{i \in \mathcal{I}}$, respectively. For example, our results can be applied to Michaelis–Menten kinetics with multiple conformations of the enzyme and of the enzyme-substrate complex [see Kou (2008)].

(d) *Other density dependent processes.* The model can also be applied to other density dependent Markov chain models, such as epidemic or ecological models. Analogous results can also be made for density dependent stochastic differential models of stochastic population growth in spatially heterogeneous environments [see Evans et al. (2013)].

Conclusions. The main conclusion of our paper is the following algorithm for determining the dynamics of a spatial chemical reaction network: assume we are given a network of the form (2.1) in a spatial context, that is, (3.1) holds with reaction rates as in Assumption 3.1; introduce a (large) scaling constant N and rewrite the dynamics of all species in the form (3.3) (for some α_i's, η_i's and β_k's) assuming (2.8) and (3.2) hold (admittedly, the choice of N, α_i's and β_k's is rather an art than a science—for simplicity, we are assuming here that this step has been done already); in addition, suppose every species moves between compartments as in Assumption 3.4; the goal is to understand the dynamics of overall normalized sums of species over compartments as given in (3.5).

There are two cases: either the system is on a single-scale, that is, (2.9) holds, or the system is two-scale, that is, (2.11) holds. (We do not treat higher order scales in this paper.)

(i) In the single-scale case Theorem 3.7 applies. Essentially, one has to average all reaction rates of reactions affecting slow species over the equilibrium distribution of movement of all species. If reaction rates are given by mass action kinetics, Corollary 3.8 applies.

(ii) The two-scale case is considerably more complicated. Here, every species is either fast or slow and we have to consider all orders of the time scale of fast reactions and movement of fast and slow species. We call S_f the overall sum of normalized fast species and S_s the overall sum of normalized slow species. Consider the submatrices of slow and fast reactions, $\underline{\underline{\zeta}}^f$ and $\underline{\underline{\zeta}}^s$ from (2.13) and (2.15), respectively. A conserved quantity for the fast reaction subnetwork is a nontrivial element of the null-space of $(\underline{\underline{\zeta}}^f)^{\mathrm{T}}$.

(ii-a) If there is no conserved quantity, we can use Theorem 3.13. Here, there are up to four time scales to consider, movement of fast and slow species, the time scale of the fast reactions and the time scale of the slow species. In all cases, in order to determine the effective rate on S_s on a slower time scale, one has to average over the equilibrium of all higher time scales. Interestingly, if all slow species are continuous (i.e., have a deterministic process as a limit), it only matters if the fast species move faster or slower than fast reactions. The speed of the movement of slow species does not matter (see Corollary 3.17).

(ii-b) If there are conserved quantities for the fast reaction subnetwork, these conserved quantities can still change on a slower time scale. Here, we are assuming that this time scale is the same as the time scale of the slow species. The main difference from the case without conserved quantities is that on the fast time scale, the equilibria we need to consider for averaging are concentrated on a fixed conserved quantity. Then, basically, the conserved quantity can be treated as new species with its own dynamics (which changes on the timescale of slow species by assumption). Again, there are four cases to consider; see Theorem 3.23. Also, if all slow quantities are continuous, it only matters if the fast species move faster or slower than the fast reactions; see Corollary 3.25.

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