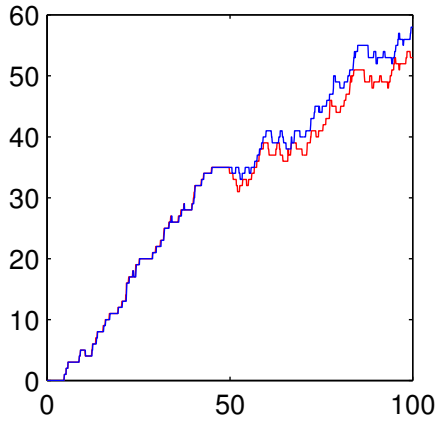
Sensitivity estimation and inverse problems in spatial stochastic models of chemical kinetics



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Outline

1. Brief overview: stochastic modeling of diffusion-controlled reactions
   (Bio-)Chemical kinetics
   Spatial chemical kinetics

2. An "All Events Method"-implementation
   Sample use: forward sensitivity estimation

3. Inverse formulation
   Sample use: "evolutionary" optimal control setup

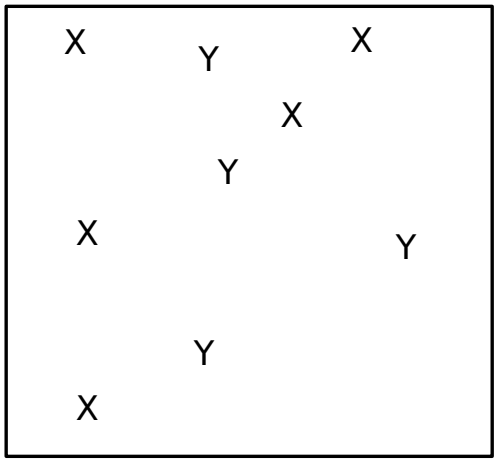
Conclusions

Stochastic modeling of biochemical reactions

The well-stirred case

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

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



V

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

Stochastic modeling of biochemical reactions

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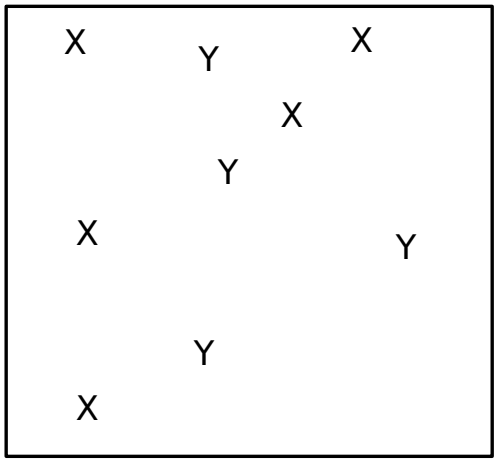

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- $P \propto n_Y$
- $P \propto 1/V$
- $P \propto \Delta t$

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

It so happens that this receipt describes a continuous-time Markov chain.

Kolmogorov's forward differential system/Master equation

(Kolmogorov '31, Nordsieck/Lamb/Uhlenbeck '40)

-State $x \in \mathbf{Z}_+^D$, the number of molecules of each of D species.

-R specified reactions defined as *transitions* between these states,

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

under a transition intensity or *propensity* w_r.

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Let $p(x,t) := P(X(t) = x|X(0))$. Then the *chemical master equation* (CME) is given by

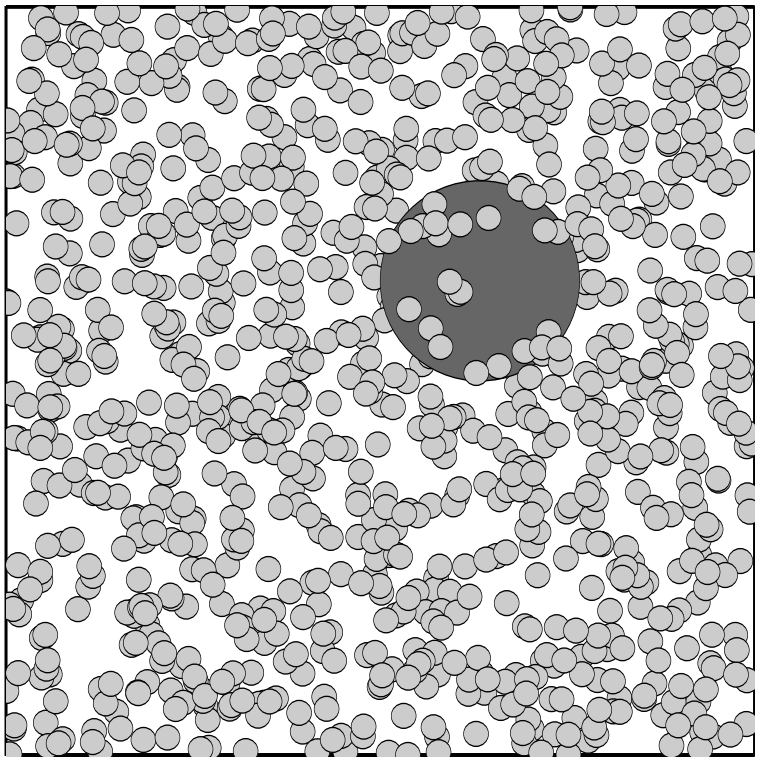
$$\begin{aligned}\frac{\partial p(x,t)}{\partial t} &= \sum_{r=1}^{R} w_r(x+\mathbb{N}_r)p(x+\mathbb{N}_r,t) - \sum_{r=1}^{R} w_r(x)p(x,t)\\ &=: \mathcal{M}p,\end{aligned}$$

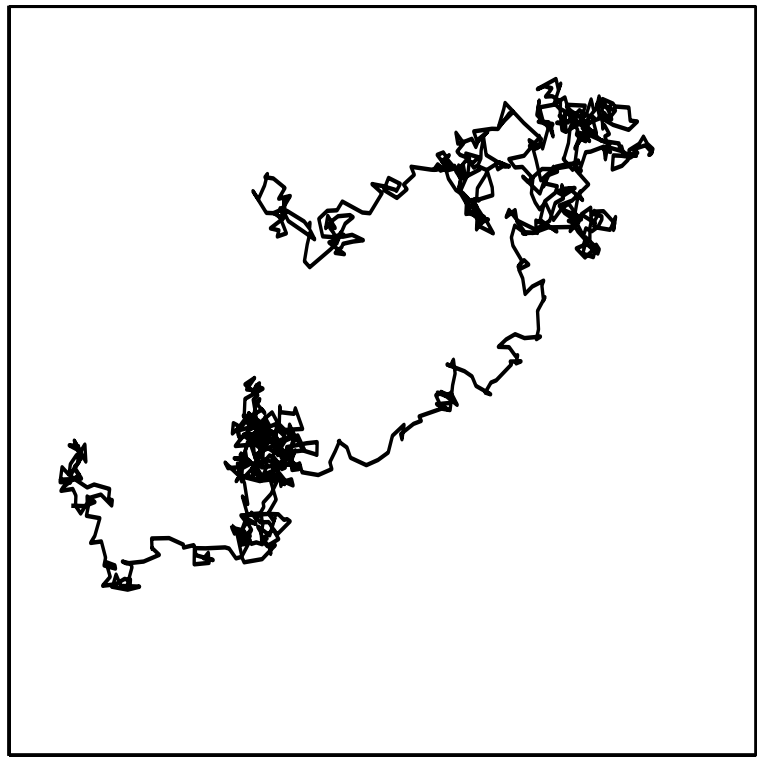
a gain-loss discrete PDE in D dimensions for the probability.

Brownian motion

Einstein 1905, & some others...

Example: Particle in a fluid.





The idea of reaction-diffusion master equations: couple well-stirred reactions with a description of diffusion.

Mesoscopic spatial kinetics

NOT well-stirred

-Generally not well-stirred in the whole volume, but if the domain Ω is subdivided into smaller computational cells Ω_j such that their individual volume $|\Omega_j|$ is small, then diffusion suffices to make each cell well-stirred.

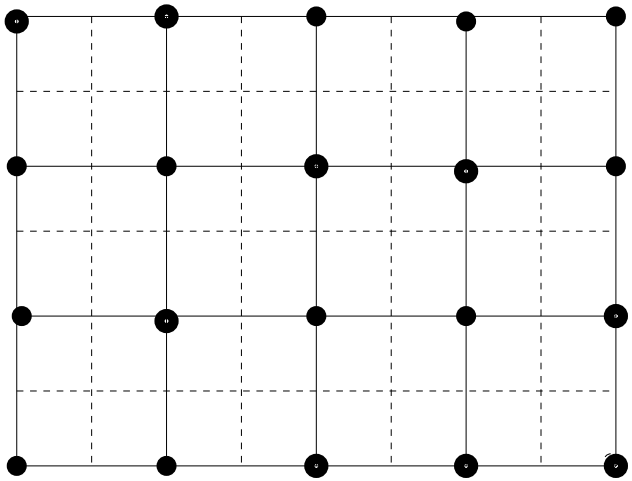


Figure: Primal mesh (solid), dual mesh (dashed). The nodal dofs are the # of molecules in each dual cell.

The reaction-diffusion master equation

"RDME"

- The state of the system is now an array $\mathbf{x}$ with $D \times K$ elements.
- This state is changed by chemical reactions occurring between the molecules in the same cell (vertically in $\mathbf{x}$) *and* by diffusion/transport where molecules move to adjacent cells (horizontally in $\mathbf{x}$).

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Hence when combining reactions with diffusions,

$$\frac{\partial p(\mathbf{x}, t)}{\partial t} = (\mathcal{M} + \mathcal{D}) p(\mathbf{x}, t).$$

Sampling the CME

(*Doob* ∼'45, *Gillespie* '76)

Simulate a single stochastic trajectory $X(t)$ "an outcome":

0. Let $t = 0$ and set the initial state x.
1. Compute the total intensity W as the sum of all reaction- and all transport intensities. Generate the *time to the next event* $\tau := -W^{-1} \log u_1$ where $u_1 \in (0, 1)$ is a uniform random number.
2. Determine the next event r by drawing u_2, again a uniform random deviate in $(0, 1)$. The probability of each event is determined by its proportion in W.
3. Update the state of the system accordingly and repeat from step 1 until some final time T is reached.

-*Complexity:* for a 3D model, 10.000 voxels with 10–100 species would be normal. Time between diffusion events scales as h^2.

Next reaction method

A version thereof...

- Note that one random number determines *when* the next event happens, another random number *what* happens.
- *An alternative*: if instead each reaction channel gets its own Poisson process, and we let them *compete*, we get the so-called *"Next Reaction Method"*.
- Events that "loose" in this process are rescaled and rescheduled for a later time.
- *Complexity:* the reason this is a viable approach is the existence of efficient data-structures (binary heap).

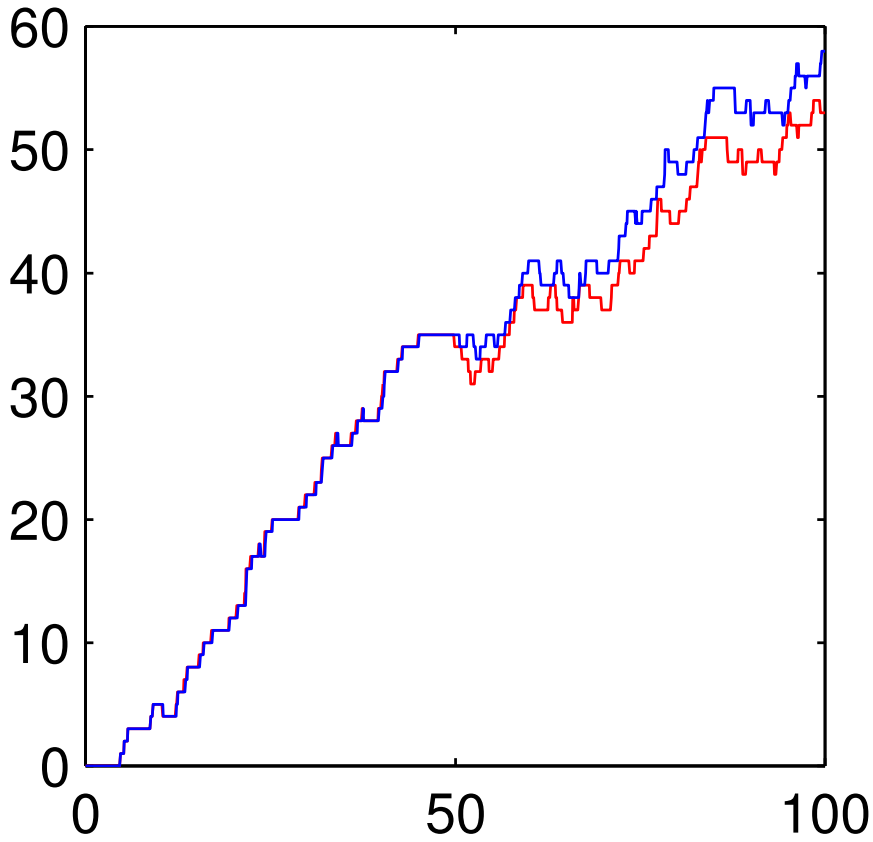
"All events method"

(..., Engblom '09, Rathinam et al. '10, Anderson '12)

In fact, if

- all events gets its own uniquely identifiable Poisson process (stream of random numbers)
- we take care of events that "go to sleep", i.e. produces a zero intensity (infinite waiting time)

then we can compare results from these types of models *per trajectory*.



$$\Longrightarrow E[X_t(\theta+\delta) - X_t(\theta)]^2 = E[X_t(\theta+\delta;\,\omega) - X_t(\theta;\,\omega)]^2 \sim O(\delta).$$

Forward sensitivity

Stochastic focusing example

Enzymatic reaction of a complex into a product,

$$C + E \xrightarrow{\nu\, C\cdot E} P + E.$$

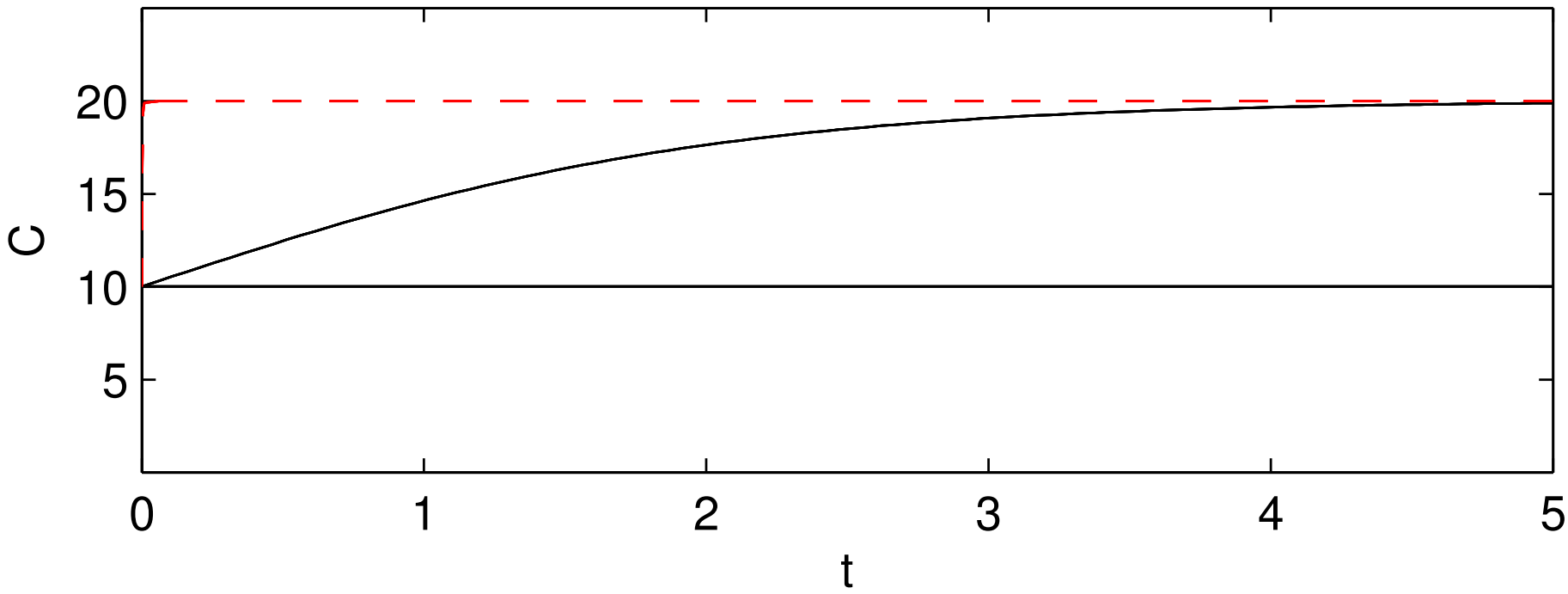
Combine with

$$\emptyset \underset{\mu_E E}{\overset{k_E}{\rightleftharpoons}} E, \quad \emptyset \underset{\mu_C C}{\overset{k_C}{\rightleftharpoons}} C, \quad P \xrightarrow{\mu_P P} \emptyset.$$

-Interested in $k_E \to (1+\delta)\cdot k_E$. *Example:* take $\delta = -1/2$.

Results in 0D (well-stirred)

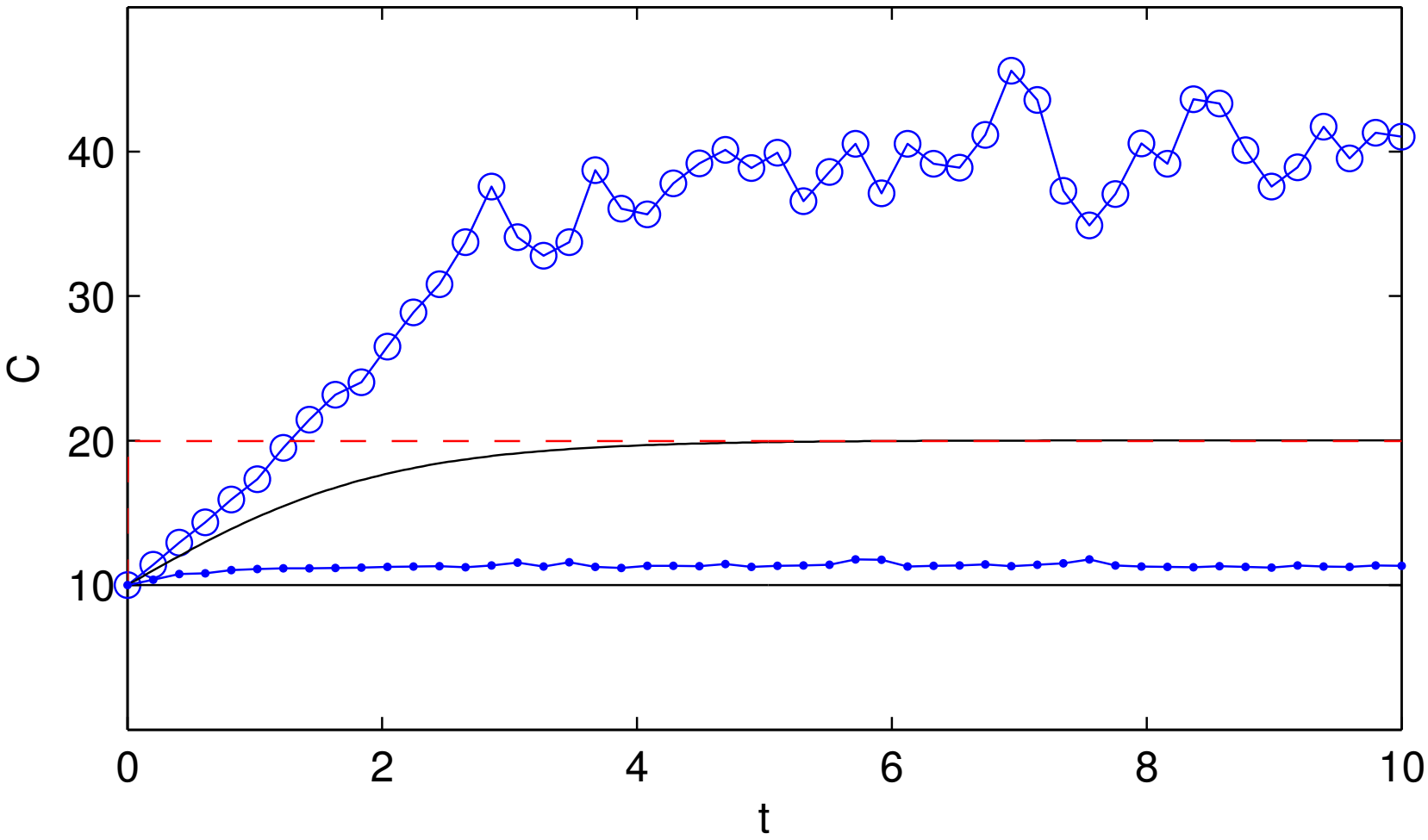
Deterministic equations



Expected: factor of 2 increase.

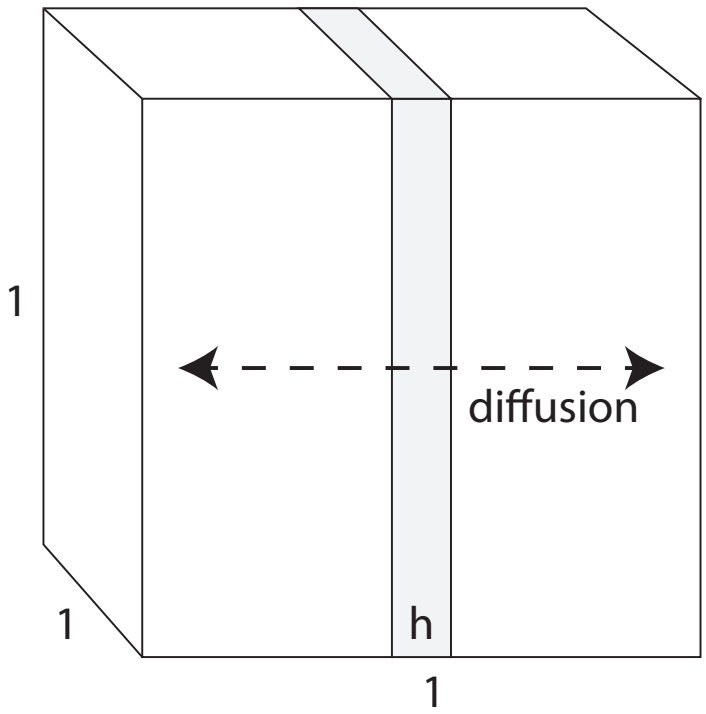
Results in 0D (well-stirred)

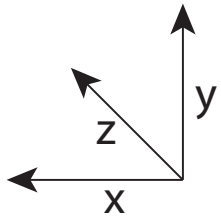
Stochastic equations - stochastic focusing effect



Results in 1D

Setup



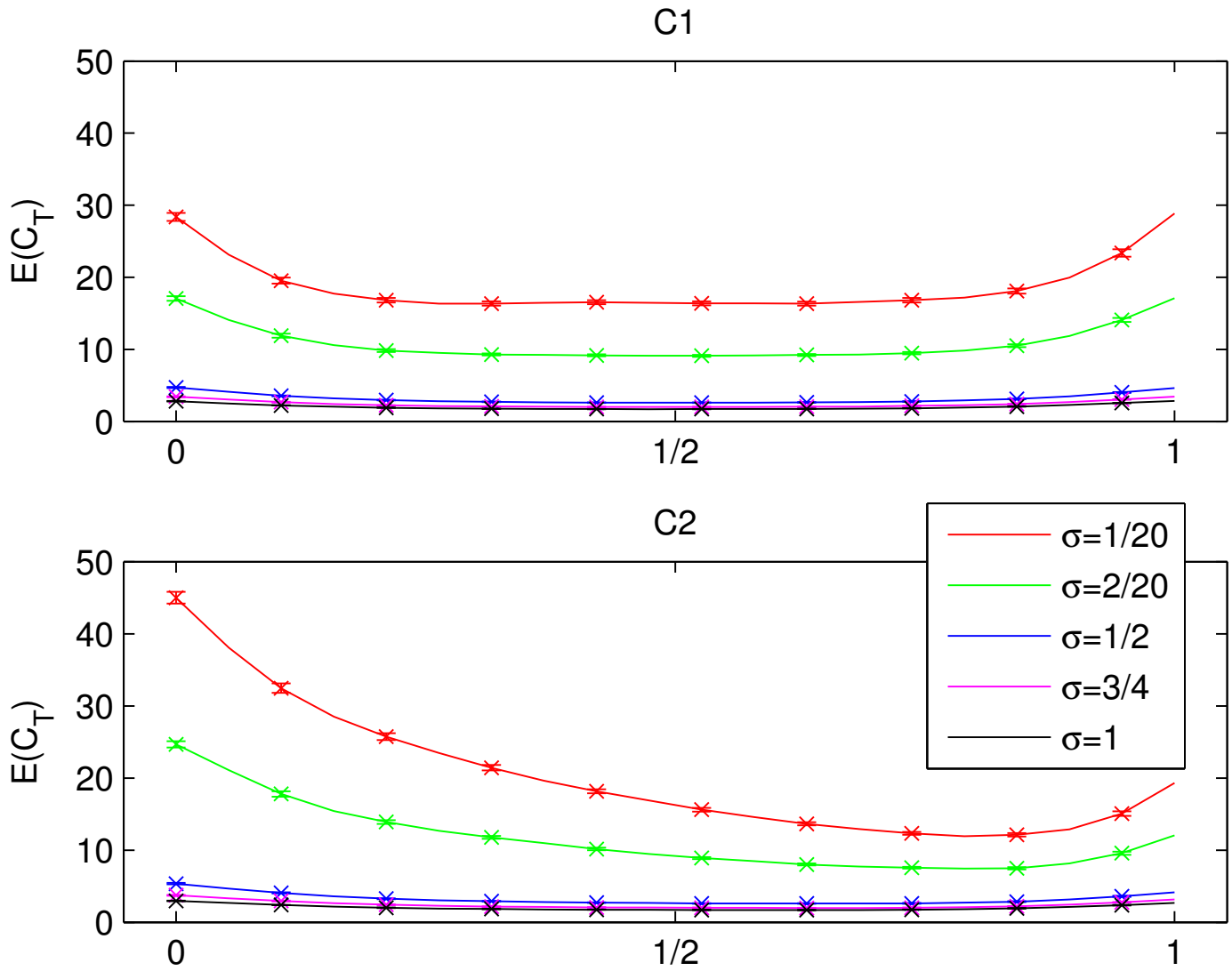


-Diffusion σ along the x-axis (assumed well-stirred in each yz-plane).

-In this case we compare with an *"unperturbed case"* with a birth-rate $k_E/2 \cdot (1 + 2x)$.
I.e. $\int k_E dV$ is unaffected and we can think of this as a *spatial* stochastic focusing.

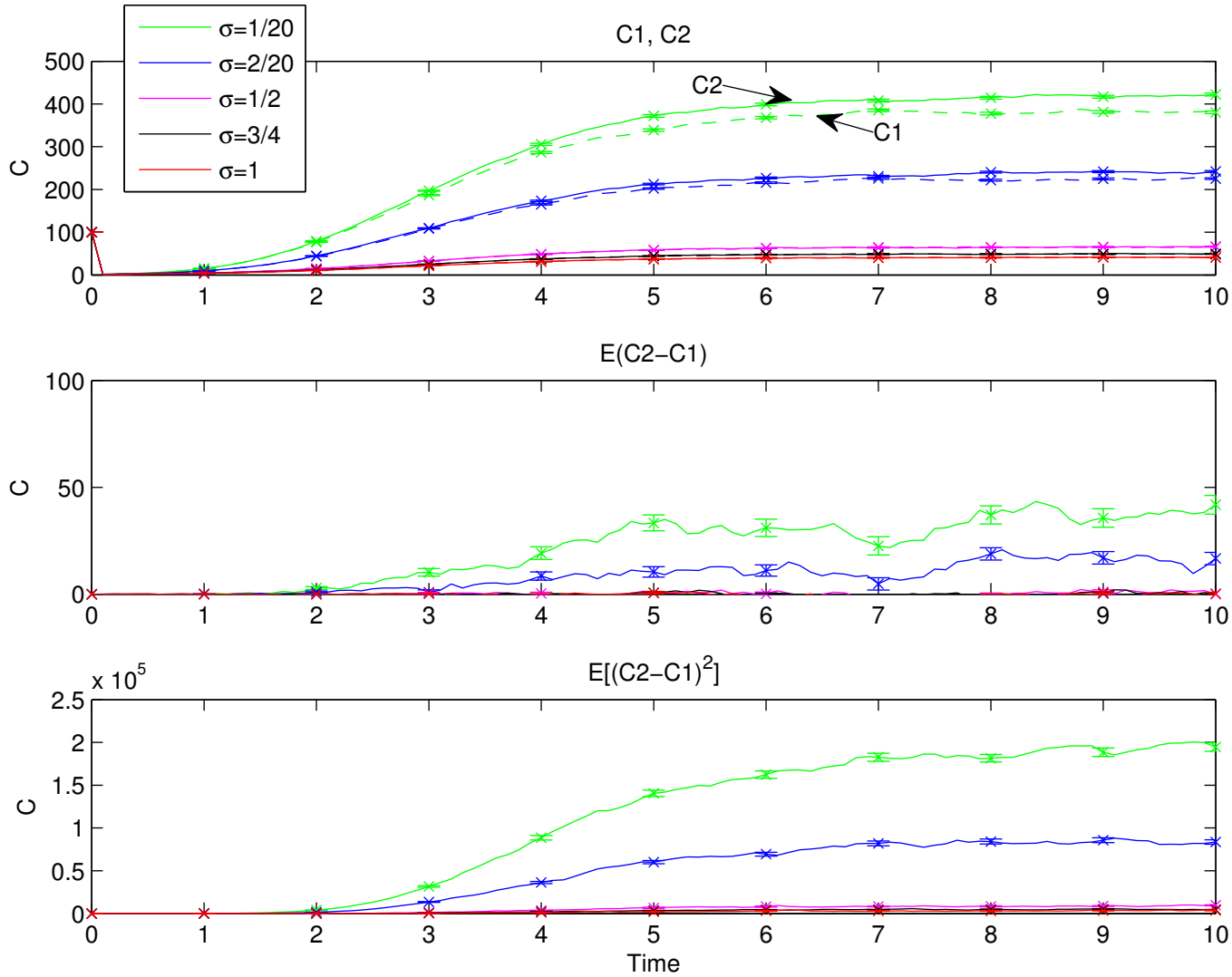
Results in 1D (cont)

Spatial profile



Results in 1D (cont)

Global effect



Optimal control of rates

As before,

$$C + E \xrightarrow{\nu\, C\cdot E} P + E,$$

$$\emptyset \underset{\mu_E E}{\overset{s(t)}{\rightleftharpoons}} E, \quad \emptyset \underset{\mu_C C}{\overset{k_C}{\rightleftharpoons}} C, \quad P \xrightarrow{\mu_P P} \emptyset,$$

hence E is now under *control* through the signal $s(t)$ (*"open-loop control"*).

-*Basic idea:* under evolutionary pressure we can expect an important chemical network inside a cell to be nearly optimal.

Optimal control of rates (cont)

Notion of optimality

Maximize

$$\mathcal{M}[P] := E\left[\int_0^T \varphi(P_t)\,dt\right],$$

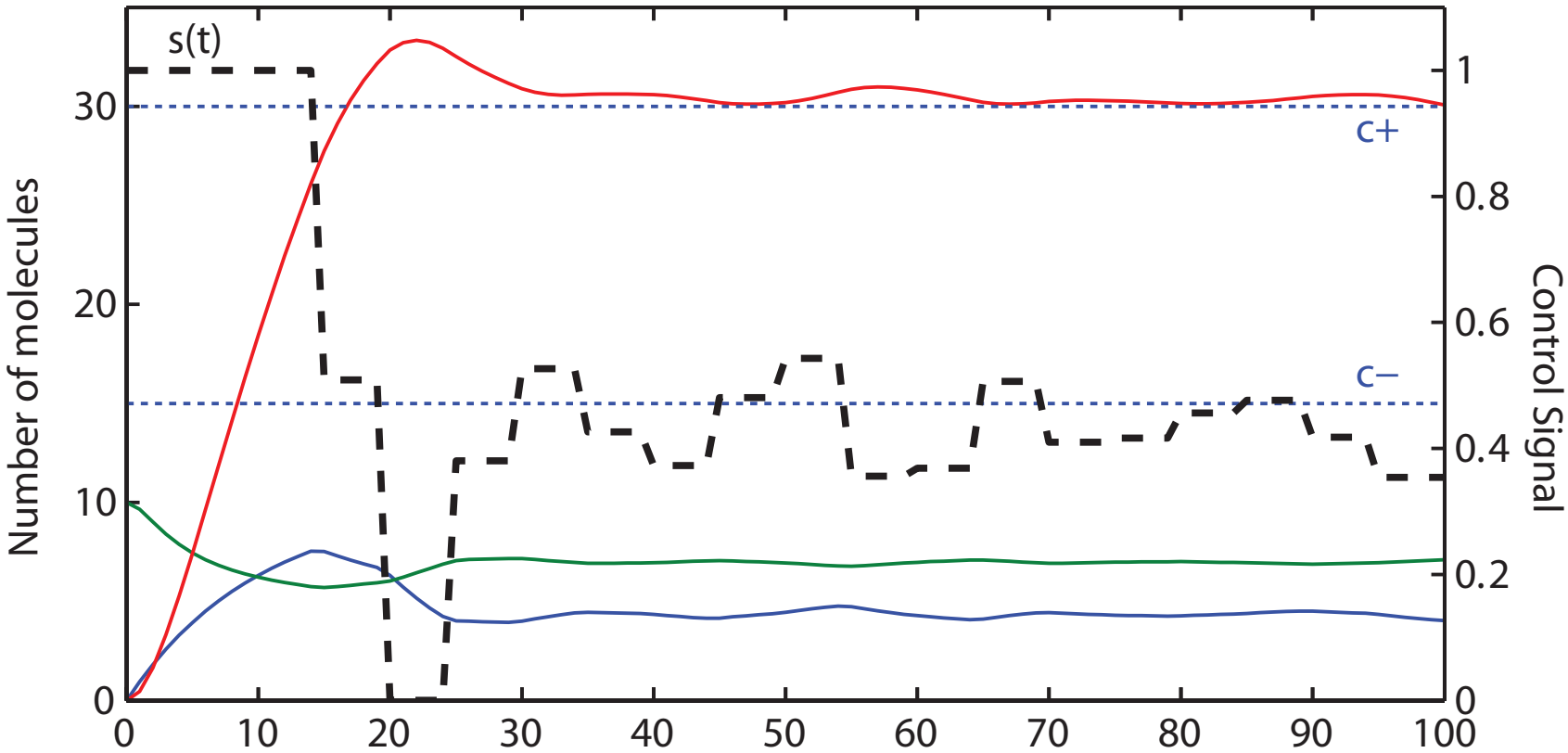
with a nonlinear *payoff function* $\varphi(P)$,

$$\left.\begin{array}{lcll} \varphi(P) & = & 0, & P \le c_- \\ \varphi(P) & = & \tau(P - c_-), & c_- < P \le C_+ \\ \varphi(P) & = & \tau(C_+ - c_-), & C_+ < P \end{array}\right\}$$

Constraints on the production signal s

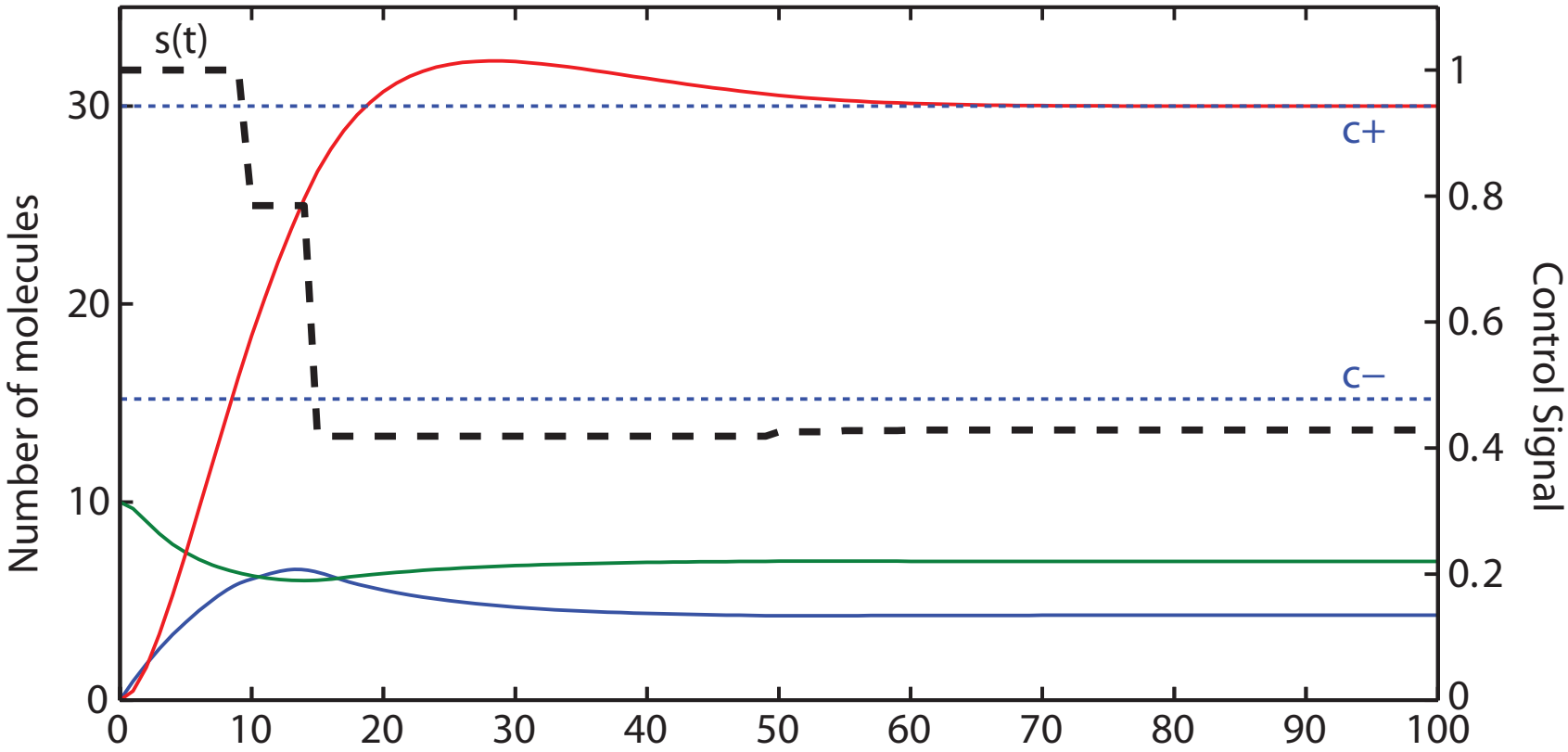
$$\left.\begin{array}{l} \max_{t\in[0,T]} s(t) \le S_\infty \\ \int_0^T s(t)\,dt \le S_1 \end{array}\right\}$$

Results



-Results from non-spatial deterministic ODE, solved by the Nelder-Mead simplex method.

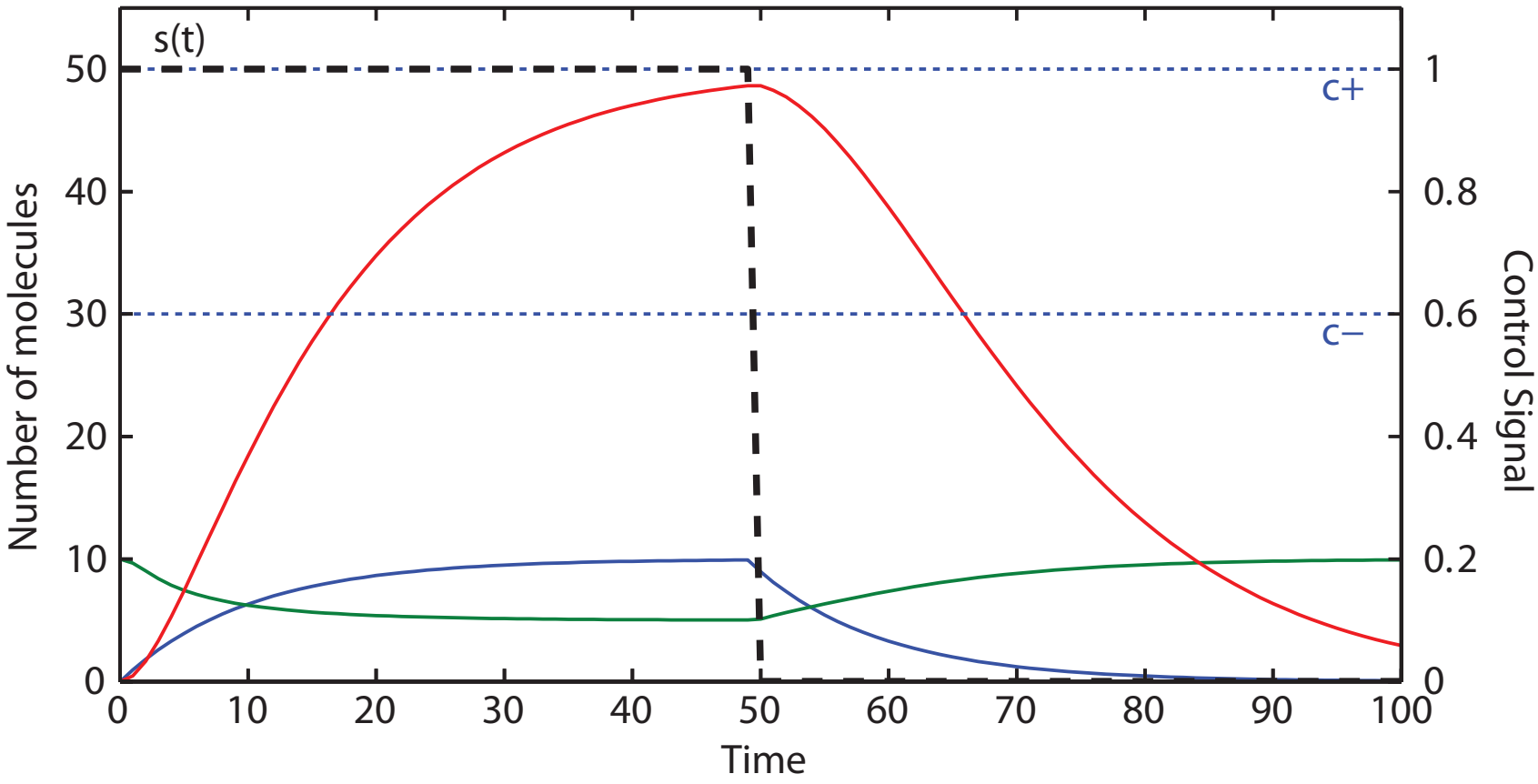
Results with penalty



$$\mathcal{M}_2[P] := \int_0^T \varphi(P_t) + \varepsilon |s'(t)| \, dt$$

Results

Boundary case



Stochastic case

Very little work to bring this particular set-up into the stochastic setting:

- Start with the solution obtained from the ODE-case.
- Fix N, the number of trajectories, *outside* the optimization routine (estimating the expectation with an average).
- Increase N after a solution was obtained.

Since we continuously evaluate small modifications to the control strategy, *removing noise is crucial* (or otherwise N must be very large).

Results: *ODE* → stochastic

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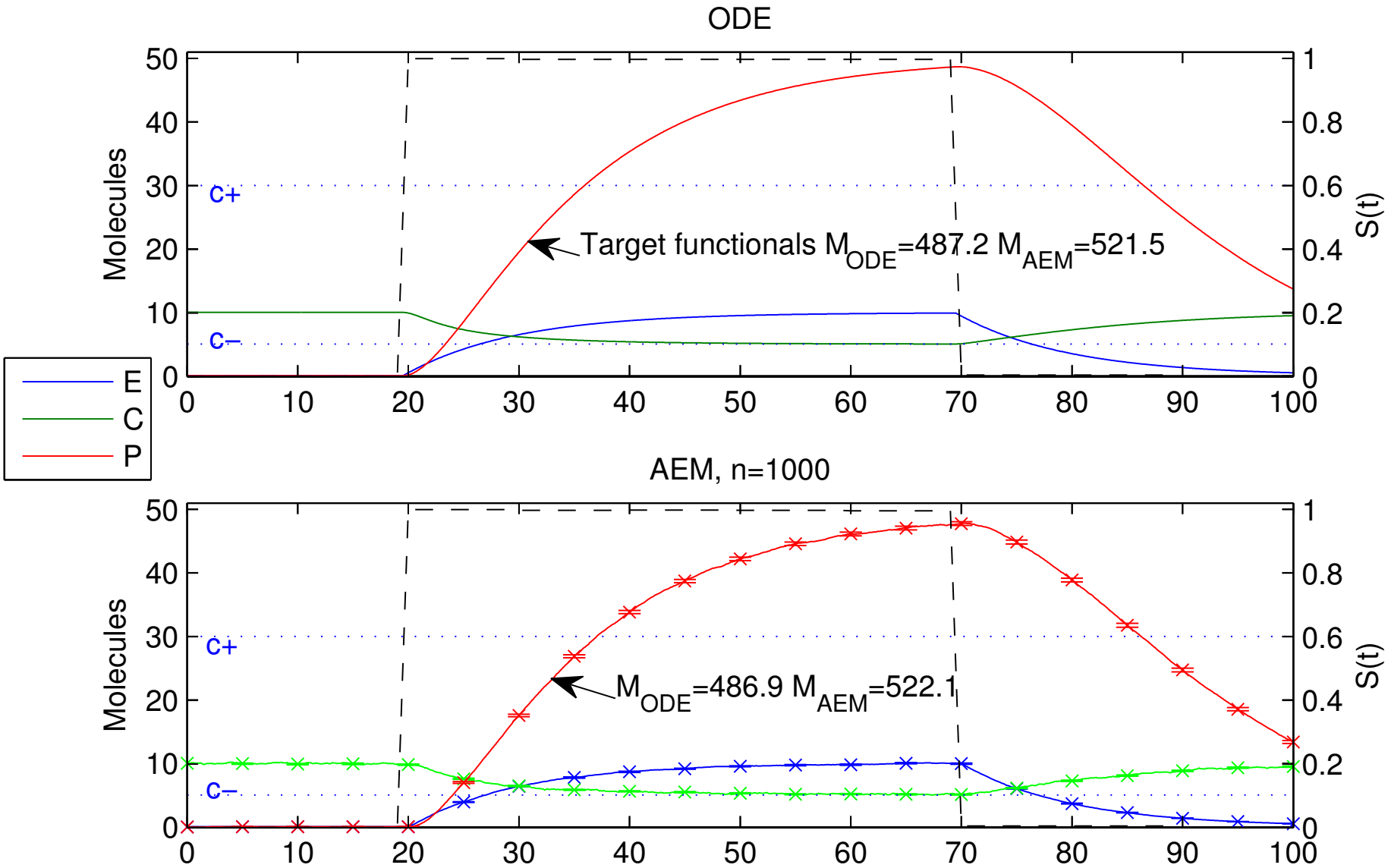

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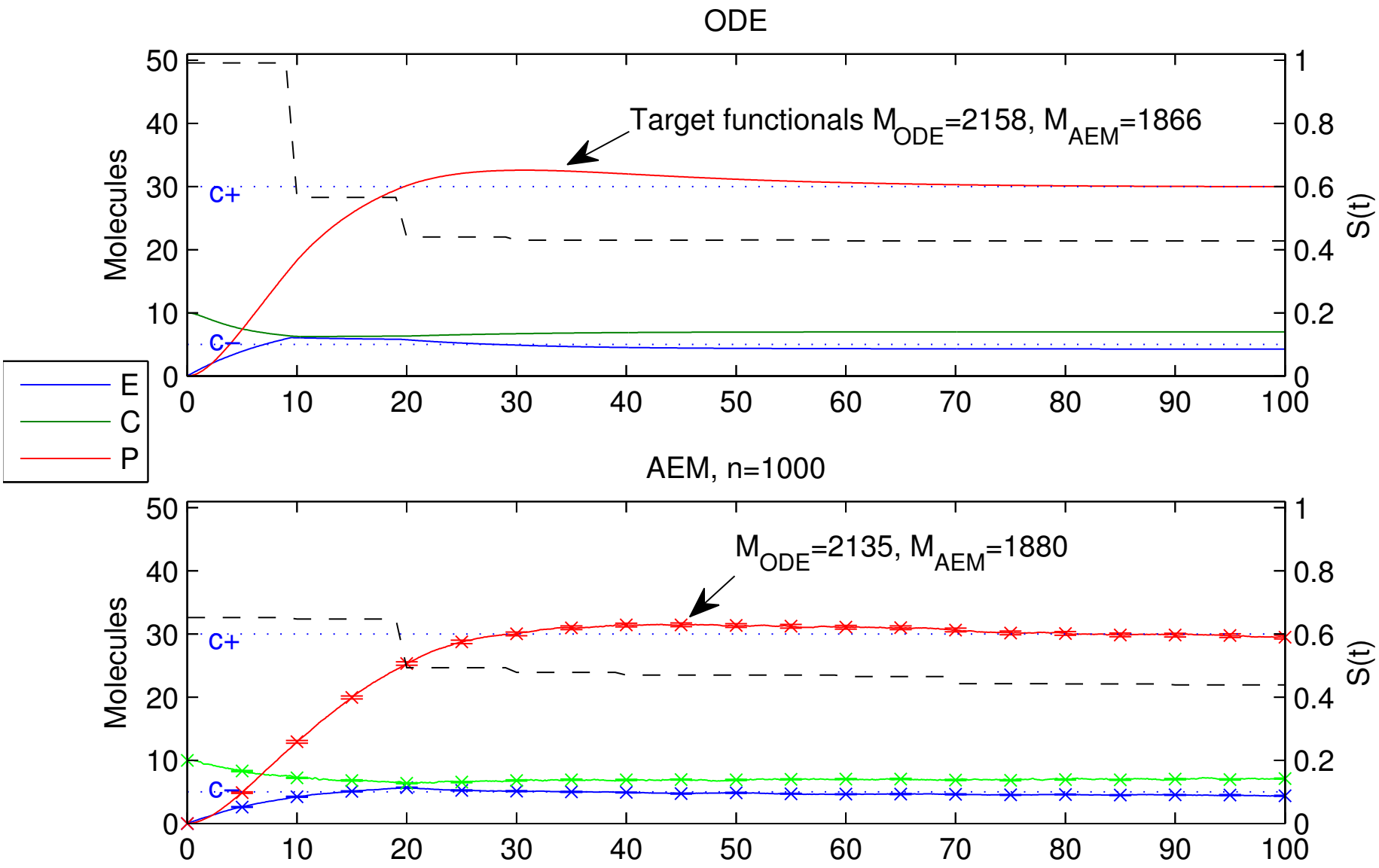

Summary & Conclusions

- (Spatial) Stochastic mesoscopic modeling in chemical kinetics can combine *simplicity* with *accuracy*
- Sensitivity computations and an implementation of an "All Events Method"; example of uses in forward computations as well as in backward/inverse formulations
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- Implemented in upcoming new release of free software URDME (`www.urdme.org`)
- Good model problems are a challenge to formulate (ideas are welcome!)...

Thank you for listening!