Numerical analysis of computational multiscale methods for kinetic equations

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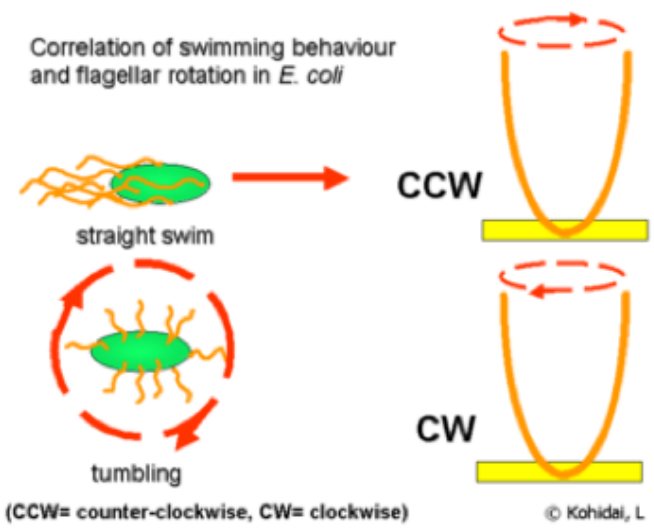
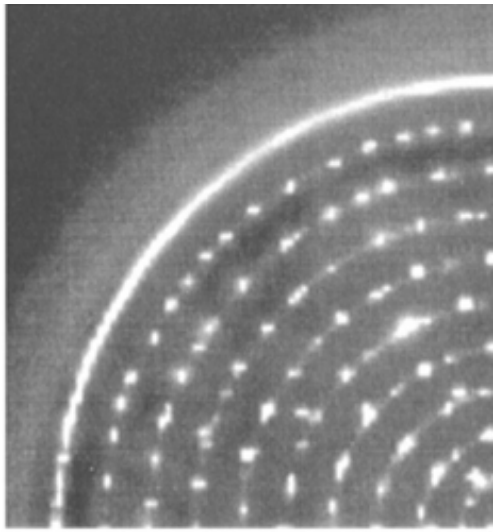
Problem statement

Discrepancy between **observation level** and **available model**

In this talk: bacterial chemotaxis and tumor growth





Macroscopic simulation with microscopic models too costly!

Widespread applications: plasma physics, radiative transfer, polymeric physics, quantitative sociology, etc.

Mathematical setting: model problem 1

- **Microscopic scale**
  - stochastic differential equation

$$dX_t = a(X_t)dt + \sigma(X_t)dW_t$$

  - equivalent Fokker-Planck equation

$$\partial_t \rho(x,t) + \partial_x \left(a(x)\rho(x,t)\right) = \partial_{xx}\left(\frac{\sigma^2(x)}{2}\rho(x,t)\right)$$

- **Macroscopic scale**
  - moments of the distribution function

$$M(t) = \int m(x)\rho(x,t)dx$$

  - ordinary differential equation for evolution not closed
- **Examples**: polymer flow, systemic risk, …

Mathematical setting: model problem 2

- **Microscopic scale**
  - High-dimensional slow-fast stochastic differential equation

$$dX_t = -\nabla V(X_t, Y_t)dt + dU_t$$

$$dY_t = \frac{1}{\epsilon}(X - Y)dt + \frac{1}{\sqrt{\epsilon}}dV_t$$

- **Macroscopic scale**
  - Marginal distribution of the slow degrees of freedom

$$\rho(x,t) = \int \phi(x,y,t)dy$$

  - Partial differential equation for evolution not closed
- **Examples**: molecular dynamics, climate, …

Mathematical setting: model problem 3

- **Microscopic scale**
  - Particles in position-velocity phase space (X_t, V_t, t)
  - Kinetic equation for evolution of distribution

$$\partial_t f(x, v, t) + v \partial_x f(x, v, t) = Q(f(x, v, t))$$

- **Macroscopic scale**
  - Moments over velocity space

$$u(x, t) = \int m(v) f(x, v, t) dv$$

  - Partial differential equation for evolution not closed
- **Examples**: bacterial chemotaxis, tumor growth, nuclear fusion,…

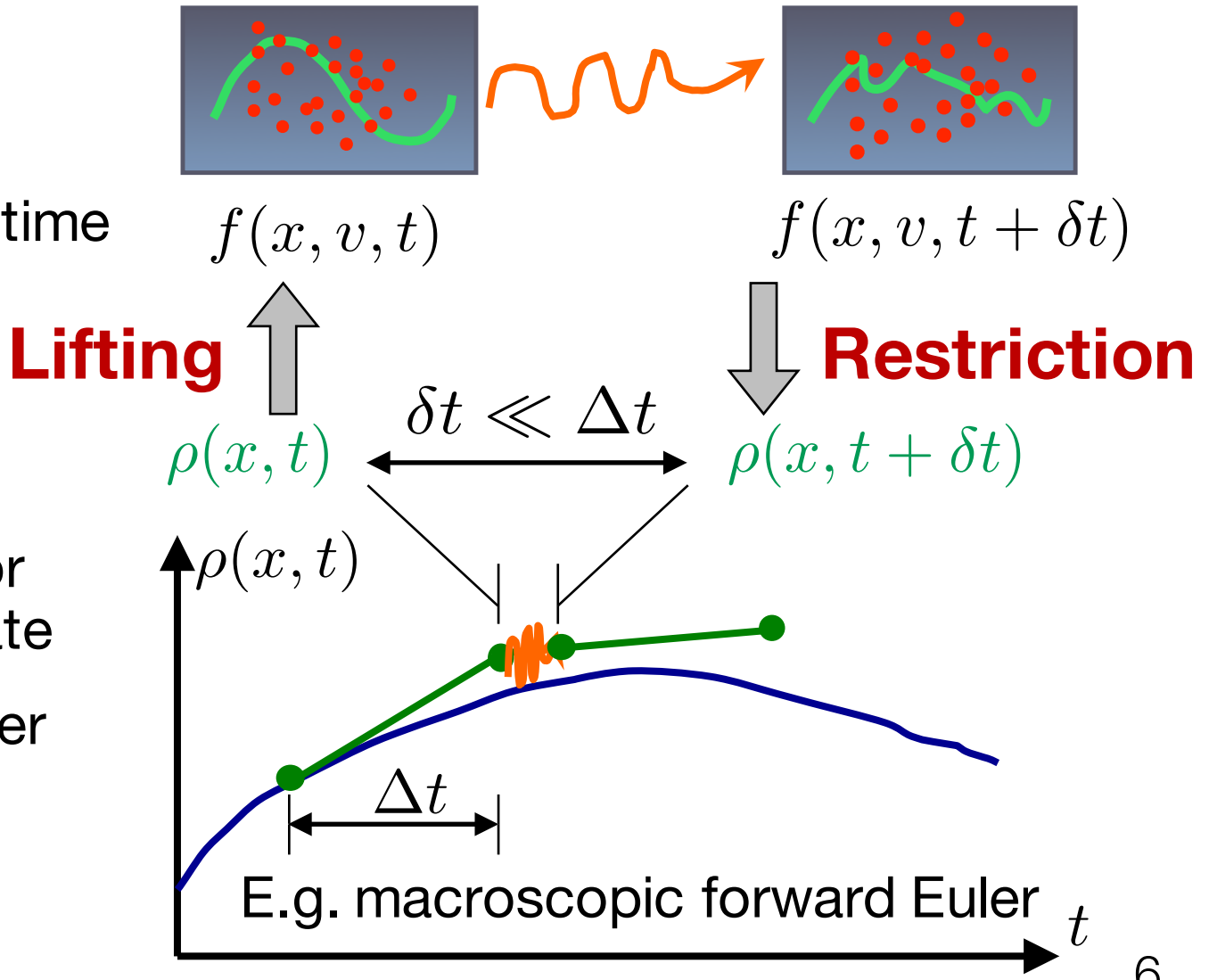
Computational multiscale framework
Based on *coarse projective integration*

Microscopic level

- model available
- simulate over short time interval

Macroscopic level

- model incomplete or insufficiently accurate
- want to simulate over long time interval



Kevrekidis et al, 2003 - …
E et al, 2003 - …

Outline of the talk

- Model problems and algorithmic framework
- **Kinetic models for bacterial chemotaxis**
- Variance-reduced stochastic simulation
- Variance reduced simulation for tumor growth
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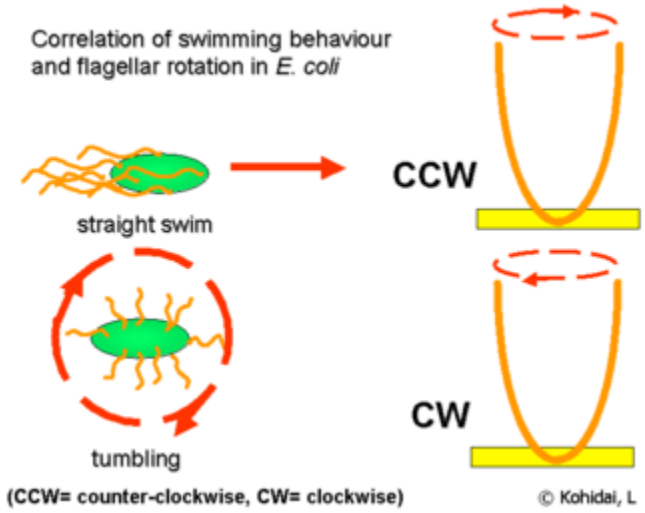
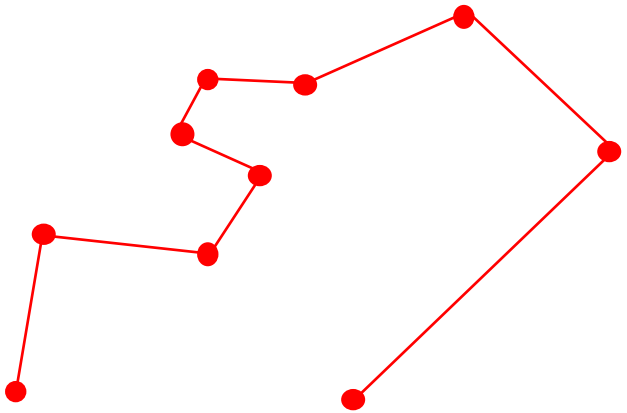
Velocity-jump models for chemotaxis



- Each bacterium moves with a constant speed in a given direction.

$$\frac{dX_t}{dt} = V_t$$

- Direction changes at jump times, generated via a Poisson process.



$$\int_{T_n}^{T_{n+1}} \lambda(t)dt = -\log(U_n), \qquad U_n = \mathcal{U}(0,1)$$

- The modeling effort goes into the definition of the intensity of the Poisson process (turning rate).

Turning rates for velocity jump models

- Constant turning rate (leads to pure diffusion)

$$\lambda(t) \equiv \lambda_0$$

- Turning rate biased by chemoattractant concentration

$$\lambda(t) \equiv \lambda_0 - g\left(\nabla_x S(X(t))\right)^T V(t)$$

- Turning rate biased by internal state (for small bacteria)

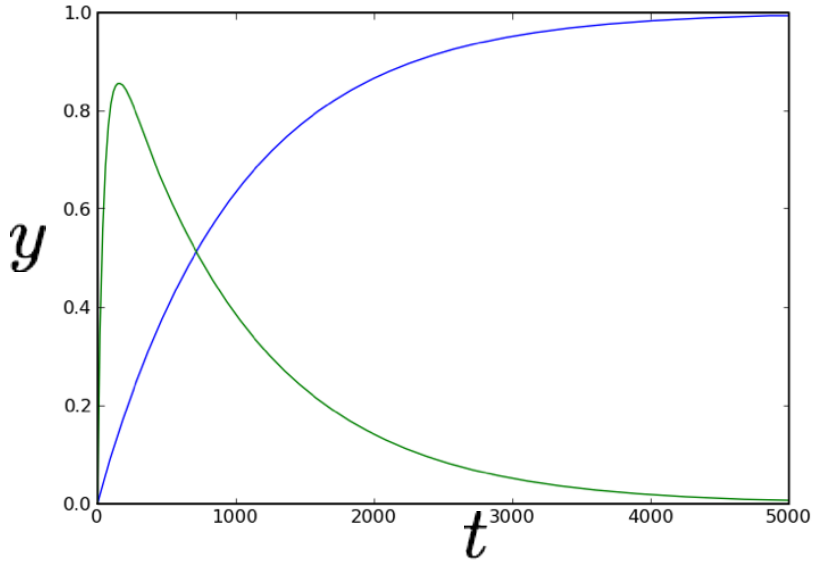
$$\lambda(t) = \lambda(y(t)), \qquad \frac{dY_t}{dt} = F(Y_t, S(X_t))$$

  - Internal state induces memory

Example: cartoon internal dynamics

- Excitation/adaptation mechanism

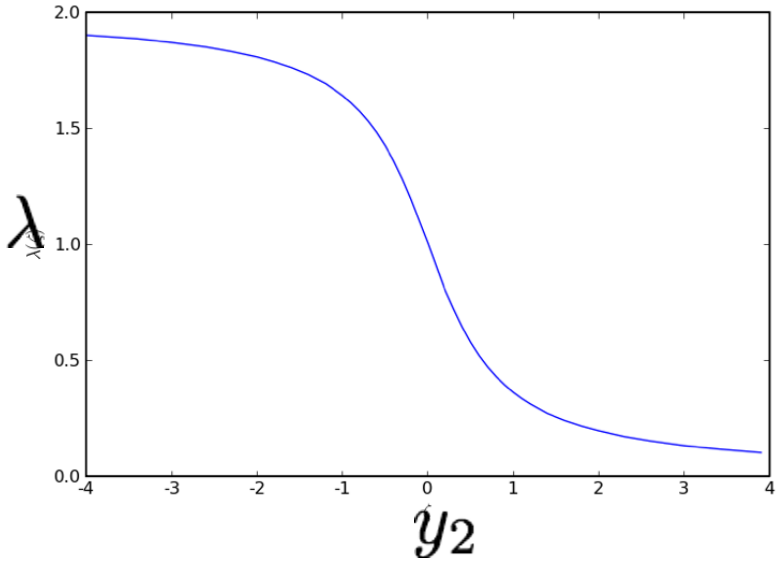
$$\begin{cases} \dfrac{\mathrm{d}y_1}{\mathrm{d}t} = \dfrac{S(x) - y_1}{t_a}, \\ \dfrac{\mathrm{d}y_2}{\mathrm{d}t} = \dfrac{S(x) - (y_1 + y_2)}{t_e}, \end{cases}$$



- Alignment with desired direction

$$\lambda(y) := \lambda_0 - by_2$$

$$\lambda(y) > \lambda_0 \text{ for } y_2 < 0$$



- Bacterium has a higher jump rate if moving in unfavorable direction.

Asymptotic regime

- Non-dimensionalize:
  - t_x : time scale associated with environmental changes
  - t_λ : typical time between two jumps
  - t_y : time scale associated with evolution of internal state

$$\epsilon := t_\lambda / t_x \qquad \tau := t_y / t_\lambda \qquad \epsilon \ll \tau^{-1} < K$$

$$\frac{dX_t}{dt} = \epsilon V_t, \qquad \|V_t\| = 1$$

$$V_t = \mathcal{V}_n \qquad t \in [T_n, T_{n+1})$$

$$Z_t = Y_t - S(X_t)$$

$$\int_{T_n}^{T_{n+1}} \lambda(Y_t)dt = \theta_n \longrightarrow \lambda(Z_t) = \lambda_0 - \epsilon b^T Z_t + O(|Z_t|^2)$$

$$\frac{dY_t}{dt} = F(Y_t, S(X_t)) \longrightarrow F(Z_t) \approx -\tau^{-1} Z_t + O(|Z_t|^2)$$

Kinetic model and macroscopic limit

- Equivalent continuum model for probability density $p(x, v, y, t)$

$$\partial_t p + \epsilon v \cdot \nabla_x p + \nabla_y (F(y, S(x))p) = Q(p)$$

advection internal dynamics collisions

- On long time scales ($t \mapsto t/\epsilon^2$), an advection-diffusion equation arises for the position density …

$$n(x,t) = \int_{\mathbb{Y}} \int_{\mathbb{V}} p(x, v, y, t) dv dy$$

- … in the limit of $\epsilon \to 0$

$$\partial_t n = \nabla_x \left(\frac{1}{2} \nabla_x n - T(x) n \right) \qquad T(x) = b^T \frac{\tau}{\lambda_0 \tau + I} \nabla_x S(x)$$

Erban and Othmer, SIAM J. Applied Math., 65(2):361–391, 2004.
Rousset and S, M3AS 23(11):2005-2037, 2013.

Macroscopic limit for gradient sensing model

- Velocity-jump process without internal dynamics

$$\frac{dX_t^c}{dt} = \epsilon V_t^c$$

$$V_t^c = \mathcal{V}_n^c \qquad t \in [T_n^c, T_{n+1}^c] \qquad \Longleftrightarrow \quad \partial_t p^c + \epsilon v \cdot \nabla_x p^c = Q(p)$$

$$\int_{T_n^c}^{T_{n+1}^c} \lambda^c(X_t, V_t) dt = \theta_n$$

$$\lambda^c(X_t, V_t) = \lambda_0 - \epsilon T(x)^T V_t$$

- For this model, we have the same macroscopic limit !

$$\partial_t n = \nabla_x \left(\frac{1}{2} \nabla_x n - T(x) n \right)$$

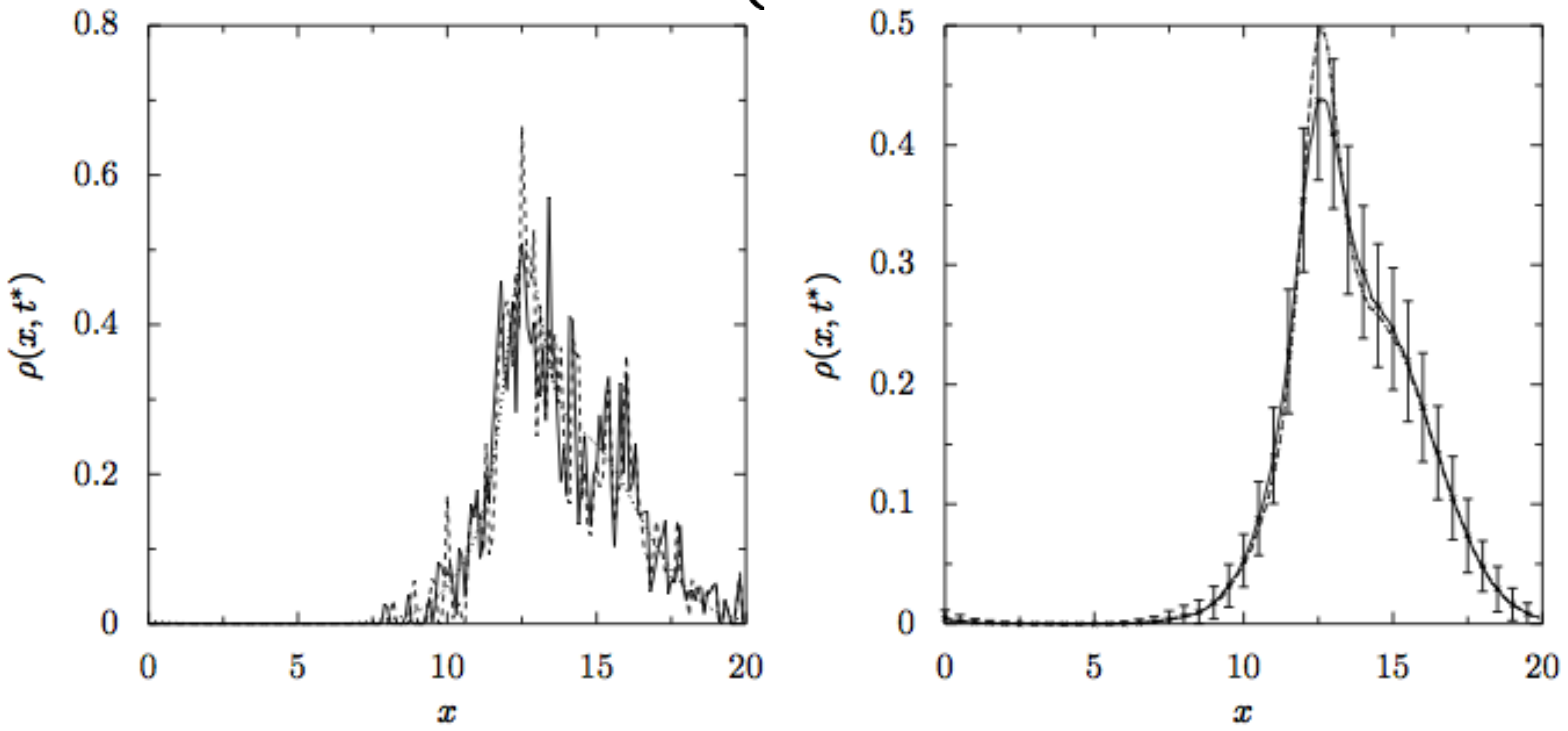
Erban and Othmer, SIAM J. Applied Math., 65(2):361–391, 2004.
Rousset and S, M3AS 23(11):2005-2037, 2013.

The numerical problem of variance

Simulation using N = 3750 particles at time t = 100, using $\epsilon = 1$

$$S(x) = \exp(-(x-7.5)^2) + \exp(-(x-12.5)^2)$$

$$n(x,0) = \begin{cases} 1 \text{ for } x \in [13,15] \\ 0 \text{ otherwise} \end{cases}$$



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- **Variance-reduced stochastic simulation**
- Variance reduced simulation for tumor growth
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Aim of asymptotic variance reduction

- Standard error on the computed density $\mathrm{Std}(\rho) = O(1/\sqrt{N})$
- Goal is to measure differences of size $O(\epsilon)$
- Two possible solutions :
  - Use $N = O(1/\epsilon^2)$ realizations (computationally expensive !)
  - **Use an asymptotic variance reduction technique such that**

$$\mathrm{Std}(\rho) = O(\epsilon/\sqrt{N})$$

Coupled simulation / control variates

Model with internal state

$$\frac{dX_t}{dt} = \epsilon V_t, \qquad \|V_t\| = 1$$
$$V_t = \mathcal{V}_n \qquad t \in [T_n, T_{n+1})$$
$$\int_{T_n}^{T_{n+1}} \lambda(Y_t)dt = \theta_n$$
$$\frac{dY_t}{dt} = F(Y_t, S(X_t))$$

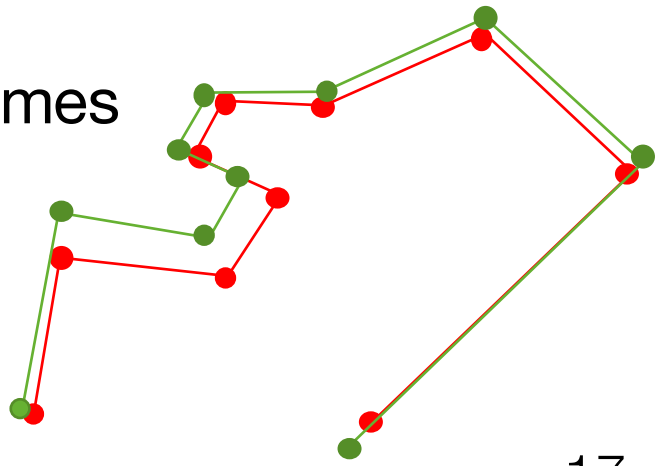
Direct gradient sensing model (control variate)

$$\frac{dX_t^c}{dt} = \epsilon V_t^c$$
$$V_t^c = \mathcal{V}_n^c \qquad t \in [T_n^c, T_{n+1}^c]$$
$$\int_{T_n^c}^{T_{n+1}^c} \lambda^c(X_t, V_t)dt = \theta_n$$

- Couple both processes by taking
  - the same random numbers for the jump times

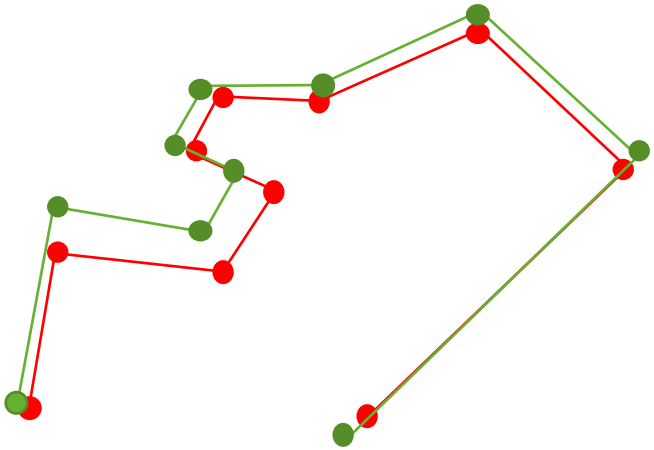
$$\int_{T_n}^{T_{n+1}} \lambda(Y_t)dt = \theta_n = \int_{T_n^c}^{T_{n+1}^c} \lambda^c(X_t, V_t)dt$$

  - the same new velocities $\mathcal{V}_n = \mathcal{V}_n^c$



Rousset and S, M3AS 23(12):2155-2191, 2013.

Coupled simulation / control variates (2)



- Density via ‘kernel density estimation’

$$\hat{n}(x,t) = \frac{1}{Nh}\sum_{i=1}^{N} K_h(x - X_t^i)$$

$$\hat{n}^c(x,t) = \frac{1}{Nh}\sum_{i=1}^{N} K_h(x - X_t^{i,c})$$

- Compute deterministic solution $n^c(x,t)$ for control variate via

$$\partial_t p^c + \epsilon v \cdot \nabla_x p^c = Q(p)$$

- Then compute variance reduced density estimate

$$\bar{n}(x,t) = \hat{n}(x,t) - \hat{n}^c(x,t) + n^c(x,t)$$

similar fluctuations

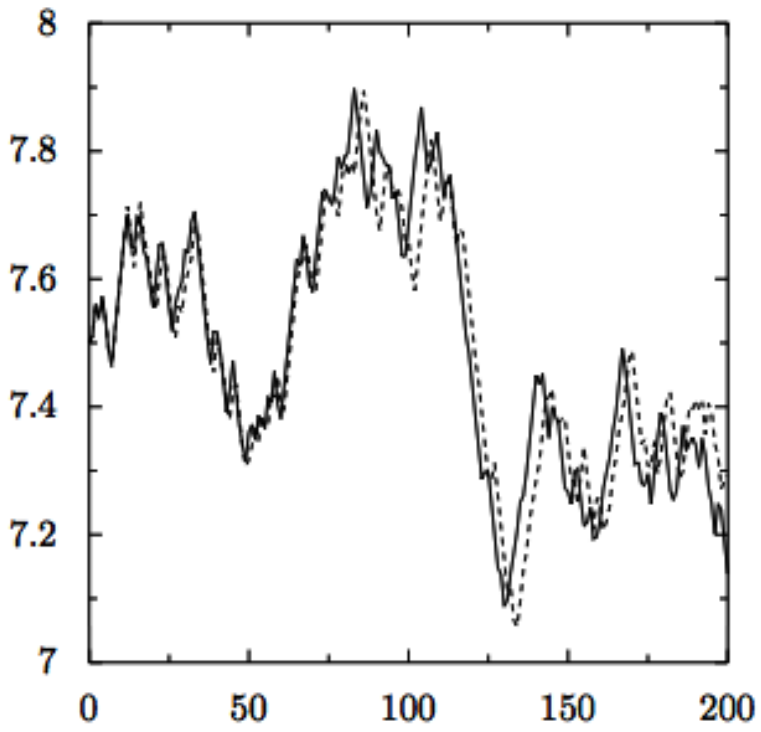
same expectation

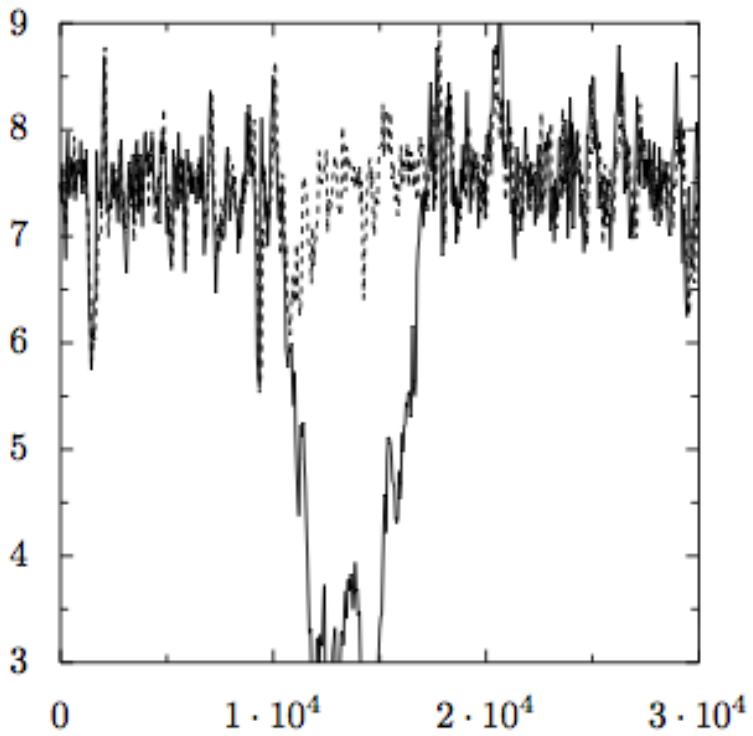
A theoretical result : asymptotic variance reduction

- The variance of the coupling behaves like

$$\mathrm{Var}\left(\hat{n}(x,t) - \hat{n}^c(x,t)\right) = O(\epsilon^2/N)$$

- The proof is pathwise, and is obtained using a random time shift argument :

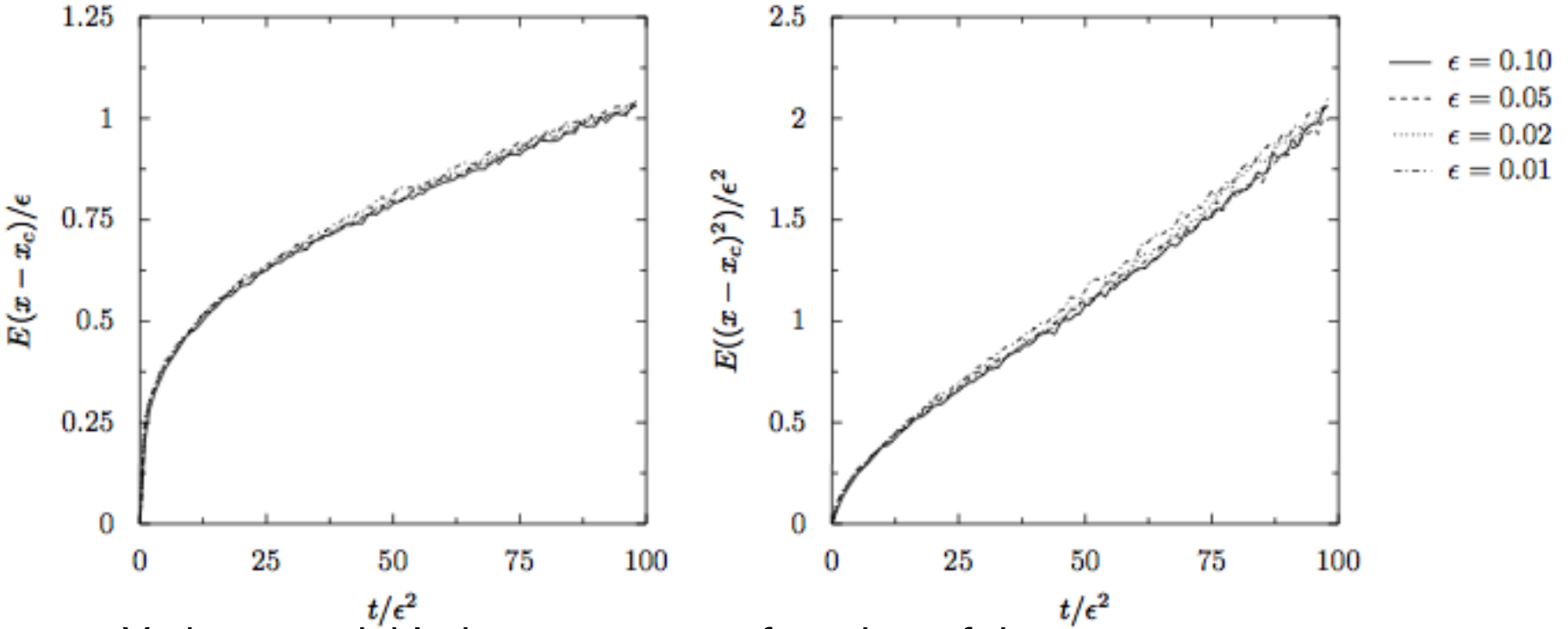




- **Watch out for time discretization effects!!**

Numerical results on the coupling (2)

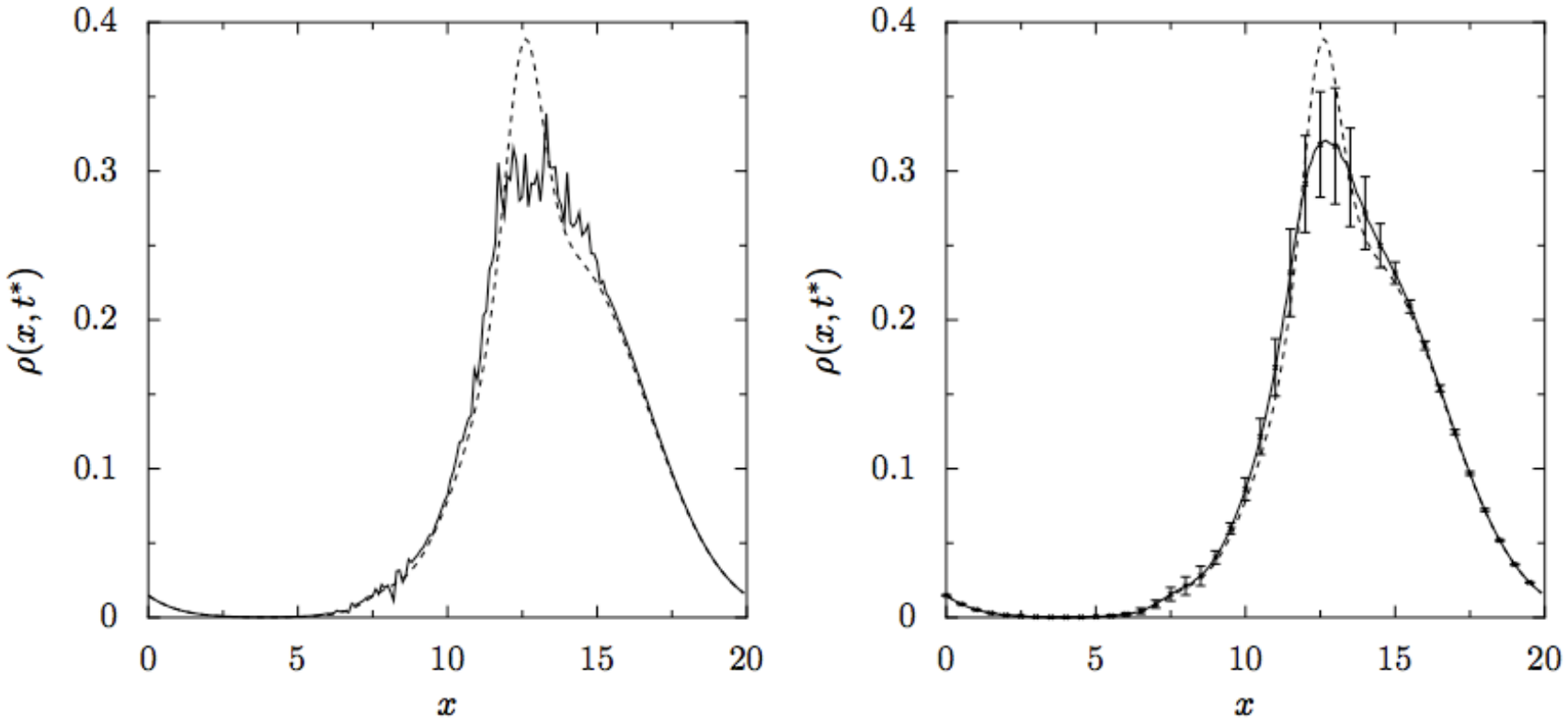
- Variance degrades a function of simulated time



- Variance quickly increases as a function of time
- Linear increase on long time scales probably due to double-well chemoattractant
- **Restore coupling frequently by reinitializing control particles**

Density computation with variance reduction

- Differences between models are statistically significant
- Variance is higher where the two models differ the most



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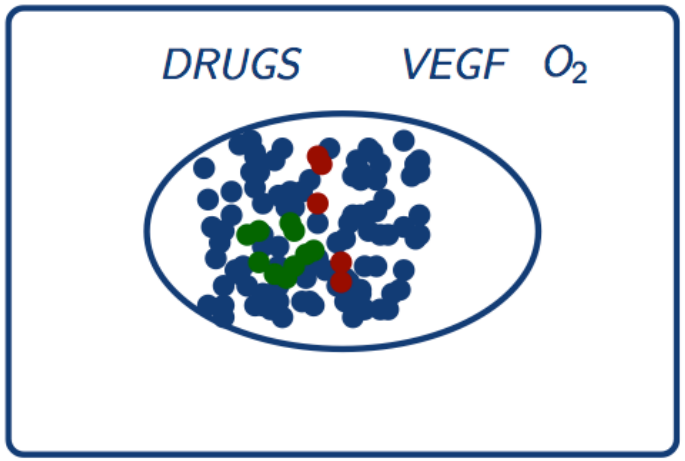
Agent-based model for tumor growth



- Normal cells (p=1)
- Cancer cells (p=2)
- Endothelial cells (p=3)

- Environment: reaction-diffusion equations, coupled with agents!

- Cell motion: biased Brownian motion

$$dX_p = \left(\sqrt{2D_p} + \chi_p \nabla V(x)\,(1 - n_p/n_{p,max})\right) dt$$

- Each cell also has internal dynamics depending on the type.

$$\frac{d\phi_p}{dt} = \frac{C(X_p,t)}{T_{p,min}(C_\phi + C(X_p,t))}$$

$$\frac{dz}{dt} = H(C_{tr} - C(X_p,t))A - BzH(C(X_p,t) - C_{tr})$$

- Environment influences motion, but also speed of cell cycle (cell division) and apoptosis (cell death)

Owen *et al.*, Cancer Res., 71(8):2826–37, 2011.
Lejon, Mortier, S, arXiv:1509.06346, submitted, 2015.

Approximate macroscopic model

- Advection-diffusion via Fokker-Planck equation

$$\partial_t n_p = D_p \nabla^2 n_p - \chi_p \nabla \cdot \left[\nabla V \left(1 - \frac{n_p}{n_{p,max}} \right) n_p \right]$$

- What about reactions?
  - Births and deaths depend on intracellular dynamics
  - Difficult to obtain as a function of density

$$\partial_t n_p = D_p \nabla^2 n_p - \chi_p \nabla \cdot \left[\nabla V \left(1 - \frac{n_p}{n_{p,max}} \right) n_p \right] + R(n_p(x,t))$$

  - Such a closure appears impossible to obtain!

Variance reduction technique (1)

- Variance due to random motion that impacts internal dynamics, and hence the precise location of reaction
- Random motion is identical in the advection-diffusion model without reactions
- Simulate simultaneously
  - Stochastic model with internal state (and hence reactions)
  - Stochastic model without reactions
  - Deterministic model without reactions
  - Use stochastic model to estimate reaction term only !

Variance reduction technique (2)

- Stochastic model with internal state (and hence reactions)

$$\hat{n}_p(t+\Delta t) = \sum_{i=1}^{I_p(t+\Delta t)} w_i(t+\Delta t)\delta_{X_i,p(t+\Delta t)}$$

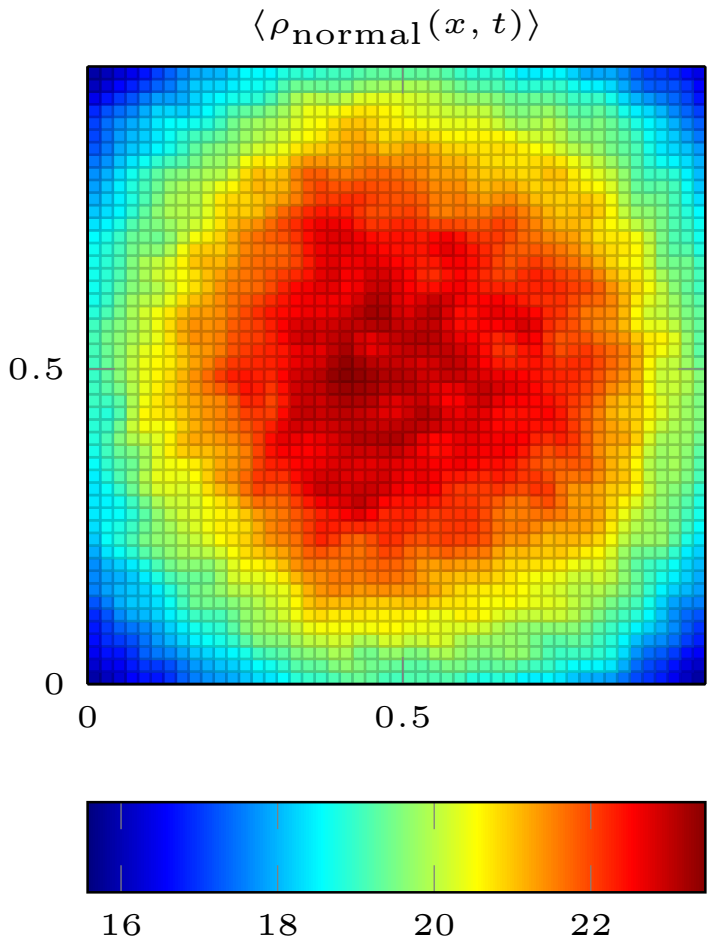
- Stochastic model without reactions

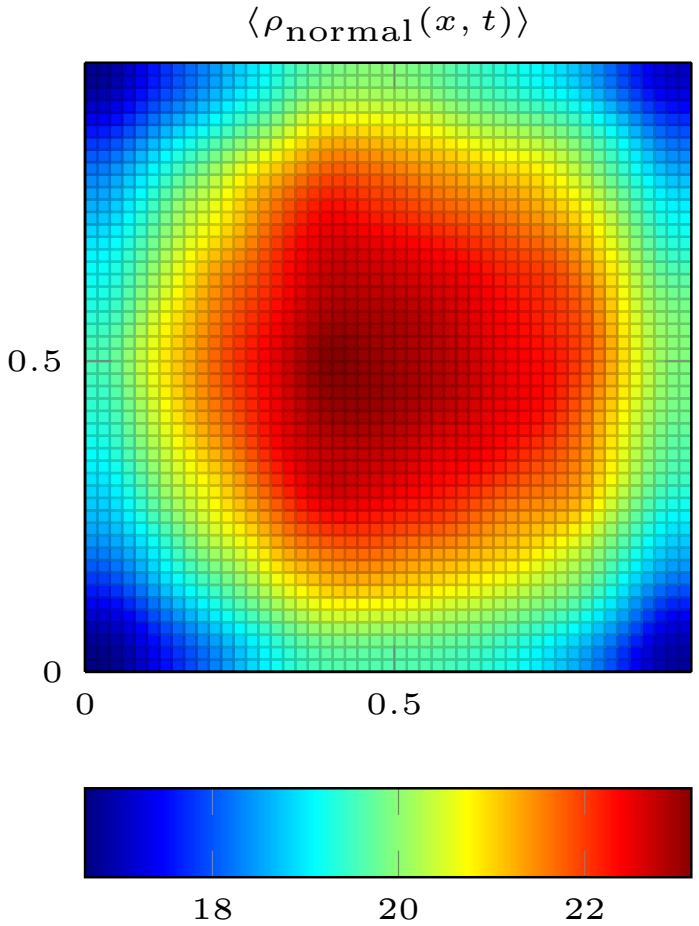
$$\hat{n}^c_p(t+\Delta t) = \sum_{i=1}^{I_p(t)} w_i(t)\delta_{X_i,p(t+\Delta t)}$$

- Use stochastic model to estimate reaction term only !

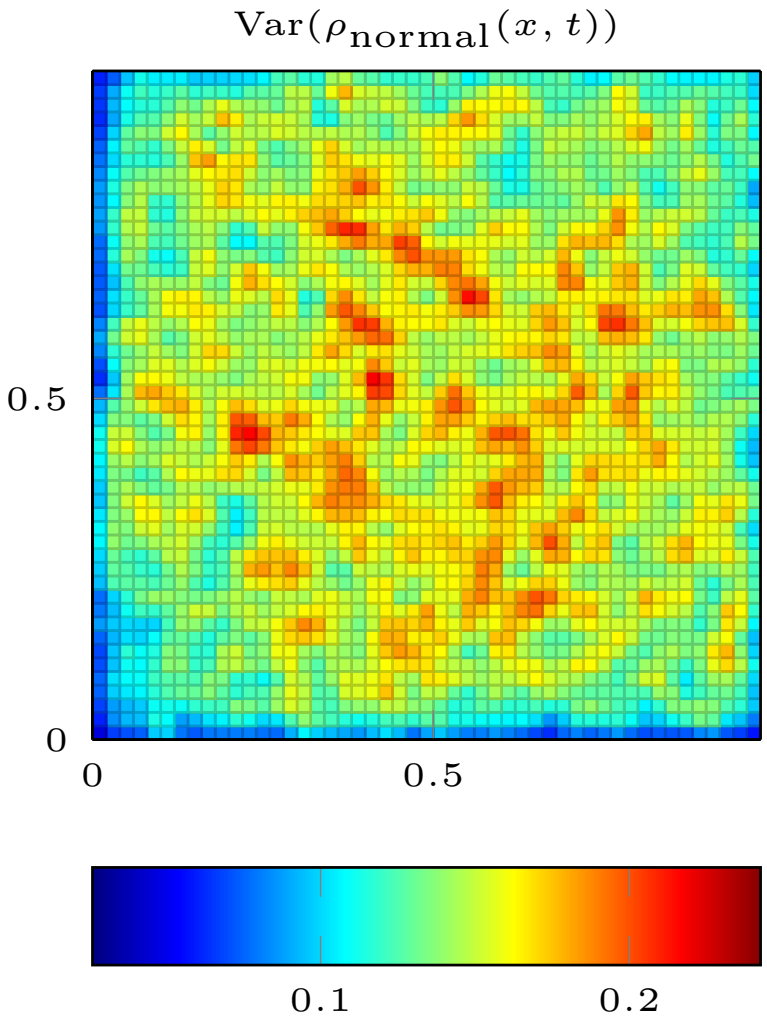
$$\bar{n}(t+\Delta t) = n^c_p(t+\Delta t) + \left(\hat{n}_p(t+\Delta t) - \hat{n}^c_p(t+\Delta t)\right)$$

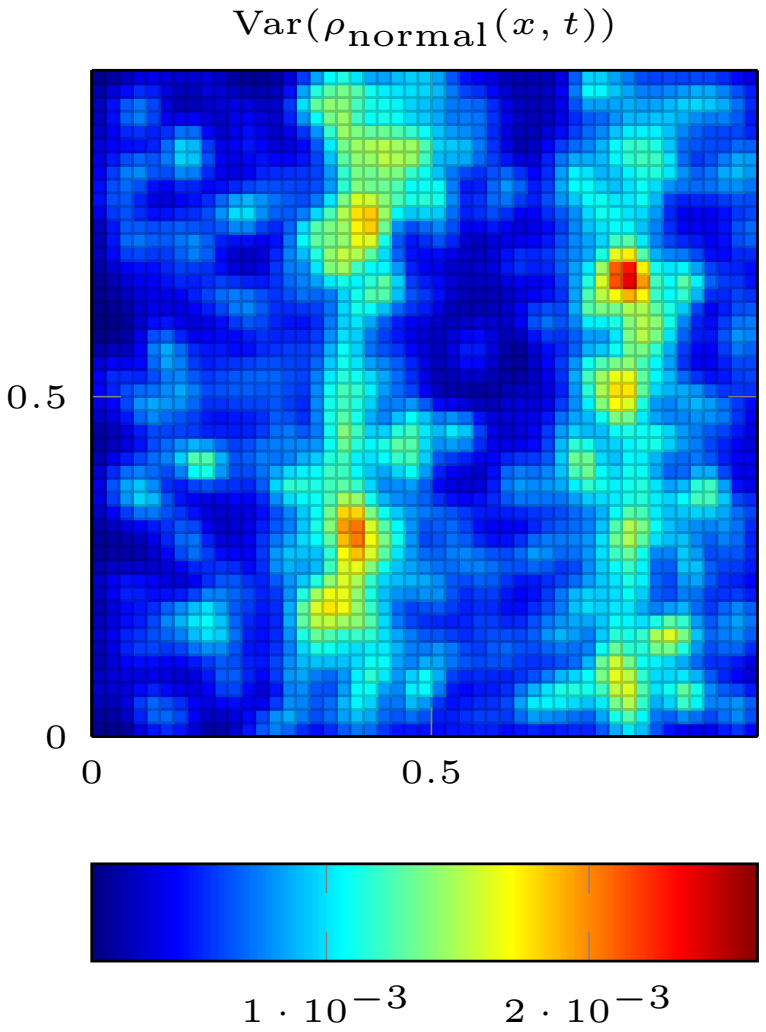
Numerical test 1: expectation





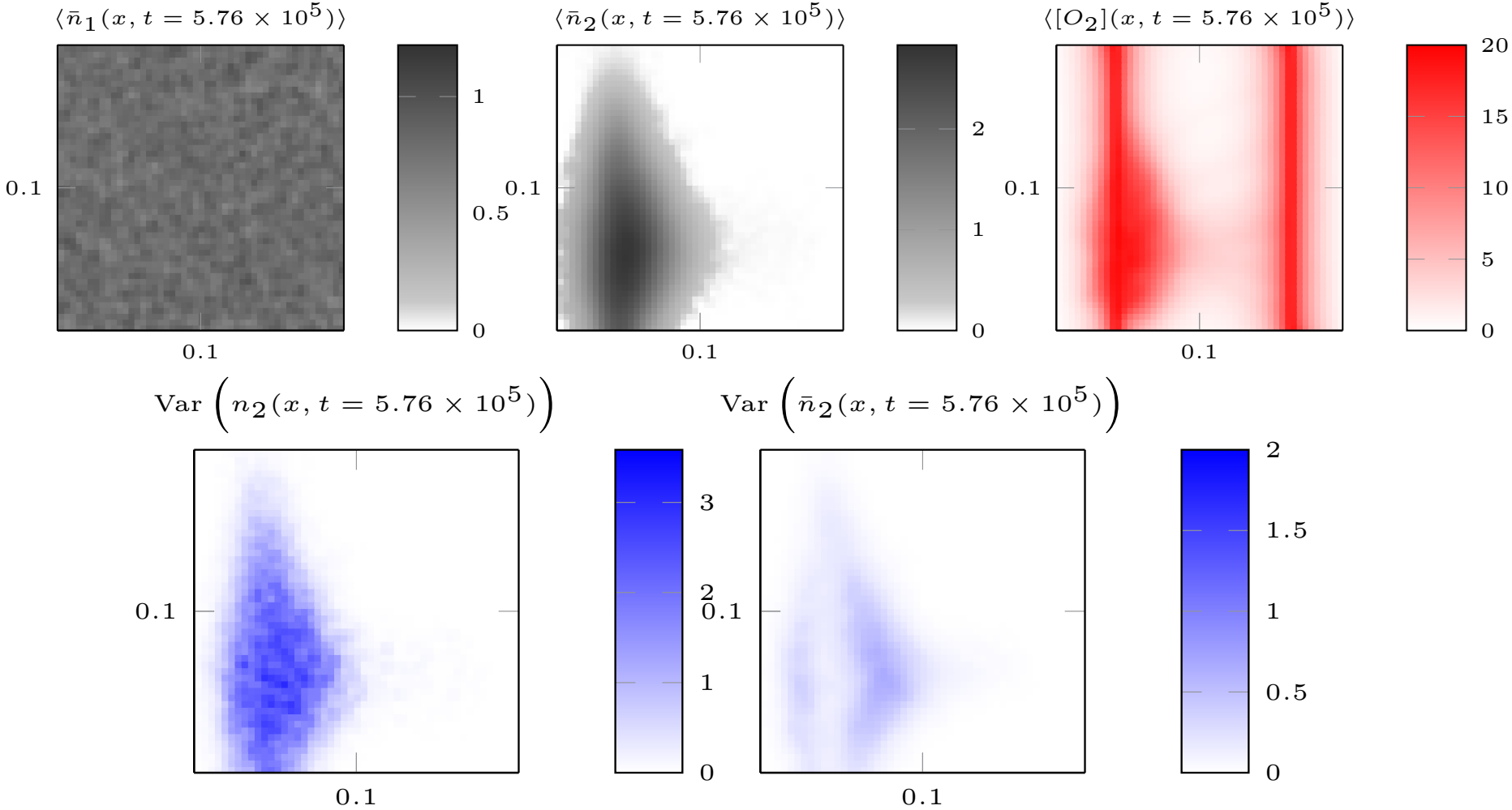
Numerical test 1: variance





Numerical test with angiogenesis

Angiogenesis modeled via tip cell that moves chemotactically and sprouts



Conclusions

- Often, microscopic simulation needs to be done via Monte Carlo simulation of stochastic models, because of high-dimensionality.
- Due to the statistical noise, the relevance of the extra modeling detail is not always very clear.
- If an approximate macroscopic model is known, it can be used for variance reduction.
- Such methods can significantly extend the size of systems that can be simulated (to the vascular case for tumor growth).

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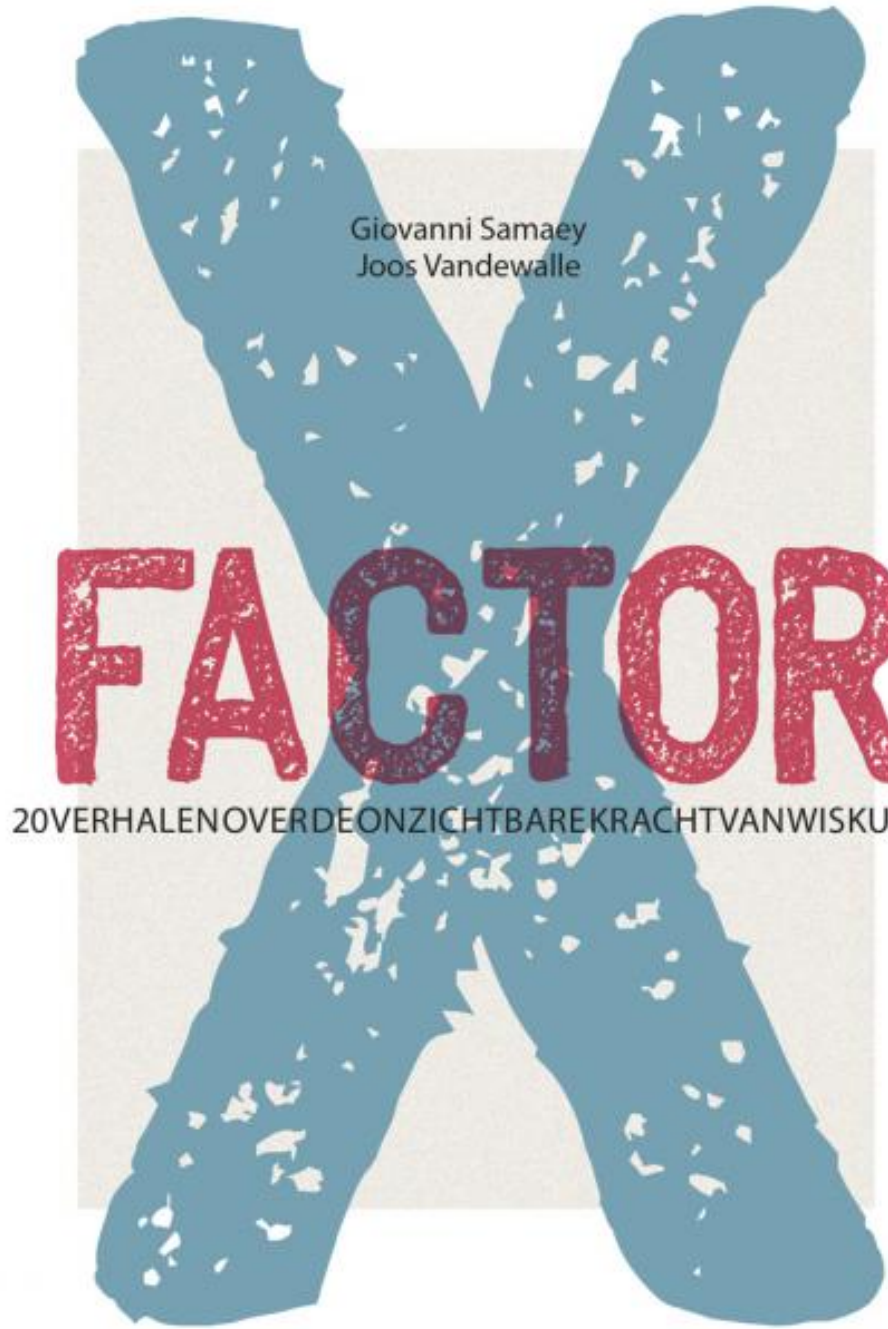
Joos Vandewalle



FACTOR

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Pelckmans Pro