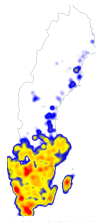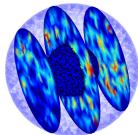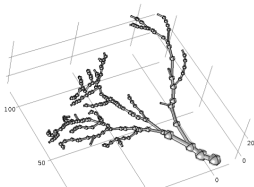# Towards consistent and effective modeling in the stochastic reaction-diffusion framework

Stefan Engblom

Div of Scientific Computing, Dept of Information Technology, Uppsala University

Mathematical Institute, University of Oxford, May 15, 2015

Outline

Outline

A kind of overview talk...

...but with several special cases/models/applications...

For details: Programs, Papers, and Preprints are available from my web-page.

Brownian motion

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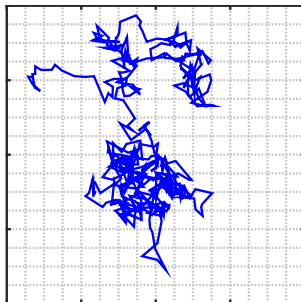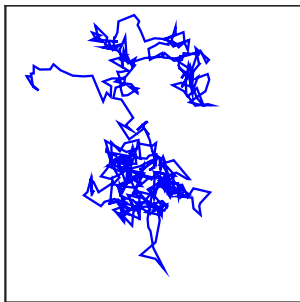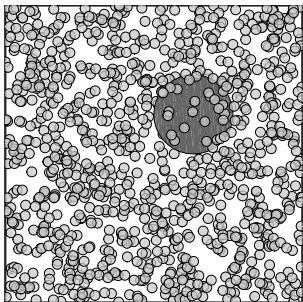
(micro) $\rightarrow$ (stoch) The stochastic model is simpler but random (*error:* microscale effects in a statistical sense only).

(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 $X + Y \rightarrow Z$.
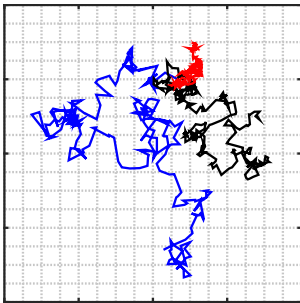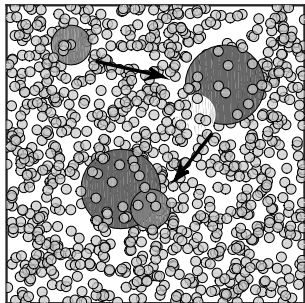
-Required: a model of physics in the zoomed in situation.

Chemical reactions

(Locally) well-stirred

Example: Bimolecular reaction $X + Y \rightarrow Z$ in a volume V.

-What is the probability $P(1X \text{ and } 1Y \text{ reacts in } [0, \Delta t])$?
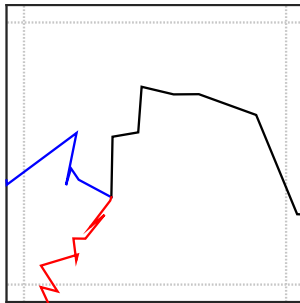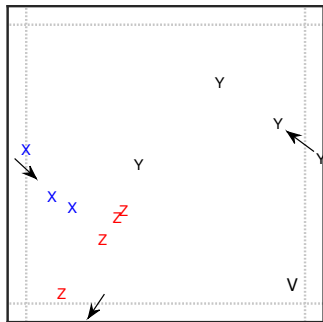

Well-stirred, then

- $P \propto n_X$ ("number of X-molecules")

- $P \propto n_Y$

- $P \propto 1/V$

- $P \propto \Delta t$

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

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

Case study: the SFE (Why noise?)

Open-loop slowly fluctuating enzyme system
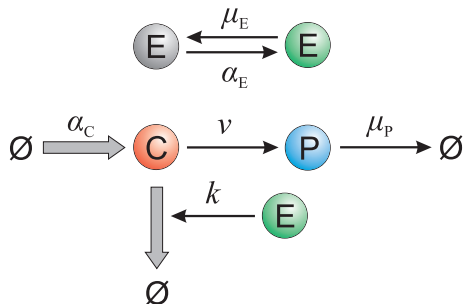
SFE-assumptions:

1. $\alpha_C \gg 1$ (high influx of C)

2. $k \gg \alpha_E + \mu_E$ (comparably slow enzyme fluctuations)

3. $k \gg 1$ (strong enzyme to substrate coupling)

4. $E^* = N \dfrac{\alpha_E}{\alpha_E + \mu_E}$ small (≤ 10)

-Very basic motif; low copy numbers, nonlinear...

Stochastic focusing
Stochastic vs. deterministic (well-stirred)
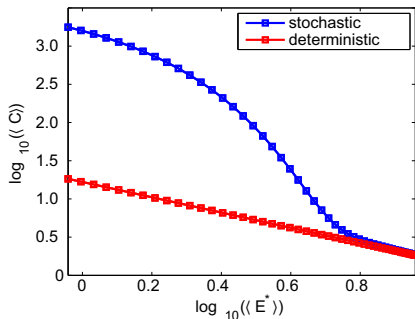
- ▶ Figure: Steady-state mean of C ("response") as a function of the mean of E^* ("signal")
- ▶ The large difference (log scale!) is a consequence of stochastic focusing
- ▶ Originally proposed as a *signal detection mechanism*

-Note: well-stirred case (no space)! Can show that there exists *spatial stochastic focusing* as well...

Stochastic focusing (cont)

Signal detection, really?
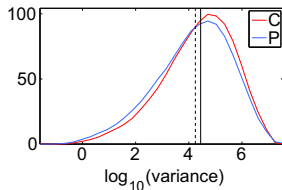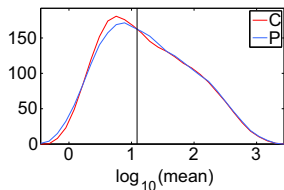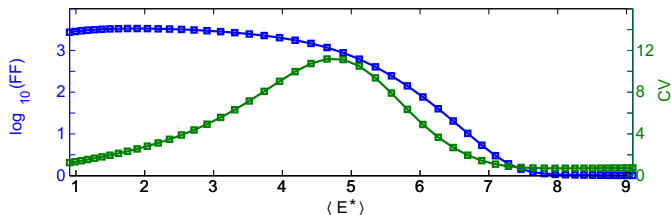
Top: output noise as a function of average E^*, *bottom:* sensitivity to parameter perturbations (histograms from 10,000 trials).

Closed-loop slowly fluctuating enzyme system

SFE with negative feedback
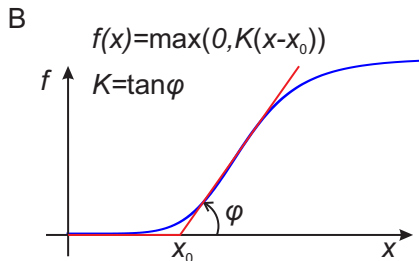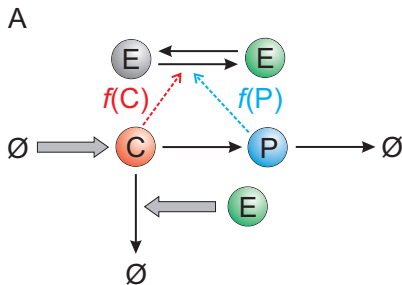
The transition $E \to E^*$ now has rate $\alpha_E(1 + f(x))$ instead, with x either C or P. *Note:* with $x = C$ this mechanism has very recently been observed experimentally!

Controlled Stochastic Focusing
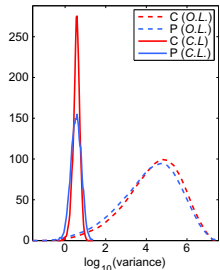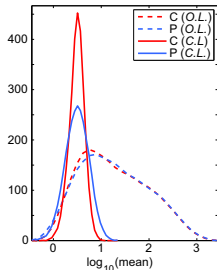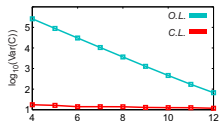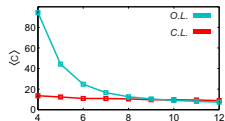
Top: Open- and Closed Loop responses to a change in $N = E + E^*$, *bottom:* responses to perturbations in parameters.

Some focused conclusions...

- Dramatic noise reduction and increased robustness, very accurate control possible (*note:* 10 molecules!)
- In fact, a certain deterministic model very closely predicts the controlled system
- Of course, this analysis and insight is only meaningful in the presence of noise

$\implies$ There are many more examples where **noise**, **discreteness**, and **nonlinearities** make a huge impact and where effective deterministic models are very difficult to derive.

Back to the details...

Mesoscopic well-stirred kinetics

Assuming a homogeneous probability of finding a molecule throughout the *local* volume (and an energy which is independent on position).

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

$$X \xrightarrow{w_r(X)} X - \mathbb{N}_r, \qquad \mathbb{N} \in \mathbf{Z}^{D \times R} \ (\textit{stoichiometric matrix})$$
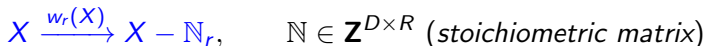
where the *propensity* $w_r : \mathbf{Z}_+^D \to \mathbf{R}_+$, $r = 1...R$, is the probability of reacting per unit of time.

$\implies$ Jump SDE formulation: $dX_t = -\mathbb{N}\boldsymbol{\mu}(dt)$

Back to the details...

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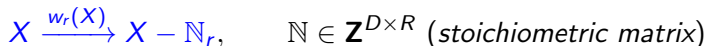
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$\implies$ Jump SDE formulation: $dX_t = -\mathbb{N}\boldsymbol{\mu}(dt) = -\mathbb{N}\boldsymbol{\mu}(w(X_{t-}); \; dt)$ such that $E[\boldsymbol{\mu}(w(x); \; dt)] = w(x) \, dt$.

Back to the details...
Mesoscopic spatial kinetics

Assuming that the domain Ω has been subdivided into small enough computational cells Ω_j such that 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.

Diffusion

A natural model of diffusion from one cell Ω_k to another cell Ω_j is

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

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

Assuming that the diffusion constants are the same for all species,

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

where $\mathbb{E}$ is D-by-K of all 1's, and $\boldsymbol{\nu}$ is K-by-K; $E[\nu_{kj}] = q_{kj}\mathbb{X}_{ik}\,dt$.

The reaction-diffusion jump SDE
"RDME"

Combining reactions with diffusions we arrive at

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

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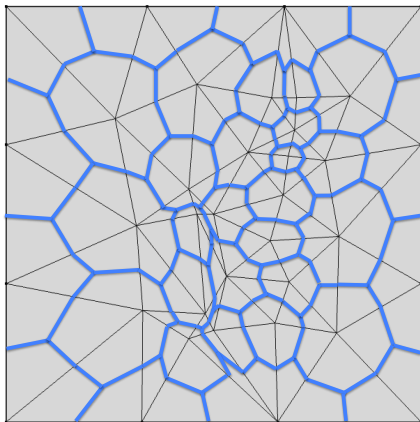
Figure: Primal mesh (thin), dual mesh (blue). The nodal dofs are the # of molecules in each dual cell.

Local physics within each small voxel, *connected* through transport mechanisms (diffusion).
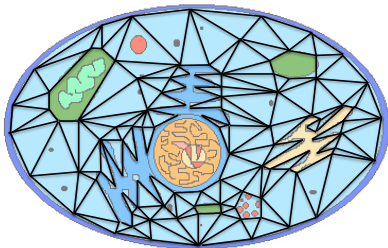
Unstructured meshes
Consistency in mean

-*Idea:* converge in expectation to the macroscopic diffusion equation. A numerical method applied to $u_t = \sigma^2/2\,\Delta u$ yields the *discretized* form

$$\frac{d\mathbf{u}}{dt} = \frac{\sigma^2}{2}D\mathbf{u}.$$

-Concentration $\varphi_{ij} = E[\Omega_j^{-1}\mathbb{X}_{ij}]$. By linearity of the diffusion intensities,

$$\frac{d\varphi_{ij}}{dt} = \sum_{k=1}^{K}\frac{|\Omega_k|}{|\Omega_j|}q_{kj}\varphi_{ik} - \left(\sum_{k=1}^{K}q_{jk}\right)\varphi_{ij},$$

$$\iff \frac{d\varphi_{i\cdot}^{T}}{dt} = Q\varphi_{i\cdot}^{T}.$$

Weak convergence
Consistency in mean

Key observation: by linearity, the diffusion CTMC/jump SDE over the unstructured grid has an expected value which coincides with the exact solution to the deterministic numerical method.

If the latter converges as the mesh $h \to 0$ (to the solution of the diffusion PDE), then the former converges in mean value.

The FEM
A **compact** summary

Consider the strong formulation $u_t = \sigma^2/2\,\Delta u$ in Ω.

Multiply by a test-function $v \in V$ and integrate...

1. Variational form (Green's theorem): find $u \in V$
   s.t. $(v, u_t) = -\sigma^2/2\,(\nabla v, \nabla u)$ for $\forall v \in V$, where $(f, g) \equiv \int_\Omega fg\,dx$.

2. A FEM is obtained by approximating $V \approx V_h = \text{span}_i\varphi_i \subset V$.

3. With $u_h = \sum_i \mathbf{u}_i(t)\varphi_i$ we get $M\mathbf{u}_t = -\sigma^2/2\,A\mathbf{u}$; $M_{ij} = (\varphi_i, \varphi_j)$,
   $A_{ij} = (\nabla\varphi_i, \nabla\varphi_j)$.

FEM convergence

$M\mathbf{u}_t = -\sigma^2/2\, A\mathbf{u}$, or, $\mathbf{u}_t = -\sigma^2/2\, M^{-1}A\mathbf{u} = \sigma^2/2\, D\mathbf{u}$.

1. Converges in L^2, $\|u_h - u\| = O(h^2)$ as $h \to 0$, under very mild assumptions on the mesh.

2. Under stringent conditions on the mesh, the maximum principle holds.

3. If these conditions are violated, "negative" diffusion take place (must be truncated).

4. Backward analysis: in this case the solution satisfies exactly a perturbed equation $\tilde{u}_t = \nabla \cdot (\tilde{\sigma}^2(x)/2 \times \nabla\tilde{u})$, where $\tilde{\sigma}$ can be explicitly obtained, $\|\tilde{\sigma} - \sigma\|$ is small, and where $\|\tilde{u} - u\| \leq C\|\tilde{\sigma} - \sigma\|$.

-*Challenges: (i)* convergence *in distribution* — retrieving the correct Brownian motion, *(ii)* convergence *with reactions*, *(iii)* getting to grip of *when it actually matters*...

Modeling of subdiffusion
Microscale random walks

Joint PDF for the jump **x** and time until the next jump t,

$$\Psi(\mathbf{x}, t) = \psi(t)\,\lambda(\mathbf{x}).$$

Expected waiting time $\tau^* \equiv \int_0^\infty t\,\psi(t)\,dt$

Jump length variance $\Sigma^2 \equiv \int_{\mathbb{R}^d} \|\mathbf{x}\|_2^2\,\lambda(\mathbf{x})\,d\mathbf{x}$

Characterization:

- τ^* and Σ^2 finite $\Rightarrow$ Brownian motion
- diverging τ^* with finite Σ^2 $\Rightarrow$ subdiffusion
- diverging Σ^2 with finite τ^* $\Rightarrow$ superdiffusion

Subdiffusion

Random walk

- Gaussian jump length PDF $\lambda(\mathbf{x}) = \dfrac{1}{(4\,\pi\,\sigma^2)^{d/2}}\, e^{-\|\mathbf{x}\|_2^2/(4\,\sigma^2)}$, $\mathbf{\Sigma}^2 = 2\,\sigma^2 < \infty$

- Mittag-Leffler waiting time PDF $\psi(t) = \dfrac{t^{\alpha-1}}{\tau^\alpha}\, E_{\alpha,\alpha}\left(-\left(\dfrac{t}{\tau}\right)^\alpha\right)$, $\tau^* = \infty$

- Mean square displacement $\left\langle \|\mathbf{x}\|_2^2(t) \right\rangle = \dfrac{2\,d\,K_\alpha}{\Gamma(1+\alpha)}\, t^\alpha$

Macroscopic model
Fractional PDE

$$\frac{\partial^\alpha}{\partial t^\alpha}\, U = K_\alpha\, \Delta U, \qquad K_\alpha \equiv \frac{\sigma^2}{\tau^\alpha}.$$

Subdiffusion

Mesoscopic model

Assuming ordinary diffusion on a mesh of interest can be simulated:

- ▶ Approximation through a Markov chain over N internal states,

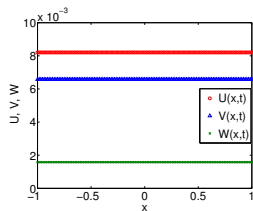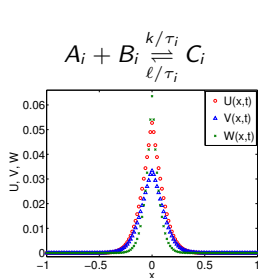$$\psi(t) = \frac{t^{\alpha-1}}{\tau^\alpha} E_{\alpha,\alpha}\left(-\left(\frac{t}{\tau}\right)^\alpha\right) \approx \sum_{i=1}^{N} \mu_i \tau_i^{-1} e^{-t/\tau_i}$$

- ▶ In the ith internal state, the diffusion of u_i is ordinary
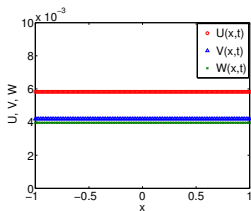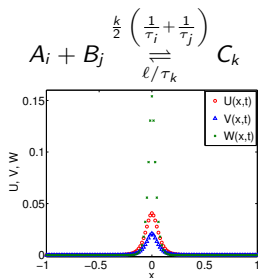- ▶ At the macroscopic level $U = \sum_{i=1}^{N} u_i$ diffuses anomalously according to the subdiffusion FPDE

-Hence again, this numerical method is *consistent in the sense of mean value with the macroscopic description* (as $(h, N) \to (0, \infty)$).

Ongoing research...

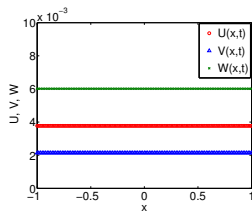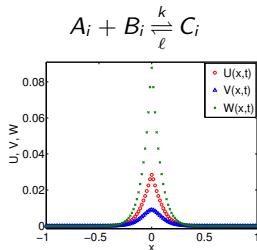Bimolecular reactions

Application: multiscale neuronal model
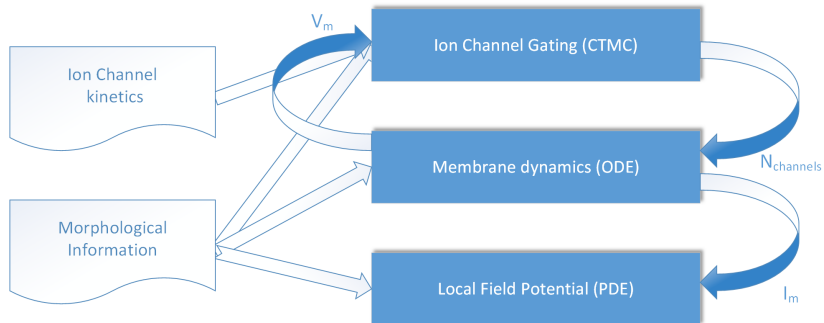
Bottom level
Ion channel gating
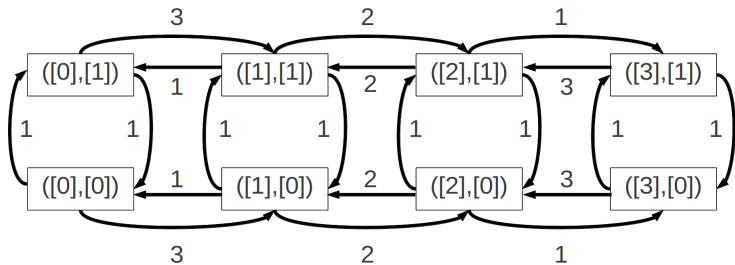
Gating process: sodium channels.

Bottom level
Ion channel gating

The gating process of ion channels can be mesoscopically described as

$$N_0 \underset{\beta_m(V_m)N_1}{\overset{3\alpha_m(V_m)N_0}{\rightleftharpoons}} N_1 \underset{2\beta_m(V_m)N_2}{\overset{2\alpha_m(V_m)N_1}{\rightleftharpoons}} N_2 \underset{3\beta_m(V_m)N_3}{\overset{\alpha_m(V_m)N_2}{\rightleftharpoons}} N_3,$$
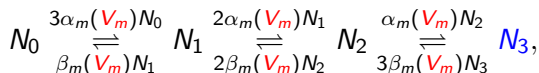
again a *continuous-time Markov chain. Output:* N_3, the number of open gates.

For efficient model coupling we freeze the voltage dependency for a short time-step τ ("Euler method/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
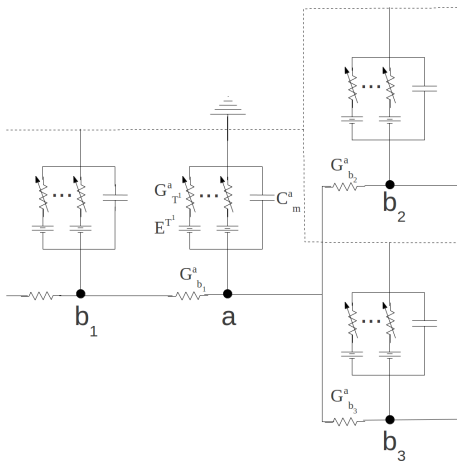
Cable equation circuit.

Middle level
Membrane dynamics

$$I_m = c_m \frac{dV_m}{dt} + \sum_{i \in C_v} \gamma_i N_3^i(t)[V_m(t) - E_i]$$
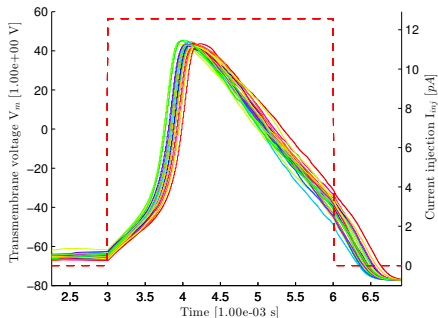
- Morphological information extracted using the *Trees toolbox*
- System of current-balance and cable equations is solved for each time step τ

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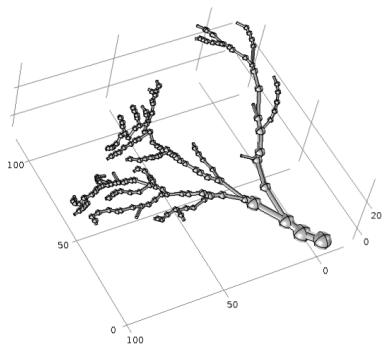
- ▶ Bottom and middle level: compartments (cylindrical volumes)
- ▶ Coupling with PDE requires a free space mesh
- ▶ Modeling the neuron via 3D curves

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 → humans) of great public health interest, causing enteroheamorrhagic colitis (EHEC) in humans (∼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

(*Note:* pop. density UK:Sweden is $\gtrsim$ 10:1)
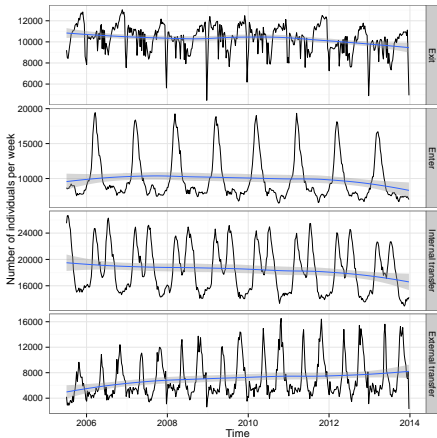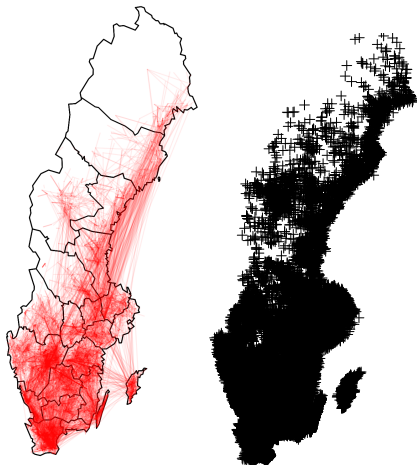
Epidemic model

"Locally well-stirred" (SIS_E)

Model states: **S**usceptible, **I**nfected, in $\sim$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,

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

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

Sample simulation

`http://user.it.uu.se/~stefane/animations/collection/siminf/`
`siminf_sample.gif`

Parallel performance
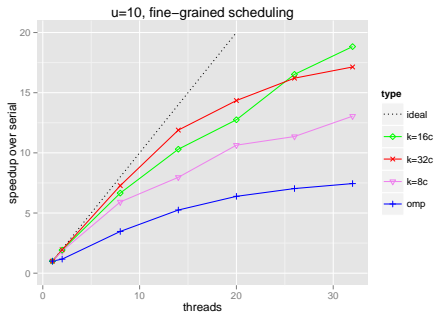
Feasibility of parameter estimation

Setup: determine $\hat{k} = \arg\min_k G(k)$,

$$G(k)^2 = M^{-1} \sum_{i=1}^{M} \| S \circ x_{\text{simulated}}^{(i)}(k) - S \circ x_{\text{input}}(k^*) \|^2,$$

S a "smoothing statistics" (...)

Using $M \in \{10, 20, 40\}$ trajectories for G and $N = 20$ iterations of an optimization routine:

M	Residual	12 cores	32 cores
10	0.174	46.6 min	30.2 min
20	0.090	94.2 min	61.5 min
40	0.036	189.3 min	123.7 min

u=10, fine−grained scheduling

Summary

- Mesoscopic stochastic R & D, **event-based computational framework**: fairly intuitive modeling, coupling and up/down-scaling, analysis of numerical methods, efficient simulation algorithms

- Terms & conditions. If used when required: accurately capturing a stochastic nonlinear phenomenon is a very hard constraint for method's development!

- **Consistency** with macroscopic equations. The numerical method's convergence to the macroscopic equation implies convergence in mean (/weak convergence) of the corresponding stochastic model, FEM, **backward analysis**

- Multiscale neuronal application solved in URDME (GitHub): coupling different types of models

- Epidemiological national-scale model solved in SimInf (GitHub): data-driven simulation, parallel performance

Acknowledgments
∼In order of appearance

- Pavol Bauer (UU)
- Andreas Milias-Argeitis, Mustafa Khammash (ETH)
- Per Lötstedt, Andreas Hellander, Lina Meinecke, Emilie Blanc (UU)
- Augustin Chevallier (ENS Cachan), Emil Berwald (UU)
- Stefan Widgren (SVA)

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