Summary for Hybrid Stochastic Simulation

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Here we summarize some thoretical results from the literature about Hybrid Stochastic Systems and approximation schemes for such systems. We mostly follow the notation in [1] and [3].

1 Description of a biochemical stochastic reaction network

We assume a stochastic reaction network consisting of

- s_0 species S_i with copy numbers x_i, with $i = 1, ..., s_0$
- r_0 reactions with corresponding stochiometry vectors $\xi_k = \nu'_k - \nu_k$ and reaction rates $\lambda_k(x)$ with $k = 1, ..., r_0$

This network can be written as a Markov Jump Process in the random-time-change representation

$$X(t) = x(0) + \sum_{k=1}^{r_0} Y_k \left(\int_0^t \lambda_k (X(s))\, ds \right) (\nu'_k - \nu_k)$$

whereas the Y_k are independent unit Poisson processes.

For the following we assume a decomposition (x_C, x_D) of the s_0 species, such that x_C represents species that are large, scaling with a parameter N, and x_D represents species that are of order $O(1)$. We define $\psi_i^C = \frac{1}{N} x_i^C$.

Additionally we partition the r_0 reactions into $\mathcal{R}_C, \mathcal{R}_{DC}, \mathcal{R}_D$, such that

- $\mathcal{R}_C$ corresponds to reactions that involve only species from x_C and whose reaction rate only depends on x_C
- $\mathcal{R}_D$ corresponds to reactions that involve only species from x_D and whose reaction rate only depends on x_D
- $\mathcal{R}_{DC}$ corresponds to reactions not belonging to $\mathcal{R}_C$ or $\mathcal{R}_D$

2 Convergence of Markov Jump Processes to Piecewise Deterministic Markov Processes

The following theorem states the convergence of a partially scaled Markov Jump Process into a PDMP (Piecewise Deterministic Markov Process) [2].

For $r \in \mathcal{R}_C$ define $\tilde{\lambda}_r = \frac{1}{N}\lambda_r$ (we can implicitely assume that λ_r is large and scales with N for $r \in \mathcal{R}_C$ because otherwise these reactions will not appear in the limit process anyway).

Define $S_1 \subseteq \mathcal{R}_{DC}$ such that for a reaction $r \in S_1$ the rate λ_r is large and scales with N and $\xi_r^D = 0$. For each $r \in S_1$ define $\tilde{\lambda}_r = \frac{1}{N}\lambda_r$.

Define $S_2 \subseteq \mathcal{R}_{DC}$ such that for a reaction $r \in S_2$ the stochiometry ξ_r^C is large and scales with N. For each $r \in S_1$ define $\tilde{\xi}_r^C = \frac{1}{N}\xi_r^C$.

Define $S = S_1 \cup S_2$.

Then we can write the random-time-change representation of the stochastic process corresponding to this reaction network as

$$
\begin{aligned}
X^N(t) = \left(\Psi_C^N, X_D^N\right)(t) &= x(0) \\
&+ \sum_{k \in \mathcal{R}_C} Y_k\left(\int_0^t \tilde{\lambda}_k\left(\Psi_C(s)\right) ds\right)\left(\frac{1}{N}\xi_k^C, 0\right) \\
&+ \sum_{k \in S_1} Y_k\left(\int_0^t N\tilde{\lambda}_k\left(X(s)\right) ds\right)\left(\frac{1}{N}\xi_k^C, 0\right) \\
&+ \sum_{k \in S_2} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right)\left(\tilde{\xi}_k^C, \xi_k^D\right) \\
&+ \sum_{k \in \mathcal{R}_{DC \setminus S}} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right)\left(\frac{1}{N}\xi_k^C, \xi_k^D\right) \\
&+ \sum_{k \in \mathcal{R}_D} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right)\left(0, \xi_k^D\right)
\end{aligned}
$$

Theorem 1. *The limit process of $X^N(t)$ for $N \to \infty$ is*

$$\begin{aligned}
X(t) &\equiv \lim_{N\to\infty} X^N(t) = (\Psi_C(t), X_D(t)) \\
&= x(0) \\
&+ \sum_{k\in\mathcal{R}_C} \int_0^t \tilde{\lambda}_k\left(\Psi_C(s)\right) ds \left(\xi_k^C, 0\right) \\
&+ \sum_{k\in S_1} \int_0^t \tilde{\lambda}_k\left(X(s)\right) ds \left(\xi_k^C, 0\right) \\
&+ \sum_{k\in S_2} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(\tilde{\xi}_k^C, \xi_k^D\right) \\
&+ \sum_{k\in\mathcal{R}_{DC\setminus S}} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(0, \xi_k^D\right) \\
&+ \sum_{k\in\mathcal{R}_D} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(0, \xi_k^D\right)
\end{aligned}$$

which is equivalent to a PDMP.

See [1] for a rigerous proof.

One should note that the distinction between $\mathcal{R}_C$ and S_1 is just a formality (the dependence of the $\tilde{\lambda}_r$) so we can define $S_3 = \mathcal{R}_C \cup S_1$ and similarly $S_4 = \mathcal{R}_D \cup (\mathcal{R}_{DC}\setminus S)$ and write the limit process as

$$\begin{aligned}
X(t) &\equiv \lim_{N\to\infty} X^N(t) = (\Psi_C(t), X_D(t)) \\
&= x(0) \\
&+ \sum_{k\in S_3} \int_0^t \tilde{\lambda}_k\left(X(s)\right) ds \left(\xi_k^C, 0\right) \\
&+ \sum_{k\in S_2} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(\tilde{\xi}_k^C, \xi_k^D\right) \\
&+ \sum_{k\in S_4} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(0, \xi_k^D\right)
\end{aligned}$$

3 Averaging of some discrete variables

Define $S_5 \subseteq \mathcal{R}_{DC}$ such that for a reaction $r \in S_1$ the rate λ_r is large and scales with N and $\xi_r^D \neq 0$. For each $r \in S_5$ define $\tilde{\lambda}_r = \frac{1}{N}\lambda_r$. Assume a decomposition $\left(x_D^1, x_D^2\right)$ of the x_D such that $\xi_r^{D,1} = 0$ and $\xi_r^{D,2} \neq 0$ (note that x_D^1 could be empty).

Define $S = S_1 \cup S_2 \cup S_5$.

Then the random-time-change representation of the stochastic process can be written as

$$
\begin{aligned}
X^N(t) = \left(\Psi_C^N, X_D^N\right)(t) = x(0) & \\
&+ \sum_{k \in \mathcal{R}_C} Y_k \left(\int_0^t \tilde{\lambda}_k \left(\Psi_C(s)\right) ds \right) \left(\frac{1}{N} \xi_k^C, 0, 0 \right) \\
&+ \sum_{k \in S_1} Y_k \left(\int_0^t N \tilde{\lambda}_k \left(X(s)\right) ds \right) \left(\frac{1}{N} \xi_k^C, 0, 0 \right) \\
&+ \sum_{k \in S_5} Y_k \left(\int_0^t N \tilde{\lambda}_k \left(X(s)\right) ds \right) \left(\tilde{\xi}_k^C, 0, \xi_k^{D,2} \right) \\
&+ \sum_{k \in S_2} Y_k \left(\int_0^t \lambda_k \left(X(s)\right) ds \right) \left(\tilde{\xi}_k^C, \xi_k^{D,1}, \xi_k^{D,2} \right) \\
&+ \sum_{k \in \mathcal{R}_{DC \setminus S}} Y_k \left(\int_0^t \lambda_k \left(X(s)\right) ds \right) \left(\frac{1}{N} \xi_k^C, \xi_k^{D,1}, \xi_k^{D,2} \right) \\
&+ \sum_{k \in \mathcal{R}_D} Y_k \left(\int_0^t \lambda_k \left(X(s)\right) ds \right) \left(0, \xi_k^{D,1}, \xi_k^{D,2} \right)
\end{aligned}
$$

If x_D^2 only takes a finite number of values (i.e. there exists a finite set K such that $X_D^2 \in K$) then the process X_D^2 given ψ_C, x_D^1 is ergodic (every state can be reached from a given state).

Define

$$
\bar{\lambda}_r \left(\psi_C, x_D^1\right) = \int_K \tilde{\lambda}_r \left(\psi_C, x_D^1, x_D^2\right) \nu_{\Psi_C, x_D^1} \left(dx_D^2\right)
$$

for $r \in S_5$ where ν_{Ψ_C, x_D^1} is the unique invariant measure of the ergodic process X_D^2 given ψ_C, x_D^1.

Theorem 2. *The limit process of $X^N(t)$ for $N \to \infty$ is*

$$\begin{aligned}
X(t) &\equiv \lim_{N\to\infty} X^N(t) = (\Psi_C(t), X_D(t)) \\
&= x(0) \\
&+ \sum_{k\in\mathcal{R}_C} \int_0^t \tilde{\lambda}_k\left(\Psi_C(s)\right) ds \left(\xi_k^C, 0, 0\right) \\
&+ \sum_{k\in S_1} \int_0^t \tilde{\lambda}_k\left(X(s)\right) ds \left(\xi_k^C, 0, 0\right) \\
&+ \sum_{k\in S_5} \int_0^t \bar{\lambda}_k\left(X(s)\right) ds \left(\xi_k^C, 0, 0\right) \\
&+ \sum_{k\in S_2} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(\tilde{\xi}_k^C, \xi_k^{D,1}, \xi_k^{D,2}\right) \\
&+ \sum_{k\in\mathcal{R}_{DC\setminus S}} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(0, \xi_k^{D,1}, \xi_k^{D,2}\right) \\
&+ \sum_{k\in\mathcal{R}_D} Y_k\left(\int_0^t \lambda_k\left(X(s)\right) ds\right) \left(0, \xi_k^{D,1}, \xi_k^{D,2}\right)
\end{aligned}$$

which is again equivalent to a PDMP.

4 Multiscale approximations of stochastic reaction networks

For the following we limit ourselves to four types of reactions

λ_k	Reaction	ν_k
κ_k'	$\emptyset \to stuff$	0
$\kappa_k' x_i$	$S_i \to stuff$	e_i
$\kappa_k' V^{-1} x_i(x_i-1)$	$2S_i \to stuff$	$2e_i$
$\kappa_k' V^{-1} x_i x_j$	$S_i + S_j \to stuff$	$e_i + e_j$

whereas V corresponds to the volume of the system and the κ_k' correspond to molecular reaction rates.

Define

- $z_i^N(t) = N^{-\alpha_i} x_i^N(t)$ with $\alpha_i \geq 0$ for $i = 1, ..., s_0$
- $\kappa_k = N^{-\beta_k}\kappa_k'$ for $k = 1, ..., r_0$

with a parameter N that is assumed to be large.

The rates of the four types of reactions can now be written as

Reaction	λ_k^N
$\emptyset \to stuff$	$N^{\beta_k}\kappa_k$
$S_i \to stuff$	$N^{\beta_k+\alpha_i}\kappa_k z_i$
$2S_i \to stuff$	$N^{\beta_k+2\alpha_i}\kappa_k V^{-1} z_i \left(z_i - N^{-\alpha_i}\right)$
$S_i + S_j \to stuff$	$N^{\beta_k+\alpha_i+\alpha_j}\kappa_k V^{-1} z_i z_j$

So we have

$$\lambda_k(x)\left(\nu_k' - \nu_k\right) = N^{\beta_k+\nu_k\cdot\alpha}\lambda_k^N(z)\left(\nu_k' - \nu_k\right)$$

whereas $\alpha = (\alpha_1, ..., \alpha_{s_0})^T$. With this we can write the corresponding multiscale Markov Jump Process as

$$Z_i^N(t) = z(0) + \sum_{k=1}^{r_0} N^{-\alpha_i} Y_k\left(\int_0^t N^{\beta_k+\nu_k\cdot\alpha}\lambda_k^N\left(Z_i^N(s)\right)ds\right)\left(\nu_{ik}' - \nu_{ik}\right)$$

The α_i and β_i should be choosen in such a way, that the z_i and κ_k are of order 1 in a loose sense.

In addition we introduce a further scaling parameter γ for the time-scale of the process and write

$$\begin{aligned} Z_i^{N,\gamma}(t) &= Z_i^N\left(N^\gamma t\right) \\ &= z(0) + \sum_{k=1}^{r_0} N^{-\alpha_i} Y_k\left(\int_0^t N^{\gamma+\beta_k+\nu_k\cdot\alpha}\lambda_k^N\left(Z_i^{N,\gamma}(s)\right)ds\right)\left(\nu_{ik}' - \nu_{ik}\right) \end{aligned}$$

See [3] for a more elaborate discussion.

5 Constraints for selection of the scaling parameters

In [3] Kang et al. derive constraints for the selection of the scaling parameters $\alpha_i, \beta_i, \gamma$ that we recapitulate here.

Condition 1. *Define* $\Gamma_i^+ = \{k : \nu_{ik}' > \nu_{ik}\}$ *and* $\Gamma_i^- = \{k : \nu_{ik}' < \nu_{ik}\}$. *Then the condition*

$$\max_{k\in\Gamma_i^-}\left(\beta_k + \nu_k\cdot\alpha\right) = \max_{k\in\Gamma_i^+}\left(\beta_k + \nu_k\cdot\alpha\right)$$

or

$$\gamma \le \alpha_i - \max_{k\in\Gamma_i^+\cup\Gamma_i^-}\left(\beta_k + \nu_k\cdot\alpha\right)$$

is called the ***species balance condition*** *and ensures that no species explodes or is driven to zero.*

We can generalize this condition to linear combinations $\Theta \cdot z$ of species with $\Theta \in [0,\infty)^{s_0}$.

Condition 2. *Define* $\Gamma^+_\Theta = \{k : \Theta \cdot \xi_k > 0\}$ *and* $\Gamma^-_\Theta = \{k : \Theta \cdot \xi_k < 0\}$. *Then the condition*

$$\max_{k\in\Gamma^-_\Theta} (\beta_k + \nu_k \cdot \alpha) = \max_{k\in\Gamma^+_\Theta} (\beta_k + \nu_k \cdot \alpha) \tag{1}$$

or

$$\gamma \le \gamma_i \equiv \max_{i:\Theta_i>0} \alpha_i - \max_{k\in\Gamma^+_\Theta\cup\Gamma^-_\Theta} (\beta_k + \nu_k \cdot \alpha) \tag{2}$$

is called the ***collective species balance condition****. It ensures that no linear combination of species explodes or is driven to zero.*

Checking this condition is not trivial but in [3] Kang et al. show a significant simplification to check for the **collective species balance condition**:

Lemma 1. *Let G be a directed graph where the nodes correspond to the species and a directed edge from $S_i \to S_j$ is drawn if there is a reaction consuming S_i and producing S_j.*

Let G_j be maximal strongly connected subgraphs such that $G = \cup_j G_j$ (this decomposition is unique).

Let $\gamma \in \mathbb{R}$ be fixed. If Condition 2 holds for each $\Theta \in [0,\infty)^{s_0}$ with supp $(\Theta) \subset G_j$ for all maximal strongly connected subgraphs G_j, then Condition 2 holds for all $\Theta \in [0,\infty)^{s_0}$.

This reduces checking Condition 2 for all $\Theta \in [0,\infty)^{s_0}$ to checking Condition 2 for all Θ with supp $(\Theta) \subset G_j$ for each of the subgraphs G_j separately.

Lemma 2. *Kang et al. continue to show that Condition 2 also holds for $c_1\Theta^1 + c_2\Theta^2$ for all $c_1, c_2 > 0$ if either*

$$\textit{(2) holds for } \Theta^1 \textit{ or } \Theta^2$$

or

$$\begin{aligned} \max_{k\in\Gamma^-_{\Theta^1}} (\beta_k + \nu_k \cdot \alpha) &= \max_{k\in\Gamma^+_{\Theta^1}} (\beta_k + \nu_k \cdot \alpha) \\ \neq \max_{k\in\Gamma^-_{\Theta^2}} (\beta_k + \nu_k \cdot \alpha) &= \max_{k\in\Gamma^+_{\Theta^2}} (\beta_k + \nu_k \cdot \alpha) \end{aligned}$$

Lemma 3. *If Lemma 2 does not apply but*

$$\Gamma^+_{\Theta^1} \cap \Gamma^-_{\Theta^2} = \emptyset$$

or

$$\Gamma^-_{\Theta^1} \cap \Gamma^+_{\Theta^2} = \emptyset$$

(i.e. the support of Θ^1 produces no species that are consumed in the support of Θ^2 and vice versa), then Condition 2 holds for $c_1\Theta^1 + c_2\Theta^2$ for all $c_1, c_2 > 0$.

Lemma 4. *If Lemma 2 does not apply and* $\Gamma^+_{\Theta^1} \cap \Gamma^-_{\Theta^2} \neq \emptyset$ *and* $\Gamma^-_{\Theta^1} \cap \Gamma^+_{\Theta^2} \neq \emptyset$ *suppose that Condition 2 also holds for* $\Theta^1 - \frac{\Theta^1 \cdot \xi_k}{\Theta^2 \cdot \xi_k}\Theta^2$ *for all* $k \in \left(\Gamma^+_{\Theta^1} \cap \Gamma^-_{\Theta^2}\right) \cup \left(\Gamma^-_{\Theta^1} \cap \Gamma^+_{\Theta^2}\right)$. *Then Condition 2 also holds for* $c_1\Theta^1 + c_2\Theta^2$ *for all* $c_1, c_2 > 0$.

The only case that is left now is that

(2) doesn't hold for both Θ^1 and Θ^2 and $\Gamma^+_{\Theta^1} \cap \Gamma^-_{\Theta^2} \neq \emptyset$ and $\Gamma^-_{\Theta^1} \cap \Gamma^+_{\Theta^2} \neq \emptyset$ and Condition 2 doesn't hold for $\Theta^1 - \frac{\Theta^1 \cdot \xi_k}{\Theta^2 \cdot \xi_k}\Theta^2$ and

$$\begin{aligned}\max_{k \in \Gamma^-_{\Theta^1}} (\beta_k + \nu_k \cdot \alpha) &= \max_{k \in \Gamma^+_{\Theta^1}} (\beta_k + \nu_k \cdot \alpha) \\ = \max_{k \in \Gamma^-_{\Theta^2}} (\beta_k + \nu_k \cdot \alpha) &= \max_{k \in \Gamma^+_{\Theta^2}} (\beta_k + \nu_k \cdot \alpha)\end{aligned}$$

all hold. We call this case *non-reducable collective species balance.* In this case Condition 2 has to be checked directly (of course this only needs to be done for all $\Theta \in [0, \infty)^{s_0}$ with support in the subgraphs G_j with a *non-reducable collective species balance*).

In all other cases it is now sufficient to check Condition 2 on a set $\Theta^{j,k}$ spanning the subgraph G_j for all j.

Theorem 3. *For completeness we state that if*

$$\gamma = \min_i \gamma_i = \min_i \left(\alpha_i - \max_{k \in \Gamma^+_\Theta \cup \Gamma^-_\Theta} (\beta_k + \nu_k \cdot \alpha) \right)$$

then each term

$$N^{-\alpha_i} Y_k \left(\int_0^t N^{\gamma + \beta_k + \nu_k \cdot \alpha} \lambda_k^N \left(Z_i^{N,\gamma}(s) \right) ds \right)$$

converges to

$$\begin{cases} 0 & \text{for } \alpha_i > \gamma + \beta_k + \nu_k \cdot \alpha \\ Y_k \left(\int_0^t \lambda_k^N \left(Z_i^{N,\gamma}(s) \right) ds \right) & \text{for } \alpha_i = \gamma + \beta_k + \nu_k \cdot \alpha = 0 \\ \int_0^t \lambda_k^N \left(Z_i^{N,\gamma}(s) \right) ds & \text{for } \alpha_i = \gamma + \beta_k + \nu_k \cdot \alpha \neq 0 \end{cases}$$

for $N \to \infty$ *which represents a PDMP of the multiscale network.*

6 Combination of convergence results and multiscale parametrization

To combine the convergence results from 2 with the multiscale Parametrization we note that the membership of a species x_i in x_C, x_D depends on α_i:

$$\begin{cases} x_i \text{ belongs to } x_C & \text{for } \alpha_i > 0 \\ x_i \text{ belongs to } x_D & \text{for } \alpha_i = 0 \end{cases}$$

We also note that $r \in S_1$ if $\gamma + \beta_r + \nu_r \cdot \alpha > 0$ and $\xi_r^D = 0$ (if $\xi_r^D \neq 0$ one can still take the approach in 3).

We can then use Theorem 1 or Theorem 2 to derive the PDMP that corresponds to the limiting process of the multiscale network.

References

[1] Alina Crudu, Arnaud Debussche, Aurélie Muller, and Ovidiu Radulescu. Convergence of stochastic gene networks to hybrid piecewise deterministic processes. *The Annals of Applied Probability*, 22(5):1822–1859, 2012.

[2] Mark HA Davis. Piecewise-deterministic markov processes: A general class of non-diffusion stochastic models. *Journal of the Royal Statistical Society. Series B (Methodological)*, pages 353–388, 1984.

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