Scaling limits of spatial chemical reaction networks

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Abstract

We study the effects of fast spatial movement of molecules on the dynamics of chemical species in a spatial heterogeneous chemical reaction network. The reaction networks we consider are either single- or multi-scale. When the dynamics is on a single-scale, fast spatial movement has the single effect of averaging the dynamics over the distribution of all the species. However, when the dynamics is on multiple scales our findings show that the spatial movement of molecules has different effects depending on whether the movement of each type of species is faster or slower then the effective dynamics of the reaction system on this molecular type. We assume the reaction dynamics separates into a fast subsystem of reactions with a stable stationary probability measure and a slow subsystem on the time scale of interest. We obtain results for both the case when the fast subsystem is without and the case with conserved quantities, where a conserved quantity is a linear combination of fast species evolving on a slower timescale.

1 Introduction

When chemical species react, they are present in some (open or closed) system with a spatial dimension. Most mathematical 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 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\textsuperscript{1970}).

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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 et al. [2010]). Deterministic spatial models (reaction-diffusion PDEs) are insufficient for this purpose, since it is clear that 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 et al. [2011]). For effective computations a mesoscopic form of the full stochastic spatial reaction model is necessary. These are essentially compartment models in which the heterogeneous system is divided into homogeneous subsystems in each of which a set of chemical reactions are performed. The molecular species are distributed across the 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 timescale, 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 et al. [2012], Ball et al. [2006], Franz et al. [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 first obtain results in non-spatial systems. Lemma 2.8 gives asymptotics for a single-scale reaction network. In Lemma 2.15 this is extended to two-scale systems without conserved quantities on the fast time-scale. Lemma 2.18 and Lemma 2.20 give extensions to three-scale systems and systems with conserved quantities, which are needed later in spatial systems. Theorem 3.9 gives the results for spatial models of single-scale systems, and results for spatial models of two-scale systems are given by Theorem 3.14 in the absence of conserved quantities, and by Theorem 3.23 in the presence of conserved quantities on the fast time-scale of chemical reactions. We also include an example of a single-scale reaction network with a self-regulating gene in Example 2.11, and an illustrative example of a reaction network with two time-scales and no conserved quantities in Example 2.16. 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 $C(E)$ ($C_b(E)$, $C_c(E)$). In general, we write $\underline{x} := (x_k)_k$ for vectors and $\underline{\underline{x}} := (x_{ik})_{i,k}$ for matrices. In addition, $\underline{x}_i$ is the $i$th line and $\underline{x}_k$ is the $k$th column of $\underline{\underline{x}}$. We denote by $D(I; E)$ 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 formulate and give basic results on reaction networks in a single compartment. Although the non-spatial results are a special case of Theorems given in Kang and Kurtz [2013], we provide our own version of the proof here since our results in the spatial case can then be formulated and proved along similar lines.
Throughout, we consider a set \( \mathcal{I} \) of different chemical species, which react in \( \mathcal{K} \) reactions of the form
\[
(\nu_{ik})_{i \in \mathcal{I}} \rightarrow (\nu'_{ik})_{i \in \mathcal{I}}
\]  
with \( \nu = (\nu_{ik})_{i \in \mathcal{I}, k \in \mathcal{K}}, \nu' = (\nu'_{ik})_{i \in \mathcal{I}, k \in \mathcal{K}} \in \mathbb{Z}^{\mathcal{I} \times \mathcal{K}} \) and \( \nu_{ik} = l \) if \( l \) molecules of the chemical species \( i \) take part in reaction \( k \) and \( \nu'_{ik} = l \) if reaction \( k \) produces \( l \) molecules of species \( i \). In the chemical reaction literature \( \zeta = \nu' - \nu \) is called the stoichiometric matrix of the system, and \( \sum_{i \in \mathcal{I}} \nu_{ik} \) the order of reaction \( k \).

In addition, we set \( \zeta_k := (\zeta_{ik})_{i \in \mathcal{I}} \).

### 2.1 The Markov chain model

Denoting by \( X_i(t) \) the number of molecules of species \( i \) at time \( t \), we assume that \( (X(t))_{t \geq 0} \) with \( X(t) = (X_i(t))_{i \in \mathcal{I}} \) is solution of
\[
X_i(t) = X_i(0) + \sum_{k \in \mathcal{K}} \zeta_{ik} Y_k \left( \int_0^t \Lambda^\text{CR}_k(X(u)) du \right)
\]  
where the \( Y\)'s are independent (rate 1) Poisson processes and \( \Lambda^\text{CR}_k(X(u)) \) is the reaction rate of reaction \( k \) at time \( u, k \in \mathcal{K} \). We will assume throughout:

**Assumption 2.1** (Dynamics of un-scaled single compartment reaction network). The reaction network dynamics satisfies the following conditions:

(i) The reaction rate \( x \mapsto \Lambda^\text{CR}_k(x) \) is a non-negative locally Lipshitz, locally bounded function, \( k \in \mathcal{K} \). In order to avoid trivial arguments, we assume that \( \Lambda^\text{CR}_k \neq 0, k \in \mathcal{K} \).

(ii) For Poisson processes \( (Y_k)_{k \in \mathcal{K}} \), the time-change equation (2.2) has a unique solution.

**Remark 2.2** (Mass action kinetics and (2.2)).

1. Probably the most important chemical reaction kinetics is given by mass action. In this case,
\[
\Lambda^\text{CR}_k(x) = \kappa_k \prod_{i \in \mathcal{I}} \frac{x_i}{\nu_{ik}} ^{\nu_{ik} - 1}
\]  
for constants \( \kappa_k \). In other words, the rate of reaction \( k \) is proportional to the number of possible combinations of reacting molecules.

2. Solutions to (2.2) can be guaranteed by using e.g. [Ethier and Kurtz, 1986, Theorem 6.2.8]; see also their Remark 6.2.9(b).
2.2 The rescaled system

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. 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 $N \in \mathbb{N}$. The rescaled versions of the original model, under certain assumptions, have a limit as $N \to \infty$. We 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. In addition we rely heavily on the stochastic averaging methods that date back to Khasminskii, for which we follow its formalism in terms of martingale problems from [Kurtz 1992].

We rescale the system as follows. Consider the solution $(X^N(t))_{t \geq 0}$ of (2.2) with the chemical reaction rates $\Lambda_{k}^{CR}$ replaced by $\Lambda_{k}^{CR,N}$. For real-valued, non-negative $\alpha = (\alpha_i)_{i \in \mathcal{I}}, \beta = (\beta_k)_{k \in \mathcal{K}}, \gamma$, we denote the $(\alpha, \beta, \gamma)$-rescaled system by

$$V_i^N(t) := N^{-\alpha_i} X_i^N(N^\gamma t), \quad i \in \mathcal{I}.$$  (2.5)

We assume that $(\alpha, \beta, \gamma)$ is chosen so that, $V_i^N = O(1)$, $i \in \mathcal{I}$ for all time (a.s. does not go infinity in finite time, but also does not have a.s. zero limit for all time). Moreover, we will occasionally restrict to the case $\gamma = 0$ which can always be achieved when considering $\beta'_k = \beta_k + \gamma, k \in \mathcal{K}$. The reaction rates satisfy the following:

Assumption 2.3 (Dynamics of scaled single compartment reaction network). There exist locally Lipshitz functions $\lambda_{k}^{CR} : \mathbb{R}^\mathcal{I}_+ \to \mathbb{R}_+$, $k \in \mathcal{K}$ with

$$N^{-\beta_k} \Lambda_{k}^{CR,N} \left( (N^{\alpha_i} v_i)_{i \in \mathcal{I}} \right) \xrightarrow{N \to \infty} \lambda_{k}^{CR} (v)$$  (2.6)

uniformly on compacts. (In the sequel, we will without loss of generality assume that the convergence in (2.6) is actually an identity. Our results easily generalize by the assumed uniform convergence on compacts.)

Remark 2.4 (Mass action kinetics). Recall from Remark 2.2 the special form of mass action kinetics. Here, if $\alpha_i = 1$ for all $i \in \mathcal{I}$ and $\kappa_k = \kappa'_k N^{-<\Sigma_i \nu_i,k>+1}$ with $\beta_k = 1$ and some $\kappa'_k > 0$ for all $k \in \mathcal{K}$, then

$$N^{-\beta_k} \Lambda_{k}^{CR,N} \left( (N^{\alpha_i} v_i)_{i \in \mathcal{I}} \right) \xrightarrow{N \to \infty} \kappa'_k \prod_{i \in \mathcal{I}} v_i^{\nu_i k}.$$  

The polynomial on the right hand side is known in the literature for deterministic chemical reaction systems as the mass-action kinetic rate.
Let $N^{-\alpha}$ be the diagonal matrix with $i$th diagonal entry $N^{-\alpha_i}$. The $(\alpha, \beta, \gamma)$-rescaled system $V_i^N(t)$, given by $V_i^N(t) = (V_i^N(t))_{i \in I} = N^{-\alpha}X_i(N^\gamma)$, is a solution to the system of stochastic equations

$$V_i^N(t) = V_i^N(0) + \sum_{k \in K} N^{-\alpha_i} \zeta_{ik} Y_k \left( N^{\beta_k + \gamma} \int_0^t \lambda_k^{CR}(V_i^N(u))du \right). \quad (2.7)$$

In vector notation, we also write

$$V^N(t) = V^N(0) + \sum_{k \in K} N^{-\alpha} \zeta \cdot k Y_k \left( N^{\beta_k + \gamma} \int_0^t \lambda_k^{CR}(V^N(u))du \right). \quad (2.8)$$

Note that Assumption 2.1 ensures that this equation has a unique solution.

**Remark 2.5** (Generator of $V^N$). In our proofs, we rely on martingale techniques. For this reason, we frequently use the generator $L^N$ of the process $(V^N(t))_{t \geq 0}$. Here, $L^N : C_b(\mathbb{R}^I_+) \to C(\mathbb{R}^I_+)$ and for $g \in C_b(\mathbb{R}^I_+)$,

$$L^N g(v) = \sum_{k \in K} N^{\beta_k + \gamma} \lambda_k^{CR}(v) \left[ g(v + N^{-\alpha} \zeta_k^{CR}) - g(v) \right]. \quad (2.9)$$

Under our assumptions on the rescaling,

$$g(V^N(t)) - g(V^N(0)) - \int_0^t L^N g(V^N(u))du$$

is a (local) martingale for all $g \in C_b(\mathbb{R}^I_+)$.

### 2.3 Single scale systems

For $i \in I$, set

$$K_i := \{ k \in K : \zeta_{ik} \neq 0 \},$$

which is the set of reactions which change the number of species $i$. (Note that a reaction of the form $A + B \rightarrow A + C$ does not change the number of species $A$.) We say that a chemical reaction network (in one compartment) is a single scale system if $(\alpha, \beta, \gamma)$ from (2.4) satisfy

$$\max_{k \in K_i} \beta_k + \gamma = \alpha_i, \quad i \in I. \quad (2.10)$$

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

$$\zeta^*_{ik} = \lim_{N \to \infty} N^{-\alpha_i} N^{\beta_k + \gamma} \zeta_{ik}. \quad (2.11)$$

Then $\zeta^*$ is the matrix whose $i \in I, k \in K_i^*$ entries are $\zeta_{ik}$ and its $i \in I, k \in K_i - K_i^*$ entries are zero. Let $I_0$ be the subset of species with $\alpha_i = 0$, called the discrete species, and let $K_0^* = \cup_{i \in I_0} K_i^*$ (called the slow reactions). Let
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| Slow reactions | Fast reactions |
|----------------|---------------|
| $k \in K^*_o$, $\beta_k = 0$ | $k \in K^*_i$, $\beta_k > 0$ |

| Discrete species, $\alpha_i = 0, i \in I_0$ | Continuous species, $\alpha_i > 0, i \in I_*$ |
|-----------------------------------------------|-----------------------------------------------|
| $\zeta_{ik} \begin{cases} \in (0, \infty), & k \in K^*_i \\ = 0, & \text{else} \end{cases}$ | $\zeta_{ik} ^* = 0$ |
| $\zeta_{ik} = \zeta_{ik} ^*$ = 0 | $\zeta_{ik} ^* \begin{cases} \in (0, \infty), & k \in K^*_i \\ = 0, & \text{else} \end{cases}$ |

Table 1: We present an overview of the different sets and possibilities here in the case $\gamma = 0$. The set $I$ is split into discrete and continuous chemical species, while the set $K^*$ is split into slow and fast 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.

Let $I_*$ be the subset of species with $\alpha_i > 0$ (called the continuous species), and let $K^*_* = \cup_{i \in I_*} K^*_i$ (called the fast reactions), so $K^* = K^*_o \cup K^*_*$. Note that by definition $I_0$ and $I_*$ are disjoint, and by definition of $K^*_i$, consequently $K^*_o$ and $K^*_*$ are also disjoint. Then in the limit of the rescaled system the species indexed by $I_0$ are $Z_+^*$–valued (hence we call them discrete species), while the species indexed by $I_*$ are $R_+^*$–valued (hence called continuous species). See also Table 1 for an overview of our notions. We must assume the following:

**Assumption 2.6.** (Dynamics of the reaction network). For Poisson processes $(Y_k)_{k \in K^*_o}$, the time-change equation

$$V(t) = V(0) + \sum_{k \in K^*_o} \zeta_{ik}^* Y_k \left( \int_0^t \lambda_{k}^{CR}(V(u)) du \right) + \sum_{k \in K^*_*} \zeta_{ik}^* \int_0^t \lambda_{k}^{CR}(V(u)) du$$

(2.12)

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

**Remark 2.7** (Reformulation of (2.12)). Actually, the last display is shorthand notation for

$$V_i(t) = V_i(0) + \sum_{k \in K^*_o} \zeta_{ik}^* Y_k \left( \int_0^t \lambda_{k}^{CR}(V(u)) du \right), \quad i \in I_0,$$

$$V_i(t) = V_i(0) + \sum_{k \in K^*_*} \zeta_{ik}^* \int_0^t \lambda_{k}^{CR}(V(u)) du, \quad i \in I_*$$
which shows that species \( i \) is either driven by Poisson processes \( (Y_k(t))_{k \in \mathbb{K}^*} \) and thus discrete, or continuous.

**Lemma 2.8** (Convergence of single-scale reaction networks). Let \( V_N := (V_N(t))_{t \geq 0} \) be the vector process of rescaled species amounts for the reaction network which is the unique solution to (2.7). Assume that \( (\alpha, \beta, \gamma) \) from (2.5) satisfy (2.10), i.e. we are dealing with a single-scale system. Suppose \( V_N(0) \Rightarrow V(0) \) and the Assumptions 2.3 and 2.6 for the rescaled reaction network are satisfied. Then \( d_{Sk}(V_N, V) \xrightarrow{N \to \infty} 0 \) in probability (in particular, \( V_N \xrightarrow{N \to \infty} V \)), where \( V \) is the solution of (2.12).

**Remark 2.9.** The proof is an extension of the classical Theorem for convergence of Markov chains to solutions of ODEs, see Kurtz [1970], Kurtz [1981], or Ethier and Kurtz [1986]. For recent related results concerning convergence to piecewise deterministic processes, see Franz et al. [2012].

**Remark 2.10** (Approximately constant species). In (2.10), we could also have required that \( \leq \) holds instead of \( = \). However, all practical examples have the property that equality holds for all \( i \in \mathcal{I} \). Otherwise, for large \( N \), species for which \( \leq \) holds in (2.10) are approximately constant and may be neglected.

**Proof of Lemma 2.8.** Without loss of generality, we set \( \gamma = 0 \) in the proof. First, we will assume that the functions \( \lambda_{k}^{CR} \) are globally bounded and globally Lipshitz continuous. Then, we will use a truncation argument to show the assertion for local boundedness and local Lipshitz conditions. So, for \( \lambda_{k}^{CR} \leq \bar{\lambda} \), and \( \hat{Y}_k(t) := Y_k(t) - t \), we set

\[
\varepsilon_N(t) := \sup_{0 \leq u \leq t} \left| V_N^N(u) - V_N^N(0) - \sum_{k \in \mathbb{K}_*^c} \xi^*_k Y_k \left( \int_0^u \lambda_{k}^{CR}(V_N^N(s)) ds \right) \right| - \sum_{k \in \mathbb{K}_*^c} \xi^*_k \left( \int_0^u \lambda_{k}^{CR}(V_N^N(s)) ds \right)
\]

such that

\[
\varepsilon_N(t) \leq \sum_{k \in \mathbb{K} - \mathbb{K}^*} \sup_{0 \leq u \leq t} \left| N^{-\alpha} \xi^*_k Y_k \left( N^\beta_k \int_0^u \lambda_{k}^{CR}(V_N^N(s)) ds \right) \right| + \sum_{k \in \mathbb{K}_0^c} \sup_{0 \leq u \leq t} \left| \xi^*_k Y_k \left( N^{-\alpha} \lambda_{k}^{CR}(V_N^N(s)) ds \right) \right| \left( \int_0^u \lambda_{k}^{CR}(V_N^N(s)) ds \right) + \sum_{k \in \mathbb{K}_*^c} \sup_{0 \leq u \leq t} \left| N^{-\alpha} \xi^*_k \hat{Y}_k \left( N^\beta_k \int_0^u \lambda_{k}^{CR}(V_N^N(s)) ds \right) \right|.
\]

The first term on the right hand side converges to 0 in \( L^1 \) since \( \alpha_i > \beta_k \) for all \( i \in \mathcal{I}, k \in \mathbb{K} - \mathbb{K}^* \) and \( \lambda_{k}^{CR} \) is bounded by \( \bar{\lambda} \). The second and third term converge to 0 by (2.11) and boundedness of \( \lambda_{k}^{CR} \). Finally, the fourth term converges to 0...
since it corresponds to a sequence of martingales with bounded jumps whose quadratic variation converges to 0 (see Theorem A.1 in Kang et al. [2012]). Now we can write, for some global Lipschitz constant $L$, 
\[
\mathbb{E}[|\mathbf{V}^N(t) - \mathbf{V}(t)|] \leq \mathbb{E}[|\mathbf{V}^N(0) - \mathbf{V}(0)|] + \mathbb{E}[\varepsilon_N(t)] + \sum_{k \in K^*} \xi_k^* \mathbb{E}\left[Y_k\left(\int_0^t \lambda_k^{\text{CR}}(\mathbf{V}^N(u)) du\right)\right] 
\]

By Gronwall’s inequality we see that 
\[
\mathbb{E}[|\mathbf{V}^N(t) - \mathbf{V}(t)|] \xrightarrow{N \to \infty} 0.
\]

From this convergence in probability of one-dimensional distributions we easily conclude convergence in probability of finite-dimensional distributions and thus \(\mathbf{V}^N \xrightarrow{N \to \infty} \mathbf{V}\).

Next, we show tightness of \((\mathbf{V}^N)_N\). By standard arguments (see e.g. Theorem 4.8.2 and Corollary 4.8.6 of Ethier and Kurtz [1986]), we have to show the compact containment condition as well as the convergence of generators. For the compact containment condition, by considering \(\sup_{0 \leq u \leq t} |\mathbf{V}^N(u)|\) on the left hand side of (2.12), and bounding the integrands by \(L'' \sup_{0 \leq u \leq t} \mathbf{V}^N(u)\) on the right hand side for some \(L''\) (which is independent of \(N\)), we obtain that 
\[
\mathbb{E}\left[\sup_{0 \leq u \leq t} |\mathbf{V}^N(u)|\right] \leq \mathbb{E}[|\mathbf{V}(0)|] + L'' \mathbb{E}\left[\sup_{0 \leq u \leq t} |\mathbf{V}^N(u)|\right]
\]

implying by Gronwall’s inequality that \(\sup_N \mathbb{E}[\sup_{0 \leq u \leq t} |\mathbf{V}^N(u)|] < \infty\) and for every \(\varepsilon > 0\) there is \(K\) such that 
\[
\sup_N P\left(\sup_{0 \leq u \leq t} |\mathbf{V}^N(u)| > K\right) \leq \varepsilon.
\]

We are left with showing convergence of generators. For this, let \(\xi^*\) be the unit vector in direction \(i \in \mathcal{I}\), and 
\[
\lim_{N \to \infty} L^N f(\mathbf{w}) = \lim_{N \to \infty} \sum_{k \in K^*} N^\beta_k \lambda_k^{\text{CR}}(\mathbf{w}) \left[ f(\mathbf{w} + N^{-\alpha_k} \xi^*_k) - f(\mathbf{w}) \right] 
\]

\[
+ \sum_{k \in K^*} \lambda_k^{\text{CR}}(\mathbf{w}) \left[ f(\mathbf{w} + \sum_{i \in \mathcal{I}_k} \xi_i \xi^*_i) - f(\mathbf{w}) \right] 
\]

\[
+ \sum_{k \in K^*} N^\beta_k \lambda_k^{\text{CR}}(\mathbf{w}) \left[ f(\mathbf{w} + \sum_{i \in \mathcal{I}_k} N^{-\alpha_i} \xi_i \xi^*_i) - f(\mathbf{w}) \right]
\]

\[
= \sum_{k \in K^*} \lambda_k^{\text{CR}}(\mathbf{w}) \left[ f(\mathbf{w} + \xi^*_k) - f(\mathbf{w}) \right] + \sum_{k \in K^*} \lambda_k^{\text{CR}}(\mathbf{w}) \nabla f(\mathbf{w}) \cdot \xi^*_k
\]

\[
= L f(\mathbf{w})
\]
Note that – on the right hand side of the first equality – in the first sum that is over $k \in K - K^*$ for all $i \in I$ we have $\alpha_i > \beta_k$; in the second sum that is over $k \in K^*$ for all $i \in I_\ast$ we have $\alpha_i > 0$; and in the last sum over $k \in K^*$ in order to have (2.10) for all $i \in I_0$ we must have $\zeta_{ik} = 0$. Hence, we have shown convergence in probability of one-dimensional distributions as well as tightness of $(V^N)_N$, so from Lemma A2.1 of Donnelly and Kurtz [1996], we conclude that $d_{Sk}(V^N, V) \xrightarrow{N \to \infty} 0$ in probability.

Let now $\lambda_k^{CR}$ be only locally bounded and locally Lipshitz. By Assumption 2.6 for every $\varepsilon > 0$ there is a compact set $\Gamma_\varepsilon$ such that $P(\sup_{0 \leq u \leq t} |V(u)| \in \Gamma_\varepsilon) > 1 - \varepsilon$. Now, change $\lambda_k^{CR}$ to $\tilde{\lambda}_k^{CR}$, such that $\lambda_k^{CR} = \tilde{\lambda}_k^{CR}$ on $B^\varepsilon(\Gamma_\varepsilon)$ (the compact $\varepsilon$-ball around $\Gamma_\varepsilon$) and $\tilde{\lambda}_k^{CR}$ is globally bounded and globally Lipshitz, $k \in K$. Moreover, call $\tilde{V}^N$ and $\tilde{V}$ the (unique) processes in (2.7) and (2.12), with $\lambda_k^{CR}$ replaced by $\tilde{\lambda}_k^{CR}$. We have already shown that $d_{Sk}(\tilde{V}^N, \tilde{V}) \xrightarrow{N \to \infty} 0$ in probability. We can now write

$$\lim_{N \to \infty} P(d_{Sk}(V^N, V) > \varepsilon) \leq P(V \notin \Gamma_\varepsilon) + \lim_{N \to \infty} P(d_{Sk}(\tilde{V}^N, \tilde{V}) > \varepsilon) \leq \varepsilon$$

and the assertion is proved. \hfill \Box

Example 2.11. (Self-regulating gene). We give a simple example of a single-scale reaction network which leads to a piecewise deterministic solution; recall also Table 1. We consider a self-regulating gene which is modeled by the set of reactions

1: $G + P \xrightarrow{\kappa_1'} G' + P$
2: $G' \xrightarrow{\kappa_2'} G$
3: $G' \xrightarrow{\kappa_3'} G' + P$
4: $P \xrightarrow{\kappa_4'} \emptyset$

where $G$ is the inactivated gene, $G'$ is the activated gene (hence $G + G'$ is conserved by the reactions), and $P$ is the protein expressed by the gene. Here, 1 describes is 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. We consider $\underline{x} = (x_G, x_{G'}, x_P)$ and the reaction rates

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

and the scaling $\alpha_G = \alpha_{G'} = 0, \alpha_P = 1$, i.e. $I_0 = \{G, G'\}$ and $I_\ast = \{P\}$, as well as

$$\beta_1 = 0, \quad \beta_2 = 0, \quad \beta_3 = 1, \quad \beta_4 = 1,$$
$$\kappa_1' = N^{-1} \kappa_1, \quad \kappa_2' = \kappa_2, \quad \kappa_3' = N \kappa_3 \quad \kappa_4' = \kappa_4.$$
such that (compare with (2.6)), with \( v_G = x_G, v_{G'} = x_{G'}, v_P = N^{-1}x_P \),
\[
\begin{align*}
\lambda_{1}^{CR}(v) &= \kappa_1 v_G v_P, \\
\lambda_{2}^{CR}(v) &= \kappa_2 v_{G'}, \\
\lambda_{3}^{CR}(v) &= \kappa_3 v_{G'}, \\
\lambda_{4}^{CR}(v) &= \kappa_4 v_P.
\end{align*}
\]
Here \( K_G^* = K_{G'} = \{1, 2\} \) and \( K_P^* = K_P = \{3, 4\} \). In this example, the matrices \( \zeta \) and \( \zeta^* \) are given by
\[
\zeta = \zeta^* = G \begin{pmatrix} -1 & 1 & 0 & 0 \\ 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}.
\]

Moreover, according to Lemma 2.8, the limit \( (V(t))_{t \geq 0} \) of \( (V^N(t))_{t \geq 0} \) solves
\[
\begin{align*}
V_{G'}(t) &= V_{G'}(0) + Y_1 \left( \kappa_1 \int_{0}^{t} V_G(u) V_P(u) du \right) - Y_2 \left( \kappa_2 \int_{0}^{t} V_{G'}(u) du \right), \\
V_P(t) &= V_P(0) + \kappa_3 \int_{0}^{t} V_{G'}(u) du - \kappa_4 \int_{0}^{t} V_P(u) du.
\end{align*}
\]

2.4 Multi-scale systems

Two-scale systems

We say that the chemical network (2.1) is a two scale system if \((\alpha, \beta, \gamma)\) from (2.4) are such that: there is a partition of \( \mathcal{I} \) in (disjoint) \( \mathcal{I}^f \) (referred to as the set of fast species) and \( \mathcal{I}^s \) (which are called the slow species) such that, for some \( \varepsilon > 0 \),
\[
\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i + \varepsilon, \quad i \in \mathcal{I}^f \\
\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i, \quad i \in \mathcal{I}^s
\]
(2.13)

We will without loss of generality assume, as before, that \( \gamma = 0 \), and that our choice of \( N \) is such that \( \varepsilon = 1 \) in (2.13), so the relative change of fast species happens at rate \( O(N) \) and the relative change of slow species happens at rate \( O(1) \).

We first consider what happens on the single faster time scale \( N \, dt \). For each \( i \in \mathcal{I}^f \), let \( \mathcal{K}^f_i \subseteq \mathcal{K}_i \) be the set of reactions with \( \beta_k = \alpha_i + 1 \). Define
\[
\mathcal{K}^f = \{ k \in \mathcal{K} : \exists i \in \mathcal{I}^f, \beta_k = \alpha_i + 1 \},
\]
(2.14)
and a matrix \( \zeta^f \) with \( |\mathcal{I}^f| \) rows and \( |\mathcal{K}^f| \) columns defined by
\[
\zeta^f_{ik} = \lim_{N \to \infty} N^{-(\alpha_i+1)} N^{\beta_k} \zeta_{ik}, \quad i \in \mathcal{I}^f, k \in \mathcal{K}^f_i.
\]
(2.15)

This matrix identifies a subnetwork of reactions and their effective change on the faster time scale \( N \, dt \). Let \( I_i^f \subseteq \mathcal{I}^f \) be the subset of fast species for which \( \alpha_i = 0 \), and let \( \mathcal{K}_i^f = \bigcup_{i \in I_i^f} \mathcal{K}^f_i \) be the subset of reactions changing discrete valued species on this time scale. Let \( I_i^s \subseteq \mathcal{I}^f \) be the subset of fast species
Table 2: As in the single-scale case, the set $I$ is split into discrete and continuous chemical species. In addition, discrete and continuous species are either changed on the fast or slow timescale. (This means that $I^f, I^s, I^{f\circ}, I^{f\bullet}$ are disjoint sets.) The set of reactions is split into several categories, which can also overlap. Here, $k \in K^f_\circ$ is a reaction which changes a discrete species on the fast timescale etc. Note that such a reaction can as well change a continuous species on the slow timescale. The separation of fast and slow time scales is determined by (2.13) with $\varepsilon = 1$. As in Table 1, we mark the cells which finally determine the dynamics of the limiting object.
for which \( \alpha_i > 0 \), also called continuous species on the fast timescale and let \( \mathcal{K}^f = \bigcup_{i \in \mathcal{I}_f} \mathcal{K}^f_i \) be the subset of reactions changing continuous valued species on this time scale. Since \( \mathcal{I}_f \) and \( \mathcal{I}_s \) are disjoint in \( \mathcal{I} = \mathcal{I}_f \cup \mathcal{I}_s \), and since \( \beta_k \) is unique for each reaction in \( \mathcal{K}^f = \mathcal{K}_f \cup \mathcal{K}_s \), it follows that \( \mathcal{K}_f^f \) and \( \mathcal{K}_s^f \) are disjoint as well.

We next consider what happens on the single slower time scale \( dt \). For each \( i \in \mathcal{I} \), let

\[
\mathcal{K}^s = \{ k \in \mathcal{K} : \exists i \in \mathcal{I}^s, \beta_k = \alpha_i \},
\]

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

\[
\zeta_{ik} = \lim_{N \to \infty} N^{-\alpha_i} N^{\beta_k} \zeta_{ik}, \quad i \in \mathcal{I}^s, k \in \mathcal{K}^s.
\]

This matrix identifies the subnetwork of reactions and their effective change on the slower time scale \( dt \). Let \( \mathcal{I}_f^s \subseteq \mathcal{I}^s \) be the subset of (discrete) slow species for which \( \alpha_i = 0 \), and \( \mathcal{K}_f^s = \bigcup_{i \in \mathcal{I}_f^s} \mathcal{K}^s_i \) the subset of reactions changing discrete valued species on this time scale. Let \( \mathcal{I}_s^s \subseteq \mathcal{I} \) be the subset of (continuous) slow species for which \( \alpha_i > 0 \), and \( \mathcal{K}_s^s = \bigcup_{i \in \mathcal{I}_s^s} \mathcal{K}^s_i \) the subset of reactions changing continuous valued species on this timescale. As before, \( \mathcal{I}_f^s \) and \( \mathcal{I}_s^s \) being disjoint in \( \mathcal{I}^s = \mathcal{I}_f^s \cup \mathcal{I}_s^s \) implies that \( \mathcal{K}^s_f \) and \( \mathcal{K}^s_s \) are disjoint in \( \mathcal{K}^s = \mathcal{K}_f^s \cup \mathcal{K}_s^s \) 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 \( \beta_k \) 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 \( N dt \), i.e. 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.

**Remark 2.12** (No generator convergence for fast species). As in the single-scale case, we rely on martingale techniques and generators in our proofs. Here, the generator \( L^N \) of the process \( (\mathcal{V}^N(t))_{t \geq 0} \) is given for \( g \in \mathcal{C}_b([0, \infty]) \) by \( \mathcal{L} \). For chemical species \( i \in \mathcal{I}^f \) and \( k \in \mathcal{K}_i \), we have \( \beta_k = \alpha_i + 1 \). Hence, if \( g \) in \( \mathcal{L} \) depends on \( v_i \), the term

\[
N^{\beta_k} \lambda_k^{CR}(v) \left[ g(v + N^{-\alpha_i} \zeta_{ik}) - g(v) \right]
\]

does not converge for all \( v \) as \( N \to \infty \). However, if \( g \) only depends on \( (v_i)_{i \in \mathcal{I}^s} \), then \( \mathcal{L} \) is zero and it can be possible to obtain a proper dynamics of the slow species. This is the content of Lemma 2.15.

**Remark 2.13** (Conserved quantities). Our initial division of species into fast and slow may include some conserved quantities, that is, there may be linear combinations of fast species that remain unchanged on the faster time scale \( N dt \). Let \( \mathcal{N}((\zeta^f)^t) \) be the null space of \( (\zeta^f)^t \). 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 \( N dt \). Probably the most prominent example in this class is Michaelis–Menten kinetics.
(see e.g. Section 6.4 of Kang and Kurtz [2013] and Section 5.2 of Kang et al. [2012]). We will discuss this in forthcoming work, and will see this feature also appearing in all spatial models in the next section. 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 we assume that the basis for the species is such that $\dim(N((\zeta^f)^t)) = 0$.

Define the fast process to be $V^N_f = (V^N_f(t))_{t \geq 0}$, $V^N_f(t) = (V^N_i(t))_{i \in I^f}$ and the slow process to be $V^N_s = (V^N_s(t))_{t \geq 0}$, $V^N_s(t) = (V^N_i(t))_{i \in I^s}$. We now give necessary assumptions on the dynamics of $V^N_f$ on the time scale $Ndt$ conditional on $V^N_s(t) \equiv \nu^s$ being constant, on the dynamics of $V^N_s$, and on the overall behavior of $V^N$ in order to obtain a proper limiting dynamics of slow species, $V^N_s$.

**Assumption 2.14 (Dynamics of a two-scale reaction network).** Recall $\lambda^{CR}_k$ from (2.6). The two-scale reaction network (2.13) with effective change $\zeta^f$ as in (2.15) on time scale $N dt$ and $\zeta^s$ as in (2.17) on time scale $dt$ satisfies the following conditions:

(i) For each $\nu_s \in \mathbb{R}^{I^s}$ there exists a well defined process $V_{f|\nu_s}$ giving the dynamics of the fast species given the vector of slow species, that is the solution of

$$
V_{f|\nu_s}(t) = V_{f|\nu_s}(0) + \sum_{k \in K^f} \zeta^f_k Y_k \left( \int_0^t \lambda^{CR}_k(V_{f|\nu_s}(u), \nu_s) du \right)
$$

with a unique stationary probability measure $\mu_{\nu_s}(d\nu)$ on $\mathbb{R}^{I^f}$, such that

$$
\bar{\lambda}^{CR}_k(\nu_s) = \int_{\mathbb{R}^{I^f}} \lambda^{CR}_k(\nu_s, \nu) \mu_{\nu_s}(d\nu) < \infty, \quad k \in K^s. \tag{2.20}
$$

(ii) There exists a well defined process that is the solution of

$$
V_s(t) = V_s(0) + \sum_{k \in K^s} \zeta^s_k Y_k \left( \int_0^t \bar{\lambda}^{CR}_k(V_s(u)) du \right)
$$

with $\bar{\lambda}^{CR}_k$ given by (2.20).

(iii) There exists a locally bounded function $\psi : \mathbb{R}^{I^f} \to \mathbb{R}$, $\psi \geq 1$ such that $\psi(x) \to \infty$ as $x \to \infty$, and
(iii-a) for each $t > 0$
\[ \sup_N E \left[ \int_0^t \psi(V^N(u))du \right] < \infty; \]

(iii-b) for all $k \in K$
\[ \lim_{K \to \infty} \sup_{|x| > K} \frac{\lambda_{k}^{CR}(x)}{\psi(x)} = 0. \]

The following Lemma can also be read off from [Kang and Kurtz, 2013, Theorem 5.1]. The proof is again given here since proofs which follow are of a similar style.

**Lemma 2.15** (Convergence of two-scale reaction networks). Let $V^N := (V^N(t))_{t \geq 0}$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to (2.7) (or (2.8)). Assume that $(\alpha, \beta, \gamma = 0)$ satisfy (2.13) for some $I$, $I_s$ and $\varepsilon = 1$, i.e., we are dealing with a two-scale system. Suppose $V^N(0) \overset{N \to \infty}{\to} V_s(0)$ and the Assumptions 2.14 are satisfied. Then the process of rescaled amounts of the slow species $V^N_s(\cdot)$ converges weakly to the solution $V_s(\cdot)$ of (2.21) with rates given by (2.20) in the Skorokhod topology.

**Proof.** Let $\Gamma^N$ be the occupation measure of the rescaled process, i.e., the measure on $\mathbb{R}_{+}^{\mathbb{Z}} \times [0, \infty)$ given by
\[ \Gamma^N(D \times [0, t]) = \int_0^t 1_D(V^N(u))du \]

Then, condition (iii-a) in Assumption 2.14 implies that $\{\Gamma^N : N \in \mathbb{N}\}$ is relatively compact. Moreover, for any continuous function $g : \mathbb{R}_{+}^{\mathbb{Z}} \to \mathbb{R}$ satisfying $\lim_{K \to \infty} \sup_{|x| > K} \frac{|g(x)|}{\psi(x)} = 0$ we have (see, for example, Lemma 2.11 of Kang et al. [2012])
\[ \int_0^t g(V^N(u))du \overset{N \to \infty}{\to} \int_{\mathbb{R}_{+}^{\mathbb{Z}}} g(z)\Gamma(dz \times [0, \cdot]), \]

where $\Gamma$ is a weak limit point of $\{\Gamma^N\}$. By the same arguments as in the proof of Lemma 2.8, $\{V^N_s : N \in \mathbb{N}\}$ satisfies the compact containment condition and we let $\underline{V}_s$ denote a weak limit point. We next show $\Gamma$ and $\underline{V}_s$ are uniquely determined.

For any function $g \in C^1_1 : \mathbb{R}_{+}^{\mathbb{Z}} \to \mathbb{R}$ of the slow species the process
\[ M^N_s g(t) = g(V^N_s(t)) - \int_0^t L^N_s g(V^N(u))du \]
is a martingale, where by \(2.9\) \(L_s^N\) is the infinitesimal generator given by

\[
L_s^N g(v) = \sum_{k \in K^f_s} \lambda_k^{CR}(v) \left[ g(v_s) + \sum_{i \in I^f_s} \zeta_{ik} e_i + \sum_{i \in I^f_s - I^f_s} N^{-\alpha_i} \zeta_{ik} e_i \right] - g(v_s)
\]

\[
+ \sum_{k \in K^s} N^{-\beta_k} \lambda_k^{CR}(v) \left[ g(v_s) + \sum_{i \in I^s} N^{-\beta_i} \zeta_{ik} e_i + \sum_{\alpha_i > \beta_k} N^{-\alpha_i} \zeta_{ik} e_i \right] - g(v_s)
\]

\[
+ \sum_{k \in K - K^f_s} N^{-\beta_k} \lambda_k^{CR}(v) \left[ g(v_s) + \sum_{i \in I^s} N^{-\alpha_i} \zeta_{ik} e_i \right] - g(v_s)
\]

\[
\text{Let } L_s \text{ be a linear operator on functions } g \in C^1_c : \mathbb{R}^{[T]}_{+} \mapsto \mathbb{R} \text{ of the slow species given by}
\]

\[
L_s g(v) = \sum_{k \in K^f_s} \lambda_k^{CR}(v) \left[ g(v_s) + \zeta_k^s - g(v_s) \right] + \sum_{k \in K^s} \lambda_k^{CR}(v) \partial_{\zeta_k^s} g(v_s) \cdot \zeta_k^s
\]

\[(2.22)\]

Conditions (iii-a) and (iii-b) in Assumption 2.14 together with the definition of the slow submatrix \(\zeta^s\), imply that for any \(t > 0\)

\[
\lim_{N \to \infty} \mathbb{E} \left[ \sup_{u \in [0,t]} \left| M_s^{N, g}(u) - g(V_s^N(u)) - \int_0^t L_s g(V_s^N(u')) du' \right| \right] = 0,
\]

as well as

\[
\sup_N \mathbb{E} \left[ \int_0^t \left| L_s g(V_s^N(u)) \right| du \right] \leq \sup_N \mathbb{E} \left[ \int_0^t \psi(V_s^N(u)) du \right].
\]

The stochastic averaging theorem of Kurtz 1992 now implies that for any \(g \in C^1_c : \mathbb{R}^{[T]}_{+} \mapsto \mathbb{R}\) the process

\[
M_s^g(t) = g(V_s(t)) - \int_0^t L_s g(V_s(u)) \Gamma(du) \times du
\]

is a martingale. Furthermore, for any function \(g \in C^1_c : \mathbb{R}^{[T]}_{+} \times \mathbb{R}^{[T]}_{+} \mapsto \mathbb{R}\) of all species the dynamics on the time scale \(N dt\) is given by

\[
N^{-1} L_s^N g(v) = \sum_{k \in K^f_s} \lambda_k^{CR}(v) \left[ g(v_s) + \sum_{i \in I^f_s} \zeta_{ik} e_i + \sum_{i \in I^f_s - I^f_s} N^{-\alpha_i} \zeta_{ik} e_i, \right.
\]

\[
\left. v_s + \sum_{i \in I^s} N^{-\alpha_i} \zeta_{ik} e_i, \right] - g(v_s)
\]

\[
+ \sum_{k \in K^s} N^{-\beta_k} \lambda_k^{CR}(v) \left[ g(v_s) + \sum_{i \in I^s} N^{-\beta_i} \zeta_{ik} e_i + \sum_{\alpha_i > \beta_k} N^{-\alpha_i} \zeta_{ik} e_i, \right.
\]

\[
\left. v_s + \sum_{i \in I^s} N^{-\alpha_i} \zeta_{ik} e_i, \right] - g(v_s)
\]

\[
+ \sum_{k \in K - K^f_s} N^{-\beta_k} \lambda_k^{CR}(v) \left[ g(v_s) + \sum_{i \in I^s} N^{-\alpha_i} \zeta_{ik} e_i, \right.
\]

\[
\left. v_s + \sum_{i \in I^s} N^{-\alpha_i} \zeta_{ik} e_i, \right] - g(v_s).
\]
For any \( \psi_v \in \mathbb{R}^{[T]}_+ \) let \( L_{f|\psi_v} \) be a linear operator on functions \( g \in C_1^1 : \mathbb{R}^{[T]} \to \mathbb{R} \) of all species (effectively changing only the fast species) given by

\[
L_{f|\psi_v} g(v) = \sum_{k \in K_2^f} \lambda_k^{CR}(v) [g(v_f + \zeta_k^f, \psi_v) - g(v_f, \psi_v)] + \sum_{k \in K_2^s} \lambda_k^{CR}(v) \partial_{v_f} g(v_f, \psi_v) \cdot \zeta_k^f.
\]

Conditions (iii-a), (iii-b) in Assumption 2.14 together with the definition of the fast submatrix \( \zeta^s \) and the assumptions on the separation of time scales (2.13), imply with \( L_{f|\psi_v} g(\psi_v) \xrightarrow{N \to \infty} V_s \),

\[
\frac{1}{N}(g(V^N(t)) - g(V^N(0)) - \int_0^t L^N g(V^N(u))du) \xrightarrow{N \to \infty} \int L_{f|\psi_v} g(\psi_v)\Gamma(d\psi_v \times du)
\]

Uniform integrability of the left hand side implies the limit on the right hand side is a continuous martingale with paths of finite variation and hence is identically zero. Condition (i) in Assumption 2.14 now implies (see Example 2.3 in Kurtz [1992]) that \( \Gamma \) can be written as

\[
\Gamma(d\psi_v \times du) = \mu_{\psi_v}(d\psi_f)\Gamma^f(d\psi_s \times du)
\]

The martingale \( M^g_s(t) \) can be rewritten as

\[
M^g_s(t) = g(V_s(t)) - \int_0^t L_s g(V_s(u))\mu_{\psi_v}(d\psi_f)\Gamma^f(d\psi_s \times du)
\]

Since \( \Gamma^f(d\psi_v \times du) = \delta_{V_s(0)}(d\psi_v)du \), we see that \( \Gamma \) is unique, and since by (2.20) in Assumption 2.14 we can integrate the rates in the operator equation (2.22) with respect to \( \mu_{\psi_v} \),

\[
M^g_s(t) = g(V_s(t)) - \int_0^t \tilde{L}_s g(V_s(u))du
\]

with \( \tilde{L}_s \) a linear operator on functions \( g \in C_1^1 \) of the slow species given by

\[
\tilde{L}_s g(V_s) = \sum_{k \in K_2^s} \lambda_k^{CR}(V_s) [g(V_s + \zeta_k^s, \psi_v) - g(V_s, \psi_v)] + \sum_{k \in K_2^s} \lambda_k^{CR}(V_s) \nabla g(V_s) \cdot \zeta_k^s
\]

and rates \( \tilde{\lambda}_k^{CR} \) as in (2.20). Now, condition (ii) of Assumption 2.14 insures that the limit of the slow process \( V_s \) can be identified as the solution of the well-posed martingale problem, namely that \( V_s \) is the solution of

\[
V_s(t) = V_s(0) + \sum_{k \in K_2^s} \zeta_k^s Y_k \left( \int_0^t \tilde{\lambda}_k^{CR}(V_s(u))du \right) + \sum_{k \in K_2^s} \zeta_k^s \int_0^t \tilde{\lambda}_k^{CR}(V_s(u))du.
\]

In particular, \( V_s \) is uniquely determined. \( \square \)
Example 2.16 (Two time-scale kinetics in a single compartment). We present here an example of a second order reaction with two time-scales. In our example, two species $A$ and $B$ react and give species $C$. Importantly, $B$ is quickly transported into the system and degrades very fast. Precisely, we have the set of reactions

1: $A + B \xrightarrow{k_1'} C$
2: $\emptyset \xrightarrow{k_2'} B$
3: $B \xrightarrow{k_3'} \emptyset$.

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 $\mathbf{x} = (x_A, x_B)$ and consider the reaction rates as given by mass action kinetics,

$$\Lambda_{1}^{CR}(\mathbf{x}) = \kappa_1' x_A x_B, \quad \Lambda_{2}^{CR}(\mathbf{x}) = \kappa_2', \quad \Lambda_{3}^{CR}(\mathbf{x}) = \kappa_3' x_B.$$ (2.23)

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

$$\beta_1 = 1, \quad \beta_2 = 1, \quad \beta_3 = 1,$$ (2.24)
i.e. with

$$\kappa_1 = \kappa_1', \quad \kappa_2 = N^{-1}\kappa_2', \quad \kappa_3 = N^{-1}\kappa_3',$$ (2.25)

we write

$$\lambda_{1}^{CR}(\mathbf{v}) = \kappa_1 v_A v_B, \quad \lambda_{2}^{CR}(\mathbf{v}) = \kappa_2, \quad \lambda_{3}^{CR}(\mathbf{v}) = \kappa_3 v_B.$$ (2.26)

Now, the process $\mathbf{v}^N = (V_A^N, V_B^N)$ is given through (2.7) by

$$V_A^N(t) = V_A^N(0) - N^{-1}Y_1\left(N \int_0^t \kappa_1 V_A^N(u) V_B^N(u) du\right),$$
$$V_B^N(t) = V_B^N(0) - Y_1\left(N \int_0^t \kappa_1 V_A^N(u) V_B^N(u) du\right) + Y_2(N \kappa_2 t) + Y_3\left(N \int_0^t \kappa_3 V_B^N(u) du\right).$$ (2.27)

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 $\mathcal{K}^s \cap \mathcal{K}^f \neq \emptyset$) $\mathcal{K}_A = \{1\}, \mathcal{K}_B = \{1, 2, 3\}$ and $\mathcal{I}_f = \mathcal{I}^o_f = \{B\}, \mathcal{I}_s = \mathcal{I}^s = \{A\}$.

The matrices describing the reaction dynamics on both scales are

$$\zeta = \begin{pmatrix} 1 & 0 \\ 1 & -1 \end{pmatrix}, \quad \zeta^f = \begin{pmatrix} 1 & 1 \\ 1 & -1 \end{pmatrix}, \quad \zeta^s = \begin{pmatrix} 1 & 0 \\ 1 & -1 \end{pmatrix}.$$
where the three columns in $\zeta$ and $\zeta^f$ give reactions 1, 2 and 3 and $\zeta^s$ is a $1 \times 1$-matrix since there is only one reaction where $A$ is involved. Note that $\mathcal{N}((\zeta^f)^t) = \{0\}$, indicating that there are no conserved quantities on the fast time-scale. In order to study the dynamics of the slow species, $V_s := V_A$, we apply Lemma 2.15 and have to check Assumption 2.14. Here, for Poisson processes $Y_1, Y_2$ and $Y_3$, and fixed $V_s = V_A = v_A$, from (2.19),

$$V_{B|v_A}(t) - V_{B|v_A}(0) = -Y_1\left(\int_0^t \kappa_1 v_A V_B(u)du\right) + Y_2(\kappa_2 t) - Y_3\left(\int_0^t \kappa_3 V_B(u)du\right)$$

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 $\kappa_2$ 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

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

which gives the desired $\mu_{v_A}(dv_B)$. Hence, (2.20) gives

$$\lambda_{2}^{\text{CR}}(v_A) = \mathbb{E}[\kappa_1 v_A X] = \frac{\kappa_1 \kappa_2 v_A}{\kappa_3 + \kappa_1 v_A}.$$

Finally, Lemma 2.15 implies that in the limit $N \to \infty$, we obtain the dynamics

$$V_A(t) = V_A(0) - \int_0^t \lambda_{2}^{\text{CR}}(V_A(u))du = V_A(0) - \int_0^t \frac{\kappa_1 \kappa_2 V_A(u)}{\kappa_3 + \kappa_1 V_A(u)}du.$$

### Three time-scales

Chemical reaction networks with more than two time-scales also appear in the literature. One example is the heat shock response in *Escherichia coli*, introduced by Srivastava et al. [2001] and studied in detail by Kang [2012]. Here, we state an extension of Lemma 2.15 to reaction networks with more than two time-scales (see Kang et al. [2012]). Namely, suppose that for some $\gamma \in \mathbb{R}$ the parameters $\alpha, \beta$ in (2.5) and (2.6) 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 $\varepsilon_2 > \varepsilon_1 > 0$,

$$\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i + \varepsilon_2, \quad i \in \mathcal{I}^f$$

$$\max_{k \in \mathcal{K}_i} \beta_k + \gamma = \alpha_i + \varepsilon_1, \quad i \in \mathcal{I}^m$$

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

(2.28)

We will assume, as before, that $\gamma = 0$, and that our choice of $N$ is such that $\varepsilon_2 = 1$ in (2.28), so the relative change of fastest species $\mathcal{I}^f$ happens at rate $O(N)$, the relative change of the middle species $\mathcal{I}^m$ happens at rate $O(N^{\varepsilon_1})$, $0 < \varepsilon_1 < 1$, and the relative change of slow species $\mathcal{I}^s$ happens at rate $O(1)$.
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 $\bar{\zeta}_i^m$ with $|\mathcal{I}^m|$ rows and $|\mathcal{K}^m|$ columns defined by

$$
\bar{\zeta}_i^m = \lim_{N \to \infty} N^{-(\alpha_i + \varepsilon_1)} N^{\beta_k} \zeta_{ik}, \quad i \in \mathcal{I}^m, k \in \mathcal{K}_i^m. \tag{2.29}
$$

which identifies a subnetwork of reactions and their effective change on the middle time scale $N^{\varepsilon_1} dt$, and we let $\mathcal{I}^m \subseteq \mathcal{I}^m$ be the subset of middle species for which $\alpha_i = 0$, $\mathcal{I}_* \subseteq \mathcal{I}^m$ be the subset of fast species for which $\alpha_i > 0$, and finally $\mathcal{K}_o^m = \cup_{i \in \mathcal{I}_*} \mathcal{K}_i^m$, and $\mathcal{K}_o^m = \cup_{i \in \mathcal{I}_*} \mathcal{K}_i^m$. We now need an additional set of assumptions on the dynamics of $V_i^N$ on the time scale $N dt$ conditional on $(V_i^N(t), V_s^N(t)) = (\mu_m, \mu_s)$ being constant, and on the dynamics of $V_i^N$ on the time scale $N^{\varepsilon_1} dt$ conditional on $V_i^N(t) = \mu_s$ being constant.

**Assumption 2.17** (Dynamics of a three-scale reaction network). The three-time scale reaction network \((2.28)\) with effective change \((2.15)\) on time scale $N dt$, \((2.29)\) on time scale $N^{\varepsilon_1} dt$ and \((2.17)\) on time scale $dt$ satisfies the following conditions:

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

$$
V_f|_{(\mu_m, \mu_s)}(t) = V_f|_{(\mu_m, \mu_s)}(0) + \sum_{k \in \mathcal{K}_f^m} \bar{\zeta}_k^f Y_k \left( \int_0^t \lambda_k^{CR}(V_f|_{(\mu_m, \mu_s)}(u), \mu_m, \mu_s) du \right) + \sum_{k \in \mathcal{K}_f^m} \bar{\zeta}_k^f \int_0^t \lambda_k^{CR}(V_f|_{(\mu_m, \mu_s)}(u), \mu_m, \mu_s) du
$$

with a unique stationary probability measure $\mu_{(\mu_m, \mu_s)}(d\bar{\mu})$ on $\mathbb{R}_{+}^{|\mathcal{I}_s^m|}$, such that

$$
\bar{\lambda}_k^{CR}(\mu_m, \mu_s) = \int_{\mathbb{R}_{+}^{|\mathcal{I}_s^m|}} \lambda_k^{CR}(\bar{\mu}, \mu_m, \mu_s) \mu_{\mu_m}(d\bar{\mu}) < \infty, \quad k \in \mathcal{K}_m. \tag{2.30}
$$

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

$$
V_m|_{\mu_s}(t) = V_m|_{\mu_s}(0) + \sum_{k \in \mathcal{K}_m^m} \bar{\zeta}_k^m Y_k \left( \int_0^t \bar{\lambda}_k^{CR}(V_m|_{\mu_s}(u), \mu_s) du \right) + \sum_{k \in \mathcal{K}_m^m} \bar{\zeta}_k^m \int_0^t \bar{\lambda}_k^{CR}(V_m|_{\mu_s}(u), \mu_s) du,
$$

which has a unique stationary probability measure $\mu_{\mu_m}(d\bar{\mu}_m)$ on $\mathbb{R}_{+}^{|\mathcal{I}_m^m|}$, such that

$$
\bar{\lambda}_k^{CR}(\mu_s) = \int_{\mathbb{R}_{+}^{|\mathcal{I}_m^m|}} \bar{\lambda}_k^{CR}(\mu_m, \mu_s) \mu_{\mu_m}(d\bar{\mu}_m) < \infty, \quad k \in \mathcal{K}_s. \tag{2.31}
$$
(ii) There exists a well defined process that is the solution of (2.21) with \( \overline{\lambda}^\text{CR}_k \) given by (2.31).

(iii) see Assumption 2.14(iii).

The extension of Lemma 2.15 then becomes

**Lemma 2.18** (Convergence of three-scale reaction networks). Let \( V^N := (V^N(t))_{t \geq 0} \) be the vector process of rescaled species amounts for the reaction network which is the unique solution to (2.7) (or (2.8)). Assume that \((\alpha, \beta, \gamma = 0)\) satisfy (2.28) for some \( I^f, I^m, I^s \) and \( 0 < \varepsilon_1 < \varepsilon_2 = 1 \), i.e. we are dealing with a three time-scale system. Suppose \( V^N(0) \xrightarrow{N \to \infty} V(0) \) and the Assumptions 2.17 are satisfied. Then the process of rescaled amounts of the slow species \( V^N_{s} \) converges weakly to the solution \( V_s \) of (2.21) with rates given by (2.31) in the Skorokhod topology.

**Proof of Lemma 2.18** The proof follows the exact same lines of argument as before with only the following adjustment when identifying the limiting occupation measure \( \Gamma \). The assumptions on the separation of time scales (2.28) imply that for any function \( g \in C^1_c \) of all species \( v \)

\[
\frac{1}{N}(g(V^N(t)) - g(V^N(0)) - \int_0^t L^N g(V^N(u))du) \xrightarrow{N \to \infty} \int_{\mathbb{R}^{|I|} \times [0,t]} L_f(v_m, v_s)g(v)\Gamma(dv \times du) = 0
\]

where \( L_f(v_m, v_s) \) is a linear operator given by

\[
L_f(v_m, v_s)g(v) = \sum_{k \in K^f} \lambda^\text{CR}_k(v) \left[ g(v_f + \zeta^f_k, v_m, v_s) - g(v) \right] + \sum_{k \in K^I} \lambda^\text{CR}_k(v) \partial_{v_f} g(v) \cdot \zeta^f_k.
\]

Condition (i-a) in Assumption 2.17 implies \( \Gamma \) can be rewritten as

\[
\Gamma(dv \times du) = \mu^f(v_m, v_s)(dv_f)\Gamma^f(dv_m, dv_s) \times du
\]

An application of the same argument also implies that for any function \( g \in C^1_c \) of only species \( v_m \) and \( v_s \)

\[
\frac{1}{N\varepsilon_1}(g(V^N(t)) - g(V^N(0)) - \int_0^t L^N g(V^N(u))du) \xrightarrow{N \to \infty} \int_{\mathbb{R}^{|I^f|} \times [0,t]} L_m(v_m)g(v)\Gamma(dv_m \times du) = 0
\]
where $L_{m|\nu}$ is a linear operator given by

$$L_{m|\nu} g(\nu) = \sum_{k \in K_m^s} \lambda^\text{CR}_k(\nu) \left[ g(\nu_f, \nu_m + \zeta^m_k, \nu_s) - g(\nu) \right] + \sum_{k \in K_m^s} \lambda^\text{CR}_k(\nu) \partial_{\nu_m} g(\nu) : \zeta^m_k.$$  

Since

$$\int_{\Re^{|I|} \times [0,t]} L_{m|\nu} g(\nu) \Gamma(d\nu \times du) = \int_{\Re^{|I|} \times [0,t]} \tilde{L}_{m|\nu} g(\nu) \Gamma_f(d(\nu_m, \nu_s) \times du)$$

where $\tilde{L}_{m|\nu}$ is the same linear operator as $L_{m|\nu}$ except with rates $\lambda^\text{CR}_k$ replaced by $\tilde{\lambda}^\text{CR}_k$ from (2.30), now condition (i-b) in Assumption 2.17 implies that $\Gamma_f$ can be rewritten as

$$\Gamma_f(d(\nu_m, \nu_s) \times du) = \mu_{\nu_s}(d\nu_m) \Gamma_{f,m}(d\nu_s \times du)$$

Since $\Gamma_f(m(d\nu_s \times du) = \delta_{\nu_n}(0)(d\nu_s)du$, the rest of the proof now proceeds as in that of Lemma 2.15 except with the rates $\tilde{\lambda}^\text{CR}_k$ in the definition of the operator $\tilde{L}_s$ on functions $g \in C^1_s$ of the slow species now given by

$$\tilde{\lambda}^\text{CR}_k(\nu_s) = \int_{\Re^{|I|}} \int_{\Re^{|I|}} \lambda^\text{CR}_k(\nu_f, \nu_m, \nu_s) \mu(\nu_m, \nu_s)(d\nu_f) \mu_{\nu_s}(d\nu_m).$$

**Conserved quantities**

We turn now to the problem of conserved quantities. Suppose we have a two-scale reaction network with $\dim(N((\zeta^f)^f)) = n^f > 0$. Then there exists linearly independent $\mathbb{Z}$-valued vectors $\theta^c_i = (\theta_1^c, \ldots, \theta_{|I|}^c)$, $i = 1, \ldots, n^f$ such that $t \mapsto \langle \theta^c_i, V_f|\nu_s(t) \rangle$ with $V_f|\nu_s$ from (2.19) is constant. In other words, the change of $\langle \theta^c_i, V_f^N(t) \rangle$ on the time scale $N dt$ goes to 0. We set $\Theta_f := (\theta^c_i)_{i=1,\ldots,n^f}$, i.e.

$$N((\zeta^f)^f) = \text{span}(\Theta_f)$$

and note that the construction implies that $\theta^c_i$ has a unique parameter $\alpha_i$ associated with it, which we denote by $\alpha_{c_i}, i = 1, \ldots, |\Theta_f|$.  

We assume that the effective changes for these combinations are on the time scale $dt$, i.e. $\sup_{k \in K_c} (\theta_{c_i}^c, \zeta_{c_i}^s) \neq 0 \beta_k \leq \alpha_{c_i}$. 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 $\tilde{V}_f^N = (V_i^N)_{i=1,\ldots,|\Theta_f|}$ be the vector of rescaled conserved quantities. For each $i = 1, \ldots, |\Theta_f|$, let $K_{\tilde{V}_i}$ be the set of slow reactions such that $\beta_k =
α_{c_i} and \langle \theta_{c_i}, \zeta_k \rangle \neq 0, and let \mathcal{K}^c := \bigcup_{i=1}^{\lvert \Theta_f \rvert} \mathcal{K}^c_{\theta_{c_i}}. Note that \mathcal{K}^c \cap \mathcal{K}^f = \emptyset by construction. Let \zeta^c be the matrix with \lvert \Theta_f \rvert rows and \lvert \mathcal{K}^c \rvert columns defined by

\begin{equation}
\zeta_{\theta_{c_i}k}^c = \lim_{N \to \infty} N^{-\alpha_{c_i}} N^{\beta_k} \langle \theta_{c_i}, \zeta_k \rangle, \quad i = 1, \ldots, \lvert \Theta_f \rvert, k \in \mathcal{K}^c_i. \tag{2.33}
\end{equation}

Let \Theta^c_{\circ} \subseteq \Theta^c be the subset of conserved quantities for which \alpha_{c_i} = 0, \mathcal{K}^c_{\circ} = \bigcup_{\theta_{c_i} \in \Theta^c_{\circ}} \mathcal{K}^c_{\theta_{c_i}}. Let \Theta^c_{\bullet} \subseteq \Theta^c be the subset of conserved quantities for which \alpha_{c_i} > 0, \mathcal{K}^c_{\bullet} = \bigcup_{\theta_{c_i} \in \Theta^c_{\bullet}} \mathcal{K}^c_{\theta_{c_i}}. As before \mathcal{K}^c_{\circ} and \mathcal{K}^c_{\bullet} are disjoint. We will also make the additional assumption that

\begin{equation}
\mathcal{K}^c \cap \mathcal{K}^s = \emptyset \tag{2.34}
\end{equation}

In other words reactions that effectively change the conserved quantities on the time scale \(t\) make no effective change on the slow species on this time scale, and vice versa. This will be the case in the compartment models of multi-scale reaction networks we consider in the next section.

We can now extend our results under obvious modifications of our earlier assumptions, as given 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 2.19** (Dynamics of a two-scale reaction network with conserved quantities). The two-scale reaction network \(2.13\) with effective change \(2.15\) on time scale \(N \, dt\) and \(2.17\) and \(2.33\) on time scale \(dt\) satisfies the following conditions:

1. For each \((v_s, v_c) \in \mathbb{R}_+^{\lvert I_f \rvert + \lvert \Theta_f \rvert}, v_c := (v_{c_i})_{i=1, \ldots, \lvert \Theta_f \rvert},\) there exists a well defined process that is the solution of

\begin{equation}
V_f_{|V_s, v_c}(t) = V_f_{|V_s, v_c}(0) + \sum_{k \in \Theta^c_{\circ}} \zeta^f_k Y_k \left( \int_0^t \lambda^{CR}_k (V_f_{|V_s, v_c}(u), v_c) du \right) + \sum_{k \in \Theta^c_{\bullet}} \zeta^f_k \int_0^t \lambda^{CR}_k (V_f_{|V_s, v_c}(u), v_c) du
\end{equation}

which satisfies the constraints

\begin{equation}
\langle \theta^c_{\circ}, V_f_{|V_s, v_c} \rangle = v_{c_i}, \quad \theta^c_{\circ} \in \Theta^c, \tag{2.35}
\end{equation}

and which has a unique stationary probability measure \(\mu_{(v_s, v_c)}(d\bar{z})\) on \(\mathbb{R}_+^{\lvert I_f \rvert}\) (concentrated on the linear subspace such that \(2.35\) is satisfied), such that

\begin{equation}
\bar{\lambda}^{CR}_k (v_s, v_c) = \int_{\mathbb{R}_+^{\lvert I_f \rvert}} \lambda_k^{CR}(z, v_c) \mu_{(v_s, v_c)}(d\bar{z}) < \infty, \quad k \in \mathcal{K}^s. \tag{2.36}
\end{equation}
satisfying (2.13), based on the joint generator for a two-scale reaction network, with 

\[ V_{c}(t) = V_{c}(0) + \sum_{k \in K_{s}} \zeta_{k}^{c} Y_{k} \left( \int_{0}^{t} \lambda_{k}^{CR}(V_{c}(u),V_{c}(u))du \right) \]

\[ + \sum_{k \in K_{s}^{*}} \zeta_{k}^{c} \int_{0}^{t} \lambda_{k}^{CR}(V_{c}(u),V_{c}(u))du, \]

i.e.

\[ V_{c}(t) = V_{c}(0) + \sum_{k \in K_{s}} \zeta_{k}^{c} Y_{k} \left( \int_{0}^{t} \lambda_{k}^{CR}(V_{c}(u),V_{c}(u))du \right) \]

\[ + \sum_{k \in K_{s}^{*}} \zeta_{k}^{c} \int_{0}^{t} \lambda_{k}^{CR}(V_{c}(u),V_{c}(u))du, \]

where the rates in both (2.21) and (2.37), (2.38) are given by (2.36).

(iii) same as in Assumptions 2.14.

**Lemma 2.20** (Convergence of two-scale reaction networks with conserved fast quantities). Let \( (V_{N}^{N}(t), t \geq 0) \) be the process of rescaled species amounts for a two-scale reaction network, with \( \alpha, \beta \) satisfying (2.13), \( \gamma = 0, \varepsilon = 1 \), and with conserved quantities \( \Theta = (\Theta_{i})_{1 \leq i \leq |\Theta|} \) (which is a basis of the null space of \( ((\zeta_{ik})_{i \in I_{f},k \in K_{f}^{e}}) \) whose effective change is on time scale \( dt \) satisfying (2.34)). Suppose \( V_{N}^{N}(0) \xrightarrow{N \to \infty} V(0) \) and Assumptions 2.14 are satisfied. Then, we have joint convergence of the process of rescaled amounts of the slow and conserved quantities \( (V_{N}^{N}(\cdot),V_{N}^{N}(\cdot)) \xrightarrow{N \to \infty} (V_{s}(\cdot),V_{c}(\cdot)) \) in the Skorohod topology, with \( V_{s} \) the solution of (2.21) and \( V_{c} \), the solution of (2.37) with rates given by (2.36).

**Proof.** The proof proceeds in exactly the same way as that of Lemma 2.15 except that now we have the martingale problem, for functions \( g \in C_{b}^{1} \) of both slow and conserved quantities \( (v_{s};v_{c}) \)

\[ M_{N}^{N_{s},g}(t) = g(V_{s}^{N}(t);V_{c}^{N}(t)) - \int_{0}^{t} L_{s,c}^{N}g(V_{s}^{N}(u))du, \]

based on the joint generator

\[ L_{s,c}^{N}g(v) = \sum_{k \in K_{s}} \lambda_{k}^{CR}(v) \left[ g (\sum_{i \in I_{s}} \zeta_{ik}^{c} + \sum_{\alpha_{i} > 0} N^{-\alpha_{i}} \zeta_{ik}^{c}) + \sum_{g_{i} \in \Theta_{i}^{f}} N^{-\alpha_{i}} (\zeta_{ik}^{c})_{g_{i}^{c}} - g(v_{s};v_{c}) \right] \]

\[ + \sum_{k \in K_{s}^{*}} N^{\beta_{k}} \lambda_{k}^{CR}(v) \left[ g (\sum_{i \in I_{s}^{*}} \zeta_{ik}^{c} + \sum_{\alpha_{i} > \beta_{k}} N^{-\alpha_{i}} \zeta_{ik}^{c}) + \sum_{g_{i} \in \Theta_{i}^{f}} N^{-\alpha_{i}} (\zeta_{ik}^{c})_{g_{i}^{c}} - g(v_{s};v_{c}) \right] \]
\[ + \sum_{k \in K^s_0} \lambda_k^{CR}(v) \left[ g(v_s + \sum_{i \in I^s, \alpha_i > 0} N^{-\alpha_i} \zeta_{ik} e_i; v_c + \sum_{g_i \in \Theta'_L} (\theta^{g_i} \zeta_k) e_{g_i}^c + \sum_{g_i \in \Theta'_L - \Theta'_L} N^{-\alpha_i} (\theta^{g_i} \zeta_k) e_{g_i}^c \right] - g(v_s; v_c) \]

\[ + \sum_{k \in K^c} N^\beta_k \lambda_k^{CR}(v) \left[ g(v_s + \sum_{i \in I^c, \alpha_i > \beta_k} N^{-\alpha_i} \zeta_{ik} e_i; v_c + \sum_{g_i \in \Theta'_L} (\theta^{g_i} \zeta_k) e_{g_i}^c + \sum_{g_i \in \Theta'_L - \Theta'_L} N^{-\alpha_i} (\theta^{g_i} \zeta_k) e_{g_i}^c \right] - g(v_s; v_c) \]
Identifying the limiting occupation measure \( \Gamma \) in terms of \( \mu_{\mathbf{v},\mathbf{v}_c} \) proceeds exactly in the same way as in Lemma 2.15 and the above can be rewritten as

\[
M^g_{s,c}(t) = g(V_s(t);V_c(t)) - \int_0^t \bar{L}_{s,c}g(V_s(u);V_c(u))du
\]

where \( \bar{L}_{s,c} \) is the linear operator obtained by replacing the rates \( \lambda^{CR}_k \) in (2.39) by averaged rates \( \bar{\lambda}^{CR}_k \) from (2.36). In addition to identifying \( V_s \) by (2.21), condition (ii) insure that \( V_c \) can also be identified as the solution of the well-posed martingale problem given by (2.37).

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, in which case (2.34) is trivially satisfied. We then only have the dynamics of conserved quantities following (2.38) with the rates \( \bar{\lambda}^{CR}_k \) obtained using the stationary probability measure for the fast species \( \mu_{\mathbf{v}_c}(\cdot) \) 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 (2.21) with \( V_c(u) = \mathbf{v}_c, u > 0 \). 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 the heterogeneous reaction network models, and we have now provided all of the tools we need for our results on models with movement between compartments.

3 Chemical reactions in multiple compartments

In this section, we assume that the chemical system is separated into a set of \( D \) compartments, and chemical species can migrate within these compartments. For species \( i \in \mathcal{I} \), movement happens from compartment \( d' \) to \( d'' \) at rate \( \Lambda^{M}_{i,d',d''} \).

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 \( (\mathbf{X}(t))_{t \geq 0} \) with \( \mathbf{X}(t) = (X_{id}(t))_{i \in \mathcal{I}, d \in \mathcal{D}} \) is solution of

\[
X_{id}(t) = X_{id}(0) + \sum_{k \in \mathcal{K}} \zeta_{ik} Y_{kd} \left( \int_0^t \Lambda^{CR}_{kd}(\mathbf{X}_d(u))du \right) + \sum_{d',d'' \in \mathcal{D}} (\delta_{d',d} - \delta_{d'',d}) Y_{d',d''} (\mathbf{X}_{id}(u)du)
\]

(3.1)

where \( \mathbf{X}_d = (X_{id})_{i \in \mathcal{I}} \) and the \( Y \)'s are independent (rate 1) Poisson processes. We now assume:

**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 \( \Lambda^{CR}_{kd} \neq 0 \).
(ii) For Poisson processes \((Y_{kd})_{k \in K, d \in D}\) and \((Y_{i',d',d''})_{i \in I, d', d'' \in D}\), the time-change equation (3.1) has a unique solution.

Remark 3.2 (Sum totals of chemical species). We stress that for \(X_i(t) := \sum_{d \in D} X_{id}(t)\),

\[
X_i(t) = X_i(0) + \sum_{k \in K} \gamma_k \sum_{d \in D} Y_{kd}(\int_0^t \Lambda_{CR, kd}(X_d(u))du)
\]

for some independent (rate 1) Poisson processes \((Y_k)_{k \in K}\). However, since \(\sum_{d \in D} \Lambda_{CR, kd}(X_d(s))\) generally depends on all entries in \(X(s)\), \(((X_i(t))_{i \in I})_{t \geq 0}\) is not a Markov process.

3.2 The rescaled system

Consider the solution of (3.1) with the chemical reaction rates \(\Lambda_{CR, kd}\) and movement rates \(\Lambda_{M, i',d',d''}\) replaced by \(\Lambda_{CR, N, kd}\) and \(\Lambda_{M, N, i',d',d''}\), respectively. For real-valued, non-negative \(\alpha = (\alpha_i)_{i \in I}, \beta = (\beta_k)_{k \in K}, \gamma, \eta = (\eta_i)_{i \in I}\),

we denote the \((\alpha, \beta, \gamma, \eta)\)-rescaled system by

\[
V_{id}^N(t) := N^{-\alpha_i} X_{id}^N(N^\gamma t), \quad i \in I, d \in D.
\]

Again, we will restrict to the case \(\gamma = 0\).

Assumption 3.3 (Dynamics of scaled multiple compartment reaction network). In addition to Assumption 2.3 within each compartment, there exist \(\lambda_{M, i',d',d''}, \gamma, i \in I, d', d'' \in D\) with

\[
N^{-m} \lambda_{M, N, i',d',d''} \xrightarrow{N \to \infty} \lambda_{M, i',d',d''} \tag{3.2}
\]

Again, we will without loss of generality assume that this convergence is actually an identity.

The \((\alpha, \beta, \gamma, \eta)\)-rescaled system \(V^N(t) = N^{-2} X(N^\gamma t)\) is the unique solution to the system of stochastic equations

\[
V_{id}^N(t) = V_{id}^N(0) + \sum_{k \in K} N^{-\alpha_i} \gamma_k Y_{kd}(N^{\beta_k + \gamma} \int_0^t \Lambda_{CR, kd}(V_d^N(u))du)
\]

\[
+ \sum_{d',d'' \in D} N^{-\alpha_i} (\delta_{d',d} - \delta_{d',d''}) Y_{d',d'',i}(N^{\alpha_i + \eta_i + \gamma} \int_0^t \Lambda_{M, N, i',d',d''} V_{id}^N(s)) \tag{3.3}
\]
In addition, (compare with Remark 3.2), we set
\[ S^N = (S^N_i)_{i \in I} \text{ with } S^N_i := \sum_{d \in D} V_{id}^N, \] (3.4)
i.e. \( S^N_i \) solves
\[ S^N_i(t) = S^N_i(0) + \sum_{k \in K} N^{-\alpha_i} \zeta_{ik} \sum_{d \in D} Y_{kd} \left( N^{\beta_k + \gamma} \int_0^t \lambda_{kd}^{CR} (V_d^N(u)) du \right). \] (3.5)

**Remark 3.4** (Heterogeneity of the Reaction Network). Our set-up does not preclude the option that different compartments may have different reaction networks all together. This is taken care of by accounting for all the possible reactions in the stoichiometric matrix \( \zeta \) and setting the individual compartment rates \( \lambda_{kd}^{CR} \) to zero in desired compartments.

**Remark 3.5** (Generator of \( V^N \)). The generator of \( (V^N(t))_{t \geq 0} \) is given by
\[ L^N f(v) = \sum_{d \in D} \sum_{k \in K} N^{\beta_k + \gamma} \lambda_{kd}^{CR} (v_d) \left[ f(v + N^{-\alpha_i} \zeta^d_k) - f(v) \right] \]
\[ + \sum_{d', d'' \in D} \sum_{i \in I} N^{\gamma_i} \lambda_{i,d',d''}^M \zeta_{id} \zeta_{id'} v_{d'} \left[ f(v + N^{-\alpha_i} \zeta^M_{i,d',d''}) - f(v) \right] \]
where \( \zeta^d_k \) is the \( |I| \times |D| \)-matrix with \( d \)th column \( \zeta^d_k \) and zero otherwise, and \( \zeta^M_{i,d',d''} \) is the \( |I| \times |D| \)-matrix with its \( i \)th row \( \zeta_i \) consisting of \( \zeta_{id''} = 1, \zeta_{id'} = -1 \) and zeros everywhere else.

### 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 \( (3.10) \) holds within every compartment. The sets \( I, I_o, I_s \) and \( K, K_s, K_o \) and \( \zeta^* \) are used as in Section 2.
We will assume that movement of species is fast, i.e. \( \eta_i > 0, i \in I \). We first make an assumption about the movement dynamics.

**Assumption 3.6** (Equilibrium for movement). For each species \( i \in I \), the movement Markov chain, given through the jump rates \( \lambda_{i,d',d''}^M \) from \( d' \) to \( d'' \), has a unique stationary probability distribution. (This is the case if the Markov chain is irreducible.) We denote this stationary probability distribution by \( (\pi_i(d))_{d \in D} \).

**Lemma 3.7** (Movement equilibrium). Let Assumption 3.4 hold.

1. Let \( i \in I \) be such that \( \alpha_i = 0 \) (i.e. \( i \in I_o \)). Consider the Markov chain of only the movement of molecules of species \( i \), i.e. the solution of
\[ V_{id}(t) = V_{id}(0) + \sum_{d', d'' \in D} (\delta_{d',d} - \delta_{d',d''}) \lambda_{i,d',d'',i} \left( \int_0^t \lambda_{i,d',d'',id}^M V_{id'}(u) du \right) \]
started with \( \sum_{d \in D} V_{id}(0) = s_i \). Then, the unique equilibrium probability distribution of this Markov chain is given as the multinomial distribution with parameters \( (s_i; (\pi_i(d))_{d \in D}) \).
2. Let \( i \in \mathcal{I} \) be such that \( \alpha_i > 0 \) (i.e. \( i \in \mathcal{I}_a \)). Consider the limiting deterministic process of only the movement of molecules of species \( i \), i.e. the solution of

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

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 \( \mathbf{P} \) and by \( \mathbb{E} \) the corresponding expectation operator. From the above, \( \mathbf{P} \) is a product of multinomial and point mass distributions.

**Proof.** The result is a simple consequence of Lemma 2.20 with sum \( S = \sum_{d \in \mathcal{D}} V_{id} \) the conserved species and \( K^s = \emptyset \).

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

(i) For Poisson processes \( (Y_k)_{k \in K^s} \), the time change equation

\[
S(t) = S(0) + \sum_{k \in K^s} \zeta_k^* Y_k \left( \int_0^t \lambda_k^{CR}(S(u)) du \right) + \sum_{k \in K^s} \zeta_k^* \int_0^t \lambda_k^{CR}(S(u)) du
\]

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

\[
\lambda_k^{CR}(s) := \mathbb{E}_s \left[ \sum_{d \in \mathcal{D}} \lambda_{kd}^{CR}(V_d) \right].
\]

(ii) same as (iii) in Assumption 2.14 for all \( d \in \mathcal{D} \).

**Theorem 3.9** (Heterogeneous single-scale system). Let \( \underline{V}_N := (V_N(t))_{t \geq 0} \) be the vector process of rescaled species amounts for the reaction network which is the unique solution to (3.3). Assume that \( (\alpha, \beta, \gamma) = (0) \) satisfy (2.10), i.e. we are dealing with a single-scale system within compartments and \( \eta_i = \eta > 0 \) for all \( i \in \mathcal{I} \). Set \( S_N(t) = (S_N(t))_{t \in \mathcal{I}} \) with \( S_i(t) := \sum_{d \in \mathcal{D}} V_{id}(t) \). Suppose \( S_N(0) \xrightarrow{N \to \infty} \underline{S}(0) \) and that Assumptions 3.6 and 3.8 for the rescaled reaction network hold. Then, the process of rescaled species sums, \( S_N(\cdot) \) converges weakly to the unique solution \( \underline{S}(\cdot) \) of (3.6) in the Skorohod topology.
Proof of Theorem 3.9. In the heterogeneous reaction network we have $|\mathcal{I}| \times |\mathcal{D}|$ species, one for each type and each compartment, with rescaled amounts $V^N_{id}$. 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 $\Lambda_{M_{i,d',d''},d,d'' \in \mathcal{D}}$. This set of reactions together with the original reactions within each compartment give an overall network in which all the species $V^N_{id}$ 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 $S^N_i := \sum_{d \in \mathcal{D}} V^N_{id}, i \in \mathcal{I}$. 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 $\zeta^*$.

In order to apply Lemma 2.20 set $\varepsilon := \eta$ and we need to check Assumptions 2.19. In this special case that 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 $s$ has a unique stationary probability measure $P_s$, which is concentrated on $\sum_{d \in \mathcal{D}} v_{id} = s_i$. This is exactly implied by Lemma 3.7 under Assumption 3.6. Conditions (ii) and (iii) in Assumptions 2.19 is assumed in the statement of the Theorem.

Let us consider the dynamics of the conserved quantities. Here, $\theta^c_i = (v_{i,j})_{j \in \mathcal{I}, d \in \mathcal{D}}$ is the $i$th 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 $\zeta^c = \zeta^*$ with overall rate equal to a sum of the individual compartment rates.

Since the equilibrium for the movement dynamics $P_\pi$ is given by

$$P_\pi(dv) = \prod_{s \in \mathcal{I}} \left( \frac{s_i}{v_i \cdots v_i[|\mathcal{D}|]} \right) \pi_i(1)^{v_i1} \cdots \pi_i(|\mathcal{D}|)^{v_i[|\mathcal{D}|]} \prod_{s \in \mathcal{I}} \delta_{\pi_i(1)s_i}(dv_i1) \cdots \delta_{\pi_i(|\mathcal{D}|)s_i}(dv_i[|\mathcal{D}|]),$$

the averaged rates for reaction dynamics in each compartment under the equi-
Equilibrium probability measure as considered in (3.7) are exactly of the form (2.36),

\[
\lambda_{CR}^k(s) = \sum_{d \in D} \kappa_{kd} \prod_{i \in I} \left( \frac{s_i}{\nu_{ik}} \right)^{V_i(d)} \prod_{i \in I} \pi_i(d)^{\nu_{ik}}.
\]  

(3.9)

This concludes the proof of the Theorem. \( \square \)

**Corollary 3.10** (Mass-action kinetics). Let \( \alpha, \beta, \gamma, \eta \) be as in Theorem 3.9. If the reaction rates are given by mass action kinetics, i.e.

\[
\lambda_{CR}^k(s) = \kappa_{kd} \prod_{i \in I} \left( \frac{s_i}{\nu_{ik}} \right)^{V_i(d)} \prod_{i \in I} \pi_i(d)^{\nu_{ik}}.
\]  

(3.10)

holds for some \( \kappa_{kd}, k \in K, d \in D \), then the limit of \( S^N(s) \) in the Skorohod topology is the solution of (3.6) with rates given by

\[
\lambda_{CR}^k(s) = \sum_{d \in D} \kappa_{kd} \prod_{i \in I} \left( \frac{s_i}{\nu_{ik}} \right)^{V_i(d)} \prod_{i \in I} \pi_i(d)^{\nu_{ik}}.
\]  

(3.11)

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

\[
\bar{\kappa}_k = \sum_{d \in D} \kappa_{kd} \prod_{i \in I} \pi_i(d)^{\nu_{ik}}.
\]  

(3.11)

If however, \( \alpha_i > 0 \) for all \( i \in I \), the limit process for the sums is the deterministic solution to an ordinary differential equation

\[
dS(t) = \sum_{k \in K} \zeta_k \lambda_{CR}^k(S(t))dt
\]

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

**Remark 3.11** (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 be all equal \( \eta_i = \eta \); as long as \( \eta_i > 0 \) for all \( i \in I \), it is easy to show that the limit dynamics of \( S^N(s) \) is as above.
Proof of Corollary 3.10. We plug (3.10) into (3.9). This gives
\[
\tilde{\lambda}_k^{\text{CR}}(\mathbf{z}) = \sum_{x_1^d=0,\ldots,1} \cdots \sum_{x_1^{|I|d}=0,\ldots,1} \sum_{d \in D} \kappa_{kd} \cdot \prod_{i \in I} \nu_{ik} \left( \frac{x_i^d}{\nu_{ik}} \right) \pi_i(d)^{x_i^{id}} (1 - \pi_i(d))^{s_i - x_i^{id}} \cdot \prod_{i \in I} (\pi_i(d)s_i)^{\nu_{ik}}
\]
\[
= \sum_{d \in D} \kappa_{kd} \prod_{i \in I} \nu_{ik} \left( \frac{s_i}{\nu_{ik}} \right) \pi_i(d)^{\nu_{ik}} \sum_{x_1^d=0,\ldots,1} \cdots \sum_{x_1^{|I|d}=0,\ldots,1} \prod_{i \in I} (\pi_i(d)s_i)^{\nu_{ik}}
\]
When \(\alpha_i = 0\) for all \(i \in I\) only the first sum in (3.6) exists, whereas when \(\alpha_i > 0\) for all \(i \in I\) only the second sum in (3.6) exists.

3.4 Spatial multi-scale systems

We next consider heterogeneous reaction networks on multiple time scales, where there is interplay between time scales on which the reaction network 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 2.4. In particular, we assume the reaction dynamics (within each compartment) has a separation of time scales (2.13) with \(\varepsilon = 1, \gamma = 0\). We set \(K^f\) and \(K^s\) as in (2.14) and (2.15), respectively, and \(I^f\) and \(I^s\) 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 \(i \in I^f\) while for all slow species is \(\eta_i = \eta_s, i \in I^s\). Considering the case \(\eta_f > 1\) for the moment, we note that for \(i \in I^f\) the variable \(V_{id}^f(\cdot)\) changes on the time-scale \(N_f dt\) (due to movement), whereas \(S_i^N(\cdot) = \sum_{d \in D} V_{id}^N(\cdot)\) only changes on the time-scale \(N dt\) (due to fast reactions). Therefore, in order to assess the interplay of dynamics on different time scales, we need to consider all possible orderings of \(\varepsilon = 1, \eta_f\) and \(\eta_s\).
In the sequel, we assume that $\eta_f, \eta_s \neq 1$ for simplicity. Moreover, the cases $\eta_s \leq \eta_f < 1$ and $\eta_f < \eta_f < 1$, as well as $1 < \eta_s \leq \eta_f$ and $1 < \eta_s < \eta_f < 1$ 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. Therefore, we are left with the four cases

$$
(1) \ 1 < \eta_s, \eta_f; \ (2) \ \eta_s < 1 < \eta_f; \ (3) \ \eta_f < 1 < \eta_s; \ (4) \ \eta_f, \eta_s < 1.
$$

(3.12)

As in the non-spatial situation, we also need to distinguish the cases when (i) there are no conserved quantities on the time scale of fast species (meaning that $\mathcal{N}((\zeta^f)')$ is the null space), and (ii) when some quantities are conserved (i.e. $\mathcal{N}((\zeta^f)') = \text{span}(\Theta^f)$, where $\Theta^f = (\theta_i^f)_{i=1, \ldots, n_f}$ is a linearly independent family of $\mathbb{R}^{[2^f]}$-valued vectors). In the latter case, the quantities $(\theta^f, V^N_i(\cdot))_{i \in I_f}$ also change on the time scale $N^{\eta_f} dt$ for $d \in D$ by movement of the fast species, but $(\theta^f, (S^N_i(\cdot))_{i \in I_f})$ is constant on the time scale $N^{\eta_f} dt$. We start with the case of $\mathcal{N}((\zeta^f)') = \text{null space}$. 

**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, $v = (v_f, v_s)$ with $v_f = (v_{id})_{i \in I_f, d \in D}, v_s = (v_{id})_{i \in I_s, d \in D}$, as well as $\mathbf{v} = (\mathbf{v}_f, \mathbf{v}_s), \mathbf{v}_f = (s_i)_{i \in I_f}, \mathbf{v}_s = (s_i)_{i \in I_s}$.

**Assumption 3.12** (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 3.6 holds, satisfies the following conditions:

(i) (1) For Poisson processes $(Y_k)_{k \in K_f^f}$, the time-change equation of the dynamics of $\mathbf{S}_f$ given the value of $\mathbf{S}_s = \mathbf{v}_s$

$$
\mathbf{S}_f|_{\mathbf{S}_s}(t) = \mathbf{S}_f|_{\mathbf{S}_s}(0) + \sum_{k \in K_f^f} \zeta_k^f Y_k \left( \int_0^t \lambda_k^{CR(1)}(\mathbf{S}_f|_{\mathbf{S}_s}(u), \mathbf{v}_s) du \right) + \sum_{k \in K_f^f} \zeta_k^f \int_0^t \lambda_k^{CR(1)}(\mathbf{S}_f|_{\mathbf{S}_s}(u), \mathbf{v}_s) du
$$

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

$$
\lambda_k^{CR(1)}(\mathbf{v}_f, \mathbf{v}_s) = \int_{\mathbb{R}_{|T_f| \times |D|} \times \mathbb{R}_{|T_s| \times |D|}} \lambda_k^{CR} (\mathbf{v}^d_{d,f}, \mathbf{v}^d_{d,s}) P_{(\mathbf{v}_f, \mathbf{v}_s)} (d\mathbf{v}_f, d\mathbf{v}_s) < \infty,
$$

(3.14)

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

(2) For Poisson processes \((Y_k)_{k \in K_f^d} \) the time-change equation of the dynamics of \( S_f \) given the value of \( V_s = v_s \)

\[
S_{f|\omega}(t) = S_{f|\omega}(0) + \sum_{k \in K_f^d} \zeta_{k} f Y_k \left( \int_{0}^{t} \lambda_{k}^{CR(2)}(S_{f|\omega}(u), v_s)du \right) 
+ \sum_{k \in K_f^d} \zeta_{k} f \int_{0}^{t} \lambda_{k}^{CR(2)}(S_{f|\omega}(u), v_s)du 
\]  

(3.15) has a unique solution, where for all \( \omega_f, v_s \)

\[
\tilde{\lambda}_{k}^{CR(2)}(\omega_f, v_s) = \int_{\mathbb{R}_+^{|I_f|} \times \mathcal{D}} \lambda_{k}^{CR}(\sum_{d \in D} \omega_{d,f}, \omega_{d,s})P_{\omega_f}(dv_f) < \infty 
\]  

(3.16) for \( P_{\omega_f} \) a product of multinomial and point mass probability distributions as in (3.8), where \( I \) is replaced by \( I_f, \omega \) by \( \omega_f \) and \( v \) by \( v_f \). In addition, 
\( S_{f|\omega}(\cdot) \) has a unique stationary probability measure \( \mu_{\omega}(d_\omega) \) on \( \mathbb{R}_+^{|I_f|} \).

(3) For Poisson processes \((Y_{kd})_{k \in K_f^d, d \in D} \) the time-change equation of the dynamics of \( V_f \) given the value of \( S_s = s_s \)

\[
V_{d,f|\omega}(t) = V_{d,f|\omega}(0) + \sum_{k \in K_f^d} \zeta_{k} d f Y_{kd} \left( \int_{0}^{t} \tilde{\lambda}_{kd}^{CR(3)}(V_{d,f|\omega}(u), s_s)du \right) 
+ \sum_{k \in K_f^d} \zeta_{k} d f \int_{0}^{t} \tilde{\lambda}_{kd}^{CR(3)}(V_{d,f|\omega}(u), s_s)du 
\]  

(3.17) has a unique solution, where for all \( \omega_f, s_s \)

\[
\tilde{\lambda}_{kd}^{CR(3)}(\omega_{d,f}, s_s) = \int_{\mathbb{R}_+^{|I_f|} \times \mathcal{D}} \lambda_{kd}^{CR}(\omega_{d,f}, \omega_{d,s})P_{\omega_f}(dv_f) < \infty 
\]  

(3.18) for \( P_{\omega_f} \) a product of multinomial and point mass probability distributions as in (3.8), where \( I \) is replaced by \( I_f, \omega \) by \( \omega_f \) and \( v \) by \( v_f \). In addition, 
\( V_{d,f|\omega}(\cdot) = (V_{id,f|\omega}(\cdot))_{i \in I_f, d \in D} \) has a unique stationary probability measure 
\( \mu_{\omega}(dv_f) \) on \( \mathbb{R}_+^{|I_f| \times |D|} \).

(4) For Poisson processes \((Y_{kd})_{k \in K_f^d, d \in D} \) the time-change equation of the dynamics of \( V_f \) given the value of \( V_s = v_s \)

\[
V_{d,f|\omega}(t) = V_{d,f|\omega}(0) + \sum_{k \in K_f^d} \zeta_{k} d f Y_{kd} \left( \int_{0}^{t} \tilde{\lambda}_{kd}^{CR(4)}(V_{d,f|\omega}(u), v_{d,s})du \right) 
+ \sum_{k \in K_f^d} \zeta_{k} d f \int_{0}^{t} \tilde{\lambda}_{kd}^{CR(4)}(V_{d,f|\omega}(u), v_{d,s})du 
\]  

(3.19)
has a unique solution with unique stationary probability measure \( \mu_{\bar{s}} \) on \( \mathbb{R}^{[\mathcal{I}] \times |\mathcal{D}|} \). Here, we set
\[
\bar{\lambda}_{kd}^{CR(4)} := \lambda_{kd}^{CR}.
\] (3.20)

(ii) There exists a well defined process \( S_s(\cdot) \) that is the unique solution of
\[
S_s(t) = S_s(0) + \sum_{k \in \mathcal{K}_s} \zeta^{s}_k Y_k \left( \int_0^t \bar{\lambda}_{k}^{CR(\ell)} (S_s(u)) du \right)
+ \sum_{k \in \mathcal{K}_s} \zeta^{s}_k \int_0^t \bar{\lambda}_{k}^{CR(\ell)} (S_s(u)) du
\] (3.21)

where rates \( (\bar{\lambda}_{k}^{CR(\ell)})_{\ell=1,2,3,4} \) are given from \( (\lambda_{k}^{CR(\ell)})_{\ell=1,2,3,4} \) in each case as for all \( s \),
\[
\bar{\lambda}_{k}^{CR(1)} (s) = \int_{\mathbb{R}^{[\mathcal{I}]}} \bar{\lambda}_{k}^{CR(1)} (s, f, s) \mu_{\bar{s}} (d_{s,f})
\] (3.22)
\[
= \sum_{d \in \mathcal{D}} \int \int \lambda_{kd}^{CR} (V_{d,f}, V_{d,s}) P_{\bar{s}} (d_{s,f}, d_{s}) \mu_{\bar{s}} (d_{s,f}) < \infty; \]
\[
\bar{\lambda}_{k}^{CR(2)} (s) = \int_{\mathbb{R}^{[\mathcal{I}] \times |\mathcal{D}|}} \int \bar{\lambda}_{k}^{CR(2)} (s, f, v) \mu_{\bar{s}} (d_{s,f}) P_{\bar{s}} (dv) \] (3.23)
\[
= \sum_{d \in \mathcal{D}} \int \int \lambda_{kd}^{CR} (V_{d,f}, V_{d,s}) P_{\bar{s}} (d_{s,f}) \mu_{\bar{s}} (dv) < \infty; \]
\[
\bar{\lambda}_{k}^{CR(3)} (s) = \sum_{d \in \mathcal{D}} \int \bar{\lambda}_{k}^{CR(3)} (s, f, s) \mu_{\bar{s}} (dv) \] (3.24)
\[
= \sum_{d \in \mathcal{D}} \int \lambda_{kd}^{CR} (V_{d,f}, V_{d,s}) P_{\bar{s}} (dv) \mu_{\bar{s}} (dv) < \infty; \]
\[
\bar{\lambda}_{k}^{CR(4)} (s) = \sum_{d \in \mathcal{D}} \int \int \bar{\lambda}_{k}^{CR(4)} (v, s) \mu_{\bar{s}} (dv) P_{\bar{s}} (dv) \] (3.25)
\[
= \sum_{d \in \mathcal{D}} \int \lambda_{kd}^{CR} (V_{d,f}, V_{d,s}) \mu_{\bar{s}} (dv) P_{\bar{s}} (dv) < \infty.
\]

(iii) same as (iii) in Assumption 2.14 in each compartment.

**Remark 3.13** (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 3.12 holds, satisfies the following condition: for Poisson processes \( (Y_k)_{k \in \mathcal{K}_s} \), the time change equation (3.21) has a unique solution, where for all \( s \),
\[
\bar{\lambda}_{k}^{CR(\ell)} (s) := E_{\bar{s}} \left[ \sum_{d \in \mathcal{D}} \lambda_{kd}^{CR} (V_{d}) \right] < \infty
\] (3.26)
and the distribution of \((V_{id})_{i \in I, d \in D}\) in (3.26) depends on the parameters \(\eta_s, \eta_f\) as follows:

\[
\begin{align*}
(\ell) &= 1 \quad P_{s_s}(dv_f, dv_s) = \int_{\ell I} \mu_{s_s}(ds_f) P_{s_s}(dv_f, dv_s), \\
(\ell) &= 2 \quad P_{s_s}(dv_f, dv_s) = P_{s_s}(dv_s) \int_{\ell I} \mu_{s_s}(ds_f) P_{s_s}(dv_f), \\
(\ell) &= 3 \quad P_{s_s}(dv_f, dv_s) = P_{s_s}(dv_s) \mu_{s_s}(dv_f), \\
(\ell) &= 4 \quad P_{s_s}(dv_f, dv_s) = P_{s_s}(dv_s) \mu_{s_s}(dv_f).
\end{align*}
\]

We can now state our results for the limiting behavior of \(S^N_f := (S^N_i, i \in I^f)\) and \(\xi^N_s := (S^N_i, i \in I^s)\) on the time scales \(N dt\) and \(dt\).

**Theorem 3.14** (Two-scale system without conserved fast quantities). Let \(\nu^N := (\nu^N(t))_{t \geq 0}\) be the vector process of rescaled species amounts for the reaction network which is the unique solution to (3.3). Assume that \((\alpha, \beta, \gamma = 0)\) satisfy (2.13) for some \(I^f, I^s\) with \(\varepsilon = 1\) and \(N((\zeta^f)^t) = 0\) (with \(\zeta^f\) from (2.15)), i.e. we are dealing with a two-scale system within compartments without conserved quantities on the fast time-scale. In addition, \(\eta_i = \eta_f > 0\) for all \(i \in I^f\) and \(\eta_i = \eta_s > 0\) for all \(i \in I^s\) and one of the cases (1)–(4) holds. Suppose Assumption 3.12 holds. Then, the rescaled sums of slow species \(S^N_s(\cdot)\) from (3.4) converges weakly to the unique solution \(\xi_s(\cdot)\) of (3.21) in the Skorohod topology.

**Remark 3.15** (Interpretation). The rates in Theorem 3.14 have an intuitive interpretation. In all cases, in order to compute \(E_{\alpha_s}[\lambda^{CR}(V_{id})]\), we have to know the distribution of \(V_{id}\) given \(S_s\).

Consider case (1) as an example. Here, since movement of particles are the fastest reactions in the system, given the value of \(S_s = s_s\), (i) \(V_{id}\) are distributed according to \(P_{s_s}(dv_s)\) from (3.8), and (ii) \(S_f\) is distributed according to the probability measure \(\mu_{s_s}(ds_f)\) from Assumption 3.12(i)(1); then, given the value of \(S_f = s_f\), the values of \(V_{idf}\) are distributed according to \(P_{s_f}(dv_{f})\) (3.8).

Another case is (3) since fast reactions within compartments and movement interacts. Here, given the value of \(S_s = s_s\), (i) again \(V_{id}\) are distributed according to \(P_{s_s}(dv_s)\) from (3.8), but (ii) \(V_{idf}\) are distributed according to \(\mu_{s_s}(dv_{f})\).

**Proof of Theorem 3.14.** The proof relies on use of Lemmas 2.18 and 2.20. 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 \(N dt\). Regarding the movement as a set of first-order reactions as in proof of Theorem 3.9 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 \( P_{(x_f, x_s)} \) from (3.8). Arguments from Lemma 2.20 imply that on the time scale \( N \cdot dt \) all rates for the reaction network dynamics \( \lambda_{CR(1)}^{i} \) are sums over compartments of rates averaged with respect to \( P_{(x_f, x_s)} \) as in (3.14), and the medium process of the sums of fast species \( S_f \) has effective change given by \( \zeta^f \). Condition (i)(1) of Assumption 3.12 ensures that on time scale \( N \cdot dt \) the medium process \( S_f(\cdot) \) is well defined and has a unique stationary probability distribution \( \mu_x(\lambda_{s}(dS_f)) \). Condition (ii) of Assumption 3.12 then ensures that, in addition to conditions (i-a) and (i-b), also condition (ii) in the Assumptions for Lemma 2.18 is met, and consequently the limiting dynamics of the slow process \( \Sigma_s(\cdot) \) with effective change given by \( \zeta^s \) 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 \( N^{\eta_f} \cdot dt \), effective change of fast species is the medium-fast process on time scale \( N \cdot dt \), movement of slow species is the medium-slow process on time scale \( N^{\eta_s} \cdot dt \), and finally effective change of slow species is the slow process on time scale \( dt \).

The fast process on time scale \( N^{\eta_f} \cdot dt \) of movement of all species has a stationary probability measure that is \( P_{(x_f, x_s)} \) (over \( i \in I^f \) only). Lemma 2.20 implies that on the next time scale \( N \cdot dt \) rates \( \lambda_{CR(2)}^{i} \) are averaged with respect to \( P_{(x_f, x_s)} \) as in (3.14), and the medium-fast process \( S_f \) has an effective change given by \( \zeta^f \). We now have that this process is well defined and has a unique stationary probability distribution \( \mu_x(\lambda_{s}(dS_f)) \). Furthermore, on the next time scale \( N^{\eta_s} \cdot dt \) we only have the movement of slow species, which has a stationary probability measure that is \( P_{(x_f, x_s)} \) (over \( i \in I^s \) only). Finally the limiting dynamics of the slow process \( \Sigma_s(\cdot) \) on time scale \( dt \), by an extension of Lemma 2.18 to four time-scales, is well defined and given by the solution of (3.21) with rates as in (3.22).

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 \( N^{\eta_s} \cdot dt \), effective change of fast species is the medium-fast process on time scale \( N \cdot dt \), movement of fast species is the medium-slow process on time scale \( N^{\eta_f} \cdot dt \), and finally effective change of slow species is the slow process on time scale \( dt \). Lemma 2.20 implies that on the medium-fast time scale \( N \cdot dt \) rates \( \lambda_{CR(3)}^{i} \) are averaged with respect to \( P_{(x_f, x_s)} \) (over \( i \in I^s \) only) as in (3.18), and the medium-fast process \( V_f \) has an effective change given by \( \zeta^f \) in each compartment \( d \in D \). This process is well defined and has a unique stationary probability distribution \( \mu_x(\lambda_{s}(dV_f)) \). On the next time scale \( N^{\eta_s} \cdot dt \) we only have the movement of slow species, which has a stationary probability measure that is \( P_{(x_f, x_s)} \) (over \( i \in I^f \) only). Finally, on time scale \( dt \), Lemma 2.18 extended to four time-scales implies the limiting dynamics of the slow process \( \Sigma_s(\cdot) \) 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 \( N \cdot dt \) in each compartment \( d \in D \) independently we have reaction dynamics of the fast species, with a unique equilibrium \( \mu_{x}(\lambda_{f}(v)) \) that must be a product distribution
over the different compartments. Similarly to case (1) when all the movement is fastest, we now have all the movement to be on the medium time-scale, with a unique stationary probability distribution $P_{(f,s)}$ (over all $i \in I$), which implies that on the slow time scale $dt$, the effective change of $F_s$ is due to reaction dynamics with rates $\tilde{\lambda}_{kd}^{\text{CR}}(v)^N$ that have been averaged over $P_{(f,s)}$, and is given by $\zeta^s$. Again Lemma 2.13 implies that $F_s(\cdot)$ is well defined and given by the solution of (3.24) with rates as in (3.25). \hfill $\square$

If the movement of fast species is slower than fast reactions (i.e. we consider case (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 3.16** (Irrelevance of movement of fast species). *In the situation of Theorem 3.14, cases (3) or (4), the limiting dynamics of $F_s$ is independent of $P_{(f,s)}$.*

**Proof.** Actually, the assertion can be seen directly from (3.29) and (3.30), since the right hand sides do not depend on $P_{(f,s)}$. \hfill $\square$

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 3.17.** *In the situation of Theorem 3.14, assume $I_s = \emptyset$, i.e. all slow species are continuous, and let $\pi_s := (\pi_i(d)s_i)_{i \in I_s, d \in D}$.\r

(i) For stationary probability measures $\mu_{(f,s)}(ds_f)$ of $F_{(f,s)}$ from Assumption 3.12(i)(1) and $\mu_{(f,s)}(ds_f)$ of $F_{(f,s)}$ from (i)(2), we have

$$\mu_{(f,s)}(ds_f) = \mu_{(f,s)}(ds_f).$$

(ii) Likewise, for stationary probability measures $\mu_{(f,s)}(dv_f)$ of $V_{(f,s)}$ from (i)(3) and $\mu_{(f,s)}(dv_f)$ of $V_{(f,s)}$ from (i)(4), we have

$$\mu_{(f,s)}(dv_f) = \mu_{(f,s)}(dv_f).$$

**Proof of Lemma 3.17.** (i) It suffices to show that $\mu_{(f,s)}$ is a stationary probability measure for the process $F_{(f,s)}(\cdot)$ from (3.13), since we assumed that this process has a unique stationary probability distribution. Clearly, the process $F_{(f,s)}(\cdot)$ is a strong Markov process with generator

$$L_{(f,s)}g(s_f) = \sum_{k \in K^f_s} \lambda^{CR}_k(s_f, s_s)[g(s_f + \zeta^f_k) - g(s_f)] + \sum_{k \in K^f_s} \lambda^{CR}_k(s_f, s_s) \partial_{s_f} g(s_f) \cdot \zeta^f_k.$$
Note that, by independence of the movement of fast and slow species, for \( k \in \mathcal{K}_f \),
\[
\tilde{\lambda}^{CR(1)}_k (\bar{s}_f, \bar{s}_s) = \int \sum_{d \in D} \lambda^{CR}_{kd} (\bar{v}_{d,f}, \bar{v}_{d,s}) P_{\bar{s}_f, \bar{s}_s} (dv_{d,f}, dv_{d,s}) \\
= \int \sum_{d \in D} \lambda^{CR}_{kd} (\bar{v}_{d,f}, \bar{v}_{d,s}) P_{\bar{s}_f} (dv_{d,f}) P_{\bar{s}_s} (dv_{d,s}) \\
= \tilde{\lambda}^{CR(2)}_k (\bar{s}_f, \bar{s}_s) = \tilde{\lambda}^{CR(2)}_k (\bar{s}_f, \pi \bar{s}_s).
\]

Hence,
\[
\int L_{f|s} g(\bar{s}_f) \mu_{\bar{\pi} s} (d\bar{s}_f) \\
= \int \sum_{k \in \mathcal{K}_f} \lambda^{CR(1)}_k (\bar{s}_f, \bar{s}_s) \left[ g(\bar{s}_f + \bar{z}_k) - g(\bar{s}_f) \right] \mu_{\bar{\pi} s} (d\bar{s}_f) \\
+ \int \sum_{k \in \mathcal{K}_f} \lambda^{CR(1)}_k (\bar{s}_f, \bar{s}_s) \bar{z}_k \cdot \nabla g(\bar{s}_f) \mu_{\bar{\pi} s} (d\bar{s}_f) \\
= \int \left( \int \sum_{k \in \mathcal{K}_f} \lambda^{CR(2)}_k (\bar{s}_f, \bar{s}_s) \left[ g(\bar{s}_f + \bar{z}_k) - g(\bar{s}_f) \right] \mu_{\bar{\pi} s} (d\bar{s}_f) \\
+ \int \sum_{k \in \mathcal{K}_f} \lambda^{CR(2)}_k (\bar{s}_f, \bar{s}_s) \bar{z}_k \cdot \nabla g(\bar{s}_f) \mu_{\bar{\pi} s} (d\bar{s}_f) \right) P_{\bar{s}_s} (dv_{d,s}) \\
= 0
\]
since \( \mu_{\bar{\pi} s} (d\bar{s}_f) \) is an equilibrium for \( S_{f|s} (\cdot) \) from (2). (ii) follows along similar lines.

\[\square\]

**Corollary 3.18.** Consider the same situation as in Theorem 3.14 and assume that \( I_{s} = \emptyset \), i.e. all slow species are continuous. 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 \( P_{s} (dv_{d,s}) \) is the delta-measure on \( \pi_{\bar{s}_s} \), all assertions can be read directly from (3.27)–(3.30) together with Lemma 3.17. \[\square\]

We end the results on multi-scale chemical reaction networks in spatial setting by noting that the case (1) (where all species move faster than the fast reactions occur) plays a special role under mass action kinetics.

**Corollary 3.19** (Homogeneous mass-action kinetics). Consider the same situation as in Theorem 3.14 and assume that the reaction rates are given by mass action kinetics with constants satisfying the homogeneity condition
\[
\kappa_k := |D| \kappa_{kd} \prod_{i \in I} \pi_i (d)^{\nu_k}.
\]

Then, the dynamics of \( \bar{s}_s \) 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 3.10 we get the first equality in

\[
\tilde{\lambda}_{k}^{CR(1)}(s_f, s_s) = \sum_{d \in D} \int_{d \in D} \lambda_{kd}^{CR}(v_{d,f}, v_{d,s}) \mathcal{P}(s_f, s_s) \left( dv_{d,f} dv_{d,s} \right)
\]

\[
= \sum_{d \in D} \kappa_{kd} \prod_{a \in I, a_i = 0} \nu_{ik} \left( s_{i} \right) \prod_{a \in I, a_i > 0} \left( \pi_{i}(d) s_{i} \right)^{\nu_{ik}}
\]

\[
= \kappa_{k} \prod_{a \in I, a_i = 0} \nu_{ik} \left( s_{i} \right) \prod_{a \in I, a_i > 0} s_{i}^{\nu_{ik}}.
\]

Since the right hand side gives the reaction rates for mass action kinetics within a single compartment, as given through \( V_f | v_{s} \) from (2.19), the equilibrium \( \mu_{v_{s}}(d) \) from Assumption 2.14(i) and \( \mu_{s}(d_{f}) \) from Assumption 3.12(i)(1) must be the same and the assertion follows in the case without conserved quantities.

Example 3.20 (Two time-scale kinetics in multiple compartments). We take up kinetics from Example 2.16 and extend it in a multi-compartment context. Recall that the chemical reaction network is given (within compartments) by the set of reactions

\[
1 : A + B \xrightarrow{\kappa'_{1d}} C, \quad 2 : \emptyset \xrightarrow{\kappa'_{2d}} B, \quad 3 : B \xrightarrow{\kappa'_{3d}} \emptyset.
\]

We consider \( \Lambda_{k}^{CR}(v) \) as in (2.23) with \( \kappa'_{k} \) replaced by \( \kappa_{kd} \), \( k \in \{1, 2, 3\} \). We have \( v = (v_{Ad}, v_{Bd}) \), and the dynamics are given by

\[
\Lambda^{CR}_{1d}(v_{d}) = \kappa'_{1d} x_{Ad} x_{Bd}, \quad \Lambda^{CR}_{2d}(v_{d}) = \kappa'_{2d}, \quad \Lambda^{CR}_{3d}(v_{d}) = \kappa'_{3d} x_{Bd}.
\]

Movement of species is given as in (3.3). The scaling in each compartment is as in the non-spatial setting (2.24), (2.25) and (2.26), so the rescaled species counts are

\[
v_{Ad} = N^{-1} x_{Ad}, \quad v_{Bd} = x_{Bd},
\]

and rates are

\[
\lambda^{CR}_{1d}(v_{d}) = \kappa_{1d} v_{Ad} v_{Bd}, \quad \lambda^{CR}_{2d}(v_{d}) = \kappa_{2d}, \quad \lambda^{CR}_{3d}(v_{d}) = \kappa_{3d} v_{Bd}.
\]

Now, the process \( V_{N} = (V_{Ad}^{N}, V_{Bd}^{N}) \) is given as in (2.27) 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 3.6) that movement of species \( A, B \) have stationary probability distributions \( (\pi_{A}(d))_{d \in D} \) and \( (\pi_{B}(d))_{d \in D} \). We derive the dynamics of \( S_{A} \) as

\[
S_{A}(t) = S_{A}(0) - \int_{0}^{t} \tilde{\lambda}^{CR}(S_{A}(u)) du
\]
for appropriate $\lambda$. Since the slow species $A$ are continuous, we are in the regime of Corollary 3.26 and we distinguish the following two cases:

**Dynamics in the cases (1)+(2):** We have

\[
S_{B|s_A}(t) - S_{B|s_A}(0) = -Y_1 \left( \int_0^t \int_{d \in D} \kappa_{1d}v_A dV_{Bd|s_A}(u) P_{s_A|s_B}(u) (dv_A, dv_B) du \right)
\]
\[+ Y_2 \left( \sum_{d \in D} \kappa_{2d} \right) - Y_3 \left( \int_0^t \int_{d \in D} \kappa_{3d}v_B dV_{Bd|s_A}(u) (dv_A, dv_B) du \right)
\]
\[= -Y_1 + \left( \sum_{d \in D} \kappa_{1d} \right) \left( s_A + \sum_{d \in D} \kappa_{3d} \right) S_{E|s_A} S_{B|s_A} du
\]
\[+ Y_2 \left( \sum_{d \in D} \kappa_{2d} \right)\]

Hence, the equilibrium of the above process is as in Example 2.16 given by

\[X \sim \mu_{s_A} (ds_B) = \text{Pois} \left( \frac{\kappa_2}{\kappa_3 + \kappa_1 s_A} \right)\]

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

\[\bar{\lambda}_{(1)+(2)}^{CR}(s_A) = -\bar{\lambda}_{1}^{CR}(s_A) = - \int \sum_{d \in D} \kappa_{1d} \pi_A(d) s_A \pi_B(d) s_B \mu_{s_A} (ds_B)
\]
\[= \sum_{d \in D} \kappa_{1d} \pi_A(d) s_A \pi_B(d) \frac{\bar{\kappa}_2}{\bar{\kappa}_3 + \kappa_1 s_A} = \frac{\bar{\kappa}_1 \bar{\kappa}_2 s_A}{\kappa_3 + \kappa_1 s_A}.
\]

**Dynamics in the cases (3)+(4):** We have in each compartment $d \in D$

\[V_{Bd|s_A}(t) - V_{Bd|s_A}(0) = -Y_1 \left( \int_0^t \int_{d \in D} \kappa_{1d}v_A dV_{Bd|s_A}(u) P_{s_A|s_B}(u) (dv_A, dv_B) du \right)
\]
\[+ Y_2 \left( \sum_{d \in D} \kappa_{2d} \right)\]
\[= -Y_1 + \left( \sum_{d \in D} \kappa_{1d} \right) \left( s_A + \sum_{d \in D} \kappa_{3d} \right) V_{Bd|s_A} du
\]
\[+ Y_2 \left( \sum_{d \in D} \kappa_{2d} \right)\]

Hence, the equilibrium of the above process is

\[X \sim \mu_{s_A} (dv_{Bd}) = \text{Pois} \left( \frac{\kappa_{2d}}{\kappa_{3d} + \kappa_{1d} \pi_A(d) s_A} \right)\]

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

\[\bar{\lambda}_{(3)+(4)}^{CR}(s_A) = - \sum_{d \in D} \int \kappa_{1d}v_A dV_{Bd|s_A} (dv_{Bd}) P_{s_A|s_B} (dv_{Ad})
\]
\[= - \sum_{d \in D} \frac{\kappa_{1d} \kappa_{2d} \pi_A(d) s_A}{\kappa_{3d} + \kappa_{1d} \pi_A(d) s_A}.
\]
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 \([3.19]\)) 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 \( \pi_A \) and \( \pi_B \). However, if we additionally suppose the slow species \( A \) are equidistributed \( \pi_A(d) = 1/|D| \) 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, i.e. we have a two-scale reaction network with \( \dim(N((\zeta^f)^t)) = n_f > 0 \). We will use the same notation as in Section \([2.3]\). In particular, \( \Theta^f := (\theta^c_j)_{j=1,\ldots,n_f} \) are linearly independent vectors which span the null space of \( (\zeta^f)^t \). Every \( \theta^c_j \) has a unique parameter \( \alpha_c_j \) associated with it, \( j = 1,\ldots,|\Theta^f| = n_f \).

Here, \( \Theta^f_0 \) is the subset of conserved quantities for which \( \alpha_c_j = 0 \), and \( \Theta^f \) is the subset of conserved quantities for which \( \alpha_c_j > 0 \). Conservation means that \( t \mapsto \langle \theta^c_j, S_f|_{\Theta^f}(t) \rangle \) with \( S_f|_{\Theta^f} \) from \([3.13]\) is constant, \( j = 1,\ldots,|\Theta^f| \). We let \( S^N_c = (\theta^c_j, S^N_f) \) and \( S^N_c = (S^N_c)_{i=1,\ldots,|\Theta^f|} \) be the vector of rescaled conserved quantities. Again, \( K_{g^f}^c \) is the set of reactions such that \( b^f_{c,j} = \alpha_{c,j} \) and \( \langle \theta^c_j, \zeta^c_k \rangle \neq 0 \), and let \( K^c := \bigcup_{j=1}^{\Theta^f_0} K_{g^f}^c \), \( K^c := \bigcup_{j=1}^{\Theta^f_0} K_{g^f}^c \) and \( K^c := \bigcup_{j=1}^{\Theta^f_0} K_{g^f}^c \). We still assume that \( K^c \cap K^f = \emptyset \) (see \([2.31]\)) and \( \zeta^c \) be the matrix defined by \([2.33]\).

Again, we consider the four cases as given in \([3.12]\). In addition, we assume that \( (\theta^c_j, S^N_f) \) changes on the time-scale \( dt \). We write here, distinguishing fast species, conserved quantities and slow species, \( v = (v_j, v_c, v_a) \) with \( v_j = (v_{id})_{i\in I^f, d\in D}, v_c = ((\theta^c_j, v_{c,d}))_{j=1,\ldots,|\Theta^f|, d\in D}, v_a = (v_{id})_{i\in I^f, d\in D}, \) as well as \( s = (s_f, s_c, s_a), s_f = (s_{id})_{i\in I^f}, s_c = (\langle \theta^c_j, s^f \rangle)_{j=1,\ldots,|\Theta^f|}, \) and \( s_a = (s_i)_{i\in I^f} \).

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 3.6 holds, satisfies the following conditions:

(i) (1) For Poisson processes \( (Y_k)_{k\in K^f_0} \), the time-change equation of the dynamics of \( S_f \) given the values of \( S_c = s_c \) and \( S_a = s_a \), denoted \( (S_f|_{(s_c, s_a)}(t))_{t\geq 0} \), given by \([3.13]\) with \( S_f|_{(s_c, s_a)} \) replaced by \( S_f|_{(s_c, s_a)} \), has a unique solution, where \( \lambda_k^{CR(1)}(s_f, s_a) \) is given by \([3.14]\). In addition, \( S_f|_{(s_c, s_a)}(\cdot) \) has a unique stationary probability measure \( \mu_{(s_c, s_a)}(d s_f) \) on \( \mathbb{R}_+^{|I^f|} \) with \( \langle \theta^c_j, s_f \rangle = s_{c,j} \), \( \mu_{(s_c, s_a)} \)-almost surely, \( j = 1,\ldots,|\Theta^f| \).

(2) For Poisson processes \( (Y_k)_{k\in K^f_0} \), the time-change equation of the dynamics of \( S_f \) given the value of \( V_c = v_c \) and \( S_a = s_a \), denoted
For Poisson processes \( (Y_{kd})_{k \in K, d \in D} \), the time-change equation of the dynamics of \( V_c \) given the values of \( \bar{s}_s = \bar{s}_s \) and \( \bar{V}_s = \bar{V}_s \), denoted by \( \langle V_f \rangle \) with \( V_{d.f} \) replaced by \( V_{d.f} \), has a unique solution, where \( \tilde{\lambda}^\text{CR(2)}(v_f, \bar{v}_s) \) is given by (3.16). In addition, \( \tilde{\lambda}^\text{CR(2)}(v_f, \bar{v}_s)(\cdot) \) has a unique stationary probability measure \( \mu_{([\bar{s}_s, \bar{v}_s], \cdot)}(d\bar{v}_f) \) on \( \mathbb{R}_{+}^{[I]} \) with \( \langle \bar{\theta}^{\bar{c}_j}, \bar{v}_f \rangle = s_{\bar{c}_j}, \mu_{([\bar{s}_s, \bar{v}_s], \cdot)}(d\bar{v}_f) \) almost surely, \( j = 1, ..., |\Theta| \).

Moreover, given \( \bar{s}_s \) and \( \bar{v}_s \), the movement dynamics of \( V_c \) is a unique solution \( \hat{V}_c = \langle V_{d.c} \rangle_{d \in D} \) of the time-change equations

\[
\langle \bar{\theta}^{\bar{c}_j}, V_{d.f} \rangle((\bar{s}_s, \bar{v}_s))(t) - \langle \bar{\theta}^{\bar{c}_j}, V_{d.f} \rangle((\bar{s}_s, \bar{v}_s))(0) = \sum_{i \in T_f} \sum_{d', v' \in D} (\delta_{d'v'} - \delta_{d'v}) \cdot Y_{d', v', i} \left( \int_{0}^{t} \lambda^M_{i, d', v} \int v_{d'} \mu_{([\bar{s}_s, \bar{v}_s], \cdot)}(du) (dv_{d'}) \right), \quad \bar{\theta}^{\bar{c}_j} \in \Theta^I, \quad (3.33)
\]

with an equilibrium probability distribution of movement \( P_{([\bar{s}_s, \bar{v}_s], \cdot)}(dv_{d'}) \) with \( \sum_{d \in D} V_{d,c} = \bar{v}_c \), \( P_{([\bar{s}_s, \bar{v}_s], \cdot)}(dv_{d'}) \) almost surely.

For Poisson processes \( (Y_{kd})_{k \in K, d \in D} \), the time-change equation of the dynamics of \( V_c \) given the values of \( \bar{v}_s = \bar{v}_s \) and \( \bar{V}_s = \bar{v}_s \), denoted by \( \langle V_f \rangle \) with \( V_{d.f} \) replaced by \( V_{d,f} \), has a unique solution, where \( \tilde{\lambda}^\text{CR(4)}(v_f, \bar{v}_s) \) is given by (3.20). In addition, \( \tilde{\lambda}^\text{CR(4)}(v_f, \bar{v}_s)(\cdot) \) has a unique stationary probability measure \( \mu_{([v_s, v_s], \cdot)}(dv_{d'}) \) with \( \langle \theta^{\bar{c}_j}, v_{d'} \rangle = v_{\bar{c}_j}, \mu_{([v_s, v_s], \cdot)}(dv_{d'}) \) almost surely, \( j = 1, ..., |\Theta| \).

Moreover, given \( \bar{v}_s \) and \( \bar{v}_s \), the movement dynamics of \( V_c \) is a unique solution \( \hat{V}_c = \langle V_{d.c} \rangle_{d \in D} \) of the time-change equations (3.33) with \( V_{d,c} = \langle \bar{v}_c, \bar{v}_s \rangle \) replaced by \( V_{d,c} \) with an equilibrium probability distribution of movement \( P_{([\bar{s}_s, \bar{v}_s], \cdot)}(dv_{d'}) \) with \( \sum_{d \in D} V_{d,c} = \bar{v}_c \), \( P_{([\bar{s}_s, \bar{v}_s], \cdot)}(dv_{d'}) \) almost surely.
(ii) From \( \{ \tilde{\lambda}^{\text{CR}(\ell)} \}_{\ell=1,2,3,4} \), we set in each case
\[
\tilde{\lambda}^{\text{CR}(1)}_{k}(s_{s}, s_{c}) = \int_{\mathbb{R}^{Z_{f}|f|}} \tilde{\lambda}^{\text{CR}(1)}_{k}(s_{f}, s_{c}) \mu_{(s_{f}, s_{c})} (ds_{f});
\]
\[
\tilde{\lambda}^{\text{CR}(2)}_{k}(s_{s}, s_{c}) = \int_{\mathbb{R}^{|Z_{f}|}} \int_{\mathbb{R}^{Z_{f}|f|}} \tilde{\lambda}^{\text{CR}(2)}_{k}(s_{f}, s_{c}) \mu_{(s_{f}, s_{c})} (ds_{f}) P_{(s_{f}, s_{c})} (dv_{f});
\]
\[
\tilde{\lambda}^{\text{CR}(3)}_{k}(s_{s}, s_{c}) = \int_{\mathbb{R}^{|\Theta_{f}| \times |Z_{f}|}} \int_{\mathbb{R}^{Z_{f}|f|}} \tilde{\lambda}^{\text{CR}(3)}_{k}(s_{f}, s_{c}) \mu_{(s_{f}, s_{c})} (ds_{f}) P_{(s_{f}, s_{c})} (dv_{f});
\]
\[
\tilde{\lambda}^{\text{CR}(4)}_{k}(s_{s}, s_{c}) = \int_{\mathbb{R}^{|Z_{f}| \times |Z_{f}|}} \int_{\mathbb{R}^{|\Theta_{f}| \times |Z_{f}|}} \tilde{\lambda}^{\text{CR}(4)}_{k}(s_{f}, s_{c}) \mu_{(s_{f}, s_{c})} (ds_{f}) P_{(s_{f}, s_{c})} (dv_{f});
\]
\[
\text{and for } j = 1, \ldots, |\Theta_{f}|,
\]
\[S_{j}(t) = S_{j}(0) + \sum_{k \in K_{s}^{d}_{c}} \zeta_{k}^{s} Y_{k} \left( \int_{0}^{t} \tilde{\lambda}^{\text{CR}(\ell)}_{k}(S_{j}(u), S_{j}(u)) du \right) + \sum_{k \in K_{c}^{d}_{j}} \zeta_{k}^{s} \int_{0}^{t} \tilde{\lambda}^{\text{CR}(\ell)}_{k}(S_{j}(u), S_{j}(u)) du,
\]
\[
S_{j}(t) = S_{j}(t)
\]

(iii) same as (iii) in Assumption 2.14 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: For Poisson processes \( (Y_{k})_{k \in K_{s}^{d}_{c}} \), the time change equations (3.21) has a unique solution, with \( \tilde{\lambda}^{\text{CR}}_{k} \) as in (3.26). The distribution of
We point out that the analogous result of Corollary 3.16 of irrelevance of the movement of fast species in cases (3.3) and (3.4) does not carry over to the case with conserved quantities. The reason is that because of the existence of conserved quantities, on the time scale of the movement of fast species, the conserved quantities of the fast reactions are still preserved.

We now derive results if all slow species and all conserved quantities are continuous. Again, we will show that the limiting dynamics for cases (1), (2) and (3), (4) are equal.

**Lemma 3.24.** In the situation of Theorem 3.23, assume $\mathcal{I}^s = \emptyset$, i.e. all slow species are continuous, and let $\pi_s := (\pi_i(0))_{i \in \mathcal{I}^s}$.

(i) For stationary probability measures $\mu(\cdot, \cdot) d\mathcal{S}_f$ and $\mathcal{S}_f(\cdot, \cdot)$ from Assumption 3.21 (i)(1) and $\mu(\cdot, \cdot) d\mathcal{S}_f$ and $\mathcal{S}_f(\cdot, \cdot)$ from (i)(2), we have

$$\mu(\cdot, \cdot) d\mathcal{S}_f = \mu(\pi_s, \cdot) d\mathcal{S}_f.$$

**Theorem 3.23** (Heterogeneous two-scale system with conserved fast quantities). Let $V^N := (V^N(t))_{t \geq 0}$ be the vector process of rescaled species amounts for the reaction network which is the unique solution to (3.3). Assume that $(\alpha, \beta, \gamma = 0)$ satisfy (2.13) for some $\mathcal{I}^f, \mathcal{I}^s$ with $\varepsilon = 1$ and $\mathcal{N}(\Theta^f) = \text{span}(\Theta^f)$ (with $\Theta^f$ from (2.15) and $\Theta^s$ from (2.32)), i.e. we are dealing with a two-scale system within compartments with conserved quantities $(\Theta^i)_{i = 1, \ldots, \lvert \Theta^f \rvert}$ 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 $i \in \mathcal{I}^s$. Suppose Assumption 3.21 holds. Then, we have joint convergence of the process of rescaled amounts of the slow and conserved quantities $(S^N_s(\cdot), S^N_c(\cdot)) \Rightarrow (S_s(\cdot), S_c(\cdot))$ in the Skorohod topology, with $S_s$ the solution of (3.38) and $S_c$ the solution of (3.39) with rates given by (3.40)–(3.43).

**Proof.** The proof follows essentially the same lines as that of Theorem 3.14. Care must be taken only with respect to the movement of conserved species in cases (3) and (4) for which extra assumption of well defined movement rates were made in Assumptions 3.21. \qed

We point out that the analogous result of Corollary 3.16 of irrelevance of the movement of fast species in cases (3) and (4) does not carry over to the case with conserved quantities. The reason is that because of the existence of conserved quantities, on the time scale of the movement of fast species, the conserved quantities of the fast reactions are still preserved.
(ii) Likewise, for stationary probability measures $\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ of $V_f(\mathcal{S},\mathcal{V})$ from $\gamma(3)$ and $\mu_{(\mathcal{S},\mathcal{W})}(d\eta_f)$ of $V_f(\mathcal{S},\mathcal{W})$ from $\gamma(4)$, we have

$$\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f) = \mu_{(\mathcal{S},\mathcal{W})}(d\eta_f).$$

**Remark 3.25** (Conserved quantities as new species). In previous results, conserved quantities on the fast time-scale can often be handled in a way as if they are new chemical species, evolving on the slow time-scale. We stress that the lemma does not require that $\Theta_f^s = \emptyset$, i.e. that there are no conserved discrete quantities. If there are conserved discrete quantities, they form a jump process on the time-scale $dt$, but the changes in the conserved quantities are made due to the movement between compartments on the time-scale $N^{th} dt$.

**Proof of Lemma 3.24**. The proof follows in full analogy with the proof of Lemma 3.17 once we exchange $\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ by $\mu_{(\mathcal{S},\mathcal{W})}(d\eta_f)$, $\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ by $\mu_{(\mathcal{S},\mathcal{W})}(d\eta_f)$, $\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ by $\mu_{(\mathcal{S},\mathcal{W})}(d\eta_f)$ and $\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ by $\mu_{(\mathcal{S},\mathcal{W})}(d\eta_f)$. ☐

**Corollary 3.26.** Consider the same situation as in Theorem 3.25 and assume that $\mathcal{I}_f^s = \emptyset$, i.e. all slow species are continuous. Then, the dynamics of (3.38) is the same in the cases (1), (2) and (3), (4).

**Proof.** Since $\mathcal{P}_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ is the delta-measure on $\pi_{\mathcal{S}}$, all assertions for (1), (2) can be read directly from (3.40)–(3.41) together with Lemma 3.24. For (3), (4) we need also to examine the effect of the equilibria of movement of the conserved species $\mathcal{P}_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ and $\mathcal{P}_{(\mathcal{S},\mathcal{W})}(d\eta_f)$ in the two cases. The movement of conserved species is determined by the expected value of the fast species with respect to the equilibrium probability measure for the faster reaction dynamics $\mu_{(\mathcal{S},\mathcal{V})}(d\eta_f)$ and $\mu_{(\mathcal{S},\mathcal{W})}(d\eta_f)$, respectively; see (3.33) and the same equation with $V_f(\mathcal{S},\mathcal{V})$ replaced by $V_f(\mathcal{S},\mathcal{W})$. By Lemma 3.24, they have the same form when $\eta_{(\mathcal{S},\mathcal{V})}$ is replaced by $\eta_{(\mathcal{S},\mathcal{W})}$. For $\theta^f \in \Theta_f^s$, the movement dynamics for $\{(\theta^f, V_f(\eta, d\eta_f)) \}_{\eta \in \mathcal{D}}$ are given by a Markov chain whose rates have the same form in (3), (4) when $\eta_{(\mathcal{S},\mathcal{V})}$ is replaced by $\eta_{(\mathcal{S},\mathcal{W})}$. Hence, the equilibrium distributions for these Markov chains have the same discrete probability distribution given the above stated replacement. For $\theta^f \in \Theta_f^s$, the movement dynamics for $\{(\theta^f, V_f(\eta, d\eta_f)) \}_{\eta \in \mathcal{D}}$ are given by solutions of ordinary differential equations whose vector fields also have the same form in (3), (4) when $\eta_{(\mathcal{S},\mathcal{W})}$ and $\eta_{(\mathcal{S},\mathcal{W})}$, and hence, their equilibria are point masses of the same form given the stated replacement. Since the overall equilibrium distribution of movement of all conserved species is a product of the multinomial and point mass distributions their forms satisfy $\mathcal{P}_{(\mathcal{S},\mathcal{V})}(d\eta_f) = \mathcal{P}_{(\mathcal{S},\mathcal{W})}(d\eta_f)$. From this the rest can be read from (3.42)–(3.43). ☐

**Corollary 3.27** (Homogeneous mass-action kinetics). Corollary 3.14 carries over to the same situation as in Theorem 3.25.

**Proof.** The proof is actually the same as in the case without conserved quantities in Corollary 3.19 because the effect of the conservation is the same for the single compartment model from Corollary 3.10 as in the proof of Corollary 3.19. ☐
A canonical application of Theorem 3.23 is a spatial version of Michaelis–Menten kinetics. Since this case also has a number of special features, we defer this application for future research.

4 Discussion

Specific features and extensions of spatial chemical reaction models.

a. Heterogeneous reaction and migration rates. The reaction rates $\Lambda_{kd}^{CR}$ in general depend on the compartment $d$. For the same reason, the outflow of species $i$ from compartment $d'$, $\sum_{d'' \in D} \Lambda_{i,d,d''}^{M}$ might depend on $i$ and $d'$. Moreover, it is possible that $\Lambda_{kd}^{CR}(x_d)$ is zero for some compartments, i.e. 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 that every reaction $k$ happens within at least one compartment.

b. Geometry of space. The geometry of the spatial system is 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 $D_i$ be the set of possible conformations of species $i$. Then, any molecule of species $i$ performs a Markov chain on $D_i$ due to changes in conformation. Moreover, in this case for each type of reaction $k$ its reaction rate $\Lambda_{k,d,d'}^{CR}$ might then depend on all conformations of reacting and produced molecules $d = (d_i)_{i \in I}$ and $d' = (d'_i)_{i \in I}$, 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, i.e. (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 $\alpha_i$’s, $\eta_i$’s and $\beta_k$’s) assuming (2.6) and (3.2) hold. (Admittedly, the choice of $N$, $\alpha_i$’s and $\beta_k$’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 3.6; 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, i.e. (2.10) holds, or the system is two-scale, i.e. (2.13) holds. (We do not treat higher order scales in this paper.)

(i) In the single-scale case Theorem 3.9 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 3.10 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, $\zeta^f$ and $\zeta^s$ from (2.15) and (2.17), respectively. A conserved quantity for the fast reaction subnetwork is a non-trivial element of the null-space of $\zeta^f$.

(ii-a) If there is no conserved quantity, we can use Theorem 3.14. Here, there are up to four timescales to consider, movement of fast and slow species, the timescale of the fast reactions, and the timescale of the slow species. In all cases, in order to determine the effective rate on $S_s$ on a slower timescale, one has to average over the equilibrium of all higher timescales. 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 3.18).

(ii-b) If there are conserved quantities for the fast reaction subnetwork, these conserved quantities can still change on a slower timescale. Here, we are assuming that: this timescale is the same as the timescale of the slow species, and that the rate-determining reactions of the dynamics of slow species and conserved quantities on the fast timescale are disjoint (2.34). The main difference from the case without conserved quantities is that on the fast timescale, 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 3.26.

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