

Limits for Reaction networks with Multiple Scales and Spatial Heterogeneity

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Introduction

Modelling Reaction Networks

Multiple Scales

Example: Michaelis-Menten Kinetics

Spatial Heterogeneity

Example: Michaelis-Menten Kinetics

Future Developments

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 $\mathbf{A}_1, \dots, \mathbf{A}_{\mathcal{I}}$

$X(t) = (X_1(t), \dots, X_{\mathcal{I}}(t)) = \text{\# of particles at time } t$

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

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

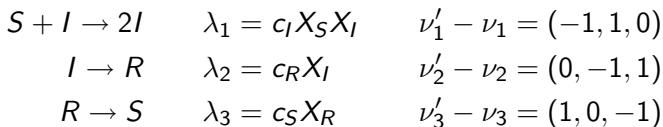
$(\nu'_{1k} - \nu_{1k}, \dots, \nu'_{\mathcal{I}k} - \nu_{\mathcal{I}k}) = \text{change due to interaction } k$

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

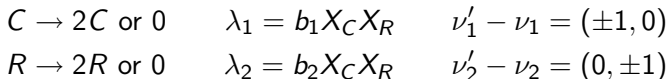
$\lambda_k(t) = \lambda_k(X(t)) = \text{rate of reaction } k \text{ at time } t$

Examples

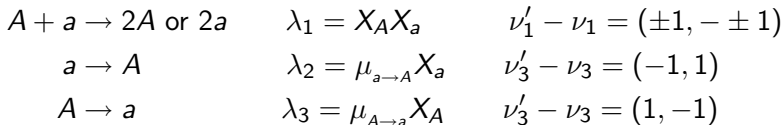
► SIRS Model :



► Catalytic Branching Process :



► Moran model with Mutations :



Stochastic dynamics

► Counting Reaction Occurrences:

$R_k(t)$ = # of times k th reaction occurs by time t

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

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

► Changes in Population Size of Components:

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

$\Delta_k = (\nu'_{1k} - \nu_{1k}, \dots, \nu'_{\mathcal{I}k} - \nu_{\mathcal{I}k})$ = 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**:

$$\begin{aligned}\lambda_k(X) &= \kappa_k \binom{X_1 \cdots X_{\mathcal{I}}}{\nu_{1k} \cdots \nu_{\mathcal{I}k}} \\ &\approx N^{\kappa_k} \prod_i \left(\frac{X_i}{N}\right)^{\nu_{ik}} \quad (\text{classical scaling})\end{aligned}$$

Rescaling of reaction networks

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

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

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

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

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

For time scale: speed-up/slow-down time by N^γ

- **Normalized system:**

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

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**:

- $\{1, 2, \dots, \mathcal{I}\} = \mathcal{I}_f + \mathcal{I}_s = \text{fast} + \text{slow}$ components s.t.:

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

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

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 $\pi_{v_s}(\mathbf{v}_f)$, then $\forall T > 0$:

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

where V_s is the solution to the system of equations:

$$V_s(t) = V_s(0) + \sum_k \int_0^t \Delta_{k|s} \bar{\lambda}_k(\mathbf{V}_s(\tau)) d\tau$$

with averaged $\bar{\lambda}_k(\mathbf{V}_s(\tau)) = \int \lambda_k(\mathbf{v}_f, \mathbf{V}_s(\tau)) \pi_{V_s(\tau)}(\mathbf{v}_f)$.

FCLT limit for slow subnetwork

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

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

Theorem [FCLT]

If $\mathbf{U}_s^N(t) = \mathbf{N}^{\delta/2}(\mathbf{V}_s^N(t) - \mathbf{V}_s(t))$, then $\forall T > 0$:

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

where U_s is the Gaussian process:

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

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

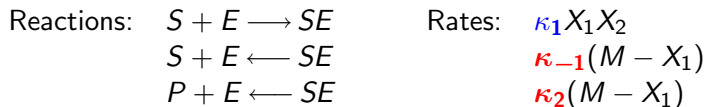
Note:

- ▶ 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



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
 $\kappa_{-1}, \kappa_2 \gg \kappa_1$, then $N = O(X_2) \gg M$ 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:

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

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

$$\begin{aligned} \sigma^2(v_2) = & M \int_0^t (1 + u_1(v_2)^2) \left(v_2 \kappa_1 p(s) + \kappa_{-1} (1 - p(s)) \right) ds \\ & + M \int_0^t u_1(v_2)^2 \kappa_2 (1 - p(s)) ds, \quad u_1(v_2) = \frac{(\kappa_1 v_2 + \kappa_{-1})}{(\kappa_1 v_2 + \kappa_{-1} + \kappa_2)} \end{aligned}$$

$u(v_1, v_2) = u_1(v_2)v_1$ 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 limiting slow subnetwork**, and averaged drift

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

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

Spatial heterogeneity in dynamics

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

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

$\lambda_{kd}(X_{\cdot d}(t))$ = **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:** $S_i^N(t) := \sum_d V_{id}^N(t)$

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

but dynamics depends on relationship between α_i, β_k and \mathbf{a}_i

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

$$S_i(t) = S_i(0) + \sum_{k \in \mathcal{K}} \Delta_{ik} Y_k \left(\int_0^t \tilde{\kappa}_k \left(\begin{matrix} S_1 \cdots S_I \\ \nu_{1k} \cdots \nu_{Ik} \end{matrix} \right) d\tau \right)$$

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

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 $\otimes_d (E_{fd} \times E_{sd})$ has generator:

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

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:

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

- **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:

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

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

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

- **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 $\tilde{\kappa}_k = \sum_d \kappa_{kd} \prod_{i \in \mathcal{I}_s} \rho_i(d)^{\nu_{ik}}$;
 - 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, $X_{1d} + X_{3d} = M_d$

$V_{2d}^N = N^{-1}X_{2d}$ 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

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

► If $\alpha_2 < 1$, then

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