∗ Women in Probability Workshop, Cornell, Ithaca, 2008

Multi-scale Markov process for interacting particles diffusing in a spatially heterogeneous system

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Interactions in continuous space

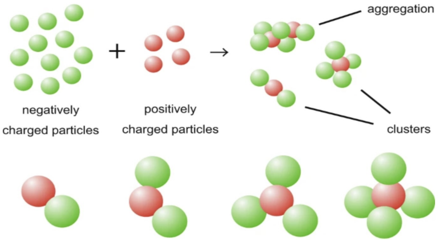
Interacting particles:

- Particles are of different types: $\tau \in \mathcal{T}$
- Interactions are from prescribed set of reactions: $r \in \mathcal{R}$, e.g.:

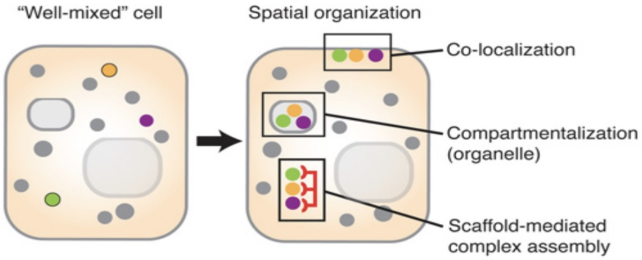
$$A \mapsto B,\ B \mapsto \emptyset,\ A{+}B \mapsto 2B,\ 2A{+}B \mapsto 3A \quad \text{(Schloegl model)}$$

$$S + I \mapsto 2I,\ I \mapsto R \quad \text{(SIR model)}$$

$$A \mapsto B,\ B \mapsto A,\ A + B \mapsto 2A,\ A + B \mapsto 2B \quad \text{(Moran model)}$$



- Rates of interactions depend on:
  - \# of particles of all input types that are close to each other
  - ⋆ proximity is determined by a kernel $\Gamma \rightarrow$ non-local operators
  - rate constants specific to the interaction that depend on the location of input types and the mass of all types
  - ⋆ allows interactions to happen only in certain locations
  - ⋆ mass of other types creates feedback in interactions

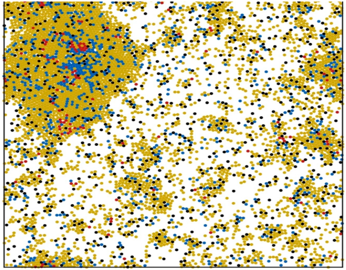


Spatial movement:

- Space is continuous: bounded $E \subset \mathbb{R}^d$
- Movement is Markovian and based on particle type
  - ⋆ some particles diffuse, some stay localized
  - - in between interactions, independently of interactions

Spatial heterogeneity:

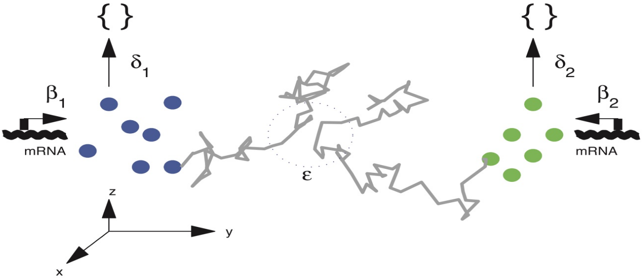
- ⋆ localization of certain reactions;
- ⋆ localization of certain particle types



∗ SIR model, Forgasz et al., Nat.Sci.Reports., 2022

Non-uniform aspects:

- some particle types are abundant, others only few counts
- some species diffuse fast, others stay almost localized



∗ Batada et al, Proc.Nat.Acad.Sci. 2004

New modelling framework:

→ allows for non-standard limits retaining relevant stochasticity

Model

Measure-valued Markov process $(M_t)_{t\geq 0}$**:**

- takes values on space of finite point measures on $\mathcal{P} = \mathcal{T} \times E$

$$\mathcal{M} = \Big\{ \sum_{i \in \mathcal{I}} \delta_{(\tau^i, x^i)} : \mathcal{I} \subset \mathbf{N}, (\tau^i, x^i) \in \mathcal{P} \Big\}$$

$\mathcal{T}$ = set of particle types, E= spatial domain, $\mathcal{I}$= indexing set,
$\delta_{(\tau,x)}$= unit mass at location $x \in E$ for particle type $\tau \in \mathcal{T}$

Flexibility of framework:

- can encode both discrete and continuous amounts in space
  $\to$ combines Individual Based Model with (S)PDE
- treating localized and non-localized particles differently
  $\to$ discrete types are localized, continuous types are either

Markov process:

*(w/ A.Véber, An.Appl.Prob.'23)

- particles w/in kernel Γ-distance interact w/ spatially dependent rates h_r - heterogeneous "mass-action"

$$\varrho_r(d\bar{y}) = \begin{cases} d\bar{y} & \text{non-localized}\,, \\ \delta_{\bar{y}} & \text{localized reac}\,. \end{cases} \qquad M^{\otimes\downarrow k_r} = \text{sampling w/o rep.}$$

$$\lambda_r(\bar{y}, M; p_1, \ldots, p_{k_r}) := h_r(\bar{y}, M) \left(\prod_{i=1}^{k_r} \mathbf{1}_{A_i^r}(x_i) \Gamma_\epsilon(y_i - \bar{y}) \right)$$

$$G_r F_f(M) = \int_{E \times \mathcal{P}^{k_r}} \varrho_r(d\bar{y}) M^{\otimes\downarrow k_r}(dp_1, \ldots, dp_{k_r}) \lambda_r(\bar{y}, M; p_1, \ldots, p_{k_r})$$

$$\left[F\left(\langle M, f \rangle - \sum_{i=1}^{k_r} f(x_i, y_i) + \sum_{i=1}^{k_r'} f(B_i^r, \bar{y}) \right) - F_f(M) \right]$$

- presented pre-limit as an Individual Based Model

- particles move according to type specific motion

$$\mathcal{D}F_f(M) = F'(\langle M, f\rangle) \sum_{x\in\mathcal{T}} \langle M, b_x \cdot \nabla_y f + \Sigma_x^2 \circ \Delta_y f\rangle$$
$$+ \; F''(\langle M, f\rangle) \sum_{x\in\mathcal{T}} \left\langle M, \Sigma_x^2 \circ \left((\nabla_y f)(\nabla_y f)^{\mathbf{t}}\right)\right\rangle.$$

Martingale problem formulation:

- for all $F_f = F(\langle \cdot, f\rangle) : F \in \mathcal{C}_b^2(\mathbf{R}), f(\tau, \cdot) \in \mathcal{C}^{0,2}(\mathcal{M})\}$

$$\left(F_f(M_t) - \int_0^t \mathcal{L}F_f(M_s)ds\right)_{t\geq 0}$$

is a martingale, where for $M \in \mathcal{M}$

$$\mathcal{L}F_f(M) = \sum_{r\in\mathcal{R}} \mathcal{L}_r F_f(M) + \sum_{\tau\in\mathcal{T}} \mathcal{D}_\tau F_f(M)$$

· can be constructed as a solution to jump-SDE

Piecewise Deterministic Markov Process (PDMP)

*(dynamical systems w/ random switching)

- (finite dim) **PDMP** - process taking values in $\underline{\mathbb{N}^d \times \mathbb{R}^c}$
- deterministic dynamics of continuous coordinates prescribed by a continuous flow
- stochastic Markov chain dynamics of discrete coordinates prescribed by jump rates

→ the flow and jump rates are fully coupled

- finite-dimensional PDMPs well studied (since Davis '84)

→ stability, inference (Costa-Dufour), ergodicity, invariant measure (Benaim et al., Cloez-Hairer)

- infinite-dimensional PDMPs: new in the literature - process in Hilbert space (Thieullen-Wainrib, neuro-science model)

Measure-Valued PDMP *(w/ A.Véber, An.Appl.Prob.'23)

- **measure-valued PDMP** - taking values in $\underline{\mathcal{M}^d \times \mathcal{M}^c}$
  $\mathcal{M}^d$= point-measures on $\mathcal{T}_{L,s} \times E$, $\mathcal{M}^c$= measures on $\mathcal{T}^c_{L,s} \times E$
  - deterministic dynamics of continuous coordinates prescribed by a measure-valued flow Φ
  - stochastic dynamics of discrete coordinates prescribed by point-measure jump rates

- can be constructed as a solution to jump-PDE

  $(\tau^i, i = 0, 1, \dots) =$ jump times of $\mathcal{M}^d$
  - for $t \in [\tau^i, \tau^{i+1})$ have the deterministic flow

$$\mathcal{M}_t := \left(\Phi_{\mathcal{M}^d_{\tau^i}}(t - \tau^i, \mathcal{M}^c_{\tau^i}), \mathcal{M}^d_{\tau^i}\right)$$

  - at τ^{i+1} have the stochastic jump due to some reaction r

$$\mathcal{M}_{\tau^{i+1}} := \left(\Phi_{\mathcal{M}^d_{\tau^i}}(\tau^{i+1} - \tau^i, \mathcal{M}^c_{\tau^i}),\ \mathcal{M}^d_{\tau^i} + \sum_{i=k'_{r^j,b}+1}^{k'_{r^j}} \delta_{(B^{r^j}_i, \bar{y}_{r^j})} - \sum_{i=k_{r^j,b}+1}^{k_{r^j}} \delta_{(A^{r^j}_i, \bar{y}_{A^{r^j}_i})}\right)$$

Limit Results

Functional LLN

- Assume subset of particles scale $\sim O(N)$ and diffuse, other particles scale $\sim O(1)$ and are localized
- Start from particles for all types, rescale mass non-uniformly:

$$M_t^N := \frac{1}{N} \sum_{x_i \in \mathcal{T}_{L,s}^c} \delta_{(x_i,y_i)} + \sum_{x_i \in \mathcal{T}_{L,s}} \delta_{(x_i,y_i)},$$

- Assume appropriate conditions on rates, and assume control on moments of mass

$$\sup_N \mathbf{E}\left[\sup_{t \in [0,T]} \langle M_t^N, 1 \rangle^{(1+\max_{r \in R} k_r) \vee 2} \right] < \infty ;$$

- If $M_0^N \Rightarrow M_0^\infty$, and the mgale problem for M^∞ is well-posed, then:

$$\left(\frac{1}{N} \sum_{\substack{i \in \mathcal{I}_t: \\ x_i \in \mathcal{T}_{NL}}} \delta_{(x_i,y_i)}, \sum_{\substack{i \in \mathcal{I}_t: \\ x_i \in \mathcal{T}_L}} \delta_{(x_i,y_i)} \right)_{t \geq 0} \underset{N \to \infty}{\Longrightarrow} \left(M_t^{\infty,c}, M_t^{\infty,d} \right)_{t \geq 0}$$

→ $M^{\infty,c}$= continuous mass coordinate is deterministic on random intervals when $M^{\infty,d}$ is constant, characterized by integro-differential equation dependent on $M^{\infty,d}$ as well

→ $M^{\infty,d}$= discrete mass coordinate is jump Markov process, jump rates are dependent on both coordinates $(M^{\infty,c}, M^{\infty,d})$

Assuming similar mass conditions:

$$\sup_N \mathbf{E}\left[\sup_{t\in[0,T]} \langle M_t^{\infty,c} \otimes M_t^{\infty,d}, 1\rangle^{(1+\max_{r\in R} k_r)\vee 2} \right] < \infty \;;$$

→ $M^{\infty} = M^{\infty,c} \otimes M^{\infty,d}$ is a measure-valued PDMP

- useful properties of the process can be derived from the particle pre-limit

Regime Switching Markov Processes

*(stochastic systems w/ random switching)

- (finite dim) **SDE w/ regime switching** - process taking values in $\underline{\mathbb{N}^d \times \mathbb{R}^c}$
  - dynamics of continuous coordinates prescribed by SDE
  - dynamics of discrete coordinates prescribed by Markov chain

→ the parameters of SDE depend on the Markov chain,
the jump rates of the Markov chain are autonomous

- (infinite-dim) **SPDE w/ regime switching**: recent in the literature

→ stability, regularity, ergodicity, invariant measure - of interest

Distribution-Valued RSMP *(w/ A.Véber, in prep.)

- **distribution-valued RSMP** - taking values in $\mathcal{S}'$
  $\mathcal{S}'$= dual of the Schwartz space of C^∞ functions on $\mathcal{T} \times E$
- paired w/ measure-valued PDMP - Markov chain = $\mathcal{M}^d$

- dynamics of continuous coordinates prescribed by a distribution-valued process $\mathcal{U}$
- dynamics of discrete coordinates prescribed by $\mathcal{M}^d$ jump rates

- can be constructed as a solution to jump-SPDE

  $(\tau^i, i = 0, 1, \dots) =$ jump times of $\mathcal{M}^d$

- for $t \in [\tau^i, \tau^{i+1})$ have the SPDE flow Ψ

$$\mathcal{U}_t := \Psi_{\mathcal{M}^d_{\tau^i}}(t - \tau^i,\ (\mathcal{U}_s)_{s \in [\tau^i, t)})$$

- at τ^{i+1} have the jump of $\mathcal{M}^d$ to $\mathcal{M}^d_{\tau^{i+1}}$ determined by PDMP

Functional CLT

- Recall

$$M^N := \Big(\frac{1}{N}\sum_{\substack{i\in\mathcal{I}_t:\\ x_i\in\mathcal{T}_{NL}}}\delta_{(x_i,y_i)}, \sum_{\substack{i\in\mathcal{I}_t:\\ x_i\in\mathcal{T}_{L}}}\delta_{(x_i,y_i)}\Big)_{t\geq 0} \underset{N\to\infty}{\Longrightarrow} M^\infty := \Big(M_t^{\infty,c}, M_t^{\infty,d}\Big)_{t\geq 0}$$

- Define normalized deviation from functional LLN limit

$$M^{N,\infty} := \text{has jumps of } M^{N,d} \text{ and continuous flow of } M^{\infty,c}$$

$$U^N := \sqrt{N}(M^N - M^{N,\infty})$$

- Assume appropriate extra conditions. If $U_0^N \Rightarrow 0$, then:

$$U^N \underset{N\to\infty}{\Longrightarrow} U^\infty$$

where U^∞ is a semi-martingale taking values in $\mathcal{S}'(\mathcal{T}\times E)$, satisfying Ornstein-Uhlenbeck type SPDE: $\forall\phi\in\mathcal{S}(\mathcal{T}\times E)$

$$\langle U_t^\infty, \phi\rangle = \int_0^t ds\,\langle U_s^\infty, \nabla_M \boldsymbol{F}(M_t^\infty(\phi)\rangle + \int_0^t dW_s^\infty \sqrt{[V^\infty(\phi)]_s}.$$

$\boldsymbol{F}(M_t^\infty, \phi)$ is the drift in the deterministic flow of $\langle M^\infty, \phi\rangle$.

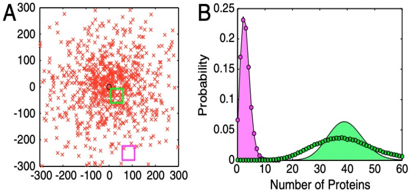
Questions

Properties of Piecewise deterministic processes:

$\rightarrow$ long-term behaviour of Measure-valued PDMP:
- regime-switching PDE driven by autonomous Markov Chain

Properties of Regime switching processes:

$\rightarrow$ statistical features of the Distribution-valued RSMP:
- evaluation on $\varphi \in \mathcal{S}(\mathcal{T} \times E)$ for useful correlations

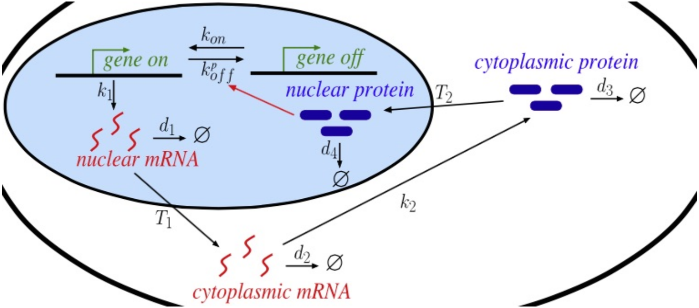


$*$ Tupper-Swain, PNAS 2012

Example

Intra-cellular transcription-translation mechanism:

*Nucleus =blue; cytoplasm = white



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Sturrock et al, J.Theor.Biol 2017

$$\emptyset \overset{\bar{h}_1(B)}{\underset{\mathbf{1}_{\bar{y}_1=0}}{\mapsto}} A, \quad A \overset{\bar{h}_2}{\mapsto} A+B, \quad B \overset{\bar{h}_3}{\mapsto} \emptyset, \quad A \overset{\bar{h}_4}{\mapsto} \emptyset$$

- A is the mRNA, B is the protein, transcription of mRNA occurs only in the nucleus at $\bar{y}_1 = 0$ w/ rate $h_1(\bar{y}_1, \langle M, \Psi_{B,\epsilon}\rangle)$
- Unregulated case: function $\bar{h}_1$ is constant;
  Self-regulated case: $\bar{h}_1(0, \langle M, \Psi_{B,\epsilon}\rangle)$ with $\Psi_{B,\epsilon} \approx \mathbf{1}_{\{B\}\times B(0,\epsilon)}$;
  e.g. $h_1(\bar{y}_1, a) = c_1/(1+(c_2 a)^k)$ for repression by B,
  or $h_1(\bar{y}_1, a) = (1+c_1 a^k)/(c_2^k + a^k)$ for activation by B

Measure-valued PDMP limit:

- $A = O(1)$, $B = O(N)$;
- A are localized at $\bar{y} = 0$, B diffuse freely:

- discrete coordinate $M_t^{\infty,c} = M_t(A, 0)$ (A molecules at $\bar{y} = 0$) is a jump Markov process w/ birth rate $=h_1$, and death rate $=h_4 M_t(A, 0)$;
- continuous coordinate $M_t^{\infty,d} = M_t \mathbf{1}_{\{B\}\times E}$ (conts mass of B) is deterministic between random jump times $\{\tau^j, j \geq 1\}$ of $M_t(A, 0)$ and its density $\mu_t(B, y) = \frac{dM_t(B,y)}{dy}$ satisfies: $\forall y, \forall t \in [\tau^j, \tau^{j+1})$

$$\partial_t \mu_t(B, y) = \sigma_B^2 \Delta_y \mu_t(B, y) + h_2 M_t(A, 0)\Gamma_\epsilon(y) - h_3 \mu_t(B, y)$$

with initial values given by $\mu_{\tau^j}(B, y) = \lim_{t \uparrow \tau^j} \mu_t(B, y)$.