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Error bound for piecewise deterministic processes modeling stochastic reaction systems*

Tobias Jahnke† and Michael Kreim†

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Abstract

Biological processes involving the random interaction of d species with integer particle numbers are often modeled by a Markov jump process on $\mathbb{N}_0^d$. Realizations of this process can, in principle, be generated with the classical stochastic simulation algorithm proposed in [19], but for very reactive systems this method is usually inefficient. Hybrid models based on piecewise deterministic processes offer an attractive alternative which can decrease the simulation time considerably in applications where species with rather low particle numbers interact with very abundant species. We investigate the convergence of the hybrid model to the original one for a class of reaction systems with two distinct scales. Our main result is an error bound which states that, under suitable assumptions, the hybrid model approximates the marginal distribution of the discrete species and the conditional moments of the continuous species up to an error of $\mathcal{O}(M^{-1})$ where M is the scaling parameter of the partial thermodynamic limit.

Keywords: Stochastic reaction systems, Gillespie algorithm, hybrid models, piecewise deterministic processes, error bounds, chemical master equation, thermodynamic limit

AMS subject classifications: 60J22, 60J27, 65C20, 65C40, 92-08, 92C42, 92D25

1 Introduction

Many processes inside living cells are characterized by low particle numbers and a high degree of randomness which brings about stochastic effects such as, e.g., the switching of a genetic toggle switch or random extinction [34, 33, 13, 39]. Such effects are crucial for the understanding of the biological system but can usually not be reproduced with the traditional deterministic reaction-rate approach where the concentrations of the species are modeled by a set of ordinary differential equations. Often much better results are obtained when the system is considered as a continuous-time Markov jump process on the state space

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of vectors of particle numbers, because this approach respects both the discreteness of the populations and the randomness of the dynamics; cf. [19, 18, 26, 16, 3]. Unbiased realizations of the Markov process can be generated with the stochastic simulation algorithm derived in D. Gillespie's seminal paper [19]. Although this algorithm is widely used, its efficiency is constrained by the fact that each single reaction event requires an update of the system, which makes the simulation of highly reactive systems very costly.

This has motivated the construction of many new numerical methods which either reformulate the original scheme in a more economical way (cf. [17]) or reduce the simulation time at the price of a a small approximation error; cf. [22, 5, 36, 32, 11, 12, 29, 2] and references therein. A second group of approaches aims to simplify the *model* by assuming, e.g., that a part of the reaction system is nearly in equilibrium [35, 7] or that the highly reactive ("fast") part of the problem can be described in terms of ordinary or stochastic differential equations which can be solved more efficiently; cf. [1, 6, 24, 23, 4, 38]. Such *hybrid models* reduce the numerical costs significantly in many applications, but a rigorous analytical investigation of the error caused by simplifying the model is missing in most cases.

The aim of this article is to prove an error bound for one of these hybrid models. In the investigated approach, a Markov jump process describing the dynamics of the species with low particle numbers is coupled to ordinary differential equations representing the highly abundant species, which removes the fast time-scales from the system and makes numerical simulations (e.g. by a Strang splitting method) much faster. Such an approach is called a *piecewise deterministic model* in the literature (cf. [10, 9, 8, 4, 37, 40]) because between two jumps of the Markov jump process the other part of the systems simply evolves according to an ordinary differential equation. Intuitively it can be expected that in a *partial thermodynamic limit* (i.e. when the abundance of the "large" species tends to infinity but the reaction constants are rescaled in a way to be explained below) the hybrid system converges to the original Markov jump process. This conjecture has recently been confirmed in [8] where convergence of the process in distribution was proved. Although the objective of our work is very similar, our analysis follows a rather different approach. In the error bound presented in Theorem 1 we only consider the error in the marginal distribution of the species described by the Markov process and the conditional expectations of the other species. In exchange, we prove not only convergence but also determine the *rate* of convergence. In fact, it will be shown that the error in the marginal distribution and in the conditional expectations is proportional to M^{-1} where M is the scaling parameter of the partial thermodynamic limit.

This goal is motivated and formulated in more detail in Section 2. As a starting point, stochastic reaction systems modeled by continuous-time Markov jump processes are considered (Section 2.1). The convergence to the classical reaction-rate equations in the thermodynamical limit (Section 2.2) motivates the use of a hybrid model based on a piecewise deterministic process (Section 2.3). Instead of discussing these concepts in an abstract setting, the derivation and the advantage of the piecewise deterministic process is first illustrated by a model problem which serves as an example throughout the paper. In Section 3 we pass from the model problem to a general class of scaled and partitioned reaction systems and define the associated Markov jump process and the corresponding piecewise deterministic process. The probability density of these processes evolve according to the chemical master equation (Section 3.3) and the Liouville-master equation (Section 3.4), and these differential equation will play a central role in the proof of the main result, which is presented

and proved in Section 4.

Throughout the article, most of the constants which appear in inequalities and which are of minor interest are denoted by the same symbol C although the value of these constants may differ from case to case.

2 Motivation

2.1 Modeling reaction systems with Markov processes

It is widely acknowledged that modeling reaction systems by ordinary differential equations (ODEs) yields qualitatively wrong results if the discreteness of the species and/or the stochastic nature of the dynamics cannot be neglected. In these cases, a significantly better approach is to consider the system as a Markov jump process on a discrete state space. This well-known model has been discussed, e.g., in [19, 18, 26, 16, 3], but in order to introduce our notation and to keep the exposition self-contained, we briefly summarize the basic facts.

Consider a discrete number of particles which move randomly in a bounded domain. It is assumed that the conditions of the environment (i.e. the temperature, the size of the domain, etc.) do not change, and that the system is well-stirred in the sense that at any time the random position of each of the particles is uniformly distributed. Each particle belongs to exactly one of $d \in \mathbb{N}$ different species $\mathcal{S}_1, \ldots, \mathcal{S}_d$, and particles of the same species are indistinguishable. It is assumed that the position of a single particle does not matter and that only the number of particles of $\mathcal{S}_k$ at time $t \geq 0$, denoted by $X_k(t) \in \mathbb{N}_0 = \mathbb{N} \cup \{0\}$, is relevant. The vector $X(t) = \big(X_1(t), \ldots, X_d(t)\big)^T$ of particle numbers changes according to r reaction channels $R_1, \ldots, R_r$ which represent events such as, e.g., a reactive collision between two particles from different species which produces a particle of another type, the decomposition of a particle into two particles, the conversion of a particle from one species to another one, the inflow of new particles into the systems from an exterior source, the "death" of particles and so on. Each reaction channel is defined by the equation

$$R_j : \kappa_{j1}^{in}\mathcal{S}_1 + \ldots + \kappa_{jd}^{in}\mathcal{S}_d \quad \xrightarrow{c_j} \quad \kappa_{j1}^{out}\mathcal{S}_1 + \ldots + \kappa_{jd}^{out}\mathcal{S}_d \tag{1}$$

with constants $\kappa_{jk}^{in}, \kappa_{jk}^{out} \in \mathbb{N}_0$ and $j \in \{1, \ldots, r\}$. If R_j fires at time t, then the particle numbers jump from the old state $X(t^-)$ to the new state $X(t) = X(t^-) + \nu_j$ where

$$\nu_j \quad = \quad \left(\kappa_{j1}^{out} - \kappa_{j1}^{in}, \ldots, \kappa_{jd}^{out} - \kappa_{jd}^{in}\right)^T \in \mathbb{Z}^d \tag{2}$$

is called the stoichiometric vector of R_j. The time of the next reaction event and the number of the reaction channel which fires are both random, but depend only on the current state, such that $X(t)$ is a realization of a Markov jump process. To be more precise, we assume that

$$X(t) \quad = \quad n_0 + \sum_{j=1}^{r} \mathcal{P}_j\left(\int_0^t \alpha_j(X(s))ds\right)\nu_j \tag{3}$$

with independent Poisson processes $\mathcal{P}_j$ (cf. [16, 4, 2]) and initial state $X(0) = n_0 \in \mathbb{N}^d$. The function α_j is called the propensity of R_j and is typically defined as

$$\alpha_j(n) \quad = \quad c_j \prod_{k=1}^{d} \binom{n_k}{\kappa_{jk}^{in}} \tag{4}$$

with a reaction constant $c_j > 0$ which depend on physical properties such as, e.g., the temperature or the volume of the domain. Here and below

$$\binom{x}{k} = \begin{cases} \dfrac{1}{k!} \displaystyle\prod_{j=0}^{k-1} (x-j) & \text{if } x > k-1 \text{ and } k \in \mathbb{N} \\ 0 & \text{if } x \leq k-1 \text{ and } k \in \mathbb{N} \\ 1 & \text{if } k = 0 \end{cases} \tag{5}$$

denotes the generalized binomial coefficient. For later use we remark that (5) is not restricted to positive integers and can also be evaluated for $x \in \mathbb{R}$.

The probability distribution $p(t, n) = \mathbb{P}(X(t) = n \mid X(0) = n_0)$ associated to $X(t)$ is the solution of the chemical master equation (CME)

$$\begin{aligned} \partial_t p(t,n) \quad &= \quad \sum_{k=1}^{r} \Big(\alpha_k(n-\nu_k) p(t, n-\nu_k) - \alpha_k(n) p(t,n) \Big) \\ p(0,n) \quad &= \quad \delta_{n_0}(n) \;=\; \begin{cases} 1 & \text{if } n = n_0 \\ 0 & \text{otherwise} \end{cases} \end{aligned} \tag{6}$$

(cf. [20]) with the convention that $p(t, n - \nu_k) = 0$ for all $n - \nu_k \notin \mathbb{N}_0^d$. Solving the CME numerically is a highly non-trivial problem because in most cases (6) has to be solved on a large state space, which excludes all standard methods. Constructing efficient *deterministic* methods for the CME is a new and very active field of research, which, in spite of its importance, is beyond the scope of this work. In this article, the CME will be used for analytical purposes only.

As a typical interpretation of the above model one may consider a *chemical* reaction system where the particles of the species correspond to the molecules of the chemical substances, but the same setting can be used to model, e.g., discrete stochastic predator-prey systems, viral kinetics, and gene regulatory networks.

The stochastic evolution of $X(t)$ can be simulated with the *Stochastic Simulation Algorithm* (SSA) derived in [19]:

1. Let $t = 0$ and $X = n_0$ where $n_0 \in \mathbb{N}_0^d$ is the initial state.
2. Compute $|\alpha(X)| = \displaystyle\sum_{j=1}^{r} \alpha_j(X)$.
3. Draw two random numbers ϱ_1 and ϱ_2 from the uniform distribution on $[0, 1]$.
4. Compute the time increment: $\tau = \ln(1/\varrho_1)/|\alpha(X)|$,

5. Determine the number of the reaction channel which fires next: find j such that

$$\sum_{k=1}^{j-1} \alpha_k(X) \;<\; \varrho_2 |\alpha(X)| \;\leq\; \sum_{k=1}^{j} \alpha_k(X).$$

6. Update the time $t \leftarrow t + \tau$ and the state $X \leftarrow X + \nu_j$.

7. If $t < t_{end}$ go to step 2.

The SSA is very popular among computational biologists but its efficiency is severely affected if the system is highly reactive, i.e. if some of the propensities are large. This happens in particular if the particle numbers of some of the species are relatively high. In this case, the expected value of the time increment τ (i.e. the waiting time between two reaction events) is so small that a huge number of steps is necessary to simulate the system over the full time-interval, and since each step requires two random numbers and an update of the state variable X, the total runtime increases considerably.

2.2 Thermodynamic limit

Before this approach is discussed, we briefly recall that the stochastic model (Markov jump process) converges to the deterministic one (reaction-rate equations, ODEs) in the thermodynamic limit. Consider the *scaled* kinetics

$$X^{[M]}(t) \;=\; Mn_0 + \sum_{j=1}^{r} \mathcal{P}_j \left(\int_0^t \alpha_j^{[M]}(X^{[M]}(s))ds \right) \nu_j, \tag{7}$$

$$\alpha_j^{[M]}(n) \;=\; M^{\left(1-|\kappa_j^{in}|_1\right)} \alpha_j(n), \qquad |\kappa_j^{in}|_1 = \sum_{i=1}^{d} \kappa_{ji}^{in} \tag{8}$$

where $M \in \mathbb{N}$ is a scaling parameter which can be thought of as the volume of the domain in which the particles move. If M increases, then the initial particle numbers $X^{[M]}(0) = Mn_0$ and thus the reactivity of the system increase, too. At the same time, the propensities (8) are rescaled in such a way that for $n \in \mathbb{N}_0^d$ one obtains

$$\begin{aligned} \alpha_j^{[M]}(Mn) \;&=\; c_j M^{\left(1-|\kappa_j^{in}|_1\right)} \prod_{k=1}^{d} \binom{Mn_k}{\kappa_{jk}^{in}} \\ &\approx\; c_j M^{\left(1-|\kappa_j^{in}|_1\right)} \prod_{k=1}^{d} \frac{(Mn_k)^{\kappa_{jk}^{in}}}{\kappa_{jk}^{in}!} = c_j M \prod_{k=1}^{d} \frac{n_k^{\kappa_{jk}^{in}}}{\kappa_{jk}^{in}!} = \mathcal{O}(M) \end{aligned}$$

for every reaction channel $j = \{1, \ldots, r\}$. For $M = 1$, the original process (3) is recovered. The thermodynamic limit is the limit dynamics of the *normalized* process $X^{[M]}(t)/M$ for $M \to \infty$. In his seminal work [30, 31, 16] T. Kurtz proved that

$$\lim_{M\to\infty} \mathbb{P}\left(\sup_{s\in[0,t_{\mathrm{end}}]} \left| \frac{X^{[M]}(t)}{M} - y(t) \right| > \varepsilon \right) = 0 \tag{9}$$

j	Reaction channel R_j	κ_{j1}^{in}	κ_{j1}^{out}	ν_j	Propensity $\alpha_j(n)$	Propensity $\alpha_j^{[M]}(n)$
1	$R_1 : \star \longrightarrow S$	0	1	1	c_1	Mc_1
2	$R_2 : S + S \longrightarrow S$	2	1	-1	$c_2 \frac{n(n-1)}{2}$	$c_2 \frac{n(n-1)}{2M}$

Table 1: Example I: A reaction system with one species $\mathcal{S} = \mathcal{S}_1$ and two reaction channels R_1 and R_2. For simplicity, we write n instead of n_1.

where $y(t)$ is the solution of the classical reaction-rate equation

$$\dot{y}(t) \quad = \quad \sum_{j=1}^{r} \nu_j c_j \prod_{k=1}^{d} \frac{y_k^{\kappa_{jk}^{in}}(t)}{\kappa_{jk}^{in}!}, \qquad y(0) = n_0. \tag{10}$$

This convergence means, roughly speaking, that for sufficiently large particle numbers the discrete, stochastic model (7) can be replaced by the deterministic ordinary differential equation (10). The advantage is that solving (10) is considerably less expensive than generating a sufficient number of realizations of the highly reactive Markov process (7).

This can be illustrated by the following simple example. Consider one single species $\mathcal{S} = \mathcal{S}_1$ which evolves according to the two reaction channels R_1 and R_2 defined in Table 1. The first reaction channel R_1 represents an inflow of new particles from an infinite source. The growth of the population is limited by R_2 which represents competition among the particles. In this example (7) takes the special form

$$X^{[M]}(t) \quad = \quad Mn_0 + \mathcal{P}_1(tMc_1) - \mathcal{P}_2\left(c_2 \int_0^t \frac{X^{[M]}(s)(X^{[M]}(s)-1)}{2M} ds\right), \tag{11}$$

and the normalized process $X^{[M]}(t)/M$ converges to the solution of the reaction-rate equation

$$\frac{dy}{dt}(t) \quad = \quad c_1 - c_2 \frac{y^2(t)}{2}, \qquad y(0) = n_0. \tag{12}$$

Equation (12) can be derived from (11) in a loose but intuitively plausible way by dividing (11) by M, by approximating $(X^{[M]}(t)-1)/M \approx X^{[M]}(t)/M \approx y(t)$, and by approximating

$$\frac{1}{M}\mathcal{P}_1(tMc_1) \approx tc_1 \quad \text{and} \quad \frac{1}{M}\mathcal{P}_2\left(M\frac{c_2}{2}\int_0^t y^2(s)ds\right) \approx \frac{c_2}{2}\int_0^t y^2(s)ds$$

according to the law of large numbers. This yields

$$y(t) \quad = \quad n_0 + tc_1 - \frac{c_2}{2}\int_0^t y^2(s)ds \tag{13}$$

which is the integral form of the reaction-rate equation (12).

j	Reaction channel R_j	Propensity $\alpha_j^{[M]}(n_1, n_2, n_3)$	Stoich. vector ν_j
1	$R_1 : \mathcal{S}_1 \longrightarrow \mathcal{S}_1 + \mathcal{S}_3$	$Mc_1 n_1$	$(0, 0, 1)^T$
2	$R_2 : \mathcal{S}_1 + \mathcal{S}_3 \longrightarrow \mathcal{S}_2$	$\frac{c_2}{M} n_1 n_3$	$(-1, 1, -1)^T$
3	$R_3 : \mathcal{S}_2 \longrightarrow \mathcal{S}_1 + \mathcal{S}_3$	$c_3 n_2$	$(1, -1, 1)^T$
4	$R_4 : \mathcal{S}_3 + \mathcal{S}_3 \longrightarrow \varnothing$	$c_4 \frac{n_3(n_3-1)}{2M}$	$(0, 0, -2)^T$

Table 2: Example II: A reaction system with three species and four reactions.

2.3 Partial thermodynamic limit and piecewise deterministic processes

In many biological systems the average particle numbers of the species can differ by several orders of magnitude, and often the dynamics of the abundant species is crucially affected by the stochastic behavior of the species with rather low particle numbers. We thus consider now a more complicated model problem consisting of three species $\mathcal{S}_1$, $\mathcal{S}_2$, $\mathcal{S}_3$ which interact via the four reaction channels defined in Table 2. $\mathcal{S}_1$ represents a gene which catalyzes the production of a protein $\mathcal{S}_3$ via R_1. For simplicity, the processes of transcription and translation are merged. The protein can auto-regulate the production of new copies by binding to the promoter region of the gene and blocking the transcription. $\mathcal{S}_2$ denotes the group of blocked genes, and the binding process is described by R_2. With a certain probability, however, the protein can be released from the gene via the third reaction channel R_3. Finally, R_4 describes dimerization of the protein to some irrelevant waste product. Since the waste product is not of any interest and does not have any feedback on $\mathcal{S}_1$, $\mathcal{S}_2$ and $\mathcal{S}_3$, its particle numbers do not have to be computed. This is the reason why this species is called $\varnothing$ instead of $\mathcal{S}_4$. Due to the particular structure of the system, the total number of genes $X_1^{[M]}(t) + X_2^{[M]}(t) = X_1^{[M]}(0) + X_2^{[M]}(0) = 10$ is constant. As a consequence, one could easily reduce the system to a two-dimensional problem by expressing $X_2^{[M]}(t)$ in terms of $X_1^{[M]}(t)$ or vice versa, but this does not matter here.

We assume that at $t = 0$ there are 10 open genes and no blocked genes, and that there are much more proteins than open or blocked genes. Thus, the scaling from the previous example is now applied to $\mathcal{S}_3$ only. To be more precise, we let

$$X^{[M]}(0) = (10, 0, M)^T$$

and scale the propensities as indicated in Table 2. For a general reaction system, the scaling rules will be defined in Section 3. At the moment, we only remark that due to this scaling we have

$$X_1(t) + X_2(t) = 10 \ll \mathbb{E}\left(X_3^{[M]}(t)\right) = \mathcal{O}(M)$$

on bounded time intervals, which means that the expected particle numbers lie on two clearly separated scales. For this reaction system, (3) takes the form

$$\begin{aligned} X^{[M]}(t) = \begin{pmatrix} 10 \\ 0 \\ M \end{pmatrix} &+ \mathcal{P}_1\left(\int_0^t M c_1 X_1^{[M]}(s)ds\right)\begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} \\ &+ \mathcal{P}_2\left(\int_0^t \frac{c_2}{M} X_1^{[M]}(s)X_3^{[M]}(s)ds\right)\begin{pmatrix} -1 \\ 1 \\ -1 \end{pmatrix} \\ &+ \mathcal{P}_3\left(\int_0^t c_3 X_2^{[M]}(s)ds\right)\begin{pmatrix} 1 \\ -1 \\ 1 \end{pmatrix} \\ &+ \mathcal{P}_4\left(\int_0^t c_4 \frac{X_3^{[M]}(s)(X_3^{[M]}(s)-1)}{2M}ds\right)\begin{pmatrix} 0 \\ 0 \\ -2 \end{pmatrix}. \end{aligned} \tag{14}$$

Now the example from 2.2 suggests that the abundant species $\mathcal{S}_3$ could be represented by a traditional reaction-rate equation while $\mathcal{S}_1$ and $\mathcal{S}_2$ should still be described in the discrete and stochastic setting. Approximating

$$y(s) \approx \frac{X_3^{[M]}(s)}{M} \approx \frac{X_3^{[M]}(s)-1}{M}$$

and proceeding as in the previous example leads to

$$\begin{aligned} Z^{[M]}(t) &= \begin{pmatrix} 10 \\ 0 \end{pmatrix} + \mathcal{P}_2\left(\int_0^t c_2 Z_1(s) y^{[M]}(s)ds\right)\begin{pmatrix} -1 \\ 1 \end{pmatrix} \\ &\quad + \mathcal{P}_3\left(\int_0^t c_3 Z_2(s)ds\right)\begin{pmatrix} 1 \\ -1 \end{pmatrix} \end{aligned} \tag{15}$$

$$\begin{aligned} y^{[M]}(t) &= 1 + \int_0^t c_1 Z_1^{[M]}(s)ds - \frac{1}{M}\int_0^t c_2 Z_1^{[M]}(s) y^{[M]}(s)ds \\ &\quad + \frac{1}{M}\int_0^t c_3 Z_2^{[M]}(s)ds - \int_0^t c_4 \left(y^{[M]}(s)\right)^2 ds \end{aligned} \tag{16}$$

where $Z_i^{[M]}(s) \approx X_i^{[M]}(s)$ for $i \in \{1,2\}$. In contrast to the previous example, the equation for $y^{[M]}(t)$ is *not* a purely deterministic ODE since the stochastic variables Z_1 and Z_2 appear on the right-hand side of (16). However, these variables only jump at discrete times and remain constant in between. If no jump occurs in the time interval $[t_1, t_2]$, then there are constants $z_1, z_2 \in \mathbb{N}_0$ such that $Z_1(s) = z_1$ and $Z_2(s) = z_2$ for all $s \in [t_1, t_2]$, and (16) is thus equivalent to the ODE

$$\frac{dy^{[M]}}{dt}(t) = c_1 z_1 - \frac{c_2 z_1}{M} y^{[M]}(t) + \frac{c_3 z_2}{M} - c_4\left(y^{[M]}(t)\right)^2 \tag{17}$$

for $t \in [t_1, t_2]$. This explains why such approaches are called *piecewise deterministic models* in the literature, see, e.g., [10, 9, 8, 37, 40] and references therein.

The piecewise deterministic model (15)-(16) can be simulated, e.g., with a stochastic Strang splitting method:

1. Choose $t_{\text{end}} > 0$ and $N \in \mathbb{N}$. Let $h = t_{\text{end}}/N$ and $t_i = ih$ for all $i = 0, \ldots, N$.
2. Initialize: Set $i = 0$, $Z_0 = (10, 0)$, $y_0 = M$.
3. Half-step in Z:
   Perform a stochastic simulation of (15) on the interval $[t_i, t_i + h/2]$ with initial state Z_i and while keeping $y^{[M]}(s) \equiv y_i$ constant. This can be done with SSA or approximate methods such as, e.g., tau-leaping [22]. Let $Z_{i+\frac{1}{2}}$ be the result of this step.
4. Full step in y:
   Solve the ordinary differential equation (17) on the interval $[t_i, t_{i+1}]$ with initial value y_i while keeping $(z_1, z_2) = Z_{i+\frac{1}{2}}$ fixed. This can be done, e.g., with a Runge-Kutta or multi-step method. Let y_{i+1} be the result of this step.
5. Half-step in Z:
   Perform a stochastic simulation of (15) on the interval $[t_i + h/2, t_{i+1}]$ with initial state $Z_{i+\frac{1}{2}}$ and while keeping $y^{[M]}(s) \equiv y_{i+1}$ constant at the updated value. Let Z_{i+1} be the result of this step.
6. If $i < N$: set $i \leftarrow i + 1$ and go to step 3.

The values Z_i and y_i are approximations to $Z^{[M]}(t_i)$ and $y(t_i)$, respectively. In addition to the *model error* which arises when the exact process $X^{[M]}(t)$ is replaced by the hybrid approach (15)-(16), there is a *splitting error* due to the fact that the two parts of the system are not propagated simultaneously, but in an alternating way. It is well-known, however, that under suitable regularity conditions the Strang splitting converges in distribution with order 2 to the exact solution; see, e.g. [29]. The main topic of this article is an analysis of the *model error*, and we will henceforth assume that the time-step h is so small that the *numerical error* can be neglected.

In order to investigate the accuracy of the piecewise deterministic process (15)-(16), the splitting method was applied to the model problem with $M = 5$, 10, 20, 30, 40, 50, 100 and

$$c_1 = 0.5,\ c_2 = 3,\ c_3 = 1,\ c_4 = 5,\ t_{\text{end}} = 0.5,\ N = 100,\ h = 0.005. \tag{18}$$

For each value of M, 10^6 realizations have been computed, with the exception of $M = 100$ where $2.5 \cdot 10^6$ realizations were generated to increase the accuracy. From this data, the marginal distribution $n_1 \mapsto \mathbb{P}(Z_1^{[M]}(t_{\text{end}}) = n_1)$ was estimated by producing a histogram and dividing by the number of samples. This approximate marginal distribution is not only affected by the model error and the splitting error, but also by the sampling error – the error due to estimating the marginal distribution from a finite number of realizations. But because of the large number of samples and the small step size h, it can be assumed[1] that the total error is dominated by the model error. The approximate marginal distribution was

[1] We have checked this by rerunning the experiment with different time-steps and a larger number of samples.

compared with a reference solution which was obtained by solving the CME (6) with high accuracy[2] and taking sums over n_2 and n_3. Figure 1 shows a considerable model error for $M = 10$ (left panel). For $M = 50$, however, the piecewise deterministic process yields a very accurate approximation to the true marginal distribution (right panel). The convergence for increasing values of M is illustrated in the left panel of Figure 2. This plot suggests that the error in the marginal distribution is proportional to M^{-1}, and the goal of this article is to prove that this is indeed the case; cf. Theorem 1.

We remark that the model problem considered here is obviously very small. This is unavoidable because a highly accurate reference solution is not available for larger problems. Moreover, in order to investigate the model error, the sampling error has to be reduced by a huge number of realizations, and the required number increases when larger problems are considered. However, our intention is not to demonstrate the efficiency of piecewise deterministic processes nor their applicability to large, complex biological systems; such applications can be found, e.g., in [9, 40]. Our example is only supposed to serve as an illustration of the somewhat abstract analysis in the second part of the paper.

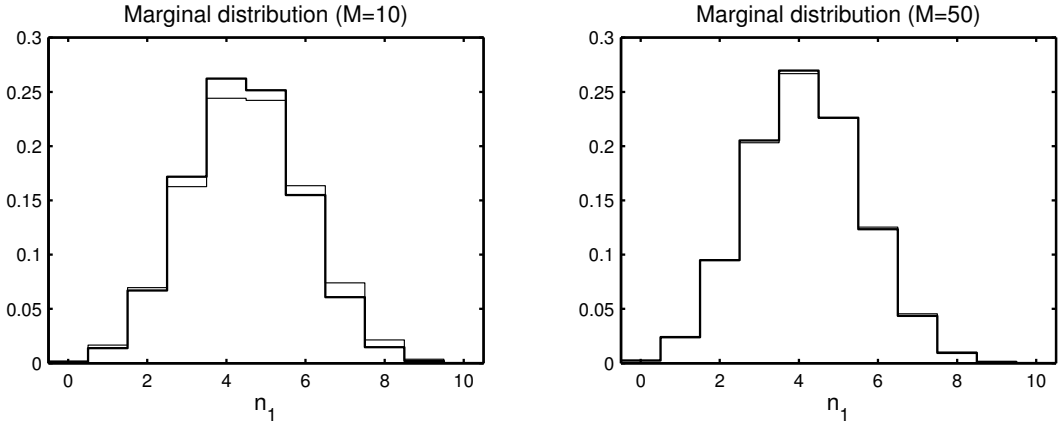

Figure 1: Marginal distributions of the piecewise deterministic model (15)-(16) (thin line) and of the exact process (14) (bold line) for $M = 10$ (left) and $M = 50$ (right) with the configuration given in (18). The marginal distribution $n_1 \mapsto \mathbb{P}(Z_1^{[M]}(t_{\mathrm{end}}) = n_1)$ of the piecewise deterministic model was estimated from the histogram of $1,000,000$ samples. The marginal distribution of the exact Markov process was obtained by solving the CME (6) with high accuracy and taking sums over n_2 and n_3.

[2]In this special case, the CME can be solved with a standard ODE integrator because the state space is small. As we have pointed out before, such a straightforward computation is not possible when larger reaction systems are investigated.

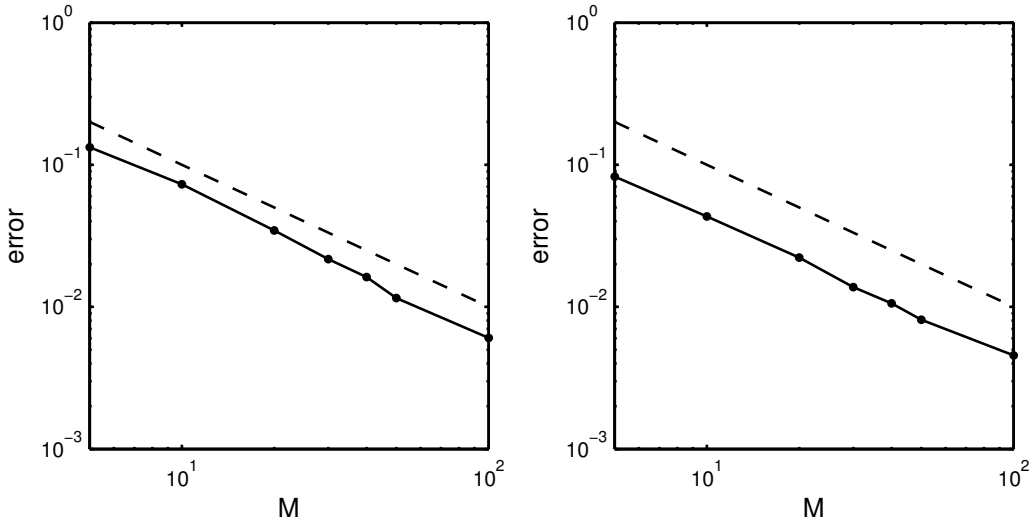

Figure 2: Illustration of Theorem 1 by the model problem defined in Table 2 with the parameters from (18). The left panel shows the convergence of the marginal distribution of the piecewise deterministic model (15)-(16) to the marginal distribution of the full process (14). The former was estimated from stochastic simulations whereas the latter was obtained by solving the CME (6) with high accuracy and taking sums over n_2 and n_3. The right panel shows the left-hand side of the inequality (43). In both panels, the comparison with the function $M \mapsto 1/M$ (dotted line) suggests that each of the two error terms decays proportional to $1/M$, which will be confirmed by the error bounds (42) and (43) from Theorem 1.

3 The general setting: two-scale reaction systems

3.1 Reaction channels, propensities and stoichiometry

Motivated by the previous section we consider reaction systems where the species are divided into two groups $\mathcal{S}_1, \ldots, \mathcal{S}_d$ and $\mathcal{S}_{d+1}, \ldots, \mathcal{S}_D$ with $d, D \in \mathbb{N}$. The particle numbers of $\mathcal{S}_1, \ldots, \mathcal{S}_d$ and $\mathcal{S}_{d+1}, \ldots, \mathcal{S}_D$ are denoted by the entries of $n \in \mathbb{N}_0^d$ and $m \in \mathbb{N}_0^D$, respectively. Later, $\mathcal{S}_{d+1}, \ldots, \mathcal{S}_D$ are supposed to be represented by real, continuous variables whereas the $\mathcal{S}_1, \ldots, \mathcal{S}_d$ will still be described by integer particle numbers. Let the j-th reaction channel be given by

$$R_j : \sum_{k=1}^{d} \kappa_{jk}^{in} \mathcal{S}_k + \sum_{k=1}^{D} \lambda_{jk}^{in} \mathcal{S}_{d+k} \quad \xrightarrow{c_j} \quad \sum_{k=1}^{d} \kappa_{jk}^{out} \mathcal{S}_k + \sum_{k=1}^{D} \lambda_{jk}^{out} \mathcal{S}_{d+k} \tag{19}$$

j	Reaction channel R_j	$\alpha_j(n)$	$\beta_j^{[M]}(m)$	$\tilde{\beta}_j^{[M]}(y)$	ν_j	μ_j
1	$R_1 : \mathcal{S}_1 \longrightarrow \mathcal{S}_1 + \mathcal{S}_3$	$c_1 n_1$	M	M	$\binom{0}{0}$	1
2	$R_2 : \mathcal{S}_1 + \mathcal{S}_3 \longrightarrow \mathcal{S}_2$	$c_2 n_1$	m/M	y	$\binom{-1}{1}$	-1
3	$R_3 : \mathcal{S}_2 \longrightarrow \mathcal{S}_1 + \mathcal{S}_3$	$c_3 n_2$	1	1	$\binom{1}{-1}$	1
4	$R_4 : \mathcal{S}_3 + \mathcal{S}_3 \longrightarrow \varnothing$	c_4	$\frac{m(m-1)}{2M}$	$M\frac{y^2}{2}$	$\binom{0}{0}$	-2

Table 3: Example II revisited. In this example, we have $d = 2$, $D = 1$, $r = 4$, $J_0 = \{2, 3\}$, $J_1 = \{1, 4\}$.

with $\kappa_{jk}^{in}, \kappa_{jk}^{out}, \lambda_{jk}^{in}, \lambda_{jk}^{out} \in \mathbb{N}_0$. The stoichiometric vectors are $(\nu_j, \mu_j) \in \mathbb{Z}^{d+D}$ with

$$\begin{aligned} \nu_j &= \left(\kappa_{j1}^{out} - \kappa_{j1}^{in}, \ldots, \kappa_{jd}^{out} - \kappa_{jd}^{in}\right)^T \in \mathbb{Z}^d \\ \mu_j &= \left(\lambda_{j1}^{out} - \lambda_{j1}^{in}, \ldots, \lambda_{jd}^{out} - \lambda_{jd}^{in}\right)^T \in \mathbb{Z}^D. \end{aligned} \tag{20}$$

For every $j = 1, \ldots, r$ the propensity of R_j is supposed to have the form $\alpha_j(n)\beta_j^{(M)}(m)$ where the entries of $n \in \mathbb{N}_0^d$ and $m \in \mathbb{N}_0^D$ are the particle numbers of $\mathcal{S}_1, \ldots, \mathcal{S}_d$ and $\mathcal{S}_{d+1}, \ldots, \mathcal{S}_D$, respectively. The function $\alpha_j(n)$ is defined by (4) as before. In order to define $\beta_j^{(M)}(m)$, we distinguish two different groups of reactions with index sets

$$J_0 = \left\{j \in \{1, \ldots, r\} : \nu_j = (0, \ldots, 0)^T\right\}, \qquad J_1 = \{1, \ldots, r\} \setminus J_0; \tag{21}$$

cf. [8]. If $j \in J_0$, then the particle numbers of $\mathcal{S}_1, \ldots, \mathcal{S}_d$ are not changed by the j-th rection channel R_j. Note that this does *not* mean that R_j is independent of these species, since any of the $\mathcal{S}_1, \ldots, \mathcal{S}_d$ could act as a catalyst of that reaction; cf. [8]. This is the case, e.g., in the first reaction channel of Table 3. With the indicator function

$$\gamma(j) = \begin{cases} 0 & \text{if } j \in J_0 \\ 1 & \text{if } j \in J_1 \end{cases}. \tag{22}$$

we define

$$\beta_j^{[M]}(x) = M^{1-\gamma(j)} M^{-|\lambda_j^{in}|_1} \prod_{k=1}^{D} \binom{x_k}{\lambda_{jk}^{in}} \tag{23}$$

for any $x \in \mathbb{R}_+^D$, where $|\lambda_j^{in}|_1 = \sum_{i=1}^d \lambda_{ji}^{in}$.

Example. For the reaction system defined in Table 2 we let $d = 2$ and $D = 1$. Thus, we have $r = 4$, $J_0 = \{1, 4\}$, and $J_1 = \{2, 3\}$. The propensities and the stoichiometric vectors are listed in Table 3; as before, we write m instead of m_1 for convenience.

In most applications, reactions between more than two particles are rather improbable events, because the probability that more than two particles collide is usually negligible.

Therefore, in most reaction systems, we have $|\lambda_j^{in}|_1 + |\kappa_j^{in}|_1 \leq 2$. In the results below, however, a weaker assumption will be made:

Assumption 1 *For every $j \in= \{1, \ldots, r\}$ we assume that $|\lambda_j^{in}|_1 \leq 2$.*

The above definitions guarantee that the particle numbers are nonnegative for all times, because a jump to a state outside of $\mathbb{N}_0^d \times \mathbb{N}_0^D$ can never occur, as the following lemma shows.

Lemma 1 *For all $j = 1, \ldots, r$, the functions α_j and $\beta_j^{[M]}$ have the following property:*

1. *If $n \in \mathbb{N}_0^d$ but one or several entries of $n + \nu_j$ are negative, then $\alpha_j(n) = 0$.*
2. *If $m \in \mathbb{N}_0^D$ but one or several entries of $m + \mu_j$ are negative, then $\beta_j^{[M]}(m) = 0$ for every $M \in \mathbb{N}$.*

Proof. Suppose that the k-th entry of $n + \nu_j$ is negative. By (20), this means that $n_k + \kappa_{jk}^{out} - \kappa_{jk}^{in} < 0$. Since $n_k, \kappa_{jk}^{in} \in \mathbb{N}_0$ it follows that $n_k \leq \kappa_{jk}^{in} - 1$ and, by definition (4), that $\alpha_j(n) = 0$. The second assertion follows analogously from the definition (23). ∎

3.2 Spaces and norms

Henceforth, $\|\cdot\|$ denotes an arbitrary vector norm on $\mathbb{R}^N$ or the induced matrix norm, respectively. For $K \in \mathbb{N}$ let

$$\ell_K^1 = \Big\{ u : \mathbb{N}_0^K \longrightarrow \mathbb{R}^N \;\Big|\; \sum_{n \in \mathbb{N}_0^K} \|u(n)\| < \infty \Big\}, \qquad \|u\|_{\ell_K^1} = \sum_{n \in \mathbb{N}_0^K} \|u(n)\|$$

be the multivariate and vector-valued counterpart of the standard ℓ^1-space, which is recovered for $K = N = 1$. In the analysis below only $N = 1$ or $N = d$ will appear, and since the latter case is a generalization of the former, the symbol ℓ_K^1 will be used in both cases. For $i \in \mathbb{N}_0$ we define the spaces $\mathcal{X}_{d,D}^{i+1}$ via the recursion

$$\mathcal{X}_{d,D}^{i+1} = \Big\{ u \in \mathcal{X}_{d,D}^i \;\Big|\; (n,m) \mapsto m_k u(n,m) \in \mathcal{X}_{d,D}^i \text{ for all } k \in \{1, \ldots, D\} \Big\}$$

with $\mathcal{X}_{d,D}^0 = \ell_{d+D}^1$. If, for example, u is a probability distribution and $u = u(n,m) \in \mathcal{X}_{d,D}^2$, then the first and second moments of the marginal distribution $m \mapsto \sum_{n \in \mathbb{N}_0^d} u(n,m)$ exist. For later use, we also define the corresponding spaces

$$\begin{aligned} \mathcal{Y}_{d,D}^0 &= \Big\{ u : \mathbb{N}_0^d \times \mathbb{R}_+^D \longrightarrow \mathbb{R}^N \;\Big|\; \sum_{n \in \mathbb{N}_0^d} \int_{\mathbb{R}_+^D} \|u(n,x)\| \, dx < \infty \Big\} \\ \mathcal{Y}_{d,D}^{i+1} &= \Big\{ u \in \mathcal{Y}_{d,D}^i \;\Big|\; (n,x) \mapsto x_k u(n,x) \in \mathcal{Y}_{d,D}^i \text{ for all } k \in \{1, \ldots, D\} \Big\}. \end{aligned}$$

for functions on a mixed discrete-continuous state space. Here and below, $\mathbb{R}_+^D$ denotes the set $[0, \infty)^D$.

3.3 Markov process and chemical master equation

The Markov process corresponding to the scaled and partitioned system is given by

$$\begin{pmatrix} X^{[M]}(t) \\ Y^{[M]}(t) \end{pmatrix} = \begin{pmatrix} n_0 \\ Mm_0 \end{pmatrix} + \sum_{j=1}^{r} \mathcal{P}_j \left(\int_0^t \alpha_j \left(X^{[M]}(s) \right) \beta_j^{[M]} \left(Y^{[M]}(s) \right) ds \right) \begin{pmatrix} \nu_j \\ \mu_j \end{pmatrix} \quad (24)$$

with $n_0 \in \mathbb{N}_0^d$ and $m_0 \in \mathbb{N}_0^D$. The probability distribution

$$p^{[M]}(t,n,m) = \mathbb{P}\Big(X^{[M]}(t) = n, Y^{[M]}(t) = m \mid X^{[M]}(0) = n_0, Y^{[M]}(0) = Mm_0 \Big)$$

is the solution of the CME

$$\begin{aligned} \partial_t p^{[M]}(t,n,m) &= \sum_{j=1}^{r} \Big(\alpha_j(n-\nu_j)\beta_j^{[M]}(m-\mu_j) p^{[M]}(t,n-\nu_j,m-\mu_j) \\ &\qquad - \alpha_j(n)\beta_j^{[M]}(m) p^{[M]}(t,n,m) \Big) \qquad (25) \\ p^{[M]}(0,n,m) &= \delta_{n_0}(n)\delta_{Mm_0}(m). \qquad (26) \end{aligned}$$

As before in (6), we let $p^{[M]}(t,n-\nu_j,m-\mu_j) = 0$ if $n-\nu_j \notin \mathbb{N}_0^d$ or $m-\mu_j \notin \mathbb{N}_0^D$. For the sake of a more compact notation we define the shift operators Δ_ν^1 and Δ_μ^2 with $\nu \in \mathbb{Z}^d$ and $\mu \in \mathbb{Z}^D$ via

$$\Delta_\nu^1 u(n,m) = \begin{cases} u(n-\nu,m) & \text{if } n-\nu \in \mathbb{N}_0^d \\ 0 & \text{else} \end{cases}, \quad (27)$$

$$\Delta_\mu^2 u(n,m) = \begin{cases} u(n,m-\mu) & \text{if } m-\mu \in \mathbb{N}_0^D \\ 0 & \text{else} \end{cases}. \quad (28)$$

The two shift operators commute, i.e.

$$\Delta_\nu^1 \Delta_\mu^2 u(n,m) = \Delta_\mu^2 \Delta_\nu^1 u(n,m) = \begin{cases} u(n-\nu,m-\mu) & \text{if } n-\nu \in \mathbb{N}_0^d, m-\mu \in \mathbb{N}_0^D \\ 0 & \text{else.} \end{cases}$$

We shall make the convention that applying a shift operator to a product $u(n,m)v(n,m)$ is to be understood as

$$\left(\Delta_\nu^1 uv\right)(n,m) = \left(\Delta_\nu^1 (uv)\right)(n,m) = u(n-\nu,m)v(n-\nu,m) = \left(\Delta_\nu^1 u\right)\left(\Delta_\nu^1 v\right)(n,m).$$

With these operators, the CME (25) can be reformulated as

$$\partial_t p^{[M]} = \sum_{j=1}^{r} (\Delta_{\nu_j}^1 \Delta_{\mu_j}^2 - 1)\alpha_j \beta_j^{[M]} p^{[M]}. \quad (29)$$

Lemma 2 *Let $\nu \in \mathbb{Z}^d$, $\mu \in \mathbb{Z}^d$, and let $u \in \ell_{d+D}^1$ be a function with the property that*

$$u(n,m) = 0 \qquad \text{if } n+\nu \notin \mathbb{N}_0^d \text{ or } m+\mu \notin \mathbb{N}_0^D. \quad (30)$$

Then, the following assertions hold:

$$\begin{aligned}
(i) \qquad & \sum_{n\in\mathbb{N}_0^d} \left((\Delta_\nu^1 - 1)u\right)(n,m) &&= 0 \\
(ii) \qquad & \sum_{m\in\mathbb{N}_0^D} \left((\Delta_\mu^2 - 1)u\right)(n,m) &&= 0 \\
(iii) \qquad & \sum_{n\in\mathbb{N}_0^d}\sum_{m\in\mathbb{N}_0^D} \left((\Delta_\nu^1\Delta_\mu^2 - 1)u\right)(n,m) &&= 0
\end{aligned}$$

If u is scalar-valued and $u \in \mathcal{X}_{d,D}^1$, then

$$(iv) \qquad \sum_{m\in\mathbb{N}_0^D} m\left((\Delta_\mu^2 - 1)u\right)(n,m) = \mu \sum_{m\in\mathbb{N}_0^D} u(n,m).$$

This lemma is not really new; similar considerations can be found, e.g., in [21, 15, 27]. However, since the lemma will be frequently used later on, we briefly recall the main argument of the proof.

Sketch of the Proof. For $\tilde{n} = n - \nu$ it follows from (27) that

$$\begin{aligned}
\sum_{n\in\mathbb{N}_0^d} \left((\Delta_\nu^1 - 1)u\right)(n,m) &= \sum_{n\in\mathbb{N}_0^d} u(n-\nu,m) - \sum_{n\in\mathbb{N}_0^d} u(n,m) \\
&= \sum_{\tilde{n}+\nu\in\mathbb{N}_0^d} u(\tilde{n},m) - \sum_{n\in\mathbb{N}_0^d} u(n,m) = 0
\end{aligned}$$

since according to (30) the two sums are identical. This proves (i), and (ii) follows by similar arguments. Then, (i) and (ii) imply (iii) via the identity

$$(\Delta_\nu^1\Delta_\mu^2 - 1)u = \Delta_\nu^1(\Delta_\mu^2 - 1)u + (\Delta_\nu^1 - 1)u.$$

Finally, (iv) is shown by substituting $\tilde{m} = m - \mu$:

$$\begin{aligned}
\sum_{m\in\mathbb{N}_0^D} m\left((\Delta_\mu^2 - 1)u\right)(n,m) &= \sum_{m\in\mathbb{N}_0^D} mu(n,m-\mu) - \sum_{m\in\mathbb{N}_0^D} mu(n,m) \\
&= \sum_{\tilde{m}\in\mathbb{N}_0^D} (\tilde{m}+\mu)u(n,\tilde{m}) - \sum_{m\in\mathbb{N}_0^D} mu(n,m) \\
&= \mu \sum_{m\in\mathbb{N}_0^D} u(n,m).
\end{aligned}$$

■

By Lemma (1), the function $\alpha_j\beta_j^{[M]}p^{[M]}$ satisfies (30). If $\alpha_j\beta_j^{[M]}p^{[M]} \in \ell_{d+D}^1$ we thus obtain that

$$\begin{aligned}
\sum_{n\in\mathbb{N}_0^d}\sum_{m\in\mathbb{N}_0^D} p^{[M]}(t,n,m) &= \sum_{n\in\mathbb{N}_0^d}\sum_{m\in\mathbb{N}_0^D} p^{[M]}(0,n,m) + \sum_{n\in\mathbb{N}_0^d}\sum_{m\in\mathbb{N}_0^D} \int_0^t \partial_t p^{[M]}(\tau,n,m)\, d\tau \\
&= 1 + \int_0^t \sum_{j=1}^r \sum_{n\in\mathbb{N}_0^d}\sum_{m\in\mathbb{N}_0^D} \left((\Delta_{\nu_j}^1\Delta_{\mu_j}^2 - 1)\alpha_j\beta_j^{[M]}p^{[M]}\right)(\tau,n,m) = 1
\end{aligned}$$

Since it can be shown with standard arguments that $p(t,n,m) \geq 0$ (cf., e.g., Section 2.4 in [28]), this shows that $p^{[M]}(t,\cdot,\cdot)$ is a probability distribution at any time $t \geq 0$.

3.4 Piecewise deterministic process and Liouville-master equation

In order to formulate the piecewise deterministic process for general reaction systems, we define

$$\tilde{\beta}_j^{[M]}(x) = M^{1-\gamma(j)} \prod_{k=1}^{D} \frac{x_j^{\lambda_{jk}^{in}}}{\lambda_{jk}^{in}!}. \tag{31}$$

For $\gamma(j) = 1$, $\tilde{\beta}_j^{[M]}(x)$ is simply the term which appears on the right-hand side of the traditional reaction-rate equation (10). The following lemma shows that $\tilde{\beta}_j^{[M]}$ is closely related to $\beta_j^{[M]}$ defined in (23).

Lemma 3 *If $x \in \mathbb{R}_+^D$ and $x_k \geq 1/M$ for all $k \in \{1,\ldots,D\}$, then there is a constant $C > 0$ such that*

$$\left|\beta_j^{[M]}(Mx) - \tilde{\beta}_j^{[M]}(x)\right| \leq CM^{-\gamma(j)}.$$

If $\lambda_{jk}^{in} \in \{0,1\}$ for all $k = 1,\ldots,D$, we even have $\beta_j^{[M]}(Mx) = \tilde{\beta}_j^{[M]}(x)$.

Proof. By Assumption 1 only the cases $\lambda_j^{in} = 0,1,2$ must be considered. If $\lambda_{jk}^{in} \leq 1$, then

$$\left| M^{-\lambda_{jk}^{in}} \binom{Mx_k}{\lambda_{jk}^{in}} - \frac{x_k^{\lambda_{jk}^{in}}}{\lambda_{jk}^{in}!} \right| \quad = \quad 0$$

for any $j \in \{1,\ldots,r\}$ and $k \in \{1,\ldots,D\}$, such that the second assertion follows from (23) and (31). If $\lambda_{jk}^{in} = 2$ and $Mx_k > 1$, then

$$\left| M^{-\lambda_{jk}^{in}} \binom{Mx_k}{\lambda_{jk}^{in}} - \frac{x_k^{\lambda_{jk}^{in}}}{\lambda_{jk}^{in}!} \right| = \left| \frac{Mx_k(Mx_k-1)}{2M^2} - \frac{x_k^2}{2} \right| = \frac{x_k}{2M},$$

whereas for $\lambda_{jk}^{in} = 2$ and $Mx_k < [0,1]$ we obtain

$$\left| M^{-\lambda_{jk}^{in}} \binom{Mx_k}{\lambda_{jk}^{in}} - \frac{x_k^{\lambda_{jk}^{in}}}{\lambda_{jk}^{in}!} \right| = \frac{x_k^2}{2!} < \frac{1}{2M^2}.$$

Hence, for every $\lambda_{jk}^{in} \in \{0,1,2\}$ we have

$$\left| \binom{M^{-\lambda_{jk}^{in}} x_k}{\lambda_{jk}^{in}} - \frac{x_k^{\lambda_{jk}^{in}}}{\lambda_{jk}^{in}!} \right| \leq \frac{C}{2M},$$

and the assertion follows from

$$\left|\beta_j^{[M]}(Mx) - \tilde{\beta}_j^{[M]}(x)\right| \quad = \quad M^{1-\gamma(j)} \cdot \left| \prod_{k=1}^{D} M^{-\lambda_{jk}^{in}} \binom{Mx_k}{\lambda_{jk}^{in}} - \prod_{k=1}^{D} \frac{x_k^{\lambda_{jk}^{in}}}{\lambda_{jk}^{in}!} \right|$$

■

Remark. According to Assumption 1, all $\beta_j^{[M]}$ and $\tilde{\beta}_j^{[M]}$ are polynomials of degree 2 or less. Hence, the Hessians $\nabla^2\beta_j^{[M]}$ and $\nabla^2\tilde{\beta}_j^{[M]}$ are both constant matrices, and higher derivatives vanish.

We are now ready to define the piecewise deterministic process corresponding to (24):

$$Z^{[M]}(t) \quad = \quad n_0 + \sum_{j=1}^{r} \mathcal{P}_j \left(\int_0^t \alpha_j \left(Z^{[M]}(s) \right) \tilde{\beta}_j^{[M]} \left(y^{[M]}(s) \right) ds \right) \nu_j \tag{32}$$

$$y^{[M]}(t) \quad = \quad m_0 + \frac{1}{M} \sum_{j=1}^{r} \left(\int_0^t \alpha_j \left(Z^{[M]}(s) \right) \tilde{\beta}_j^{[M]} \left(y^{[M]}(s) \right) ds \right) \mu_j \tag{33}$$

Example. For the reaction system defined in Table 3 with $n_0 = (10, 0)$ and $m_0 = 1$, the process (32)-(33) reduces to (15)-(16).

As before, the second equation (33) is piecewise deterministic in the sense that (33) is locally equivalent to the ODE

$$\dot{y}^{[M]}(t) \quad = \quad \frac{1}{M} \sum_{j=1}^{r} \alpha_j \left(z \right) \tilde{\beta}_j^{[M]} \left(y^{[M]}(t) \right) \mu_j$$

on time intervals where $Z^{[M]}(s) = z$ does not jump. The coupled equations (32)-(33) can be simulated, e.g., by adapting the Strang splitting method from Section 2.3.

The probability distribution associated to the original Markov process (24) evolves according to the CME (25) defined in the previous subsection. Now the question arises what the counterpart of the CME in case of the piecewise deterministic process (32)-(33) is. The answer can be found in [25, 8]: If

$$\int_S q^{[M]}(t, n, x)\, dx \quad = \quad \mathbb{P}\Big(X^{[M]}(t) = n,\ y^{[M]}(t) \in S \mid X^{[M]}(0) = n_0,\ y^{[M]}(0) = m_0 \Big)$$

for all measurable sets $S \subset \mathbb{R}_+^D$, then the density $q^{[M]}(t, n, x)$ is the solution of the Liouville-master equation (LME)

$$\begin{aligned} \partial_t q^{[M]}(t, n, x) \quad = \quad & \sum_{j \in J_1} \tilde{\beta}_j^{[M]}(x) \Big(\alpha_j(n - \nu_j) q^{[M]}(t, n - \nu_j, x) - \alpha_j(n) q^{[M]}(t, n, x) \Big) \\ & - \frac{1}{M} \sum_{j=1}^{r} \alpha_j(n) \nabla \left(\tilde{\beta}_j^{[M]}(x) q^{[M]}(t, n, x) \right)^T \mu_j \end{aligned} \tag{34}$$

for $n \in \mathbb{N}_0^d$, $x \in \mathbb{R}_+^D$, $t \geq 0$, where ∇ acts on the x-variables only, i.e.

$$\nabla u(t, n, x) = \left(\frac{\partial u}{\partial x_1}(t, n, x) \ , \ \ldots \ , \ \frac{\partial u}{\partial x_D}(t, n, x) \right)^T .$$

The LME is provided with the boundary condition

$$q^{[M]}(t,n,x) \quad = \quad 0 \quad \text{ if } x_i = 0 \text{ for one or more } i \in \{1,\ldots,D\}. \tag{35}$$

and the initial data

$$q^{[M]}(0,n,x) \quad = \quad \delta_{n_0}(n) q_0(x). \tag{36}$$

Specifying $q_0(x)$ is somewhat delicate: since the process (32)-(33) starts in (n_0, m_0) with probability 1, $q_0(x)$ must be the corresponding Dirac delta, and then the question arises if a solution of (34)-(36) actually exists or in which sense the word "solution" has to be understood. Such analytical difficulties can be avoided if we choose $q_0 : \mathbb{R}_+^D \to \mathbb{R}$ to be a smooth nonnegative function with the properties

$$q_0(x) = 0 \text{ if } \|x - m_0\|_\infty > \varepsilon, \qquad \int_{\mathbb{R}_+^D} q_0(x) = 1, \qquad \int_{\mathbb{R}_+^D} x q_0(x) = m_0 \tag{37}$$

for some $0 < \varepsilon \ll 1$. If ε is sufficiently small, then the additional error caused by the modified initial data can be neglected.

With the shift operator defined in (27), the LME (34) can be reformulated as

$$\partial_t q^{[M]} \quad = \quad \sum_{j \in J_1} \tilde{\beta}_j^{[M]} (\Delta_{\nu_j}^1 - 1) \alpha_j q^{[M]} - \frac{1}{M} \sum_{j=1}^{r} \alpha_j \nabla \left(\tilde{\beta}_j^{[M]} q^{[M]} \right)^T \mu_j. \tag{38}$$

4 Error bound for the approximation by the piecewise deterministic process

In this section an error bound for the difference between the original Markov process and the piecewise deterministic process is presented. Convergence in distribution has recently been shown in [8]. In our analysis, only the *marginal* distribution of the discrete species $\mathcal{S}_1, \ldots, \mathcal{S}_d$ and the conditional moments of the continuous species $\mathcal{S}_{d+1}, \ldots, \mathcal{S}_D$ are considered, but in exchange, the *rate* of convergence will be established.

4.1 Marginal distributions, conditional expectations, and regularity assumptions

Assumption 2 *We assume that the CME (29) with initial condition (26) has a unique classical solution $p^{[M]}(t,\cdot,\cdot) \in \mathcal{X}_{d,D}^3$ for $t \in [0, t_{end}]$ and that*

$$(n,m) \mapsto \alpha_j(n) p^{[M]}(t,n,m) \in \mathcal{X}_{d,D}^3 \qquad \textit{for all } j \in \{1,\ldots,r\}.$$

Moreover, we assume that the LME (38) with boundary condition (35) and initial data (36) has a unique classical solution $q^{[M]}(t,\cdot,\cdot) \in \mathcal{Y}_{d,D}^3$ for $t \in [0, t_{end}]$ and that

$$(n,x) \mapsto \alpha_j(n) q^{[M]}(t,n,x) \in \mathcal{Y}_{d,D}^3 \qquad \textit{for all } j \in \{1,\ldots,r\}.$$

The marginal distribution of the discrete species $\mathcal{S}_1, \ldots, \mathcal{S}_d$ is given by

$$p_1^{[M]}(t,n) = \sum_{m \in \mathbb{N}_0^D} p^{[M]}(t,n,m),$$

and we define

$$p_2^{[M]}(t,m|n) = \begin{cases} \dfrac{p^{[M]}(t,n,m)}{p_1^{[M]}(t,n)} & \text{if } p_1^{[M]}(t,n) > 0 \\ 0 & \text{else} \end{cases}.$$

If $p_1^{[M]}(t,n) > 0$, then $p_2^{[M]}(t,m|n)$ is the conditional probability that $Y^{[M]}(t) = m$ under the constraint that $X^{[M]}(t) = n$. Moreover, let

$$\eta^{[M]}(t,n) \quad = \quad \sum_{m \in \mathbb{N}_0^D} m p_2^{[M]}(t,m|n)$$

be the conditional expectation, and let

$$\sigma^{[M]}(t,n) \quad = \quad \sum_{m \in \mathbb{N}_0^D} \Big(m - \eta^{[M]}(t,n)\Big) \Big(m - \eta^{[M]}(t,n)\Big)^T p_2^{[M]}(t,m|n)$$

be the associated covariance matrix. The corresponding quantities for $q^{[M]}$ are defined as follows:

$$\begin{aligned} q_1^{[M]}(t,n) &= \int_{\mathbb{R}_+^D} q^{[M]}(t,n,x)\, dx \\ q_2^{[M]}(t,x|n) &= \begin{cases} \dfrac{q^{[M]}(t,n,x)}{q_1^{[M]}(t,n)} & \text{if } q_1^{[M]}(t,n) > 0 \\ 0 & \text{else} \end{cases} \\ \theta^{[M]}(t,n) &= \int_{\mathbb{R}_+^D} x q_2^{[M]}(t,x|n)\, dx \\ \varsigma(t,n) &= \int_{\mathbb{R}_+^D} \Big(x - \theta^{[M]}(t,n)\Big) \Big(x - \theta^{[M]}(t,n)\Big)^T q_2^{[M]}(t,x|n)\, dx \end{aligned}$$

Assumption 2 guarantees the existence of $\eta^{[M]}(t,n)$, $\sigma^{[M]}(t,n)$, $\theta^{[M]}(t,n)$, and $\varsigma(t,n)$ for all $n \in \mathbb{N}_0^d$ and $t \in [0, t_{\text{end}}]$

Assumption 3 *There is a constant $C > 0$ such that*

$$\|\eta^{[M]}(t,n)\| \le C \cdot M, \qquad \|\theta^{[M]}(t,n)\| \le C \qquad \textit{for all } t \in [0,t_{end}], n \in \mathbb{N}_0^d \tag{39}$$

and

$$\|\sigma^{[M]}(t,n)\| \le C \cdot M, \qquad \|\varsigma^{[M]}(t,n)\| \le \frac{C}{M} \qquad \textit{for all } t \in [0,t_{end}], n \in \mathbb{N}_0^d. \tag{40}$$

Moreover, all third central moments of $p_2^{[M]}(t,\cdot|n)$ are bounded by CM^2, and all third central moments of $q_2^{[M]}(t,\cdot|n)$ are bounded by C/M for all $t \in [0, t_{end}]$ and $n \in \mathbb{N}_0^d$.

It follows from (26), (36), and (37) that $\eta^{[M]}(0|n) = \mathcal{O}(M)$, $\theta^{[M]}(0,n) = \mathcal{O}(1)$, and $\sigma^{[M]}(0|n) = 0$, and $\varsigma^{[M]}(0|n) = \mathcal{O}(\varepsilon^2)$. By a continuity argument, it can be shown that for every single M there is a $t_{\text{end}}^{[M]} > 0$ such that the above bounds hold for all $t \in [0, t_{\text{end}}^{[M]}]$. However, Assumption 3 is slightly stronger, because it is assumed that t_{end} does not depend on M.

At first sight, the assumptions on $\varsigma^{[M]}(t,n)$ and the third moments of $q_2^{[M]}(t,\cdot|n)$ seem to be somewhat restrictive. A closer inspection reveals, however, that the first term on the right-hand side of the LME (34) does not change these objects, and due to the factor M^{-1} of the second term, the above assumptions are reasonable.

Assumption 4 *Suppose that there is a constant $C > 0$ such that for all $t \in [0, t_{end}]$ and $j \in \{1, \ldots, r\}$ the bound*

$$\|\alpha_j(\cdot)u(t,\cdot)\|_{\ell_d^1} \quad \leq \quad C\,\|u(t,\cdot)\|_{\ell_d^1} \tag{41}$$

holds for

$$\begin{aligned} u(t,n) &= \left(\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right)(t,n) \\ \text{or} \quad u(t,n) &= \left(M^{-1}\beta_j^{[M]}(\eta^{[M]})\eta^{[M]}p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]}q_1^{[M]}\right)(t,n). \end{aligned}$$

Remark.

1. In both cases we have $\alpha_j(\cdot)u(t,\cdot) \in \ell_n^1$ according to Assumption 2.
2. Assumption 4 is true if $u(t,\cdot)$ decays sufficiently fast as $n \to \infty$. In the model problem discussed in Section 2.3 the assumption is true because there the state space is bounded in the n-direction.

4.2 A bound for the modeling error

After these preparations, the main result of this article can be formulated.

Theorem 1 *Let $p(t,n,m)$ be the solution of the CME (29) with initial condition (26), and let $q(t,n,x)$ be the solution of the LME (38) with boundary condition (35) and initial condition (36). Under the assumptions 1, 2, 3, and 4, there is a constant $C > 0$ such that the approximation error is bounded by*

$$\|p_1^{[M]}(t,\cdot) - q_1^{[M]}(t,\cdot)\|_{\ell_d^1} \quad \leq \quad \frac{C}{M} \tag{42}$$

$$\left\| \frac{1}{M}\eta^{[M]}(t,\cdot)p_1^{[M]}(t,\cdot) - \theta^{[M]}(t,\cdot)q_1^{[M]}(t,\cdot) \right\|_{\ell_d^1} \quad \leq \quad \frac{C}{M} \tag{43}$$

for all $t \in [0, t_{end}]$.

Remarks.

1. The choice of the parameter ε in (37) may alter the constants in the error bound and the value of t_{end} in Assumption 3. The convergence rate, however, is not affected by ε.
2. For the model problem from Section 2.3 the terms on the left-hand side of (42) and (43) have been estimated by numerical simulations for different values of M. The result was shown in Figure 2 and confirms that both errors are proportional to M^{-1}.

An immediate consequence of Theorem 1 is the following

Corollary 1 *If there is a constant $C_n^{\min} > 0$ such that*

$$p_1^{[M]}(t,n) \geq C_n^{\min} \qquad \text{for all } t \in [0, t_{end}] \text{ and } M \in \mathbb{N},$$

then, under the assumptions of Theorem 1, the bound

$$\left\| \frac{1}{M}\eta^{[M]}(t,n) - \theta^{[M]}(t,n) \right\| \leq \frac{C}{C_n^{\min} M}$$

hold for the error in the conditional expectations.

Proof. Since

$$\frac{1}{M}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]} \quad = \quad \left(\frac{1}{M}\eta^{[M]} - \theta^{[M]}\right) p_1^{[M]} + \theta^{[M]}\left(p_1^{[M]} - q_1^{[M]}\right),$$

it follows from (43) that

$$\begin{aligned} & \left\| \frac{1}{M}\eta^{[M]}(t,n) - \theta^{[M]}(t,n) \right\| \\ = \quad & \frac{1}{p_1^{[M]}(t,n)} \left(\left\| \frac{1}{M}\eta^{[M]}(t,n)p_1^{[M]}(t,n) - \theta^{[M]}(t,n)q_1^{[M]}(t,n) \right\| \right. \\ & \qquad \left. + \|\theta^{[M]}(t,n)\| \cdot \left| p_1^{[M]}(t,n) - q_1^{[M]}(t,n) \right| \right) \\ \leq \quad & \frac{C}{M p_1^{[M]}(t,n)}, \end{aligned}$$

and the assumption that $p_1^{[M]}(t,n) \geq C_n^{\min}$ yields the assertion. ∎

For those n where $p_1^{[M]}(t,n) \approx 0$, the constant $C_n^{\min}$ must be very small, and hence the difference between $\frac{1}{M}\eta^{[M]}(t,n)$ and $\theta^{[M]}(t,n)$ can be very large. However, this error is not relevant because $p_1^{[M]}(t,n) \approx 0$ means that these states are only visited with a very small probability.

Proof of Theorem 1. It will be shown in Lemma 5 and Lemma 6 that

$$E(t) = \|p_1^{[M]}(t,\cdot) - q_1^{[M]}(t,\cdot)\|_{\ell_d^1} + \left\| \frac{1}{M}\eta^{[M]}(t,\cdot)p_1^{[M]}(t,\cdot) - \theta^{[M]}(t,\cdot)q_1^{[M]}(t,\cdot) \right\|_{\ell_d^1}$$

satisfies the Gronwall inequality

$$E(t) \leq \frac{C_1}{M} + C_2 \int_0^t E(\tau)\, d\tau$$

for some constants $C_1, C_2 > 0$. Then, the Gronwall lemma yields

$$E(t) \leq \frac{C_1}{M} e^{C_2 t}$$

which implies (42) and (43). ■

Lemma 4 *Let $y : \mathbb{N}_0^d \longrightarrow \mathbb{R}^d$, $z : \mathbb{N}_0^d \longrightarrow \mathbb{R}^d$ with*

$$\max_{n\in\mathbb{N}_0^d} \|y(n)\| \leq CM, \qquad \max_{n\in\mathbb{N}_0^d} \|z(n)\| \leq C, \tag{44}$$

and let $u \in \ell_d^1$ and $v \in \ell_d^1$. Then for every $j \in \{1,\ldots,r\}$, there is a constant $C > 0$ such that

$$\left\|\beta_j^{[M]}\big(y\big)u - \tilde\beta_j^{[M]}\big(z\big)v\right\|_{\ell_d^1} \quad\leq\quad CM^{1-\gamma(j)}\Big(\|M^{-1}yu - zv\|_{\ell_d^1} + \|u-v\|_{\ell_d^1}\Big) + CM^{-\gamma(j)}$$

with $\gamma(j)$ defined in (22). Products of sequences are to be understood entry-wise, e.g.

$$\left[\beta_j^{[M]}(y)u\right](n) = \beta_j^{[M]}(y(n))u(n),$$

and so on. Note that the assumption (44) implies that $M^{-1}yu - zv \in \ell_d^1$.

Proof. We investigate the propensities corresponding to the reaction scheme (1) and treat three cases separately:

- If $|\lambda_j^{in}|_1 = 0$, then $\beta_j^{[M]}(y) = \tilde\beta_j^{[M]}(y) = M^{1-\gamma(j)}$ is constant, and hence

$$\left\|\beta_j^{[M]}\big(y\big)u - \tilde\beta_j^{[M]}\big(z\big)v\right\|_{\ell_d^1} \quad=\quad M^{1-\gamma(j)}\,\|u-v\|_{\ell_d^1}\,.$$

- If $|\lambda_j^{in}|_1 = 1$, then there is a $k \in \{1,\ldots,d\}$ such that $\beta_j^{[M]}(y) = M^{-\gamma(j)}y_k$ and $\tilde\beta_j^{[M]}(y) = M^{1-\gamma(j)}y_k$, and hence

$$\begin{aligned}\left\|\beta_j^{[M]}\big(y\big)u - \tilde\beta_j^{[M]}\big(z\big)v\right\| &= M^{1-\gamma(j)}\left\|M^{-1}y_ku - z_kv\right\|_{\ell_d^1}\\ &\leq M^{1-\gamma(j)}\left\|M^{-1}yu - zv\right\|_{\ell_d^1}\end{aligned}$$

- If $|\lambda_j^{in}|_1 = 2$, then the propensity $\tilde\beta_j^{[M]}(y)$ takes the form

$$\tilde\beta_j^{[M]}(y) = \hat c_j M^{1-\gamma(j)} y_k y_l \qquad \text{with } \hat c_j = \begin{cases} c_j & \text{if } k \neq l \\ \frac{1}{2}c_j & \text{if } k = l \end{cases}$$

for some $k, l \in \{1, \ldots, d\}$. The assumption (44) allows to apply Lemma 3, which gives

$$\left\| \beta_j^{[M]}(y)u - \tilde{\beta}_j^{[M]}(y/M)u \right\|_{\ell_d^1} \quad \leq \quad CM^{-\gamma(j)} \|u\|_{\ell_d^1}. \tag{45}$$

Thus, we only have to bound the difference

$$\begin{aligned} & \tilde{\beta}_j^{[M]}(y/M)u - \tilde{\beta}_j^{[M]}(z)v \\ = \quad & \hat{c}_j M^{1-\gamma(j)} \left(M^{-2} y_k y_l u - z_k z_l v \right) \\ = \quad & \hat{c}_j M^{1-\gamma(j)} \left(M^{-1} y_k \left(M^{-1} y_l u - z_l v \right) + z_l \left(M^{-1} y_k u - z_k v \right) - M^{-1} y_k z_l \left(u - v \right) \right). \end{aligned}$$

Since (44) implies that $|y_k(n)/M| \leq C$ and $|z_l(n)| \leq C$, it follows that

$$\left\| \tilde{\beta}_j^{[M]}(y/M)u - \tilde{\beta}_j^{[M]}(z)v \right\|_{\ell_d^1} \leq CM^{1-\gamma(j)} \left(\|M^{-1}yu - zv\|_{\ell_d^1} + \|u - v\|_{\ell_d^1} \right)$$

which, together with (45), proves the assertion. ∎

Lemma 5 *Under the assumptions of Theorem 1 there is a constant $C > 0$ such that*

$$\begin{aligned} \|p_1^{[M]}(t,\cdot) - q_1^{[M]}(t,\cdot)\|_{\ell_d^1} \leq \frac{C}{M} \quad & + \quad C \int_0^t \left\| \left(\frac{1}{M} \eta^{[M]} p_1^{[M]} - \theta^{[M]} q_1^{[M]} \right)(\tau,\cdot) \right\|_{\ell_d^1} d\tau \\ & + \quad C \int_0^t \left\| p_1^{[M]}(\tau,\cdot) - q_1^{[M]}(\tau,\cdot) \right\|_{\ell_d^1} d\tau. \end{aligned}$$

for all $t \in [0, t_{end}]$.

Proof. Step 1: From the definition of the marginal distribution $p_1^{[M]}$ it follows that

$$\partial_t p_1^{[M]} \quad = \quad \sum_{j \in J_0} \sum_{m \in \mathbb{N}_0^D} (\Delta_{\nu_j}^1 \Delta_{\mu_j}^2 - 1) \alpha_j \beta_j^{[M]} p^{[M]} + \sum_{j \in J_1} \sum_{m \in \mathbb{N}_0^D} (\Delta_{\nu_j}^1 \Delta_{\mu_j}^2 - 1) \alpha_j \beta_j^{[M]} p^{[M]}.$$

The first sum vanishes, because $\Delta_{\nu_j}^1 = I$ for $j \in J_0$, and

$$\sum_{m \in \mathbb{N}_0^D} (\Delta_{\mu_j}^2 - 1) \alpha_j \beta_j^{[M]} p^{[M]} = 0$$

by Lemma 1 and Lemma 2. Since

$$\Delta_{\nu_j}^1 \Delta_{\mu_j}^2 - 1 = \Delta_{\nu_j}^1 (\Delta_{\mu_j}^2 - 1) + (\Delta_{\nu_j}^1 - 1)$$

and, again by Lemma 1 and Lemma 2,

$$\sum_{j \in J_1} \sum_{m \in \mathbb{N}_0^D} \Delta_{\nu_j}^1 (\Delta_{\mu_j}^2 - 1) \alpha_j \beta_j^{[M]} p^{[M]} = 0$$

we obtain

$$\begin{aligned}\partial_t p_1^{[M]} &= \sum_{j\in J_1}\sum_{m\in\mathbb{N}_0^D}(\Delta_{\nu_j}^1-1)\alpha_j\beta_j^{[M]}p^{[M]} \\ &= \sum_{j\in J_1}(\Delta_{\nu_j}^1-1)\alpha_j\sum_{m\in\mathbb{N}_0^D}\beta_j^{[M]}p_2^{[M]}p_1^{[M]}. \end{aligned} \tag{46}$$

Following the ideas of [14] we represent $\beta_j^{[M]}$ by the Taylor expansion

$$\begin{aligned}\beta_j^{[M]}(m) &= \beta_j^{[M]}(\eta^{[M]})+\nabla\beta_j^{[M]}(\eta^{[M]})^T(m-\eta^{[M]}) \\ &\quad +\frac{1}{2}(m-\eta^{[M]})^T\left(\nabla^2\beta_j^{[M]}\right)(m-\eta^{[M]})\end{aligned} \tag{47}$$

where $\eta^{[M]}=\eta^{[M]}(t,n)$. The usual remainder term vanishes because $\beta_j^{[M]}$ is at most quadratic due to Assumption 1. This yields

$$\sum_{m\in\mathbb{N}_0^D}\beta_j^{[M]}(m)p_2^{[M]}(t,m|n) = \beta_j^{[M]}(\eta^{[M]})+\operatorname{trace}\left(\sigma^{[M]}(t,n)\nabla^2\beta_j^{[M]}\right) \tag{48}$$

because $\sum_{m\in\mathbb{N}_0^D}p_2^{[M]}(t,m|n)=1$ and $\sum_{m\in\mathbb{N}_0^D}(m-\eta^{[M]}(t,n))p_2^{[M]}(t,m|n)=0$. According to (23) we have

$$\nabla^2\beta_j^{[M]}=\begin{cases}0 & \text{if } |\lambda_j^{in}|_1<2\\ M^{-1-\gamma(j)} & \text{if } |\lambda_j^{in}|_1=2\end{cases}. \tag{49}$$

Since $\gamma(j)=1$ for all $j\in J_1$ and $\sigma^{[M]}=\mathcal{O}(M)$ by assumption (40), it follows that $\sigma^{[M]}\nabla^2\beta_j^{[M]}=\mathcal{O}\big(M^{-1}\big)$ and thus (48) becomes

$$\sum_{m\in\mathbb{N}_0^D}\beta_j^{[M]}(m)p_2^{[M]}(t,m|n) = \beta_j^{[M]}(\eta^{[M]})+\mathcal{O}\big(M^{-1}\big) \tag{50}$$

Substituting (50) into (46) gives

$$\partial_t p_1^{[M]} = \sum_{j\in J_1}(\Delta_{\nu_j}^1-1)\alpha_j\beta_j^{[M]}(\eta^{[M]})p_1^{[M]}+\mathcal{O}\big(M^{-1}\big). \tag{51}$$

Step 2: Now the same steps are carried out *mutatis mutandis* for $q^{[M]}$. By definition of the marginal distribution $q_1^{[M]}$ and (38) we have

$$\begin{aligned}\partial_t q_1^{[M]} &= \sum_{j\in J_1}\int_{\mathbb{R}_+^D}(\Delta_{\nu_j}^1-1)\alpha_j\tilde{\beta}_j^{[M]}q^{[M]}\,dx-\frac{1}{M}\sum_{j=1}^r\alpha_j\int_{\mathbb{R}_+^D}\nabla\left(\tilde{\beta}_j^{[M]}q^{[M]}\right)^T\mu_j\,dx \\ &= \sum_{j\in J_1}(\Delta_{\nu_j}^1-1)\alpha_j\int_{\mathbb{R}_+^D}\tilde{\beta}_j^{[M]}q^{[M]}\,dx\end{aligned}$$

because the second term vanishes due to the boundary condition (36). Substituting the Taylor expansion

$$\begin{aligned}\tilde{\beta}_j^{[M]}(x) = \tilde{\beta}_j^{[M]}(\theta^{[M]}) &+ \nabla\tilde{\beta}_j^{[M]}(\theta^{[M]})^T(x-\theta^{[M]}) \\ &+ \frac{1}{2}(x-\theta^{[M]})^T\left(\nabla^2\tilde{\beta}_j^{[M]}\right)(x-\theta^{[M]})\end{aligned} \tag{52}$$

and proceeding similar as before yields the counterpart of (48), namely

$$\int\limits_{\mathbb{R}_+^D} \tilde{\beta}_j^{[M]}(x) q_2^{[M]}(t,x|n)\,dx = \tilde{\beta}_j^{[M]}(\theta^{[M]}) + \operatorname{trace}\left(\varsigma^{[M]}\nabla^2\tilde{\beta}_j^{[M]}\right). \tag{53}$$

Since $\varsigma^{[M]}\nabla^2\tilde{\beta}_j^{[M]} = \mathcal{O}\big(M^{-1}\big)$ by Assumption 3, it follows that

$$\partial_t q_1^{[M]} = \sum_{j\in J_1}(\Delta_{\nu_j}^1 - 1)\alpha_j\tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]} + \mathcal{O}\big(M^{-1}\big). \tag{54}$$

Step 3: Finally, we subtract (54) from (51) and integrate from 0 to t. Since $p_1^{[M]}(0) = q_1^{[M]}(0)$ and $\|(\Delta_{\nu_j}^1 - 1)\|_{\ell_d^1} \le 2$, we obtain

$$\begin{aligned}&\|p_1^{[M]}(t,\cdot) - q_1^{[M]}(t,\cdot)\|_{\ell_d^1} \\ \le\ & 2\int_0^t \sum_{j\in J_1}\left\|\alpha_j\left(\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right)(\tau,\cdot)\right\|_{\ell_d^1} d\tau + \mathcal{O}\big(M^{-1}\big) \\ \le\ & C\int_0^t \sum_{j\in J_1}\left\|\left(\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right)(\tau,\cdot)\right\|_{\ell_d^1} d\tau + \mathcal{O}\big(M^{-1}\big).\end{aligned}$$

The second inequality follows from Assumption 4. Now Lemma 4 can be applied, and since $M^{1-\gamma(j)} = 1$ for all $j \in J_1$, the assertion follows. ∎

Lemma 6 *Under the assumptions of Theorem 1 there is a constant $C > 0$ such that*

$$\begin{aligned}\|M^{-1}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]}\|_{\ell_d^1} \le \frac{C}{M} &+ C\int_0^t \left\|\left[M^{-1}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell_d^1} d\tau \\ &+ C\int_0^t \left\|\left[p_1^{[M]} - q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell_d^1} d\tau\end{aligned}$$

for all $t \in [0, t_{end}]$.

Proof. Step 1: From the definition of $\eta^{[M]}$ and $p_1^{[M]}$ and the CME (29) it follows that

$$\partial_t\left(\eta^{[M]}p_1^{[M]}\right)(t,n) = \sum_{m\in\mathbb{N}_0^D} m\,\partial_t p(t,n,m)$$

$$
\begin{aligned}
&= \sum_{j=1}^{r} \sum_{m\in\mathbb{N}_0^D} m\left((\Delta^1_{\nu_j}\Delta^2_{\mu_j}-1)\alpha_j\beta_j^{[M]}p^{[M]}\right)(t,n,m)\\
&= \sum_{j=1}^{r} \sum_{m\in\mathbb{N}_0^D} m\left(\Delta^1_{\nu_j}(\Delta^2_{\mu_j}-1)\alpha_j\beta_j^{[M]}p^{[M]}\right)(t,n,m)\\
&\quad + \sum_{j=1}^{r} \sum_{m\in\mathbb{N}_0^D} m\left((\Delta^1_{\nu_j}-1)\alpha_j\beta_j^{[M]}p^{[M]}\right)(t,n,m)\\
&= \sum_{j=1}^{r} \mu_j \sum_{m\in\mathbb{N}_0^D} \left(\Delta^1_{\nu_j}\alpha_j\beta_j^{[M]}p^{[M]}\right)(t,n,m) \qquad (55)\\
&\quad + \sum_{j\in J_1} \sum_{m\in\mathbb{N}_0^D} m\left((\Delta^1_{\nu_j}-1)\alpha_j\beta_j^{[M]}p^{[M]}\right)(t,n,m) \qquad (56)
\end{aligned}
$$

due to Lemma 2 (iv) and the fact that $\Delta^1_{\nu_j}-1=0$ for all $j\in J_0$. For the first term (55), it follows from (48) that

$$
\begin{aligned}
&\sum_{j=1}^{r} \mu_j \sum_{m\in\mathbb{N}_0^D} \left(\Delta^1_{\nu_j}\alpha_j\beta_j^{[M]}p^{[M]}\right)(t,n,m)\\
&= \sum_{j=1}^{r} \mu_j \left(\Delta^1_{\nu_j}\alpha_j\left[\beta_j^{[M]}(\eta^{[M]}) + \operatorname{trace}\left(\sigma^{[M]}\nabla^2\beta_j^{[M]}\right)\right]p_1^{[M]}\right)(t,n,m)\\
&= \sum_{j=1}^{r} \mu_j \left(\Delta^1_{\nu_j}\alpha_j\beta_j^{[M]}(\eta^{[M]})p_1^{[M]}\right)(t,n,m) + \mathcal{O}(1)
\end{aligned}
$$

because (49) and Assumption (40) yield that

$$
\left\|\operatorname{trace}\left(\sigma^{[M]}(t,n)\nabla^2\beta_j^{[M]}\right)\right\| \le CM^{-\gamma(j)} \le C
$$

for all $t\in[0,t_{\text{end}}]$ and $n\in\mathbb{N}_0^d$. We remark that in the proof of Lemma 5, the same trace term only caused an error of $\mathcal{O}\big(M^{-1}\big)$; cf. (50). This was due to the fact that in (51) we have $j\in J_1$ and hence $\gamma(j)=1$, but this is not the case in (55)

For the second term (56), we use the Taylor expansion (47) to obtain

$$
\sum_{m\in\mathbb{N}_0^D} m\beta_j^{[M]}(m)p^{[M]}(t,n,m) \;=\; \left(\beta_j^{[M]}(\eta^{[M]})\eta^{[M]} + R_1(t,n)\right)p_1^{[M]}(t,n)
$$

with $\eta^{[M]}=\eta^{[M]}(t,n)$ and the remainder term

$$
\begin{aligned}
R_1(t,n) \;=\; \sum_{m\in\mathbb{N}_0^D} m\Bigg(&\nabla\beta_j^{[M]}(\eta^{[M]})^T(m-\eta^{[M]})\\
&+\frac{1}{2}(m-\eta^{[M]})^T\left(\nabla^2\beta_j^{[M]}\right)(m-\eta^{[M]})\Bigg)p_2^{[M]}(t,m|n)
\end{aligned}
$$

$$
\begin{aligned}
&= \sigma^{[M]}\nabla\beta_j^{[M]}(\eta^{[M]}) + \frac{1}{2}\eta^{[M]}\mathrm{trace}\left(\sigma^{[M]})\nabla^2\beta_j^{[M]}\right) \\
&\quad + \frac{1}{2}\sum_{m\in\mathbb{N}_0^D}(m-\eta^{[M]})\left((m-\eta^{[M]})^T\left(\nabla^2\beta_j^{[M]}\right)(m-\eta^{[M]})\right)p_2^{[M]}(t,m|n)
\end{aligned}
$$

which depends on the third moment of $p_2^{[M]}(t,\cdot|n)$. Now the crucial observation is that the sum in (56) is only taken over J_1. For all $j\in J_1$, it follows from (23) and assumption (39) that

$$
\nabla\beta_j^{[M]}(\eta^{[M]}) = \mathcal{O}\big(M^{-1}\big)\,, \qquad \nabla^2\beta_j^{[M]} = \mathcal{O}\big(M^{-2}\big)\,,
$$

and Assumption 3 yields that $\|R_1(t,n)\|\le C$ for all $n\in\mathbb{N}_0^d$ and $t\in[0,t_{\mathrm{end}}]$. All in all, we have shown in step 1 that

$$
\begin{aligned}
\partial_t\left(\eta^{[M]}p_1^{[M]}\right)(t,n) &= \sum_{j=1}^r \mu_j\left(\Delta_{\nu_j}^1\alpha_j\beta_j^{[M]}(\eta^{[M]})p_1^{[M]}\right)(t,n) \\
&\quad + \sum_{j\in J_1}\left((\Delta_{\nu_j}^1-1)\alpha_j\beta_j^{[M]}(\eta^{[M]})\eta^{[M]}p_1^{[M]}\right)(t,n) + \mathcal{O}(1)\,.
\end{aligned} \tag{57}
$$

Later this equation will be multiplied by M^{-1} such that the rest term $\mathcal{O}(1)$ becomes $\mathcal{O}\big(M^{-1}\big)$.

Step 2: Now an analogous equation is derived for $\partial_t\left(\theta^{[M]}q_1^{[M]}\right)$. According to the LME (38) we have

$$
\begin{aligned}
\partial_t\left(\theta^{[M]}q_1^{[M]}\right) &= \int_{\mathbb{R}_+^D} x\partial_t q^{[M]}\,dx \\
&= \sum_{j\in J_1}\int_{\mathbb{R}_+^D} x\tilde\beta_j^{[M]}(\Delta_{\nu_j}^1-1)\alpha_j q^{[M]}\,dx - \frac{1}{M}\sum_{j=1}^r\int_{\mathbb{R}_+^D} x\alpha_j\nabla\left(\tilde\beta_j^{[M]}q^{[M]}\right)^T\mu_j\,dx
\end{aligned}
$$

with $\tilde\beta_j^{[M]} = \tilde\beta_j^{[M]}(x)$ and $q^{[M]} = q^{[M]}(t,n,x)$. Integration by parts yields

$$
\int_{\mathbb{R}_+^D} x\nabla\left(\tilde\beta_j^{[M]}q^{[M]}\right)^T\mu_j\,dx = -\mu_j\int_{\mathbb{R}_+^D}\tilde\beta_j^{[M]}q^{[M]}\,dx
$$

because the boundary terms cancel due to the boundary condition (35) and $\lim_{x\to\infty}\tilde\beta_j^{[M]}(x)q^{[M]}(t,n,x) = 0$ (since $\tilde\beta_j^{[M]}(\cdot)q^{[M]}(t,n,\cdot)\in\ell_{d+D}^1$ due to Assumption 2). This gives

$$
\partial_t\left(\theta^{[M]}q_1^{[M]}\right) = \sum_{j\in J_1}(\Delta_{\nu_j}^1-1)\alpha_j\int_{\mathbb{R}_+^D} x\tilde\beta_j^{[M]}q^{[M]}\,dx \tag{58}
$$

$$
+\frac{1}{M}\sum_{j=1}^r\mu_j\int_{\mathbb{R}_+^D}\alpha_j\tilde\beta_j^{[M]}q^{[M]}\,dx. \tag{59}
$$

Next, we insert the Taylor expansion (52) into (58) and obtain

$$\int\limits_{\mathbb{R}_+^D} x\tilde{\beta}_j^{[M]} q^{[M]}\, dx = \left(\tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]} + R_2(t,n)\right) q_1^{[M]}(t,n)$$

with $\theta^{[M]} = \theta^{[M]}(t,n)$ and the rest term

$$\begin{aligned} R_2(t,n) &= \int\limits_{\mathbb{R}_+^D} x\Bigg(\nabla\tilde{\beta}_j^{[M]}(\theta^{[M]})^T(x-\theta^{[M]}) \\ &\qquad\qquad +\frac{1}{2}(x-\theta^{[M]})^T\left(\nabla^2\tilde{\beta}_j^{[M]}\right)(x-\theta^{[M]})\Bigg) q_2^{[M]}\, dx \\ &= \varsigma(t,n)\nabla\tilde{\beta}_j^{[M]}(\theta^{[M]}) + \frac{1}{2}\theta^{[M]}\mathrm{trace}\left(\varsigma^{[M]}(t,n)\nabla^2\tilde{\beta}_j^{[M]}\right) \\ &\quad +\frac{1}{2}\int\limits_{\mathbb{R}_+^D}(x-\theta^{[M]})(x-\theta^{[M]})^T\left(\nabla^2\tilde{\beta}_j^{[M]}\right)(x-\theta^{[M]})q_2^{[M]}\, dx. \end{aligned}$$

Again we note that the sum in (58) is only taken over J_1, such that (31) and Assumption (39) imply that $\nabla\tilde{\beta}_j^{[M]}(\theta^{[M]})$ and its derivatives are uniformly bounded with respect to M. Combining this with Assumption 3 implies that $\|R_2(t,n)\| \leq C/M$ for all $n \in \mathbb{N}_0^d$ and $t \in [0, t_{\mathrm{end}}]$.

Next, the second term (59) is investigated. The Taylor expansion (52) yields

$$\begin{aligned} &\frac{1}{M}\sum_{j=1}^r \mu_j \int\limits_{\mathbb{R}_+^D} \alpha_j\tilde{\beta}_j^{[M]} q^{[M]}\, dx \\ &= \frac{1}{M}\sum_{j=1}^r \mu_j\alpha_j\left[\tilde{\beta}_j^{[M]}(\theta^{[M]}) + \mathrm{trace}\left(\varsigma^{[M]}\nabla^2\tilde{\beta}_j^{[M]}\right)\right] q_1^{[M]} \\ &= \frac{1}{M}\sum_{j=1}^r \mu_j\alpha_j\tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]} + \mathcal{O}\big(M^{-1}\big) \end{aligned}$$

because due to (31) and (40)

$$\left\|\mathrm{trace}\left(\varsigma^{[M]}(t,n)\nabla^2\tilde{\beta}_j^{[M]}\right)\right\| \leq CM^{-\gamma(j)} \leq C$$

for all $t \in [0, t_{\mathrm{end}}]$ and $n \in \mathbb{N}_0^d$. We thus obtain

$$\begin{aligned} \partial_t\left(\theta^{[M]}q_1^{[M]}\right) &= \sum_{j\in J_1}(\Delta_{\nu_j}^1 - 1)\alpha_j\tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]}q_1^{[M]} \\ &\quad +\frac{1}{M}\sum_{j=1}^r \mu_j\left(\alpha_j\tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right)(t,n,x) + \mathcal{O}\big(M^{-1}\big). \end{aligned} \tag{60}$$

Step 3: Multiplying (57) with M^{-1}, subtracting (60) and integrating from 0 to t yields, with $\|(\Delta^1_{\nu_j} - 1)\|_{\ell^1_d} \leq 2$, that

$$\begin{aligned}
&\|M^{-1}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]}\|_{\ell^1_d} \\
\leq\ & \frac{C}{M} + \frac{C}{M}\int_0^t \sum_{j=1}^r \left\| \alpha_j \left[\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} d\tau \\
&+C\int_0^t \sum_{j\in J_1} \left\| \alpha_j \left[M^{-1}\beta_j^{[M]}(\eta^{[M]})\eta^{[M]}p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]}q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} d\tau \\
\leq\ & \frac{C}{M} + \frac{C}{M}\int_0^t \sum_{j=1}^r \left\| \left[\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} d\tau \\
&+C\int_0^t \sum_{j\in J_1} \left\| \left[M^{-1}\beta_j^{[M]}(\eta^{[M]})\eta^{[M]}p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]}q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} d\tau.
\end{aligned}$$

The second inequality follows from Assumption 4. Applying Lemma 4 yields

$$\begin{aligned}
&\frac{1}{M}\left\| \left[\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} \\
&\leq C\left\| \left[M^{-1}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} + C\left\| \left[p_1^{[M]} - q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} + \frac{C}{M}.
\end{aligned}$$

Hence, it remains to show that for all $j \in J_1$

$$\begin{aligned}
&\left\| \left[M^{-1}\beta_j^{[M]}(\eta^{[M]})\eta^{[M]}p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]}q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} \\
\leq\ & \frac{C}{M} + C\left\| \left[M^{-1}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]}\right](\tau,\cdot)\right\|_{\ell^1_d} + C\left\| p_1^{[M]}(\tau,\cdot) - q_1^{[M]}(\tau,\cdot)\right\|_{\ell^1_d} \qquad (61)
\end{aligned}$$

for all $\tau \in [0, t_{\text{end}}]$. We decompose

$$\begin{aligned}
&M^{-1}\beta_j^{[M]}(\eta^{[M]})\eta^{[M]}p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})\theta^{[M]}q_1^{[M]} \\
=\ & \beta_j^{[M]}(\eta^{[M]})\cdot\left[M^{-1}\eta^{[M]}p_1^{[M]} - \theta^{[M]}q_1^{[M]}\right] + \beta_j^{[M]}(\eta^{[M]})\theta^{[M]}\left[q_1^{[M]} - p_1^{[M]}\right] \\
&+\theta^{[M]}\left[\beta_j^{[M]}(\eta^{[M]})p_1^{[M]} - \tilde{\beta}_j^{[M]}(\theta^{[M]})q_1^{[M]}\right],
\end{aligned}$$

take the ℓ^1-norm on both sides, apply the triangle inequality and use that

$$\begin{aligned}
\max_{\tau\in[0,t_{\text{end}}]}\max_{n\in\mathbb{N}_0^d}\left|\beta_j^{[M]}\big(\eta^{[M]}(\tau,n)\big)\right| &\leq C \qquad \text{for all } j \in J_1, \\
\max_{\tau\in[0,t_{\text{end}}]}\max_{n\in\mathbb{N}_0^d}\left|\theta^{[M]}(\tau,n)\right| &\leq C
\end{aligned}$$

due to Assumption (39). The last term can be bounded by applying Lemma 4 (with $\gamma(j) = 1$ since $j \in J_1$). This proves (61) and completes the proof of Lemma 6. ∎

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