Limits for Reaction networks with Multiple Scales and Spatial Heterogeneity

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Reaction networks

- **Set-up:**
  - population consists of different **types** of 'particles'
  - they are involved in a system of **interactions**
  - rates of interactions depend on the **current number** of types

- **Examples:**
  - **epidemic** models, e.g. SIR or SIRS
  - **branching** models, e.g. catalytic branching
  - **neutral genetic** models, e.g. Moran model with mutation
  - **chemical reaction** models,
    e.g. molecular interactions in biological cells

Multiple scales and space

- **Scaling issues:**
  - **amounts** of particles are in different **orders of abundance**
  - **rates** of interactions are of different **orders of magnitude**

- **Spatial issues:**
  - different **spatial locations** = discrete compartments
  - each particle type **moves** between compartments

Goals:

- how can one **reduce network complexity** without losing **essential randomness**
- how does **effect of spatial heterogeneity** interact with the **multiple scales** on the network reaction dynamics

Notation

- **Particles**: $\mathcal{I}$ distinct types $\mathbf{A_1}, \ldots, \mathbf{A}_\mathcal{I}$

  $$X(t) = (X_1(t), \ldots, X_\mathcal{I}(t)) \;= \textbf{\# of particles at time } t$$

- **Reactions**: $\mathcal{K}$ distinct interactions

  $$\sum_{i=1}^{\mathcal{K}} \nu_{ik}\mathbf{A_i} \mapsto \sum_{i=1}^{\mathcal{K}} \nu'_{ik}\mathbf{A_i}, \quad \nu_{ik}, \nu'_{ik} \in \mathbb{Z}^+ \;= \textbf{interaction k}$$

  $$(\nu'_{1k} - \nu_{1k}, \ldots, \nu'_{\mathcal{I}k} - \nu_{\mathcal{I}k}) \;= \text{change due to interaction } k$$

- **Rates**: depend on current **state of system**

  $$\lambda_k(t) = \lambda_k(X(t)) \;= \textbf{rate of reaction k} \text{ at time } t$$

Examples

- **SIRS Model** :

$$\begin{aligned} S + I &\to 2I & \lambda_1 &= c_I X_S X_I & \nu_1' - \nu_1 &= (-1, 1, 0) \\ I &\to R & \lambda_2 &= c_R X_I & \nu_2' - \nu_2 &= (0, -1, 1) \\ R &\to S & \lambda_3 &= c_S X_R & \nu_3' - \nu_3 &= (1, 0, -1) \end{aligned}$$

- **Catalytic Branching Process** :

$$\begin{aligned} C &\to 2C \text{ or } 0 & \lambda_1 &= b_1 X_C X_R & \nu_1' - \nu_1 &= (\pm 1, 0) \\ R &\to 2R \text{ or } 0 & \lambda_2 &= b_2 X_C X_R & \nu_2' - \nu_2 &= (0, \pm 1) \end{aligned}$$

- **Moran model with Mutations** :

$$\begin{aligned} A + a &\to 2A \text{ or } 2a & \lambda_1 &= X_A X_a & \nu_1' - \nu_1 &= (\pm 1, - \pm 1) \\ a &\to A & \lambda_2 &= \mu_{a \to A} X_a & \nu_3' - \nu_3 &= (-1, 1) \\ A &\to a & \lambda_3 &= \mu_{A \to a} X_A & \nu_3' - \nu_3 &= (1, -1) \end{aligned}$$

Stochastic dynamics

- **Counting Reaction Occurrences**:

  $R_k(t)$ = **# of times kth reaction** occurs by time t

  $$R_k(t) = Y_k(\int_0^t \lambda_k(X(s))ds)$$

  $\{Y_k\}_{k\in\mathcal{K}}$= independent rate 1 Poisson processes

- **Changes in Population Size of Components**:

  $$X(t) = X(0) + \sum_{k\in\mathcal{K}} \Delta_k R_k(t)$$
  $$= X(0) + \sum_{k\in\mathcal{K}} \Delta_k Y_k(\int_0^t \lambda_k(X(s))ds)$$

  $\Delta_k = (\nu'_{1k} - \nu_{1k}, \ldots, \nu'_{\mathcal{I}k} - \nu_{\mathcal{I}k})$= **change** due to reaction k

Reaction rates

- **Reaction rates**:
  $\lambda_k(X(t))$ depends on the state of the whole system
  when some input components are missing $\lambda_k = 0$
  at least some λ_k in the system are non-linear

- Commonly used - **mass action kinetics**:
  based on uniform mixing assumption, infinitesimal rates of interactions come from **collision probabilities**:

$$\lambda_k(X) = \kappa_k \binom{X_1 \cdots X_{\mathcal{I}}}{\nu_{1k} \cdots \nu_{\mathcal{I}k}}$$

$$\approx N\kappa_k \prod_i \left(\frac{X_i}{N}\right)^{\nu_{ik}} \quad (\textbf{classical scaling})$$

Rescaling of reaction networks

- **Scaling parameters**: N = scaling paramter

  For each type: $\alpha_i \geq 0$ chosen s.t.

  $$V_i^N(t) := \mathbf{N}^{-\alpha_i} X_i(t) = \mathbf{O(1)}$$

  For each reaction: $\beta_k \geq 0$ chosen s.t.

  $$\mathbf{N}^{\beta_k} \lambda_k(X) = \mathbf{O(1)}$$

  For time scale: speed-up/slow-down time by $\mathbf{N}^{\gamma}$

- **Normalized system**:

  $$V_i^N(t) = V_i^N(0) + \mathbf{N}^{-\alpha_i} \sum_k \Delta_k Y_k\Big(\int_0^t \mathbf{N}^{\beta_k + \gamma} \lambda_k(V^N(s)) ds\Big)$$

  dynamics depends on the **relationship between α_i & β_k**

Separating scales

- Goal: **Reduction of Network Complexity**
  exploit **multiscale aspect** to get simpler system in limit

Suppose on well chosen time scale γ the normalized components fall into two groups:
V_1^N = vector of **'fast varying'** components
V_2^N = the vector of **'slow varying'** components

Let $\delta > 0$, be the **scale along which the system separates**:

- $\{1, 2, \ldots, \mathcal{I}\} = \mathcal{I}_\mathbf{f} + \mathcal{I}_\mathbf{s} =$ **fast** + **slow** components s.t.:

$$V_f^N(t) = V_f^N(0) + \mathbf{N}^{-\alpha_{i_f}} \sum_k \Delta_{k|f} Y_k(\mathbf{N}^{\alpha_{i_f}} \mathbf{N}^{\delta} \int_0^t \lambda_k(V^N(s))ds),$$

$$V_s^N(t) = V_s^N(0) + \sum_k \mathbf{N}^{-\alpha_{i_s}} \Delta_{k|s} Y_k(\mathbf{N}^{\alpha_{i_s}} \int_0^t \lambda_k(V^N(s))ds),$$

Averaging of fast and LLN for slow subnetwork

- Suppose fast varying components have unique partial stationary measure, for each value of slow varying components
- then **limit of the slow varying components** depends only on the **partial stationary distribution** of the fast components

Theorem [Averaging and LLN]

If $\forall t > 0$, *when* $V_s^N(t) = v_s$ *is fixed,* V_f^N *has a unique stationary distribution* $\boldsymbol{\pi_{v_s}(v_f)}$, *then* $\forall T > 0$*:*

$$\lim_{N\to\infty} \mathbf{P}\Big[\sup_{t\in[0,T]} |\mathbf{V_s^N(t) - V_s(t)}| \geq \epsilon\Big] = \mathbf{0}, \quad \forall \epsilon > \mathbf{0}$$

where V_s *is the solution to the system of equations:*

$$V_s(t) = V_s(0) + \sum_k \int_0^t \Delta_{k|s} \overline{\boldsymbol{\lambda}_{\mathbf{k}}}(\mathbf{V_s}(\boldsymbol{\tau}))d\tau$$

with averaged $\overline{\boldsymbol{\lambda}_{\mathbf{k}}}(\mathbf{V_s}(\boldsymbol{\tau})) = \int \boldsymbol{\lambda}_{\mathbf{k}}(\mathbf{v_f}, \mathbf{V_s}(\boldsymbol{\tau}))\boldsymbol{\pi}_{\mathbf{V_s}(\boldsymbol{\tau})}(\mathbf{v_f})$.

FCLT limit for slow subnetwork

For the **fluctuations of the slow varying components**:

- follow a centered Gaussian process
- diffusion coefficient $\overline{\boldsymbol{\sigma}}$ of this process depends on the **interaction of slow and fast components**

Theorem [**FCLT**]

If $\mathbf{U_s^N(t) = N^{\delta/2}\big(V_s^N(t) - V_s(t)\big)}$, *then* $\forall T > 0$*:*

$$\mathbf{(U_s^N(t), t \in [0, T]) \Rightarrow (U_s(t), t \in [0, T])}$$

where U_2 *is the Gaussian process:*

$$U_s(t) = \int_0^t \overline{\boldsymbol{\sigma}}(\mathbf{V_s}(\boldsymbol{\tau}))dW(\tau) + \int_0^t \overline{\boldsymbol{\mu}}(\mathbf{V_s}(\boldsymbol{\tau}))U_s(\tau)d\tau$$

with $W = |\mathcal{I}_s|$*-dimensional BM,* $\overline{\boldsymbol{\sigma}}(v_s), \overline{\boldsymbol{\mu}}(v_s)$ *are averaged*

Note:

- expression for $\overline{\mu}(\mathbf{v_s})$ is simple $\rightarrow$ **gradient of the drift** of V_s
- expression for $\overline{\sigma}(\mathbf{v_s})$ is more complicated $\rightarrow$ combines the fluctuations of V_s^N about its mean V_s with the **gradient of the solution of Poisson equation** for the generator of V_f w.r.t. to the drift of V_s, i.e. the fluctuations of the partial stationary distribution $\pi_{V_s}(v_f)$ of V_f in drift direction of V_s

General Theorems:

- fclt results for **general multiscale Markov Chain models** by: an iterative application of separation of the network into subnetworks on progressive time scales - Kurtz-Popovic '11
- analogous fclt results for **two time scale SDEs** - Pardoux-Veretennikov '01, '03, '05

Example: Michaelis-Menten enzymatic reactions

Reactions:

$$S + E \longrightarrow SE$$
$$S + E \longleftarrow SE$$
$$P + E \longleftarrow SE$$

Rates:

$$\kappa_1 X_1 X_2$$
$$\kappa_{-1}(M - X_1)$$
$$\kappa_2(M - X_1)$$

Species:

$X_1 = \#$ of **unbound enzymes E**
$X_2 = \#$ of **unbound substrate S**
$X_3 = \#$ of **enzymatic product P**
$M - X_1 = \#$ of **bound enzymes SE**

$\#$ of unbound enzymes $+$ $\#$ of bound enzymes $= M$
$\kappa_{-1}, \kappa_2 >> \kappa_1$, then $N = O(X_2) >> M$ while $X_1 + X_3 = M$

Fast species: bound & unbound enzymes SE, E
Slow species: unbound substrate S

Stationary distribution for $V_1^N(s)$ (# of unbound enzymes) is:

$$\pi_{V_2(s)}(v_1) \sim \text{Binomial}(M, p(V_2(s)))$$

$$p(V_2(s)) = (\kappa_{-1} + \kappa_2)/(\kappa_{-1} + \kappa_2 + \kappa_1 V_2(s))$$

LLN limit for V_2^N (# of unbound substrate) is:

$$V_2(t) = V_2(0) - M \int_0^t \frac{\kappa_1 \kappa_2 V_2(s)}{\kappa_{-1} + \kappa_2 + \kappa_1 V_2(s)} ds$$

FCLT for the deviation of V_2^N from V_2 satisfies:

$$U_2(t) = \int_0^t \sqrt{\sigma^2(V_2(s))} dW(s) + \int_0^t \mu(V_2(s)) U_2(s) ds$$

$$\boldsymbol{\mu}(v_2) = \frac{-M\kappa_1\kappa_2(\kappa_{-1}+\kappa_2)}{(\kappa_{-1}+\kappa_2+\kappa_1 v_2)^2}$$

$$\boldsymbol{\sigma}^2(v_2) = M\int_0^t (1+u_1(v_2)^2)\Big(v_2\kappa_1 p(s)+\kappa_{-1}(1-p(s))\Big)ds$$

$$+ M\int_0^t u_1(v_2)^2\kappa_2(1-p(s))ds, \quad u_1(v_2) = \frac{(\kappa_1 v_2+\kappa_{-1})}{(\kappa_1 v_2+\kappa_{-1}+\kappa_2)}$$

$u(v_1, v_2) = u_1(v_2)v_1$ solves **Poisson equation** $Lu(v_1, v_2) = F - \bar{F}$,

$$F = -\kappa_1 v_1 v_2 + \kappa_{-1}(M - v_1) + M\frac{\kappa_1\kappa_2 v_2}{\kappa_{-1}+\kappa_2+\kappa_1 v_2}, \quad \bar{F} = \int F\pi_{v_2}(v_1)$$

$=$ **drift of the limitting slow subnetwork**, and averaged drift

$$Lf(v_1, v_2) = \Big[\kappa_1 v_1 v_2\big(f(v_1-1)-f\big)+(\kappa_{-1}+\kappa_2)(M-v_1)\big(f(v_1+1)-f\big)\Big]$$

$=$ **generator for fast subnetwork** with fixed slow vars

Spatial heterogeneity in dynamics

- **Spatial compartments**: $\mathcal{D}$ distinct subdivisions of space

  $X_{\cdot d}(t) = (X_{1d}(t), \ldots, X_{\mathcal{I}d}(t))$ = particles in **compartment d**

  $\lambda_{\mathbf{kd}}(X_{\cdot d}(t))$ = **spatially dependent** rate of reaction k

- **Movement between compartments**:

  μ_i = movement **rate per particle** of type i

  $p_i(d', d'')$ = **probability** of movement from $d' \mapsto d''$

  $\rho_i = (\rho_i(d))_{d \in \mathcal{D}}$ = **stationary distribution** of $\{p_i(d', d'')\}_{d', d'' \in \mathcal{D}}$

- **Speed of movement**:
  For each type $i \in \mathcal{I}$: $a_i > 0$ chosen s.t. $\mathbf{N^{a_i}} \mu_i^N = \mathbf{O(1)}$

- **System sums**: $S_i^N(t) := \sum_d V_{id}^N(t)$

$$S_i^N(t) = S_i^N(0) + \mathbf{N}^{-\alpha_i} \sum_d \sum_k \Delta_k Y_k\left(\int_0^t \mathbf{N}^{\beta_k + \gamma} \lambda_k(\mathbf{V}^\mathbf{N}(s)) ds \right)$$

  but dynamics depends on relationship between $\boldsymbol{\alpha_i}, \boldsymbol{\beta_k}$ and $\mathbf{a_i}$

- **Mass action kinetics**: If reaction rates have **mass action** form on a **single scale** and movement is and on a **faster scale**

$$S_i(t) = S_i(0) + \sum_{k \in \mathcal{K}} \Delta_{ik} Y_k \left(\int_0^t \widetilde{\kappa}_k \binom{S_1 \cdots S_{\mathcal{I}}}{\nu_{1k} \cdots \nu_{\mathcal{I}k}} d\tau \right)$$

$$\widetilde{\kappa}_k = \sum_d \kappa_{kd} \prod_i \rho_i(d)^{\nu_{ik}}$$

  if **all** species move faster than they interact, **mass action in compartments** becomes **mass action of system sums**

Spatially heterogeneous multi-scale networks

- **Reactions**: dynamics of reactions separate species into 'fast' and 'slow' components: the normalized amounts change due to reactions at **rates $O(N^\delta)$ and $O(1)$**, respectively

- **Movement**: 'fast' and 'slow' components move between compartments at **speeds $O(N^{a_f})$ and $O(N^{a_s})$**, respectively

$V^N = (V_f^N, V_s^N)$ with values in $\otimes_d \big(E_{fd} \times E_{sd}\big)$ has generator:

$$L_N \text{ "}\approx\text{" } \sum_{d\in\mathcal{D}} \big(N^\delta L_{fd}^{cr} + L_{sd}^{cr}\big) + N^{a_f} L_f^{mov} + N^{a_s} L_s^{mov}$$

where $\mathcal{D}(L_{fd}^{cr}) \subset \mathcal{C}_c(E_{fd} \times E_{sd})$, while $\mathcal{D}(L_{sd}^{cr}) \subset \mathcal{C}_c(E_{sd})$ only, and:

$$L_{sd}^{cr} = F_d \cdot \nabla, \qquad \text{with } F_d = \sum_{k\in\mathcal{K}} \Delta_k \lambda_{kd}$$

- **Assumption on the reactions**: reaction dynamics in each compartment is s.t., when the normalized amount of slow components is kept fixed, the **fast components have a unique partial stationary distribution $\otimes_d \pi_{v_{sd}}(v_{fd})$**

- **Assumption on the effect of movement on reactions**: movement has a stationary distribution $\rho = \rho_f \otimes \rho_s$ s.t., when all the components, as well as, when only the fast components are distributed over compartments according to ρ, **reaction dynamics still has unique partial stationary distributions $\pi_{s_s}(s_f)$, and $\int (\otimes_d \pi_{v_{sd}}(v_{fd}))\, \rho_f(v_{fd})$**, respectively

- **Theorem [Spatial limits]**: Under **assumptions**, $\forall T > 0$ the normalized sum of slow components S_s^N converges on $[0, T]$ to the solution of:

$$S_s(t) = S_s(0) + \sum_{k \in \mathcal{K}} \int_0^t \Delta_k \bar{\lambda}_k^{cr}(S_s(\tau)) d\tau$$

where if $a_s > 0, a_f > \delta$ then:

$$\bar{\lambda}_k^{cr}(s_s) = \int \Big(\sum_{d \in \mathcal{D}} \int \lambda_{kd}^{cr}(v_{fd}, v_{sd}) \rho_f(v_{fd}) \rho_s(v_{sd}) \Big) \pi_{s_s}(s_f)$$

while if $a_s > 0, a_f < \delta$ then:

$$\bar{\lambda}_k^{cr}(s_s) = \sum_{d \in \mathcal{D}} \int \Big(\int \lambda_{kd}^{cr}(v_{fd}, v_{sd}) \pi_{v_{sd}}(v_{fd}) \Big) \rho_f(v_{fd}) \rho_s(v_{sd})$$

- **Interplay of scales**: The dynamics of total normalized amount of slow particles depends on how **speed scale a_f** of fast components compares to the **scale of separation of reactions δ**, and **not** on **speed scale a_s** of slow components.

- **Theorem [Spatially heterogeneous mass action kinetics]**: If reaction rates have **mass action** form, then:

  if $a_f > \delta$, the dynamics of sum of slow components takes on the **same form as the dynamics in a homogeneous environment** with rate constants $\widetilde{\kappa}_k = \sum_d \kappa_{kd} \prod_{i \in \mathcal{I}_s} \rho_i(d)^{\nu_{ik}}$;

  if $a_f < \delta$ the dynamics of sum of slow components can take on a completely **different form** from that in a homogeneous environment (unless all the reactions are linear).

Example: heterogeneous Michaelis-Menten

- **Michaelis-Menten in compartment** d:
  X_{1d}, X_{3d} are 'fast' components, $\quad X_{1d} + X_{3d} = M_d$
  $V_{2d}^N = N^{-1} X_{2d}$ is 'slow' component
  λ_{kd} are mass action with parameters $\kappa_{1d}, \kappa_{-1d}, \kappa_{2d}$

- **Without movement**: V_{2d}^N converges to the solution of:

$$V_{2d}(t) = V_{2d}(0) - M_d \int_0^t \frac{\kappa_{1d}\kappa_{2d} V_{2d}(s)}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d} V_{2d}(s)} ds$$

- **Separation of scales in reaction dynamics**: $\delta = 1$
- **Speed of movement**: $\alpha_1, \alpha_3 > 0$, and
  $\alpha_2 < 1$ **vs** $\alpha_2 > 1$

$M := \sum_d M_d$ is conserved
$\rho_1(d) = \rho_3(d), \rho_2(d)$ are stationary distributions of movement

$S_2^N = \sum_d V_{2d}^N$ converges to the solution of:

- If $\alpha_2 > 1$, then

$$S_2(t) = S_2(0) - M \int_0^t \frac{\sum_d \kappa_{1d}\rho_2(d)\rho_1(d) \sum_d \kappa_{2d}\rho_1(d)\ S_2(s)}{\sum_d \left(\kappa_{-1d} + \kappa_{2d}\right)\rho_1(d) + \sum_d \kappa_{1d}\rho_2(d)\rho_1(d)\ S_2(s)} ds$$

- If $\alpha_2 < 1$, then

$$S_2(t) = S_2(0) - M \int_0^t \sum_d \left(\frac{\kappa_{1d}\kappa_{2d}\rho_2(d)S_2(s)}{\kappa_{-1d} + \kappa_{2d} + \kappa_{1d}\rho_2(d)S_2(s)} \right) \rho_1(d) ds$$