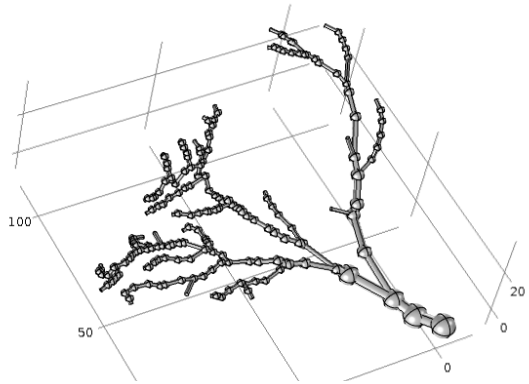
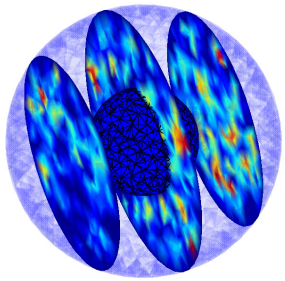
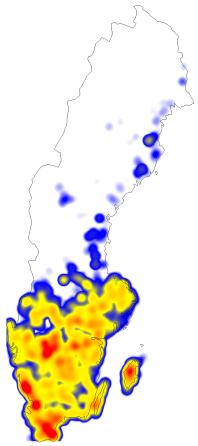
Pathwise analysis for split-step methods and multiscale variable splitting in spatial stochastic kinetics



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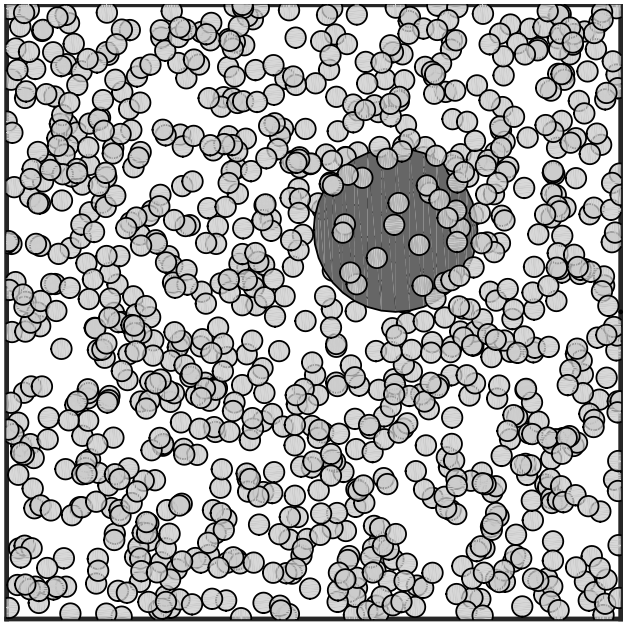
KTH/NA, October 22, 2015

Outline

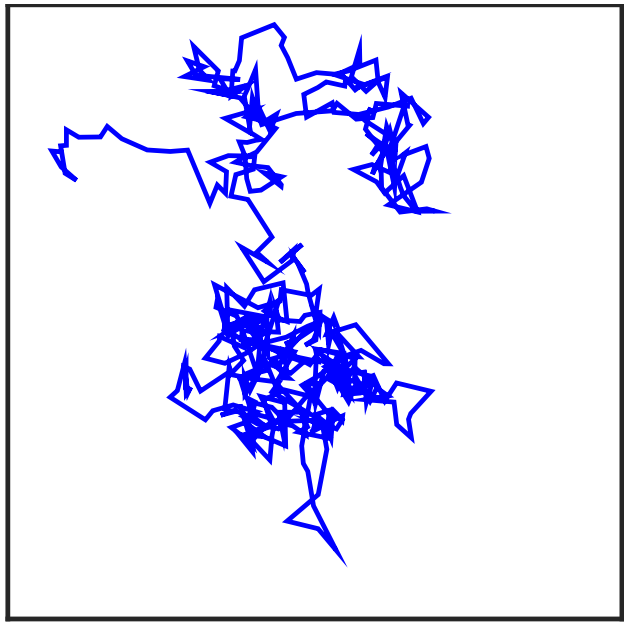
Brownian motion

Example: Particle diffusing in a fluid

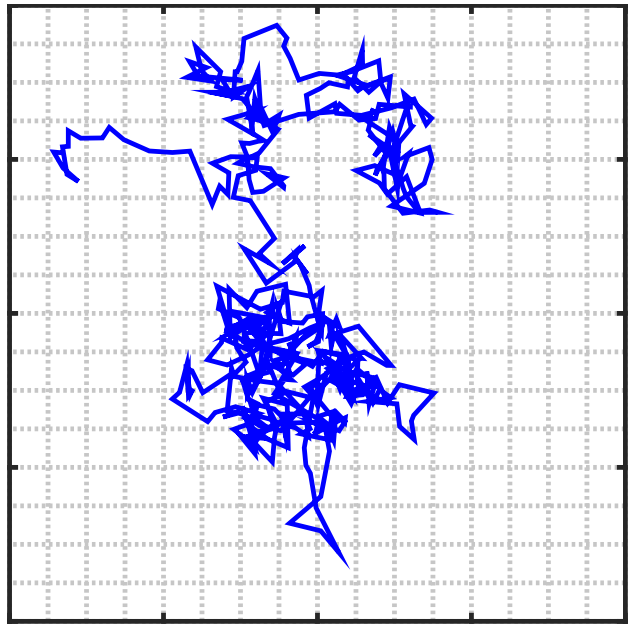
microscopic



stochastic



mesoscopic



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

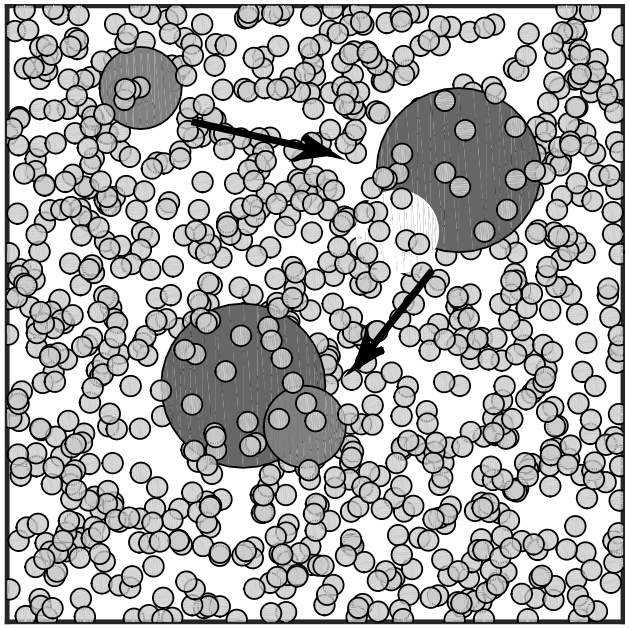
(stoch) $\rightarrow$ (meso) Discrete space approximation (*error:* finite $h > 0$).

The mesoscopic stochastic model is a continuous-time Markov chain.

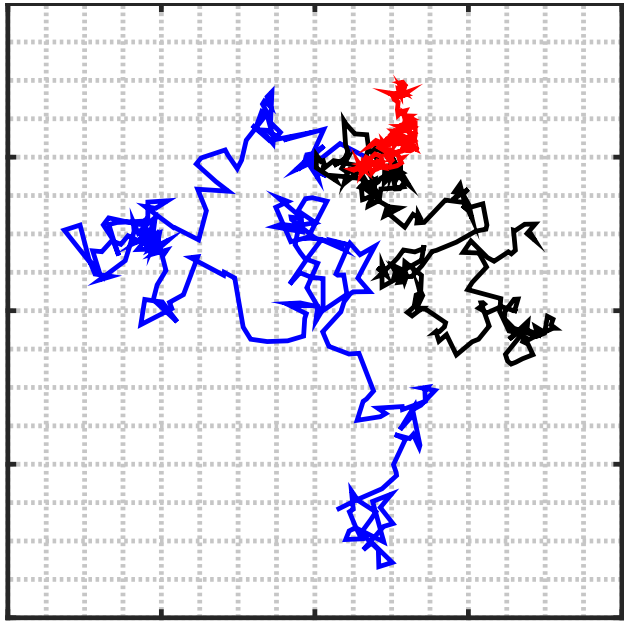
Chemical reactions

Example: Bimolecular reaction $X + Y \rightarrow Z$

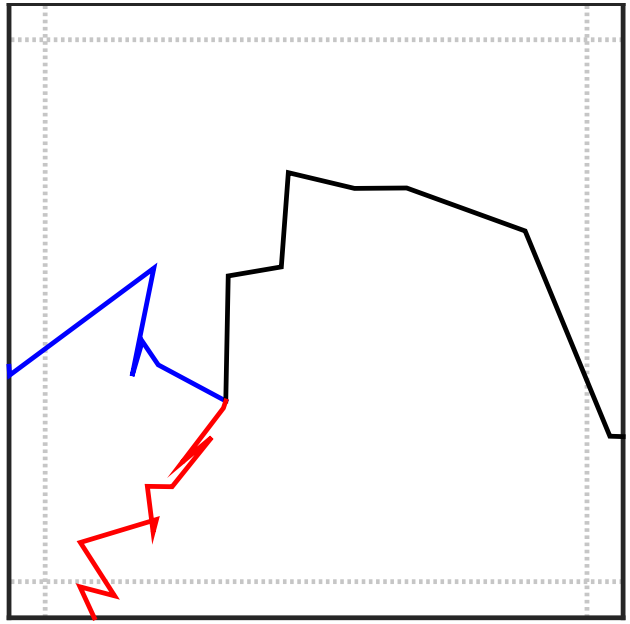
microscopic



mesoscopic/spatial



mesoscopic/"0D"



-Required: a model of physics in the zoomed in situation.

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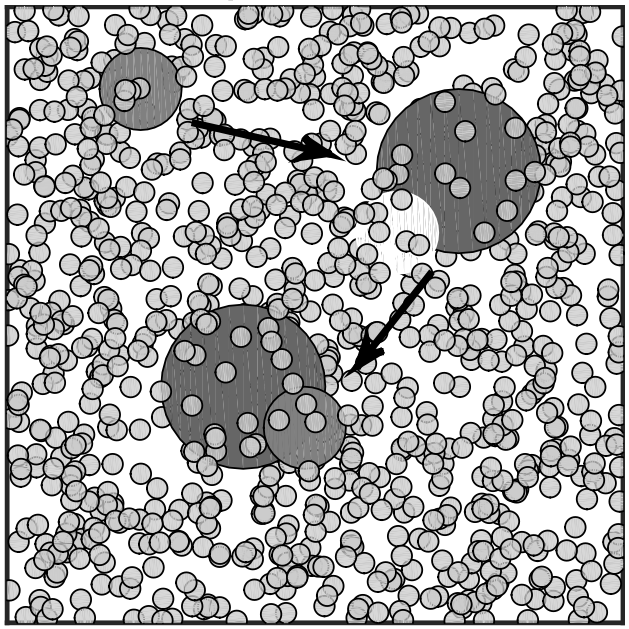
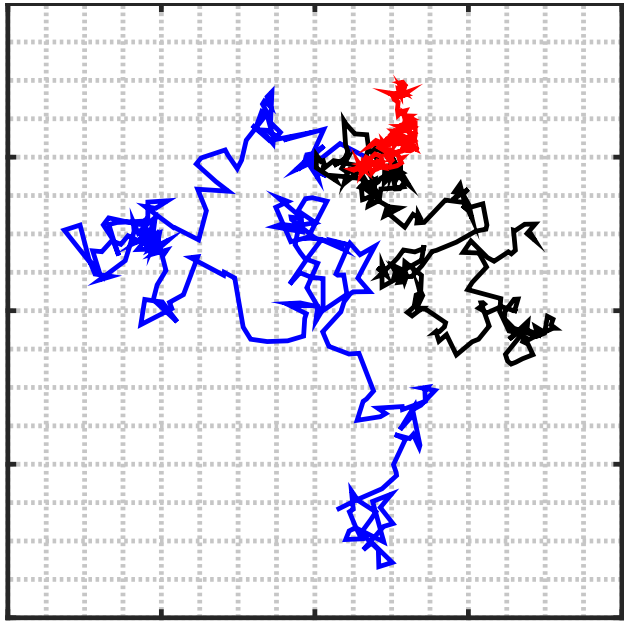


mesoscopic/spatial



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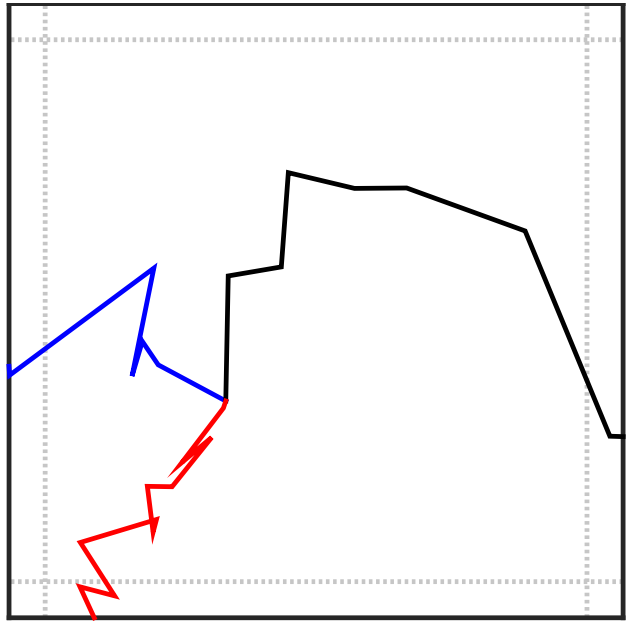


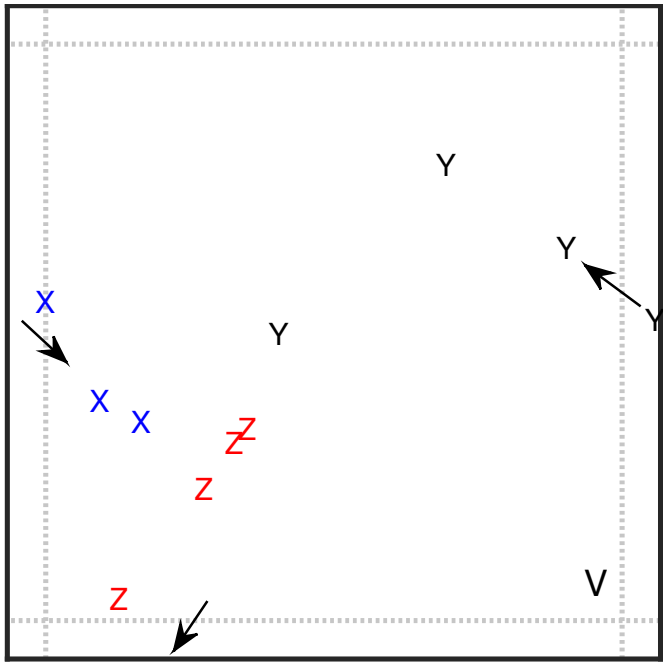
-Required: a model of physics in the zoomed in situation.

-Assuming well-stirred locally (0D), what is the probability $P(1X \text{ and } 1Y \text{ reacts in } [0, \Delta t])$ in a volume V?

Chemical reactions

Example: Bimolecular reaction $X + Y \to Z$

-$P(1X$ and $1Y$ reacts in $[0, \Delta t])$ in a well-stirred local volume V...



Well-stirred, then

- $P \propto n_X$ ("number of X-molecules")
- $P \propto n_Y$
- $P \propto 1/V$
- $P \propto \Delta t$

$\Longrightarrow P(X + Y \to Z \text{ in } [0, \Delta t]) =$ const $\cdot\, n_X n_Y \, \Delta t / V$.

As $\Delta t \to 0$ we recover again a continuous-time Markov chain.

Back to the details...

Mesoscopic well-stirred kinetics (0D)

Assuming a homogeneous probability of finding a molecule throughout the *local* volume.

-State $X \in \mathbf{Z}_+^D$, counting the number of molecules of each of D species.
-Reactions are transitions between these states,

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

where the *propensity* $w_r : \mathbf{Z}_+^D \to \mathbf{R}_+$, $r = 1...R$, is the probability of reacting per unit of time.

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Jump SDE formulation: $dX_t = -\mathbb{N}\boldsymbol{\mu}(dt)$,
(where $E[\mu_r(w_r(X);\, dt)] = E[w_r(X)]\, dt$),

Poisson representation: $X_t = X_0 - \mathbb{N}\Pi(\int_0^t w(X_{s-})\, ds)$,
(with Π_r a unit-rate Poisson process).

Back to the details...

Mesoscopic spatial kinetics

Assuming that the domain V has been subdivided into small enough computational cells V_j such that eg. diffusion suffices to make each cell well-stirred.

- The state of the system is now an array $\mathbb{X}$ with $D \times K$ elements; D chemically active species $\mathbb{X}_{ij}$, $i = 1, \ldots, D$, counted separately in K cells, $j = 1, \ldots, K$.
- This state is changed by chemical reactions occurring between the molecules in the same cell (vertically in $\mathbb{X}$) *and* by diffusion/transport where molecules move to adjacent cells (horizontally in $\mathbb{X}$).

Reactions

By assumption, each cell is well-stirred and consequently the jump SDE is valid as a description of *reactions*,

$$d\mathbb{X}_t = -\mathbb{N}\boldsymbol{\mu}(dt),$$

where $\boldsymbol{\mu}$ is now R-by-K; $E[\mu_{rj}]dt^{-1}$ = propensity of the rth reaction in the jth cell.

Transport/diffusion

A natural model of diffusion from one cell V_k to another cell V_j is

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

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

For a certain array multiplication $\otimes$ (...),

$$d\mathbb{X}_t = \mathbb{S} \otimes (-\boldsymbol{\nu}^T + \boldsymbol{\nu})(dt),$$

where $\mathbb{S}$ is 1-by-K of all 1's, and $\boldsymbol{\nu}$ is K-by-K-by-D; $E[\nu_{kji}]dt^{-1} =$ diffusion rate of the ith species from cell V_k to cell V_j.

The reaction-diffusion jump SDE

"RDME"

Combining reactions with diffusions we arrive at

$$d\mathbb{X}_t = -\mathbb{N}\boldsymbol{\mu}(dt) + \mathbb{S} \otimes (-\boldsymbol{\nu}^T + \boldsymbol{\nu})(dt).$$

-An *approximation*, valid when

$$\rho^2 \ll h^2 \ll \sigma^2 \tau_\Delta,$$

ρ the molecular radius, τ_Δ average molecular survival time.

Outlook

Event-based mesoscopic framework

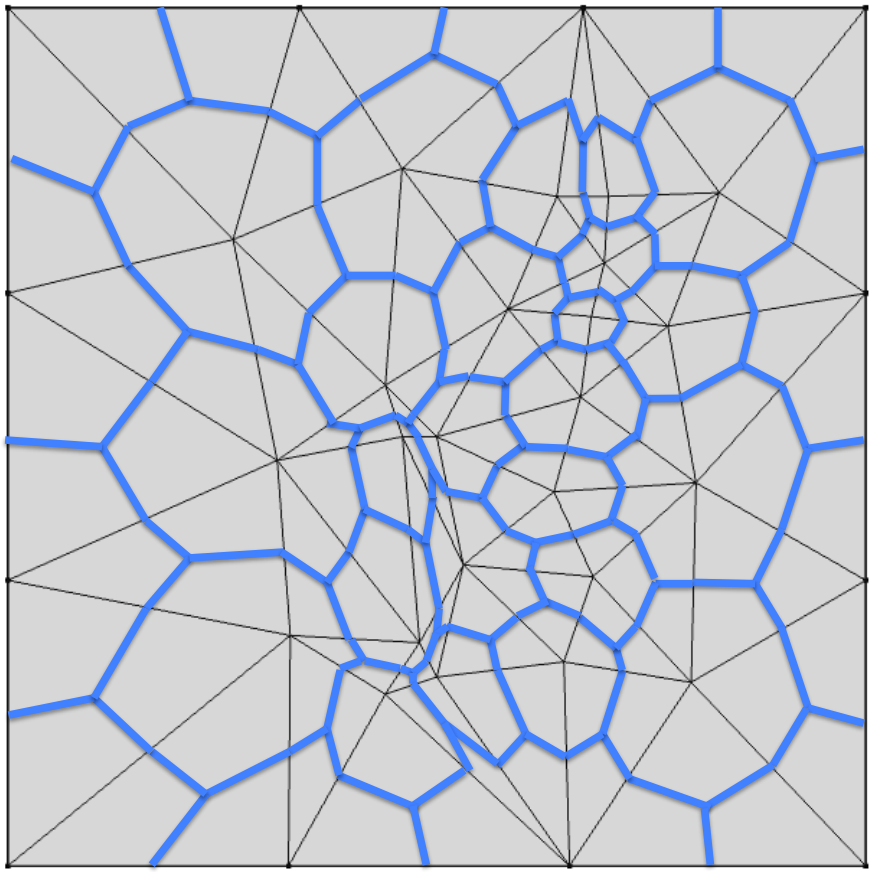
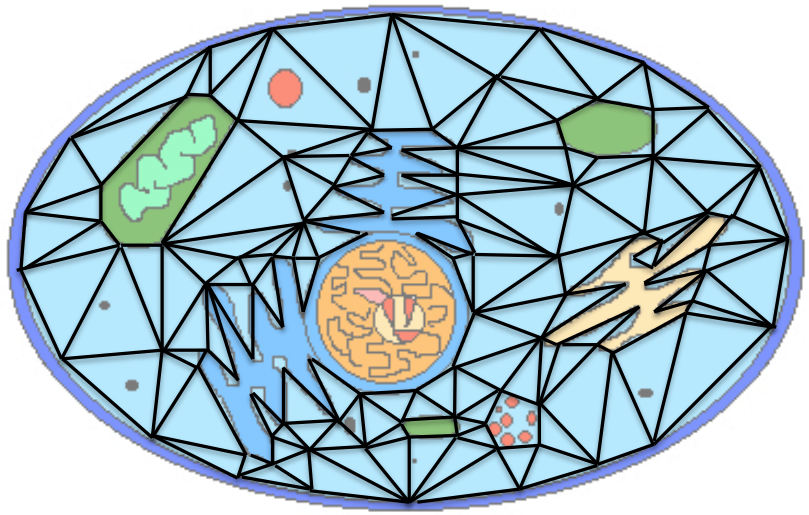


Figure: Primal mesh (thin), dual mesh (blue). The nodal dofs are the # of molecules in each dual cell.

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



Motivation...

...for the effort with stating assumptions and *a priori* results

Scalar ODE+Euler forward,

$$y' = f(y),$$
$$y_{n+1} = y_n + hf(y_n), \quad y_n \approx y(t_n) = y(n \cdot h).$$

Assume:

1. f is (locally) Lipschitz, ($|f(x) - f(y)| \leq L_Y|x - y|$ whenever $|x| \vee |y| \leq Y$),
2. *a priori* stability, $|y| \vee |y_n| \leq Y$

Then, straightforwardly, $e_n = |y_n - y(t_n)|$ is $O(h)$.

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Problem: assumptions and analysis are both incomplete without a verification of the 2nd assumption above.

-Additional complications in the stochastic setting (...).

Assumptions & *a priori*: well-stirred case

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, "$x'(t) = -\mathbb{N}w(x)$", $x \approx E[X]$.

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

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

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

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

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

Assumptions & *a priori*: well-stirred case

Results

With suitable initial data...

- $E \sup_{s\in[0,t]} \|X_s\|_{\boldsymbol{I}}^p$ bounded, any $p \geq 1$
- if $X_0 = Y_0$ almost surely, then $E\|X_t - Y_t\|^2 = 0$
- if $\alpha + \beta_2(p-1) < 0$, then $E\,\|X_t\|_{\boldsymbol{I}}^p$ bounded as $t \to \infty$

-Can also elaborate on continuity wrt parameter perturbations (...)

Split-step method

Set-up

Split into two sets of reaction pathways

$$\mathbb{N} = \left[\mathbb{N}^{(1)}\ \mathbb{N}^{(2)}\right], \qquad w(x) = \left[w^{(1)}(x);\ w^{(2)}(x)\right],$$

where $\mathbb{N}^{(i)}$ is D-by-R_i, $i \in \{1,2\}$, $R_1 + R_2 = R$.

Method:

$$Y_{t+h/2} = Y_t - \sum_{r\in\mathcal{R}_1} \mathbb{N}_r \Pi_r \left(\int_t^{t+h/2} 2w_r(Y_{s-})\, ds \right),$$

$$Y_{t+h} = Y_{t+h/2} - \sum_{r\in\mathcal{R}_2} \mathbb{N}_r \Pi_r \left(\int_{t+h/2}^{t+h} 2w_r(Y_{s-})\, ds \right).$$

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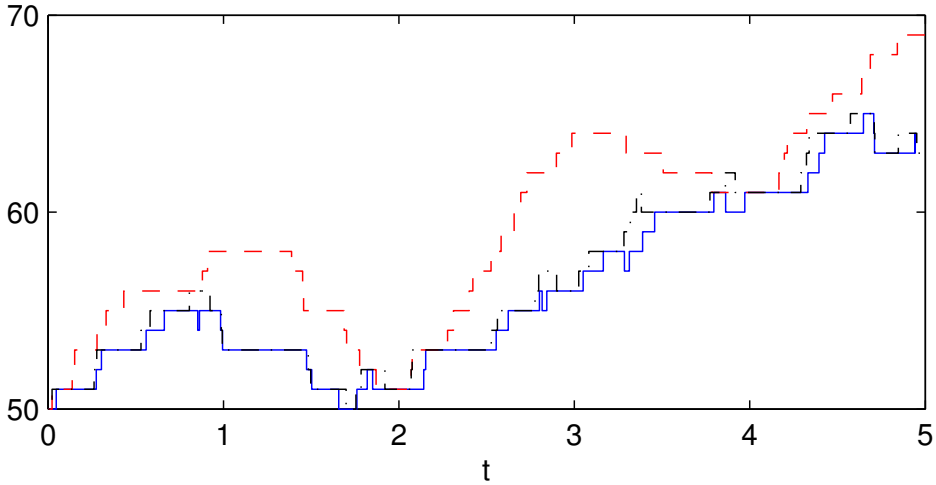
In closed form: $$Y_t = Y_0 - \sum_{r\in\mathcal{R}_1,\mathcal{R}_2} \mathbb{N}_r \Pi_r \left(\int_0^t (1 \pm \sigma_h(s)) w_r(Y_{s-})\, ds \right).$$

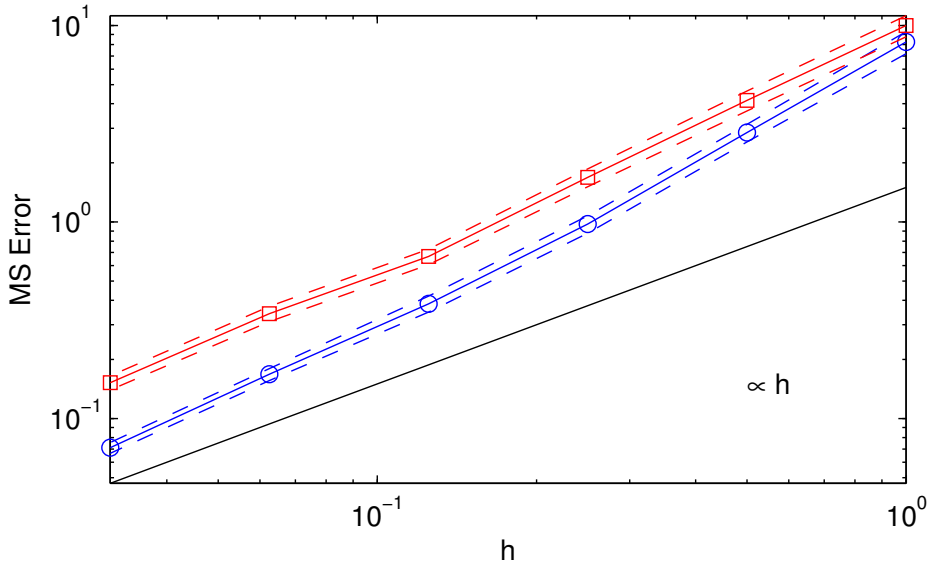
Split-step method

Results

Assume the (Assumptions) hold for *both* sub-systems. Then

- $E \sup_{s\in[0,t]} \|Y_s\|_I^p$ bounded, any $p \geq 1$
- $E\|Y_t - X_t\|^2 = O(h)$, any finite t (*Proof:* "Riemann-Lebesgue" with kernel σ_h...)





Assumptions & *a priori*: R&D case

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

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

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

$$\mathbf{v}_t = -\mathbb{N}u(\mathbf{v}) + \underbrace{Q}_{\approx\nabla\cdot\Sigma\nabla}\mathbf{v}, \quad \mathbf{v} \approx E[V^{-1}\mathbb{X}]$$

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Assumptions:

- on the mesh, some natural and quite weak assumptions (...)
- reactions, as before, *plus*
  (iv) $w_{rk}(x) = V_k u_r(V_k^{-1}x)$, "density dependent"
- diffusion:
  (v) $(x^{p-1}\odot V)^T Qx \le R_p\|x\|_p^p$, $p \ge 1$, $x \in \mathbf{R}_+^K$, (implies the pure transport bounds $\|\mathbf{v}\|_p \le \|\mathbf{v}_0\|_p \exp(R_p t)$)

Assumptions & *a priori*: R&D case

Results

Norm $\|\mathbb{X}\|_{\boldsymbol{I},p}^p \equiv \sum_{k=1}^K \|\mathbb{X}_{\cdot,k}\|_{\boldsymbol{I}}^p \, V_k^{1-p} \quad (\approx \int_V \|\mathbf{v}\|_{\boldsymbol{I}}^p \, dV)$.

With suitable initial data...

- only reactions: as before
- pure transport: $E\,\|\mathbb{X}_t\|_{\boldsymbol{I},p}^p$ bounded in finite time, or even grows very slowly for $R_p = 0$
- full R&D: $E \sup_{s\in[0,t]} \|\mathbb{X}_s\|_{\boldsymbol{I},p}^p$ bounded, any $p \geq 1$

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 *(possibility: on a per voxel basis)*
- rate- and diffusion constants are either fast ~ 1, or slow ϵ *(per reaction/per species)*

$\Longrightarrow$ 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", $\bar{\mathbb{Y}}_t^{(h)}$ 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 $[t, t+h)$

Multiscale variable splitting

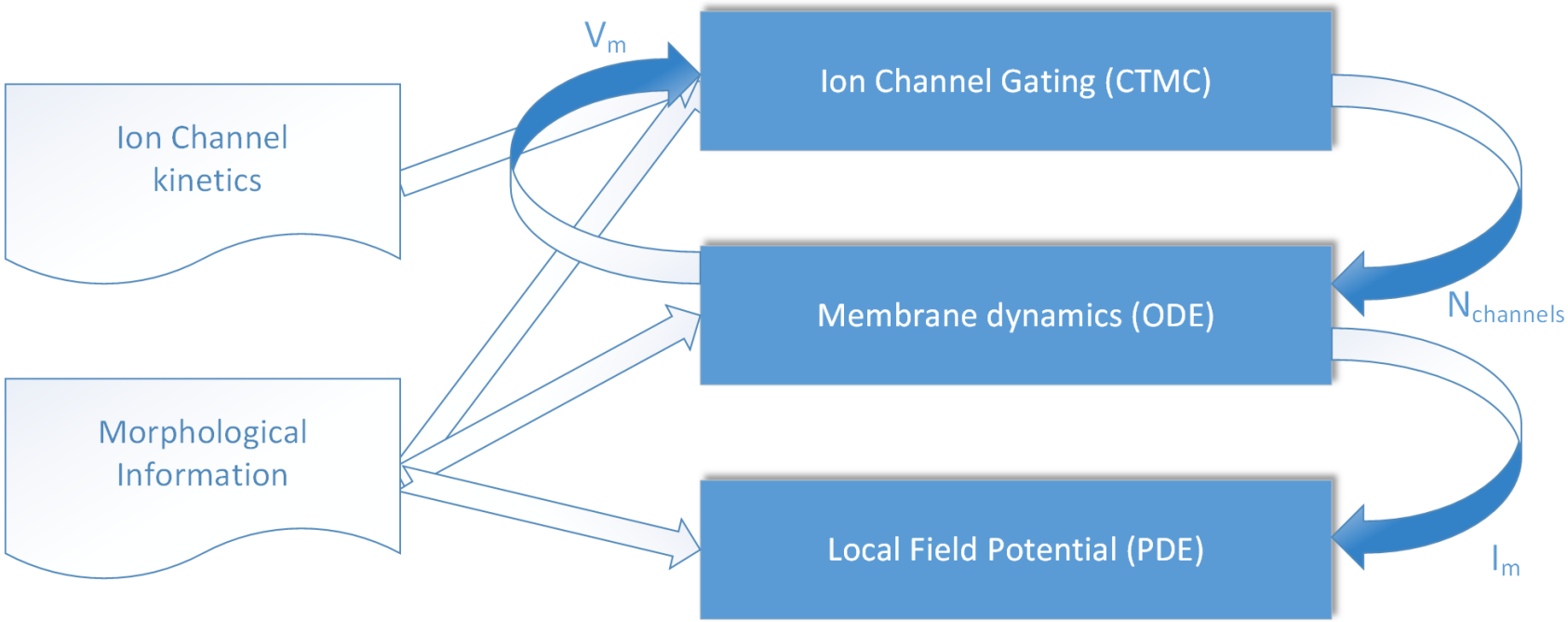
Results

Under the *a priori* conditions above and under similar (Assumptions) for the splitted system $\bar{\mathbb{Y}}_t^{(h)}$ (...), then

- $E \sup_{s\in[0,t]} \left\|\bar{\mathbb{Y}}_s\right\|_{\boldsymbol{I},p}^p$ bounded, any $p \geq 1$
- $E\|\bar{\mathbb{Y}}_t - \bar{\mathbb{X}}_t\|^2 = O(\epsilon)$, any finite t
- $E \sup_{s\in[0,t]} \left\|\bar{\mathbb{Y}}_s^{(h)}\right\|_{\boldsymbol{I},p}^p$ bounded, any $p \geq 1$
- $E\|\bar{\mathbb{Y}}_t^{(h)} - \bar{\mathbb{Y}}_t\|^2 = O(h)$, any finite t

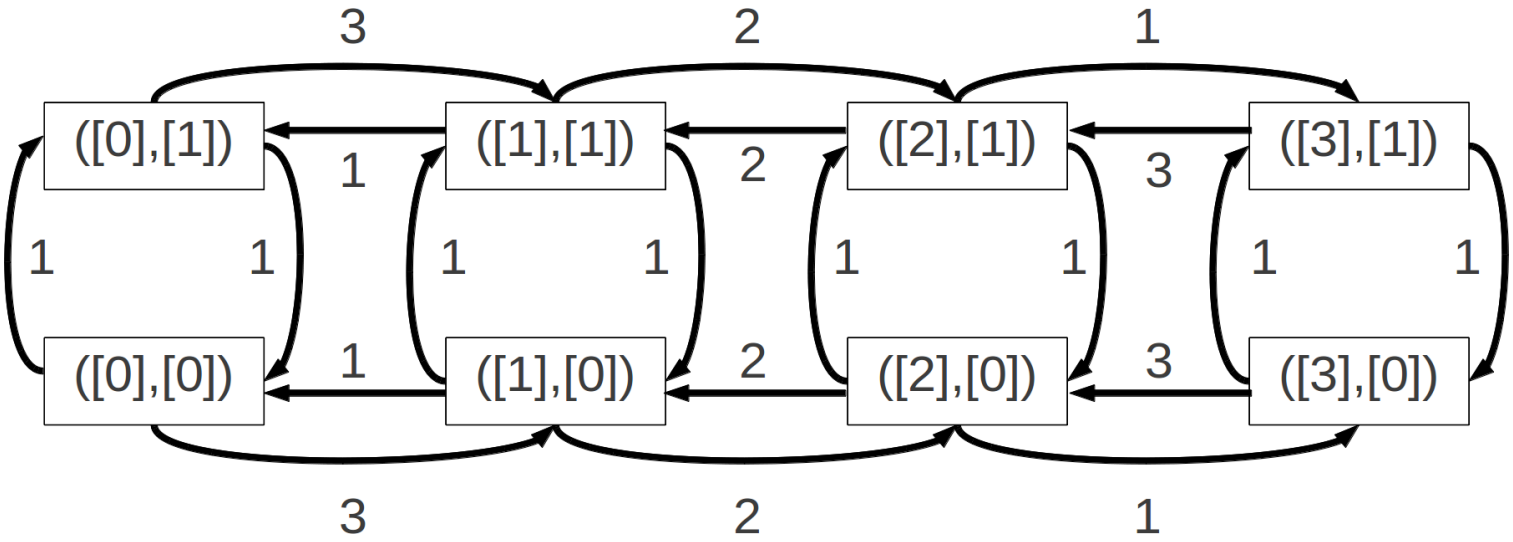
-Additional (Conditions) for this concerns the reaction topology: effectively fast reactions must not affect low copy number species (...)

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

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

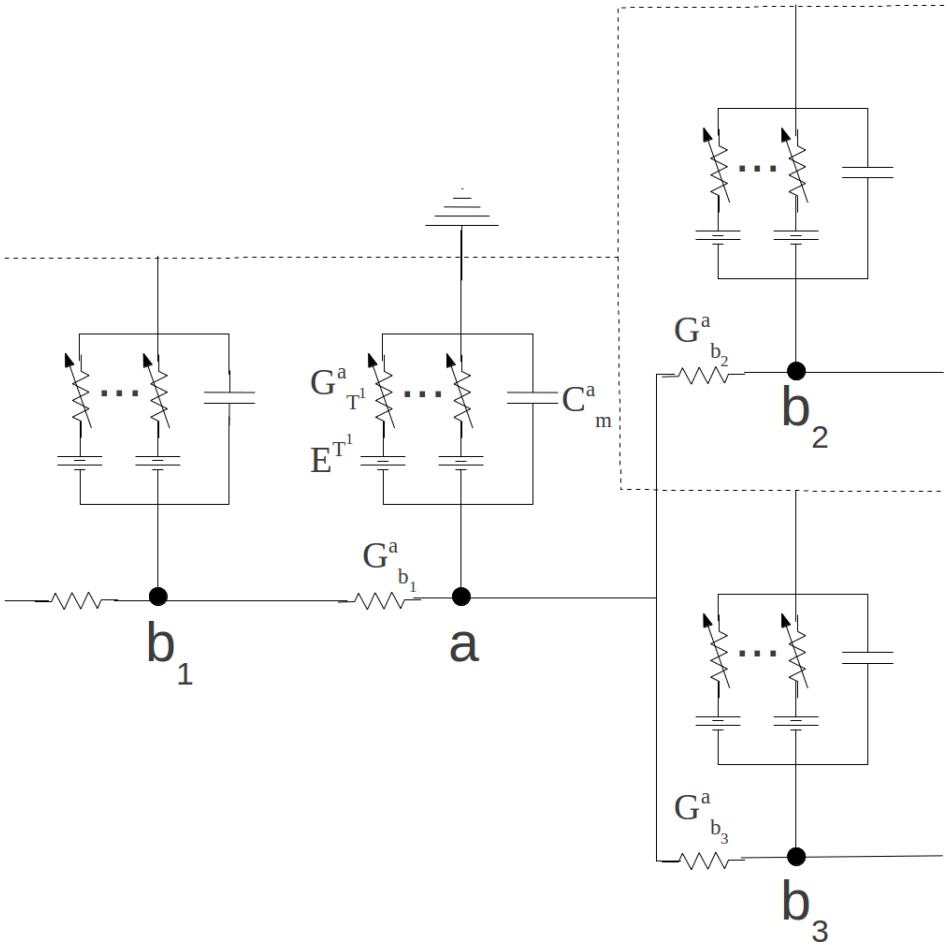
again a *continuous-time Markov chain*. *Output:* N_3, the number of open gates.

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

$$X_{t+\tau} = X_t - \int_t^{t+\tau} \mathbb{N}\boldsymbol{\mu}(V_m(t), w(X_{s-});\ ds).$$

Middle level

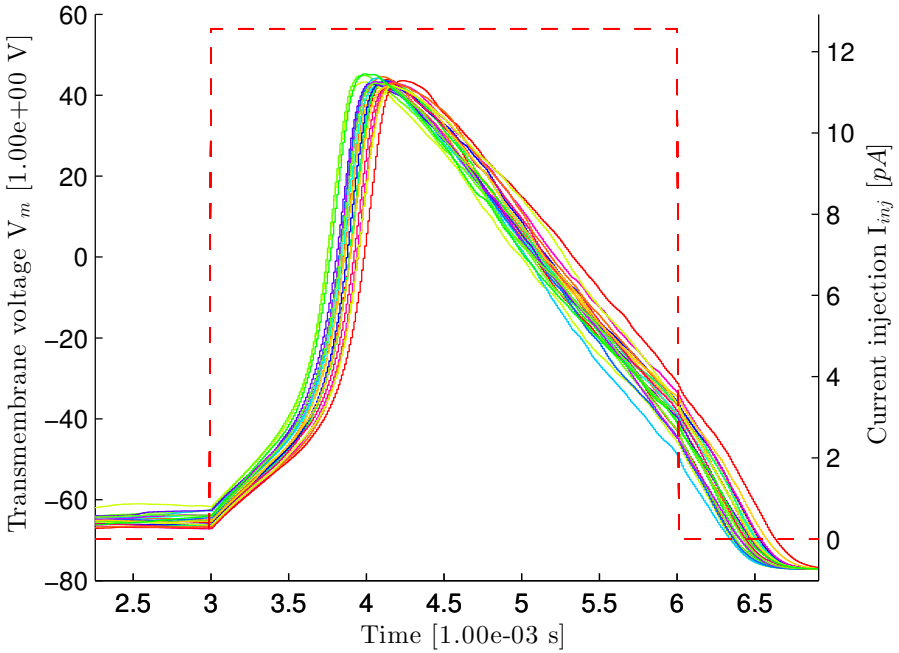
Membrane dynamics



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 **E** in terms of the *electric scalar potential* V,

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

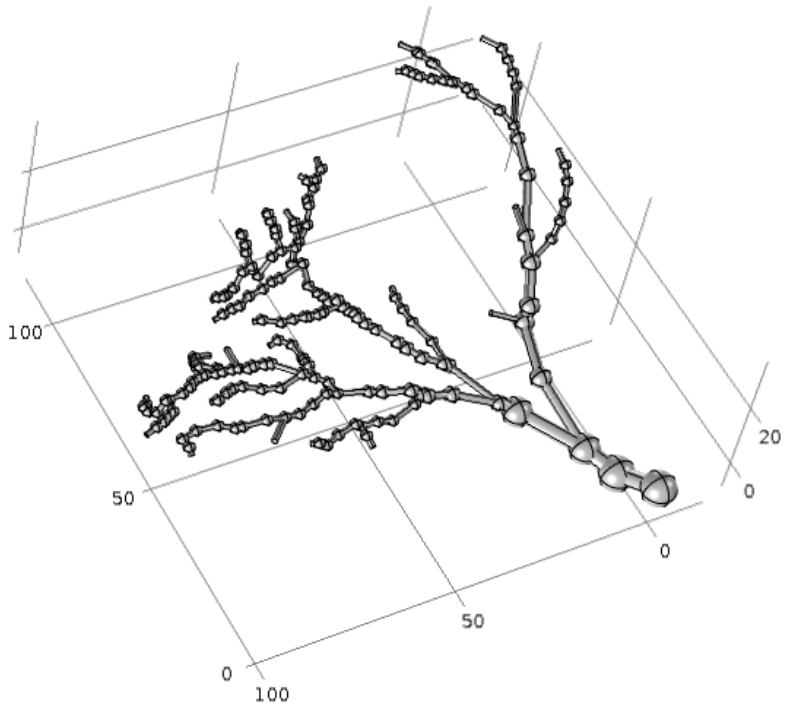
Trans-membrane current I_m is scaled with the compartement surface area and coupled as a current source,

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

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

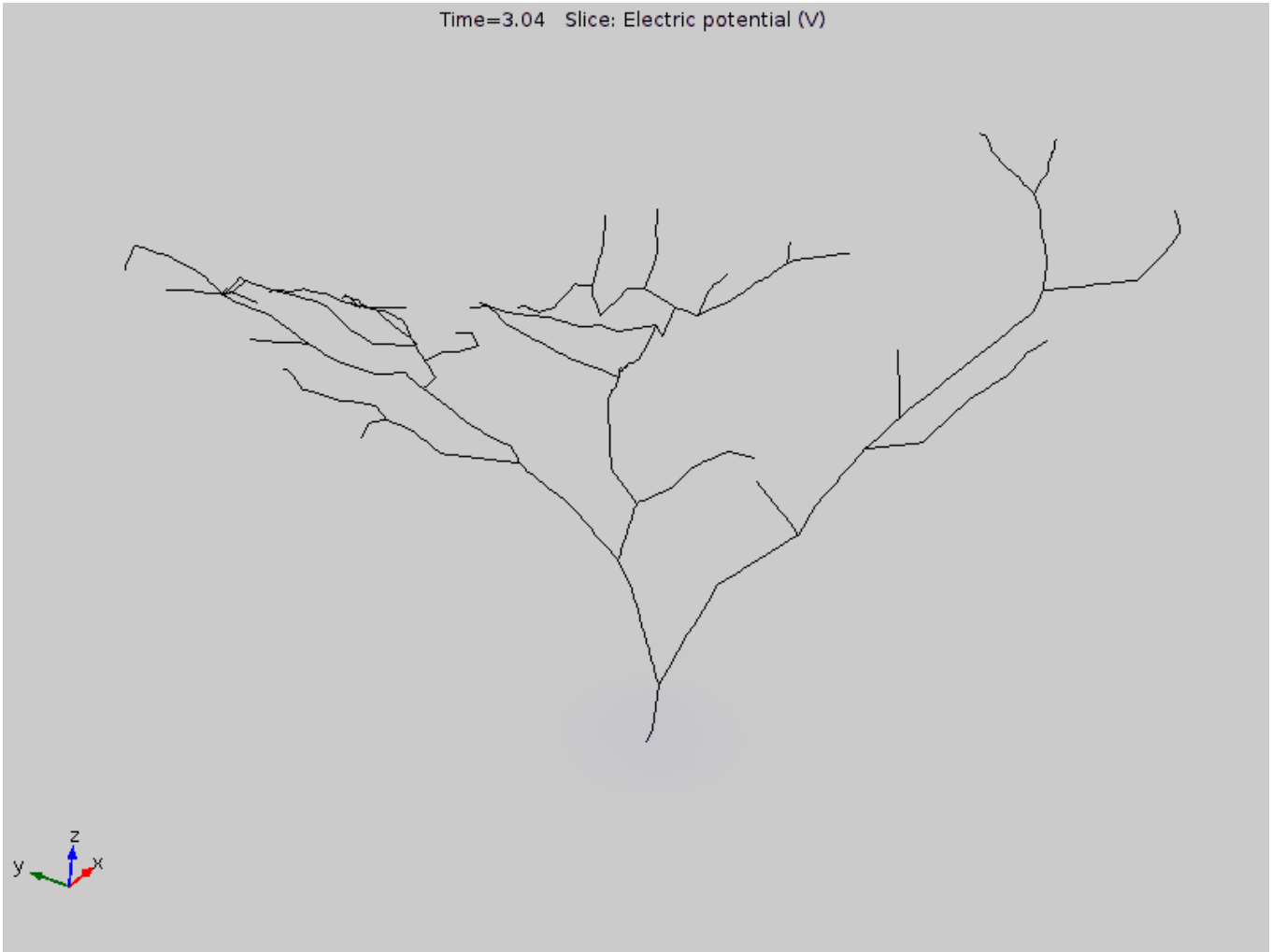
Top level

Geometry coupling



- Bottom and middle level: compartments (cylindrical volumes)
- Coupling with PDE requires a free space mesh
- Modeling the neuron via 3D curves

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).
- *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

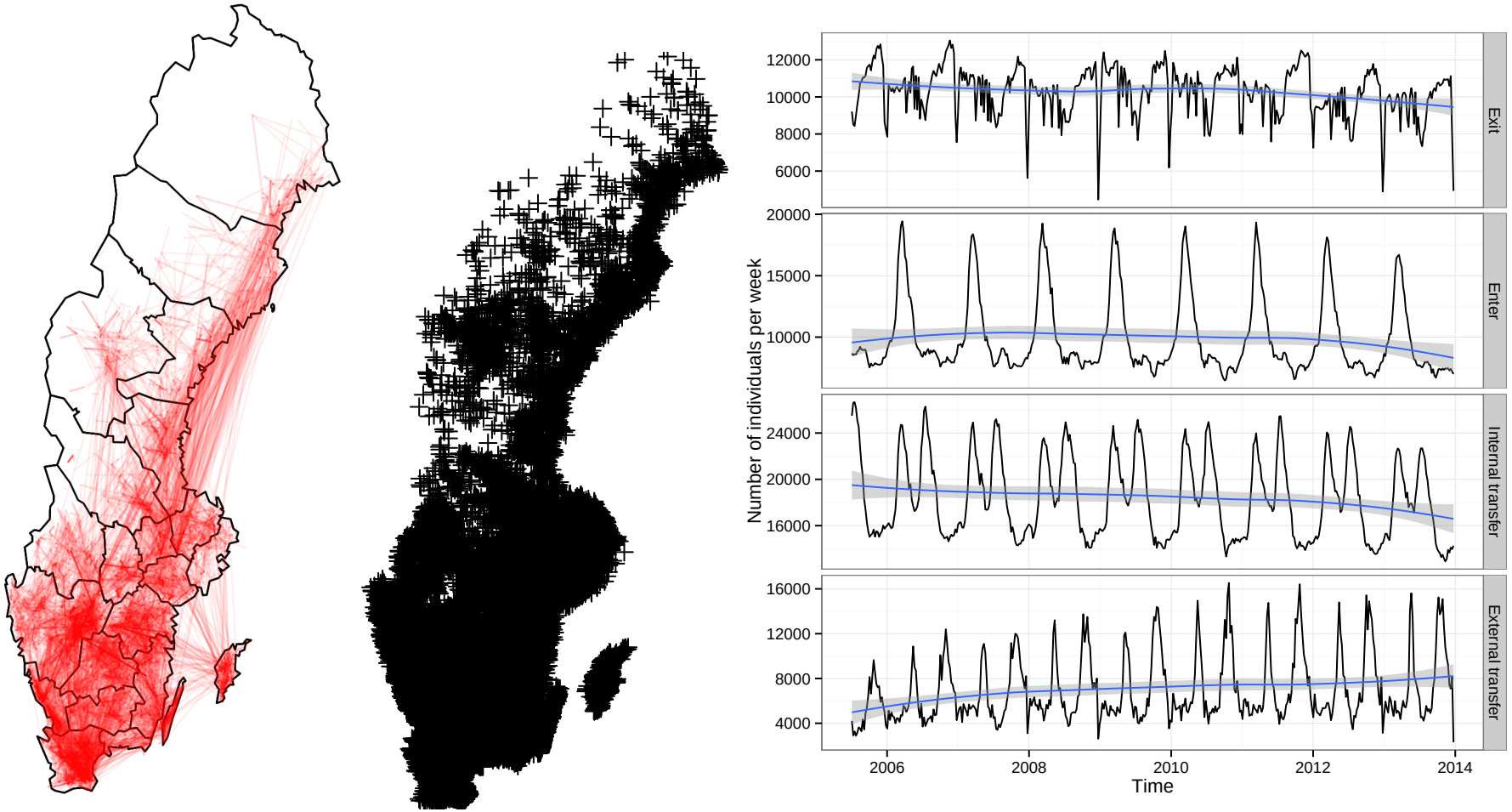
REPORTER	WHERE	ABATTOIR	DATE	EVENT	ANIMALID	BIRTHDATE
83466	83958	0	2009-10-01	2	SE0834660433	1997-04-04
83958	83466	0	2009-10-01	1	SE0834660433	1997-04-04
83958	83829	0	2012-03-15	2	SE0834660433	1997-04-04
83829	83958	0	2012-03-15	1	SE0834660433	1997-04-04
83829	83958	0	2012-03-15	4	SE0834660433	1997-04-04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


Number of individuals per week
Exit
Enter
Internal transfer
External transfer
Time
2006
2008
2010
2012
2014

Epidemic model

"Locally well-stirred" (SIS_E)

Model states: **S**usceptible, **I**nfected, in ∼40,000 holdings and in 3 age categories $\{calves, youngstock, adults\}$.

Environmental infectious pressure

$$\frac{d\varphi_i}{dt} = \frac{\alpha \sum_j I_{i,j}(t)}{\sum_j S_{i,j}(t) + I_{i,j}(t)} - \beta(t)\varphi_i(t)$$

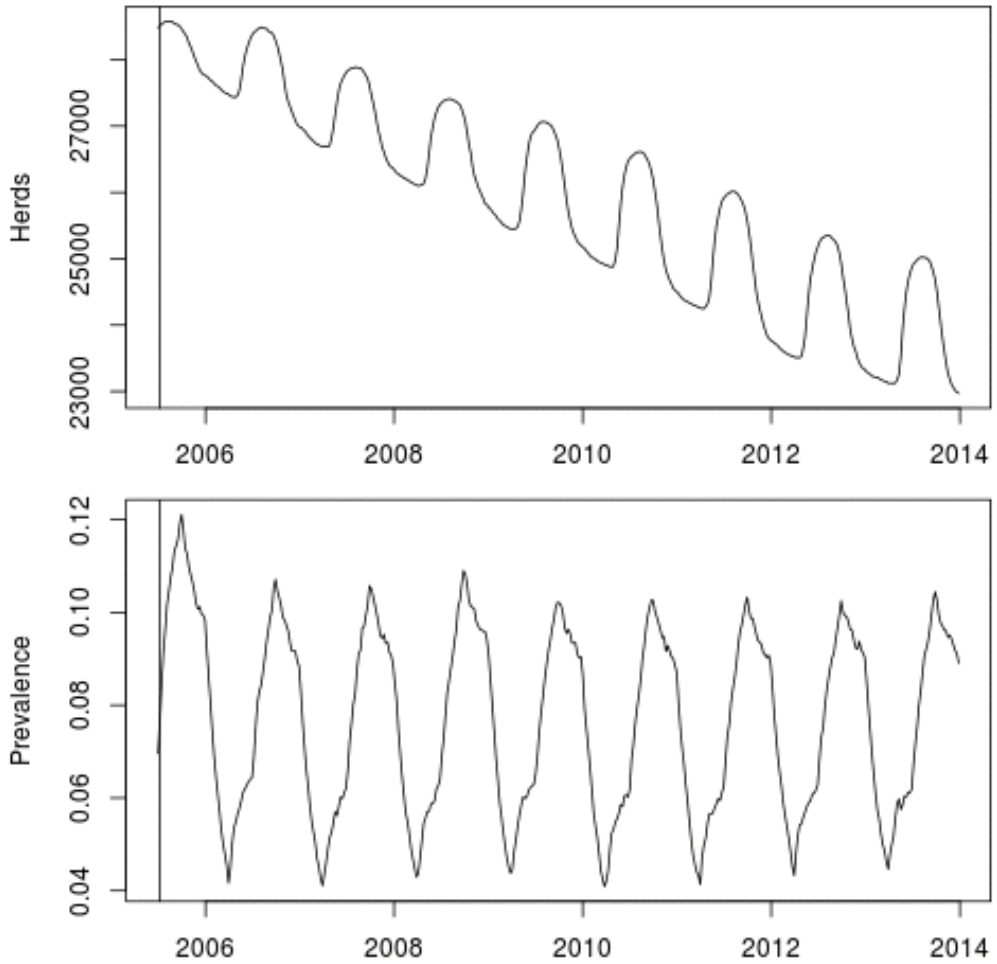
Finding: $\beta = \beta(t)$ required in the Swedish climate.

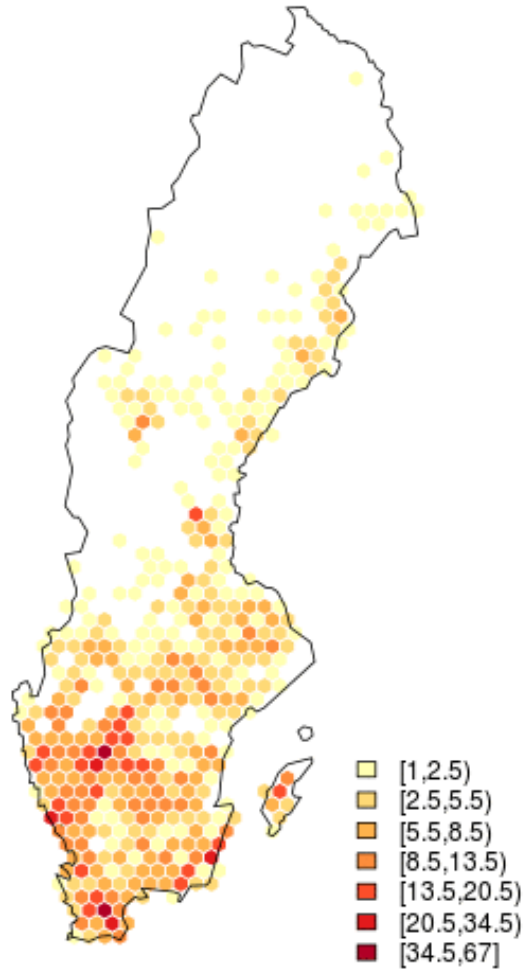
State transitions at node i in the jth age category,

$$Rate\ S_{i,j} \to I_{i,j} = \gamma_j \varphi_i(t) S_{i,j}(t)$$

$$Rate\ I_{i,j} \to S_{i,j} = \frac{I_{i,j}(t)}{\delta_j}$$

Sample simulation





Summary

- Mesoscopic stochastic R & D, **event-based computational framework**: fairly intuitive modeling, coupling and up/down-scaling, simulation algorithms
- Terms & conditions. If used when required: accurately capturing a stochastic nonlinear phenomenon is a very hard constraint for method's development!
- Well-posedness, stability, convergence... of simple numerical methods
- Multiscale neuronal application solved in URDME (GitHub): coupling different types of models
- Epidemiological national-scale model solved in SimInf (GitHub): data-driven simulation

Acknowledgments

~In order of appearance

- Augustin Chevallier (ENS Cachan)
- Pavol Bauer (UU)
- Emil Berwald (UU)
- Stefan Widgren (SVA)

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