Model Reduction for Density Dependent Population Processes on Multiple Scales

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Density-dependent Population Processes

Stochastic framework

Multi-scale model

Fluid Limit

Diffusion Limit

Example: Michaelis-Menten

Density-dependent Population Processes

Population Models:

- different **types** in the population
- **interactions** between the types
- rates of interactions depend on the current **density of types**

Examples/Applications:

- **epidemic** models
- catalytic **branching** processes
- **chemical** reaction networks

- **Population Types**: **m** distinct types $\mathbf{A_1}, \ldots, \mathbf{A_m}$

  $$X(t) = (X_1(t), \ldots, X_m(t)) \ = \text{\# of individuals at time } t$$

- **Interactions Between Them**: **M** distinct interactions

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

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

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

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

- Example - **SIRS Model** :

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

- Example - **Catalytic Branching Process** :

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

- **Example** - **Chemical Reaction Networks** :
  viral infection model in B-Kurtz-Popovic-R '05
  typically: large # of species **&** large system of reactions

Stochastic framework

- **Counting Processes**:

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

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

$(Y_1, \ldots, Y_M)$ = independent Poisson rate 1 processes

Lemma [Meyer '71, Kurtz '80]

If $R_1, \ldots, R_M$ are counting processes with no common jumps and λ_k is the intensity of R_k, then there exist independent unit Poisson processes $Y_1, \ldots, Y_m$ such that

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

- **Evolution of the system**:

$$\begin{aligned} X(t) &= \text{ \textbf{\# of types} in the system at time } t \\ &= X(0) + \sum_k R_k(t)(\nu'_k - \nu_k) \\ &= X(0) + \sum_k Y_k\Big(\int_0^t \lambda_k(X(s))ds\Big)(\nu'_k - \nu_k) \end{aligned}$$

- **Scaling Laws**:
  - if the total # of particles X is **large** $=$ O(N)
  - the interaction rates λ_k are **fast** $=$ O(N)

- **Classical** scaling laws can **NOT** be applied if:
  - amounts $X_1, \ldots, X_m$ are in different **orders of abundance**
  - rates $\lambda_1, \ldots, \lambda_M$ are of different **orders of magnitude**

Multi-scale model

- **Scaling parameters**: N = order of most abundant species

  For each species: $\alpha_i \in [0,1]$ chosen s.t. $\mathbf{N^{-\alpha_i}} X_i(t) = \mathbf{O(1)}$
  For each reaction: $\beta_k \in [0,1]$ 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** stochastic system:

$$V_i^N(t) = V_i^N(0) + \sum_k \mathbf{N^{-\alpha_i}} Y_k\left(\int_0^t \mathbf{N^{\beta_k+\gamma}} \lambda_k(V^N(s))ds\right)(\nu_k' - \nu_k)$$

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

- **Model reduction**: approximate system by a simpler one

Two time scales

Suppose the normalized abundances on a well chosen time scale fall essentially into two groups:

- V_1^N = vector of all the **'fast'** components in the system
- V_2^N = the vector of all the **'slow'** components in the system

Let N^δ be the **scale along which the system separates**:

$$\{1,2,\ldots,m\} = \mathcal{I}_f + \mathcal{I}_s = \textbf{fast} + \textbf{slow} \text{ components}$$

$$V_{i_1}^N(t) = V_{i_1}^N(0) + \sum_k Y_k\left(\mathbf{N}^\delta \int_0^t \lambda_k(V^N(s))ds\right)(\nu'_{i_1 k} - \nu_{i_1 k}),\ i_1 \in \mathcal{I}_f$$

$$V_{i_2}^N(t) = V_{i_2}^N(0) + \sum_k \mathbf{N}^{-\delta} Y_k\left(\mathbf{N}^\delta \int_0^t \lambda_k(V^N(s))ds\right)(\nu'_{i_2 k} - \nu_{i_2 k}),\ i_2 \in \mathcal{I}_s$$

Fluid limit

Suppose fast species are ergodic with unique stationary measure:

- limiting evolution of the slow species depends only on the **stationary distribution of the fast** quantities

Theorem 1 [**Averaging and deterministic approximation**]

If $\forall s > 0$, *when* $V_2^N(s) = v_2$ *is fixed,* $V_1^N(s)$ *has a stationary distribution* $\boldsymbol{\pi}_s(\cdot|v_2)$, *then we have a* **LLN result** *for* $V_2^N(s)$*:*

$$\forall \epsilon > 0, \quad \lim_{N\to\infty} P\Big[\sup_{s\in[0,t]} |V_2^N(s) - V_2(s)| \geq \epsilon\Big] = 0$$

where V_2 *is the deterministic process:* $\forall i_2 \in \mathcal{I}_s$

$$V_{i_2}(t) = V_{i_2}(0) + \sum_k \int_0^t (\nu'_{i_2 k} - \nu_{i_2 k}) \boldsymbol{\lambda}_k(V_2(s))ds$$

and $\boldsymbol{\lambda}_k(V_2(s)) = \int \lambda_k(v_1, V_2(s))\boldsymbol{\pi}_s(dv_1|V_2(s))$.

proof of Theorem 1

- separate evolution of "fast" process in generator L^N of V^N, L_1 is N independent and operates on f as a function of v_1 alone:

$$L^N f(v_1, v_2) = N^\delta L_1 f(v_1, v_2) + L_2^N f(v_1, v_2)$$

- let Γ_1^N be the occupation measure for the "fast" process:

$$f(V_1^N(t), V_2^N(t)) - N^\delta \int_{[0,t]\times E_1} L_1 f(v_1, V_2^N(s))\Gamma_1^N(dv_1 \times ds) - \int_{[0,t]\times E_1} L_2^N f(v_1, V_2^N(s))\Gamma_1^N(dv_1 \times ds) = M_f^N(t)$$

- if (V_2^N, Γ_1^N) is tight then for every limit point (V_2, Γ_1):

$$\int_{[0,t]\times E_1} L_1 f(v_1, V_2(s))\Gamma_1(dv_1 \times ds) = 0$$

if for each v_2 $\exists!$ $\boldsymbol{\pi}_s(\cdot|v_2)$ so that $\int_0^t L_1 f(v_1, v_2)\boldsymbol{\pi}_s(dv_1|v_2) = 0$:

$$\Gamma_1(dv_1 \times ds) = \boldsymbol{\pi}_s(dv_1|V_2(s))ds$$

- apply the Stochastic Averaging Theorem (Kurtz '91) - limit of:

$$f(V_2^N(t)) - \int_{[0,t]\times E_1} L_2^N f(v_1, V_2^N(s))\Gamma_1^N(dv_1 \times ds)$$

  is a martingale for each function f of v_2 where:

$$L_2^N f(v_1, V_2^N) = \sum_k \lambda_k(V^N)N^\delta\Big(f(V^N + N^{-\delta}(\nu'_{2k} - \nu_{2k})) - f(V^N)\Big)$$

- so for each function f of v_2 the limit of V_2^N satisfies:

$$f(V_2(t)) - \sum_k \int_0^t \partial_{v_2} f(V_2(s))(\nu'_{i_2k} - \nu_{i_2k})\boldsymbol{\lambda}_k(V_2(s))ds = f(V_2(0))$$

  where:

$$\boldsymbol{\lambda}_k(V_2(s)) = \int \lambda_k(v_1, V_2(s))\boldsymbol{\pi}_s(dv_1|V_2(s))$$

Diffusion limit

For the variability correction to this LLN deterministic approximation:

- we get a centered Gaussian process that is mean-reverting
- diffusion coefficient $\boldsymbol{\sigma}$ in the FCLT law depends on the **interaction of slow and fast** quantities

Theorem 2 [**Diffusion correction to the fluid limit**]

If $U_2^N(t) = N^{\frac{\delta}{2}}\big(V_2^N(t) - V_2(t)\big)$, *then we have a* **FCLT result**:

$$U_2^N \Rightarrow U_2$$

where U_2 *is the Ornstein-Uhlenbeck process:* $\forall i_2 \in \mathcal{I}_s$

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

with $W = |\mathcal{I}_s|$*-dimensional BM,* $\boldsymbol{\sigma}^2(v_2), \boldsymbol{\mu}(v_2)$ *matrix functions*

Note:

- expression for $\mu(v_2)$ is simple $\rightarrow$ gradient of the drift of V_2
- expression for $\sigma^2(v_2)$ is more complicated $\rightarrow$ uses the gradient of the solution of the Poisson equation for the fast process V_1

Note:

- analogous results for diffusion approximation of multi-scale SDEs - Pardoux-Veretennikov '01, '03, '05
- results for more general scaling exponents - separation into slow set and a fast set, but the vector of slow/fast components can have different exponents $\alpha_{i_1}/\alpha_{i_2}$ - Kurtz-Popovic '09

proof of Theorem 2

- let $m(v_1, v_2)$ and $\mathbf{m}(v_2)$ be the drift of the slow process and of its limit:

$$m_{i_2}(v_1, v_2) = \sum_k (\nu'_{i_2 k} - \nu_{i_2 k}) \lambda_k(v_1, v_2)$$

$$\mathbf{m}_{i_2}(v_2) = \sum_k (\nu'_{i_2 k} - \nu_{i_2 k}) \boldsymbol{\lambda}_k(v_2)$$

- let $\tilde{Y}_k^N(t) = Y_k(t) - t$ and $\tilde{R}_k(t) = \tilde{Y}_k(N^\delta \int_0^t \lambda_k(V^N(s))ds)$:

$$N^{\frac{\delta}{2}}(V_{i_2}^N(t) - V_{i_2}(t)) = N^{\frac{\delta}{2}}(V_{i_2}^N(0) - V_{i_2}(0))$$

$$+ \sum_k (\nu'_{i_2 k} - \nu_{i_2 k}) N^{-\frac{\delta}{2}} \tilde{R}_k(t) + N^{\frac{\delta}{2}} \int_0^t (m_{i_2}(V^N(s)) - \mathbf{m}_{i_2}(V_2(s)))ds$$

- let $u(v_1, v_2)$ be the solution to Poisson equation:

$$L_1 u(v_1, v_2) = m(v_1, v_2) - \mathbf{m}(v_2)$$

where L_1 is the generator of the "fast" process v_1 with v_2 fixed

- then the deviation from the fluid limit can be written as:

$$U^N_{i_2}(t) = U^N_{i_2}(0) + \sum_k (\nu'_{i_2 k} - \nu_{i_2 k}) N^{-\frac{\delta}{2}} \tilde{R}_k(t)$$

$$+ N^{\frac{\delta}{2}} \int_0^t L_1 u_{i_2}(V^N(s)) ds + N^{\frac{\delta}{2}} \Big(\int_0^t \mathbf{m}_{i_2}(V^N_2(s)) ds - \int_0^t \mathbf{m}_{i_2}(V_2(s)) ds \Big)$$

- when $U^N_2 \Rightarrow U_2$ the last term converges to the drift of U_2:

$$\int_0^t \nabla \mathbf{m}_{i_2}(V_2(s)) U_2(s) ds$$

- the second term can be expressed as

$$N^{\frac{\delta}{2}} \int_0^t L_1 u_{i_2}(V^N(s)) ds = M^N_{u,i_2}(t) + O(N^{-\frac{\delta}{2}})$$

for $M^N_u(t)$ a martingale correlated with $\sum_k (\nu'_{2k} - \nu_{2k}) N^{-\frac{\delta}{2}} \tilde{R}_k(t)$

- to find $M_u^N(t)$ let $\Delta_{i_1 k} = \nu'_{i_1 k} - \nu_{i_1 k}, \Delta_{i_2 k} = N^{-\delta}(\nu'_{i_2 k} - \nu_{i_2 k})$ and use Ito's formula:

$$u(V^N(t)) = u(V^N(0)) + \sum_k \int_0^t \Big(u(V^N(s^-) + \Delta_k) - u(V^N(s^-)) \Big) d\tilde{R}_k^N(s)$$

$$+ \int_0^t \Big(L^N u(V^N(s)) - N^\delta L_1 u(V^N(s)) \Big) ds + \int_0^t N^\delta L_1 u(V^N(s)) ds$$

$$\Rightarrow N^{\frac{\delta}{2}} \int_0^t L_1 u_{i_2}(V^N(s)) ds = -M_{u,i_2}^N(t) - \varepsilon_{u,i_2}^N(t) + O(N^{-\frac{\delta}{2}})$$

- where $M_{u,i_2}^N(t)$ is the i_2 coordinate of the martingale:

$$M_u^N(t) = N^{-\frac{\delta}{2}} \sum_k \int_0^t \Big(u(V^N(s^-) + \Delta_k) - u(V^N(s^-)) \Big) d\tilde{R}_k^N(s)$$

- and $\varepsilon_{u,i_2}^N(t)$ is the i_2 coordinate of the error term:

$$\varepsilon_u^N(t) = N^{-\frac{\delta}{2}} \int_0^t \Big(L^N u(V^N(s)) - N^\delta L_1 u(V^N(s)) \Big) ds = O(N^{-\frac{\delta}{2}})$$

- the deviation from the fluid limit can now be written as:

$$U_{i_2}^N(t) = U_{i_2}^N(0) + \sum_k \Delta_{i_2 k} N^{-\frac{\delta}{2}} \tilde{R}_k(t) - M_{u,i_2}^N(t)$$
$$+ O(N^{-\frac{\delta}{2}}) + N^{\frac{\delta}{2}} \Big(\int_0^t \mathbf{m}_{i_2}(V_2^N(s))ds - \int_0^t \mathbf{m}_{i_2}(V_2(s))ds \Big)$$

- let $\Delta_{2k} = (\Delta_{i_2 k})_{i_2 \in \mathcal{I}_s}$ and $\Delta_{1k} = (\Delta_{i_1 k})_{i_1 \in \mathcal{I}_f}$
the fluctuations of $U^N(t)$ follow from the quadratic variation of two martingale terms above:

$$\sigma^2(V^N(t)) = \Big[\sum_k \int_0^{\cdot} \Delta_{2k} N^{-\frac{\delta}{2}} d\tilde{R}_k^N(s)$$
$$- \sum_k \int_0^{\cdot} \Big(u(V^N(s^-) + \Delta_k) - u(V^N(s^-)) \Big) N^{-\frac{\delta}{2}} d\tilde{R}_k^N(s) \Big](t)$$

$$\tilde{R}_k(t) = \tilde{Y}_k(N^{\delta} \int_0^t \lambda_k(V^N(s))ds), \Delta_{1k} = O(1), \Delta_{2k} = O(N^{-\delta})$$

- when $U_2^N \Rightarrow U_2$ the diffusion coefficient is:

$$\sigma^2(V^N(s)) \Rightarrow \int \sum_k \mathbf{S}(v_1, v_2)^t \mathbf{S}(v_1, v_2) \lambda_k(v_1, v_2) \pi_s(v_1|v_2)$$

for $\quad \mathbf{S}(v_1, v_2) = \Delta_{2k} - \partial_{v_1} u(v_1, v_2) \Delta_{1k}$

- while the drift coefficient is:

$$\mu(V_2^N(s)) \Rightarrow \int \sum_k \Delta_{2k}\, \partial_{v_2} \lambda_k(v_1, v_2) \pi_s(v_1|v_2) = \nabla \mathbf{m}(v_2)$$

Note: the expression for σ^2 depends on solving the Poisson equation $L_1 u(v_1, v_2) = m(v_1, v_2) - \mathbf{m}(v_2)$ for $u(v_1, v_2)$ explicitly

- when the rates $\lambda_k(v_1, v_2)$ are polynomial in v_1, v_2

$$\lambda_k(v_1, v_2) = c_k \prod_{i_1 \in \mathcal{I}_f, i_2 \in \mathcal{I}_s} v_{i_1}^{n_{i_1 k}} v_{i_2}^{n_{i_2 k}}$$

this may be done using a polynomial for $u(v_1, v_2)$

Example: Michaelis-Menten enzymatic reactions

Reactions:

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

Rates:

$$\kappa_1 X_1 X_2$$
$$\kappa_2 (M - X_1)$$
$$\kappa_3 (M - X_1)$$

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 $= M$

$\kappa_2, \kappa_3 >> \kappa_1$, 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:

$$\boldsymbol{\pi}_s(\cdot|V_2(s)) \sim \text{Binomial}(M, p(V_2(s)))$$

$$p(V_2(s)) = (\kappa_2 + \kappa_3)/(\kappa_2 + \kappa_3 + \kappa_1 V_2(s))$$

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

$$V_2(t) = V_2(0) - M \int_0^t \frac{\kappa_1 \kappa_3 V_2(s)}{\kappa_2 + \kappa_3 + \kappa_1 V_2(s)} ds$$

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

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

where we can explicitly calculate:

$$\boldsymbol{\mu}(v_2) = \frac{-M\kappa_1\kappa_3(\kappa_2+\kappa_3)}{(\kappa_2+\kappa_3+\kappa_1 v_2)^2}$$

$$\begin{aligned}\boldsymbol{\sigma}^2(v_2) &= M\int_0^t (1+u_1(v_2)^2)\Big(v_2\kappa_1 p(s)+\kappa_2(1-p(s))\Big)ds \\ &+ M\int_0^t u_1(v_2)^2\kappa_3(1-p(s))ds\end{aligned}$$

for $\quad u_1(v_2) = (\kappa_1 v_2+\kappa_2)/(\kappa_1 v_2+\kappa_2+\kappa_3)$

since $u^{v_2}(v_1) = v_1 u_1(v_2)$ solves

$$L_1^{v_2}u(v_1) = -\kappa_1 v_1 v_2 + \kappa_2(M-v_1) + M\frac{\kappa_1\kappa_3 v_2}{\kappa_2+\kappa_3+\kappa_1 v_2}$$

$$L_1^{v_2}f(v_1) = \Big[\kappa_1 v_1 v_2\Big(f(v_1-1)-f\Big)+(\kappa_2+\kappa_3)(M-v_1)\Big(f(v_1+1)-f\Big)\Big]$$