Summary for Hybrid Stochastic Simulation

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1 Theory

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].

1.1 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 $\mathcal{R}_D$

1.2 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

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

1.3 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 $\xi_r^{D,2} \neq 0$ (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.

1.4 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
$\emptyset \to stuff$	$N^{\beta_k}\kappa_k$
$S_i \to stuff$	$N^{\beta_k+\alpha_i}\kappa_k z_i$
$2S_i \to stuff$	$N^{\beta_k+2\alpha_i}\kappa_k V^{-1} z_i(z_i - N^{-\alpha_i})$
$S_i + S_j \to stuff$	$N^{\beta_k+\alpha_i+\alpha_j}\kappa_k V^{-1} z_i z_j$

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

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

See [3] for a more elaborate discussion.

1.5 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

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

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 $\mathrm{supp}\,(\Theta) \subset G_j$ 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*

(2) holds for Θ^1 *or* Θ^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

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

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

1.6 Combination of convergence results and multiscale parametrization

To combine the convergence results from 1.2 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 1.3).

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

2 Implementation

Here we summarize how the adaptive multiscale network is implemented as a PDMP, how to simulate the PDMP and then go into more details about the steps of the adaptation.

2.1 Adaptive Multiscale Network as a PDMP

To distinguish between stochastic and deterministic reactions we follow the theoretical foundation stated further up with an additional threshold parameter $\delta \geq 0$

$$\begin{cases} Y_k\left(\int_0^t \lambda_k^N\left(Z_i^{N,\gamma}(s)\right) ds\right) & \text{for } \alpha_i < \delta \\ \int_0^t \lambda_k^N\left(Z_i^{N,\gamma}(s)\right) ds & \text{for } \alpha_i \geq \delta \end{cases}$$

If any term of a reaction is stochastic by the previous definition, then the whole reaction is treated stochastically, as we have to simulate the stochastic event anyway.

The α_i and β_k are computed by solving the following linear program:

$$\begin{array}{lccc} \text{maximize} & \sum_{i=1}^{Q} \frac{\alpha_i}{A_i} + \sum_{i=1}^{W} \frac{\beta_k}{B_k} & & \\ \text{subject to} & 0 \leq \alpha_i \leq A_i & \text{for each } i \in \{1,...,Q\} & \\ \text{and} & \beta_k \leq B_k & \text{for each } k \in \{1,...,W\} & \\ \text{and} & \alpha_i \geq \beta_k + \alpha \cdot \nu_k & \text{for each } i \in \{1,...,Q\},\ k \in \{1,...,W\} & \end{array} \tag{3}$$

whereas $A_i = \frac{\log(x_i)}{\log(N)} + 1$ and $B_i = \frac{log(\kappa'_k)}{\log(N)} + 1$.

If a species i has $\alpha_i \geq \delta$ it is a scaled species, otherwise it is an unscaled species.

In the next step the reaction graph is searched for subnetworks that can be averaged (see section 2.4).

2.2 Simulation of a PDMP with adaptation

2.3 Copy number bounds

As stated in the algorithm 2.2 an adaptation procedure is performed whenever the copy number bounds are crossed. These bounds are defined by two parameters $\delta \geq 0$ and $\eta > 0$. The copy number bounds for an unscaled species i are $0 \leq x_i < N^\delta$ and the bounds for a scaled species j are $N^{-\eta} < z_j = N^{-\alpha_j} x_j < N^\eta$.

An unscaled species i that crosses it's upper copy number bound N^δ can be a scaled species after the adaptation. Only when the copy number of the

$t \leftarrow t_0$
$X \leftarrow x_0$
$i \leftarrow 0$
$Y \leftarrow [\text{exprnd}(1), 0]$
while $t_0 \leq t_1$ **do**
  evolve
    X according to $X'(t) = \sum_{M_D} \lambda_k(X(t))(\nu'_k - \nu_k)$
    Y according to $Y'(t) = [0, \sum_{M_S} \lambda_k(X(t))]$
  until either $t = t_1$ or $Y_1 = Y_2$ or *copy number bounds have been crossed*
  if *copy number bounds have been crossed* **then**
    Adapt scaling parameters and update scaled copy numbers
  else if $Y_1 = Y_2$ **then**
    $Y \leftarrow [\text{exprnd}(1), 0]$
    $r \leftarrow k$ with probability $p_k \propto \lambda_k(X)$
    $X \leftarrow X + \nu'_k - \nu_k$
  end if
end while

scaled species crosses it's lower bound $N^{-\eta}$ will the species revert to an unscaled species. This means that there is a hysteresis-like effect for the switching between unscaled and scaled copy numbers for a species. In the range $(N^{-\eta}N^{\delta}, N^{\delta})$ of real copy numbers a species can be either scaled or unscaled depending on whether the species was unscaled or scaled before the switching. This might seem like an inconvenience of the implementation but actually this is necessary to prevent endless adaptation and thus a high performance penalty due to numerical errors and small changes in the copy numbers and also to enable the detection of crossings of copy number bounds by root finding during the ODE integration in the first place.

2.4 Averaging

After the α_i and β_k have been computed a timescale τ_i is computed for each species as follows:

$$\tau_i := \frac{q_i}{\sum_{k \ s.t. \ v'_{ik} \neq 0} \sum_j |q\nu_{jk}|}$$

whereas $q_i = \max(x_i, 1)$.

Now for each possible subset S of species we compute the timescale of the subset τ_S and the timescale of the outside network $\tau_{\bar{S}}$ as follows:

$$\tau_S = max_{i \in S}(\tau_i)$$

$$\tau_{\bar{S}} = min_{i \in \bar{S}}(\tau_i)$$

whereas $\bar{S}$ is the set of species j that are directly involved in reactions with species $i \in S$. That is either

$$\bar{S} = \bar{S}_1 \cup \bar{S}_2$$

$$\bar{S}_1 = \{j : \nu'_{kj} \neq 0 \text{ and } \nu_{ki} \neq 0 \text{ for some } i \in S \text{ and } k\}$$

$$\bar{S}_2 = \{j : \nu_{kj} \neq 0 \text{ and } \nu'_{ki} \neq 0 \text{ and } l \text{ is connected to } j \text{ for some } i, l \in S \text{ and } k\}$$

If $\frac{\tau_{\bar{S}}}{\tau_S} \geq \theta$ and for all reactions k there is no $i \in S$ s.t. $\nu_{ki} > 1$ and no $i, j \in S$ s.t. $\nu_{ki} > 0$ and $\nu_{kj} > 0$ then we remember S as a candidate subnetwork for averaging.

Finally we start with an empty list L_A of species to average and an empty list L of subnetworks to average and iterate in order of decreasing number of species over the candidate subnetworks. If $L_A \cap S = \emptyset$ we add all the species from S to L_A and add S to L. After the iteration L contains all the subnetworks to average so we treat the copy numbers of all species of those subnetworks as continuous and all the reactions within those subnetwork as deterministic.

References

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