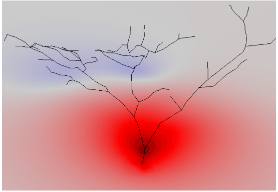
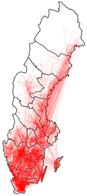
Stability and strong convergence in multiscale methods for spatial stochastic kinetics





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Spatially Distributed Stochastic Dynamical Systems in Biology

Isaac Newton Institute for mathematical Sciences, University of Cambridge, June 20, 2016

Outline

Local physics + transport mechanism

= Event-based mesoscopic & stochastic computational framework

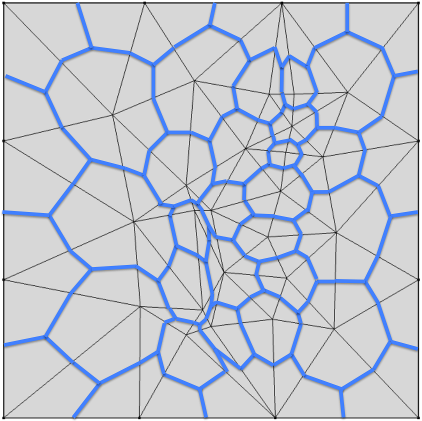
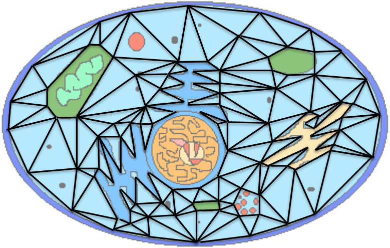


Figure: Primal mesh (thin), dual mesh (blue). The *state* is the # of agents (eg. molecules) in each dual voxel.

Local physics within each voxel, *connected* through transport mechanisms (eg. diffusion).

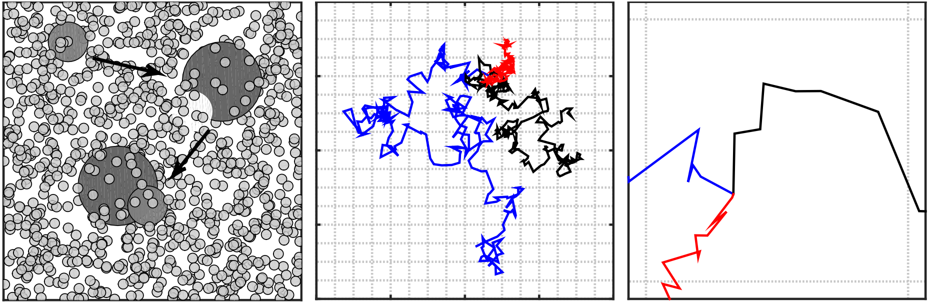


Like PDEs, but better!

"Local physics" first...

Well-stirred kinetics

Example: Bimolecular reaction $X + Y \to Z$. *Or* infection spread $S + I \to 2I$. *Or*...

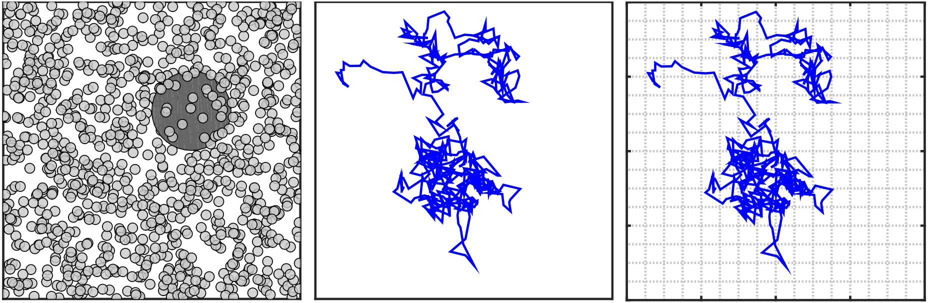


-When counting individual species/agents, a continuous-time Markov chain is the most immediate model of the physics in the zoomed in situation.

..."transport physics" next

Space-discrete, time-continuous model of moving particle

Example: Brownian motion.



(micro) → (stoch) The stochastic model is simpler but random (*error:* microscale effects in a statistical sense only).

(stoch) → (meso) Discrete space approximation (*error:* finite $h > 0$).

Why stochastic? Why discrete? Why space?

SE '06 *"The situation is clearly different when biological systems inside living cells are considered. [—] It is intuitively clear that under such circumstances the inherent stochasticity of the system plays a vital role"*

SE & others '09 *"Intrinsic noise in biochemical networks can have a large impact [—] The extremely complex ... microscopic behavior paired with the fact that the copy number is a small nonnegative integer make a discrete, stochastic description of the system necessary"*

SE & others '15 *"...spatial stochastic models based on a Markov process formalism are popular due to their high level of biological realism compared to [PDEs], with only a moderate increase in computational complexity..."*

-And a great many similar remarks have been made by several many others...! *(everybody "knows")*

The main message

Just to rub it in...

Terms & conditions. Want to use these models when either one of

- stochasticity
- nonlinearities
- species discreteness
- spatial inhomogeneities

make a big, or at least an interesting difference. Hence the physical model itself is *sensitive to perturbations* in anyone of these.

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Designing/understanding computational models: either we do

- An analysis by analogy/fingerspitzengefühl...
- Or, using the **Lax principle**: *if the numerical physics $\approx$ the wanted "true" physics (consistency), then the numerical solution $\to$ the true solution (convergence) IFF the numerical physics is stable*

Notation

Local physics

-State $X \in \mathbf{Z}_+^D$, counting the number of each of D species/agents/compartments.

-Events/reactions are transitions between these states,

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r, \qquad \mathbb{N} \in \mathbf{Z}^{D \times R} \text{ (\textit{stoichiometric matrix})}$$

with *propensity* $w_r : \mathbf{Z}_+^D \to \mathbf{R}_+$, $r = 1...R$.

-Poisson representation

$$X(t) = X(0) - \sum_r \mathbb{N}_r \Pi_r \left(\int_0^t w_r(X(s))\, ds \right),$$

each Π_r a unit-rate Poisson process.

Notation (cont)

Mesoscopic spatial kinetics

Total volume Ω subdivided into small enough computational cells Ω_j such that the local physics is an accurate model.

- The state of the system is now an array $\mathbb{X}$ with $D \times K$ elements; D species $\mathbb{X}_{ij}$, $i = 1, \ldots, D$, counted separately in K cells, $j = 1, \ldots, K$.
- This state is changed by local physics events (vertically in $\mathbb{X}$) *and* by transport into adjacent cells (horizontally in $\mathbb{X}$).

Local physics

(eg. reactions)

Same model in K cells, $j = 1, \ldots, K$,

$$\mathbb{X}_{ij}(t) = \mathbb{X}_{ij}(0) - \sum_r \mathbb{N}_{ri} \Pi_{rj} \left(\int_0^t w_{rj}(\mathbb{X}_{\cdot,j}(s)) \, ds \right),$$

for $i = 1, \ldots, D$ species.

Transport mechanism
(eg. diffusion)

Linear model (convection/diffusion, but also crowding): transport from one cell Ω_j to another cell Ω_k according to

$$\mathbb{X}_{ij} \xrightarrow{q_{ijk}\mathbb{X}_{ij}} \mathbb{X}_{ik},$$

where q_{ijk} is non-zero only for connected cells.

$$\mathbb{X}_{ij}(t) = \mathbb{X}_{ij}(0) - \sum_k \Pi'_{ijk}\left(\int_0^t q_{ijk}\mathbb{X}_{ij}(s)\,ds\right) + \sum_k \Pi'_{ikj}\left(\int_0^t q_{ikj}\mathbb{X}_{ik}(s)\,ds\right).$$

Stochastic reaction-transport framework

"RDME"

Combining reactions with transport events we arrive at

$$\begin{aligned}\mathbb{X}_{ij}(t) = &\mathbb{X}_{ij}(0) - \sum_r \mathbb{N}_{ri} \Pi_{rj} \left(\int_0^t w_{rj}(\mathbb{X}_{\cdot,j}(s)) \, ds \right) \\ &- \sum_k \Pi'_{ijk} \left(\int_0^t q_{ijk} \mathbb{X}_{ij}(s) \, ds \right) + \sum_k \Pi'_{ikj} \left(\int_0^t q_{ikj} \mathbb{X}_{ik}(s) \, ds \right).\end{aligned}$$

-Formulated in already discrete space! The limit when the cell size $\to 0$ is not straightforward.

Assumptions & *a priori*: well-stirred case

Local physics first...

Recall: CTMC $X(t) \in \mathbf{Z}_+^D$ governed by transitions

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r, \quad r = 1...R, \quad \mathbb{N} \in \mathbf{Z}^{D \times R},$$

or, to get some ODE-feeling, "$X'(t) = -\mathbb{N}w(X)$".

Norm $\|x\|_{\boldsymbol{l}} := \boldsymbol{l}^T x$, $x \in \mathbf{Z}_+^D$, normalized so $\min_i \boldsymbol{l}_i = 1$.

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Assumptions: $x, y \in \mathbf{Z}_+^D$,

(i) $-\boldsymbol{l}^T \mathbb{N} w(x) \le A + \alpha \|x\|_{\boldsymbol{l}}$ ("$\boldsymbol{l}$-outward bound")

(ii) $(-\boldsymbol{l}^T \mathbb{N})^2 w(x)/2 \le B + \beta_1 \|x\|_{\boldsymbol{l}} + \beta_2 \|x\|_{\boldsymbol{l}}^2$ ("$\boldsymbol{l}$-outward absolute bound")

(iii) $|w_r(x) - w_r(y)| \le L_r(P)\|x - y\|$, $r = 1, \ldots, R$, and $\|x\|_{\boldsymbol{l}} \vee \|y\|_{\boldsymbol{l}} \le P$

The "blue assumptions".

Assumptions & *a priori*: local physics

Summary of results

With suitable initial data...

- This $\mathbb{E}[\sup_{s\in[0,t]} \|X(s)\|_{\boldsymbol{l}}^p]$ bounded, any $p \geq 1$
- if $X(0) = Y(0)$ almost surely, then $\mathbb{E}[\|X(t) - Y(t)\|^2] = 0$
- if $\alpha + \beta_2(p-1) < 0$, then $\mathbb{E}[\|X(t)\|_{\boldsymbol{l}}^p]$ bounded as $t \to \infty$

Assumptions & *a priori*: local physics

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-In fact, if $X(0) = Y(0)$ almost surely, and if $Y(t)$ is obtained by δ-perturbing the transition intensities ($w_r \to (1 \pm \delta)w_r$), then $\lim_{\delta\to 0} \mathbb{E}[\|X(t) - Y(t)\|^2] = 0$.

-Actually, if both X and Y are bounded, then $\mathbb{E}[\|X(t) - Y(t)\|^2] = O(\delta)$.

Assumptions & *a priori*: spatial case

Recall: CTMC $\mathbb{X}(t) \in \mathbf{Z}_+^{D \times K}$ with transitions

$$\mathbb{X}_{\cdot,k} \xrightarrow{w_{rk}(\mathbb{X}_{\cdot,k})} \mathbb{X}_{\cdot,k} - \mathbb{N}_r, \quad \mathbb{X}_{ij} \xrightarrow{q_{ijk}\mathbb{X}_{ij}} \mathbb{X}_{ik},$$

$k = 1...K$, $i = 1...D$, $r = 1...R$. To get "PDE-feeling",

$$\mathbf{v}_t = -\mathbb{N}u(\mathbf{v}) + \underbrace{Q}_{\text{eg. } \approx \nabla \cdot \Sigma \nabla} \mathbf{v}.$$

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Assumptions:

- on the mesh, some natural and quite weak assumptions (...)
- reactions, as before, *plus*
  (iv) $w_{rk}(x) = \Omega_k u_r(\Omega_k^{-1} x)$, "density dependent"

Assumptions & *a priori*: spatial case

Summary of results

Norm $\|\mathbb{X}\|_{\boldsymbol{l},1} \equiv \sum_{k=1}^{K} \|\mathbb{X}_{\cdot,k}\|_{\boldsymbol{l}} = \boldsymbol{l}^T \mathbb{X}\mathbf{1}$.

With suitable initial data...

- only reactions: as before
- pure transport: $\|\mathbb{X}(t)\|_{\boldsymbol{l},1} = \|\mathbb{X}(0)\|_{\boldsymbol{l},1}$, so bounded by initial data
- coupled spatial model: $\mathbb{E}[\sup_{s \in [0,t]} \|\mathbb{X}(s)\|_{\boldsymbol{l},1}^p]$ bounded, any $p \geq 1$
- (strong) continuous dependence on parameters as before

Application: Multiscale variable splitting

Set-up: ϵ, h

Consider the separation of scales:

- species are either abundant $\sim \epsilon^{-1}$, or appear in low copy numbers ~ 1 *(on a per voxel basis!)*
- rate constants are either fast ~ 1, or slow ϵ (...)

$\Longrightarrow$ rescaled variable $\bar{\mathbb{X}}(t) = \bar{\mathbb{X}}_{ij}(t) \sim 1$.

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Multiscale splitting methods:

"Exact", $\bar{\mathbb{Y}}(t)$ all Poisson processes driving an abundant species are replaced with mean drift terms, $\Pi(t) \approx t$

"Numerical", $\bar{\mathbb{Y}}^{(h)}(t)$ discrete steps h; low copy number variables are first simulated in $[t, t+h)$ letting abundant species be frozen at time t, next abundant species are integrated in $[t, t+h)$

Scale separation

Details

Scale vector $S \in \mathbf{R}^D$,

$$\mathbb{X}_{i,\cdot}(t) = S_i \bar{\mathbb{X}}_{i,\cdot}(t), \qquad S_i = 1 \text{ or } \epsilon^{-1}.$$

The rates are assumed to obey the scaling laws

$$\begin{aligned} q_{ijk}x &= \epsilon^{-\mu_i} \bar{q}_{ijk} S^{-1} x, \\ u_r(x) &= \epsilon^{-\nu_r} \bar{u}_r(S^{-1}x). \end{aligned}$$

The scaled rates $\{\bar{q}_{ijk}, \bar{u}_r(\cdot)\}$ are understood to be $O(1)$ with respect to ϵ.

Scale separation
Existence

If the following scaled assumptions hold,

$$-\boldsymbol{l}^T S^{-1}\mathbb{N}u(x) \le A + \alpha \left\|S^{-1}x\right\|_{\boldsymbol{l}} \quad (1)$$

$$(-\boldsymbol{l}^T S^{-1}\mathbb{N})^2 u(x)/2 \le B + \beta_1 \left\|S^{-1}x\right\|_{\boldsymbol{l}} + \beta_2 \left\|S^{-1}x\right\|_{\boldsymbol{l}}^2 \quad (2)$$

$$|\bar{u}_r(x) - \bar{u}_r(y)| \le L_r(P)\|x-y\|,\; r = 1\ldots R, \text{ and } \|x\|_{\boldsymbol{l}} \vee \|y\|_{\boldsymbol{l}} \le P \quad (3)$$

for $\{\boldsymbol{l}, A, \alpha, B, \beta_1, \beta_2, L\}$ all *independent of* ϵ.

Then in an $O(1)$ interval of time, with $O(1)$ initial data, $\mathbb{E}[\sup_{s\in[0,t]} \left\|\bar{\mathbb{X}}(s)\right\|_{\boldsymbol{l},1}^p]$ is also $O(1)$.

Scale separation

Existence (cont)

1. Replace (2) with

$$\left(-\boldsymbol{I}_1^T\mathbb{N}^{(1)}\right)^2 u(x)/2 \le B + \beta_1 \left\|S^{-1}x\right\|_{\boldsymbol{I}} + \beta_2 \left\|S^{-1}x\right\|_{\boldsymbol{I}}^2$$

($\boldsymbol{I}$-outward absolute bound for stochastic part only)

$\Longrightarrow$ Then $\bar{\mathbb{Y}}(t)$ is also $O(1)$.

2. Additionally replace (1) with

$$\max\left(-\boldsymbol{I}_1^T\mathbb{N}^{(1)}u(x), -\boldsymbol{I}_2^T\epsilon\mathbb{N}^{(2)}u(x)\right) \le A + \alpha \left\|S^{-1}x\right\|_{\boldsymbol{I}}$$

($\boldsymbol{I}$-outward bound for deterministic/stochastic parts individually)

$\Longrightarrow$ Then $\bar{\mathbb{Y}}^{(h)}(t)$ is also $O(1)$.

Multiscale split

Terms & conditions

Species in low numbers $i \in G_1$, in large numbers $i \in G_2$. Put

$$R(G_1) := \{r;\ \text{transition } r \text{ affects a species } i \in G_1\}$$

(and same for $R(G_2)$).

Define also

$$u := \min_{r \in R(G_1)} -\nu_r \wedge \min_{i \in G_1} -\mu_i \text{ ('worst' } \epsilon\text{-scaling of transition affecting } G_1)$$

$$v := 1 + \min_{r \in R(G_2)} -\nu_r \wedge \min_{i \in G_2} -\mu_i \text{ ('worst' } \epsilon\text{-scaling of transition affecting } G_2 \textit{ plus } 1)$$

Errors

Convergence results

Under the (Assumptions) above, then

- $\mathbb{E}[\|\bar{\mathbb{Y}}(t) - \bar{\mathbb{X}}(t)\|^2] = O(\epsilon^{1+v} + \epsilon^{1/2+v/2+u})$
- Bounded/unbounded case: *almost* the same result...

Under the (Assumptions) above, then *if the processes are bounded*,

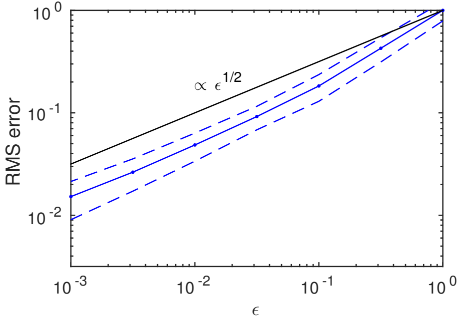
- $\mathbb{E}[\|\bar{\mathbb{Y}}^{(h)}(t) - \bar{\mathbb{Y}}(t)\|^2] = O\left(h(\epsilon^{2u} + \epsilon^{u+v})\right) + O\left(h^2\epsilon^{2v}\right)$
- Unbounded case: only convergence as $h \to 0$ remains...

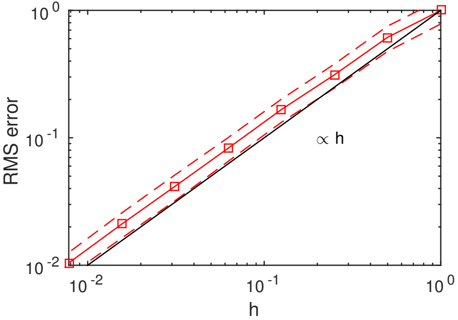
Example: catalytic process

"Stress test" of theory

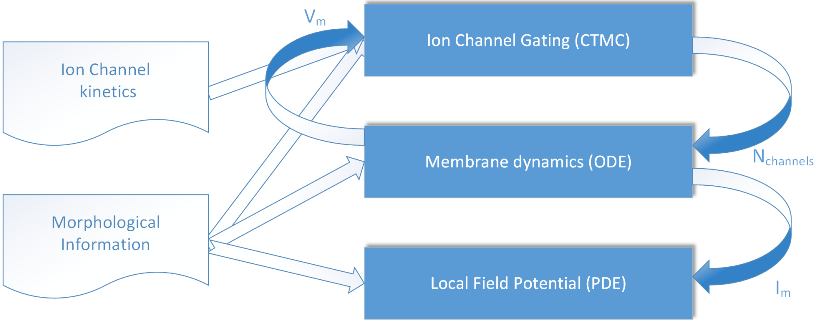
$(A, C) \sim \epsilon^{-1}$, $(B, D) \sim 1$, diffusion$_{A,C} \sim \epsilon$, diffusion$_{B,D} \sim 1$.

$$
\begin{aligned}
A + B &\xrightarrow{kAB} C + B & \qquad A &\underset{b_a}{\overset{\epsilon d_a A}{\rightleftharpoons}} \emptyset \\
C + D &\xrightarrow{kCD} A + D & \qquad B &\underset{b_b}{\overset{d_b AB}{\rightleftharpoons}} \emptyset \\
B + B &\underset{k_d D}{\overset{k_b B(B-1)}{\rightleftharpoons}} D & &
\end{aligned}
$$



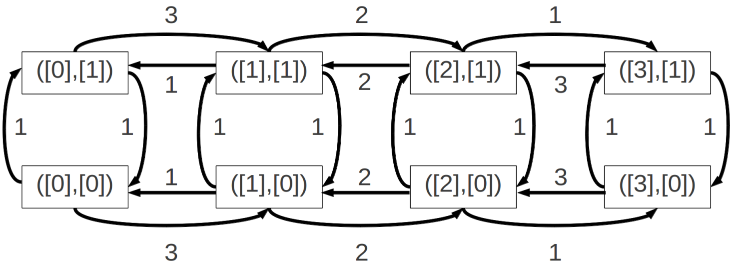


Application: multiscale neuronal model



Bottom level

Ion channel gating



Gating process: sodium channels.

Bottom level

Ion channel gating

The gating process of ion channels can be mesoscopically described as

$$N_0 \underset{\beta_m(V_m)N_1}{\overset{3\alpha_m(V_m)N_0}{\rightleftharpoons}} N_1 \underset{2\beta_m(V_m)N_2}{\overset{2\alpha_m(V_m)N_1}{\rightleftharpoons}} N_2 \underset{3\beta_m(V_m)N_3}{\overset{\alpha_m(V_m)N_2}{\rightleftharpoons}} N_3,$$

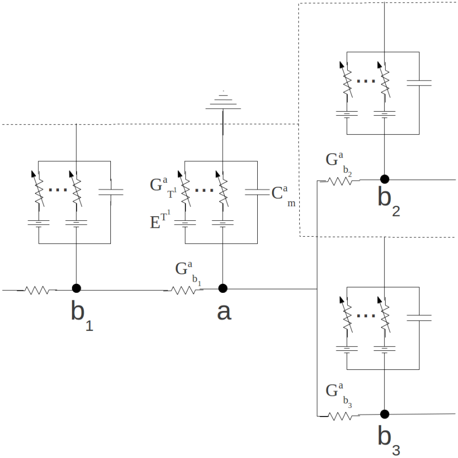
again a *continuous-time Markov chain*. *Output:* N_3, the number of open gates.

For efficient model coupling we freeze the voltage dependency for a short time-step τ ("split-step" or "1st order Strang split"):

$$X(t+\tau) = X(t) - \mathbb{N}\Pi\left(\int_t^{t+\tau} w(X(s), V_m(t))\, ds\right).$$

Middle level

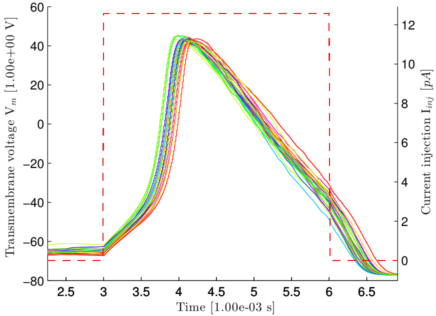
Membrane dynamics



Cable equation circuit.

Middle level

Membrane dynamics



$$I_m = c_m \frac{dV_m}{dt} + \sum_{i \in C_v} \gamma_i N_3^i(t)[V_m(t) - E_i]$$

- Morphological information extracted using the *Trees toolbox*
- System of current-balance and cable equations is solved for each time step τ

Top level

Maxwell's equations, potential form

Electric field intensity $\mathbf{E}$ in terms of the *electric scalar potential* V,

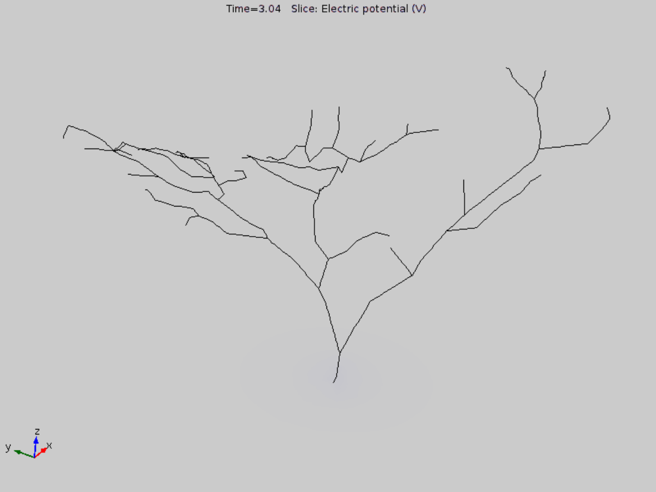
$$\mathbf{E} = -\nabla V.$$

Trans-membrane current I_m is scaled with the compartement surface area and coupled as a current source,

$$-\nabla \cdot \left(\sigma \nabla V + \varepsilon_0 \varepsilon_r \frac{\partial}{\partial t} \nabla V \right) = \frac{1}{\Omega_c} I_m,$$

with conductivity σ and permittivity ε. The time dependent potential V is solved via finite element methods.

Sample simulation



Application: national-scale epidemics

- Modeling the spread of verotoxinogenic *E. coli* O157:H7 (VTEC O157:H7) in the Swedish cattle population
- Important *zoonotic pathogen* (animal $\rightarrow$ humans) of great public health interest, causing enteroheamorrhagic colitis (EHEC) in humans ($\sim$500 cases anually in Sweden).

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- Important *zoonotic pathogen* (animal $\to$ humans) of great public health interest, causing enteroheamorrhagic colitis (EHEC) in humans ($\sim$500 cases anually in Sweden).
- In Germany during the summer 2011, a particularly aggressive variant emerged, with 3,816 reported cases and 54 deceased.
- *Infected animals show no signs of the disease!*
- Cattle is a main reservoir of the bacteria, ongoing research to better understand the epidemiology of VTEC O157:H7 in the cattle population
- Mixed event-based approach:
    - Data-driven simulation using all registred cattle events 2005-2013
    - Stochastic simulation of within-herd dynamics (i.e. mesoscopic)

Data-driven

REPORTER	WHERE	ABATTOIR	DATE	EVENT	ANIMALID	BIRTHDATE
83466	83958	0	2009-10-01	2	SE0834660433	1997-04-04
83958	83466	0	2009-10-01	1	SE0834660433	1997-04-04
83958	83829	0	2012-03-15	2	SE0834660433	1997-04-04
83829	83958	0	2012-03-15	1	SE0834660433	1997-04-04
83829	83958	0	2012-03-15	4	SE0834660433	1997-04-04
54234	83829	0	2012-04-11	1	SE0834660433	1997-04-04
83829	54234	0	2012-04-11	2	SE0834660433	1997-04-04
83829	83958	0	2012-04-11	5	SE0834660433	1997-04-04

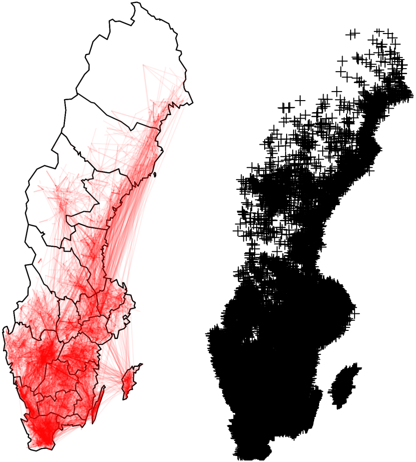
Total: 18 649 921 reports and 37 221 holdings

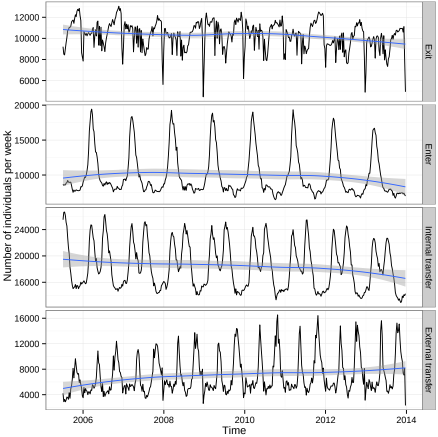
Events

- Exit (n=1 438 506)
- Enter (n=3 479 000)
- Internal transfer (n=6 593 921)
- External transfer (n=732 292)

Events

(Population UK:Sweden is $\sim$ 10:1, area $\sim$ 5:9)





Epidemic model

"Locally well-stirred" (SIS_E)

Model states: **S**usceptible, **I**nfected, in $i = 1, \ldots, \sim$40,000 holdings and in 3 age categories $j \in \{calves, youngstock, adults\}$.

State transitions at node i in the jth age category,

$$Rate\ I_{ij} \to S_{ij} = \gamma_j I_{ij}(t)$$
$$Rate\ S_{ij} \to I_{ij} = \upsilon_j S_{ij}(t)\varphi_i(t)$$

Environmental infectious pressure

$$\frac{d\varphi_i}{dt} = \frac{\alpha \sum_j I_{ij}(t)}{\sum_j S_{ij}(t) + I_{ij}(t)} - \beta(t)\varphi_i(t) + \epsilon$$

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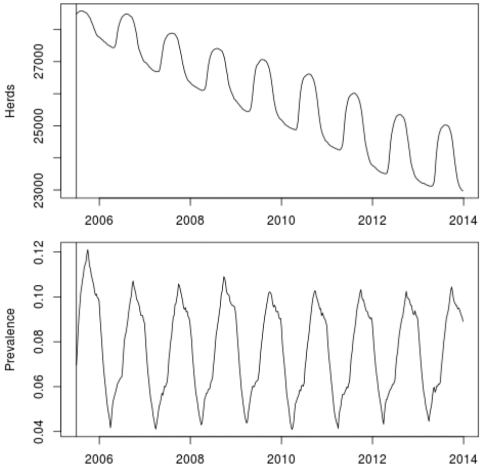
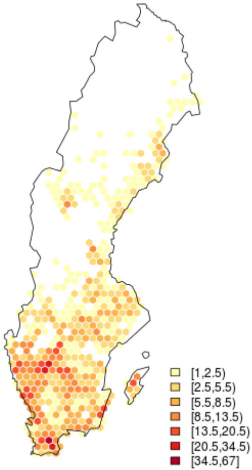
Finding #1: $\beta = \beta(t)$ required in the Swedish climate.

Finding #2: finite-time extinction for $\epsilon = 0$, contrary to the corresponding ODE-model.

Sample simulation

Connected through ∼9 years of actual transport data





Summary

- Mesoscopic stochastic reaction-transport, **event-based computational framework**: fairly intuitive modeling & coupling
- Terms & conditions. If used when required: accurately capturing a stochastic nonlinear phenomenon is a very hard constraint for method's development!
- The **Lax principle** $\Longrightarrow$ Well-posedness, stability, consistency, convergence
- Analysis of simple numerical methods
- Multiscale neuronal application solved in URDME (GitHub): proof of concept for coupling different types of models
- Epidemiological national-scale model solved in SimInf (GitHub): data-driven simulation, some findings when attempting to fit parameters to data

Thanks

Programs, Papers, and Preprints are available from my web-page.
Thank you for the attention!