"Wireless" Networks of Systems Biology

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1. Interacting Networks Inside and Outside the Cell

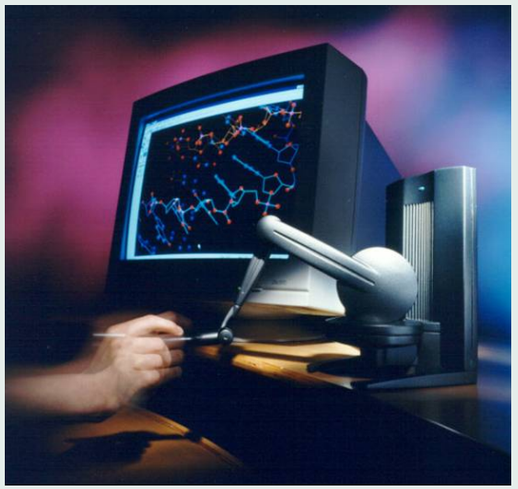
Systems biology brings ideas from engineering disciplines such as control theory and signal processing into molecular biology at the level of interaction networks or pathways.

Interesting details:

- Biological phenomena occurring in a living cell span over 8 orders of magnitude in space
- In addition: broad range of time scales
- Mixture of populations with different copy-numbers (high and low)
- Uncertainty in parameters due to the current limitations of experiential techniques

Goals:

- Call for *hybrid* and /or *multi-scale* simulation techniques
- Uncertainty must be incorporated into the simulation procedure as an inherent part of the process



2. Classical Reaction Kinetics

$$\mathsf{S}_1 + \mathsf{S}_2 \xrightarrow{k_r} \mathsf{S}_3,$$
$$\boldsymbol{\nu}_r = (-1, -1, +1)$$

From [TKurtz71,DTGillespie2001]:

$$\text{RandomCollisions} + \text{Well mixed} + \text{Large Populations} \Rightarrow \text{ClassicalChem.Kinetics}, \tag{1a}$$

$$\frac{dX_i}{dt} = \sum_{r=1}^{R} \nu_{ir} k_r h_r(\{X_i\}),\ X_i(t) \in \mathbb{R} \tag{1b}$$

- Simulations can be casted in terms of ODEs
- Classical CK works for conventional problems but biochemical networks have *stochastic effects as an intrinsic part of the problem*.

3. Stochastic Chemical Kinetics

In classical CK proteins are discrete objects, yet their effects are often modeled in terms of concentrations. This dichotomy must be resolved.

Populations are discrete and reaction events are random:

$$\mathsf{S}_1 + \mathsf{S}_2 \xrightarrow{k_r} \mathsf{S}_3$$

Now:

$$P(X_1 - 1, X_2 - 1, X_3 + 1, t + \Delta t | X_1, X_2, X_3, t) = k_r h(X_1, X_2)\Delta t + O(\Delta t^2), \tag{2}$$

$$X_i(t) = X_i(0) + \sum_{r=1}^{R} \nu_{ir} \underbrace{N_r(t)}_{counter} \tag{3}$$

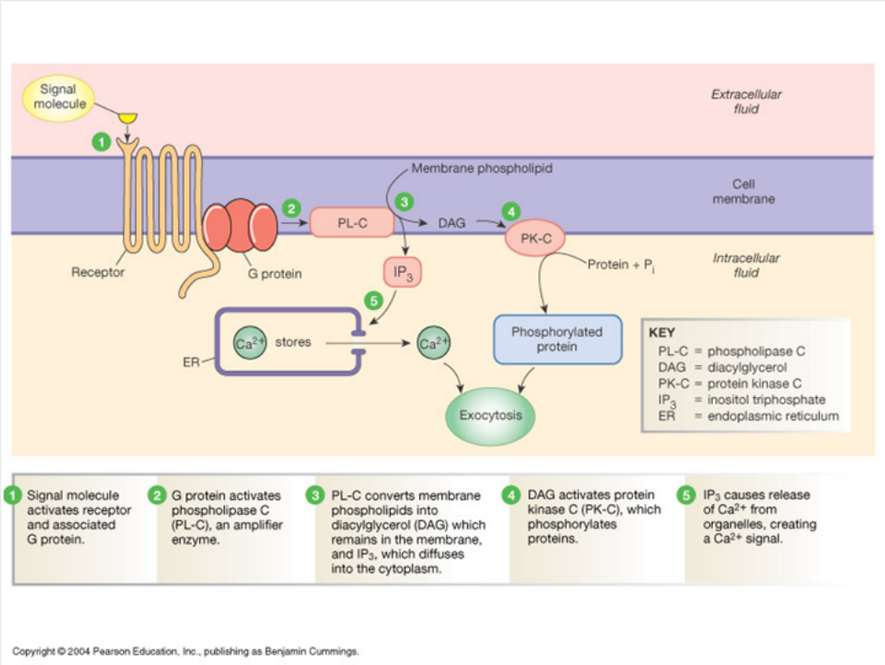
Reaction counters $N_r(t)$ are random and state dependent (think of 20$ “Rolex”)
Simulation technique:

- “Well-mixed” assumption is still important
- Kinetic Monte Carlo/Stochastic Simulation Algorithm [Bortz et.al.75, DTGillespie76]

4. Well-mixed Assumption: Reality or Fiction?

Importance of diffusion effects was known for a long time but was usually downplayed.

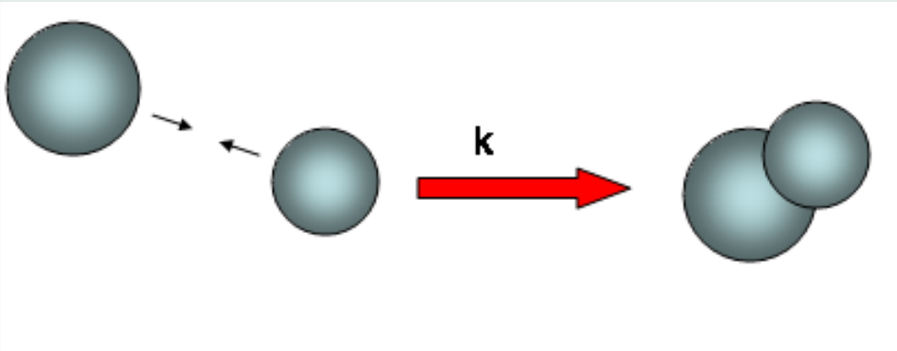
- The Stocks-Einstein relations implies slow liquid phase diffusion for many signal proteins
- Aspects of cell's physiology depend on the spatial signal range of secreted molecules
- "Join the Crowd" (cells are packed with proteis, complex sugars and nucleic acids)



- Most of the parameters required for the successful use of the current simulation techniques are not directly accessible from the experiments

5. Kinetic Rates

- the rate of reaction for proximate molecules, "intrinsic" k_0
- the facility with which molecules can diffuse



Kinetic rate [Smoluchowski35,Szabo89,AgmonSzabo91]:

$$k(t)|_{t\to\infty} \approx \frac{k_0 k_D}{k_0 + k_D}, \tag{4}$$

$k_0 -$ intrinsic binding rate, $k_D = 4\pi D r_\sigma$

$$k(t) = \begin{cases} k_D, & \text{if } \mathrm{k_0} \gg \mathrm{k_D} \\ k_0, & \text{if } \mathrm{k_D} \gg \mathrm{k_0} \end{cases} \tag{5}$$

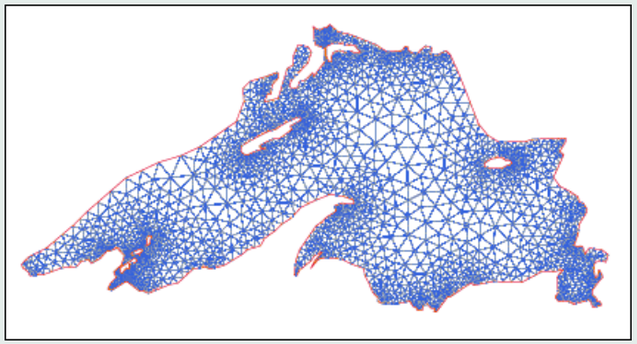
- Reversible reactions are "many body problems" [AgmonSzabo91,SAndrews2004]

6. Two poles of the (computational) world

6.1. Space

Spatial dynamics of the concentration $u(t, \mathbf{x})$ (PDE):

$$du/dt = \underbrace{\mathcal{A}u}_{D\Delta u - \mathbf{V}\nabla u}$$

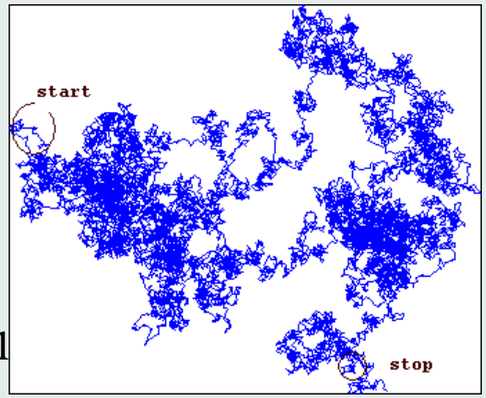


- Discrete finite elements; finite time steps
- Requires adaptive mesh generation
- Boundary conditions included as linear constrains
- Solves *spectral problem* $\{\lambda_n, e_n(\mathbf{x}), \mathbf{x} \in \mathcal{D}\}$:

$$\mathcal{A}e_n(\mathbf{x}) = -\lambda_n^2 e_n(\mathbf{x}), \langle e_n, e_m \rangle = \int_{\mathcal{D}} d\mathbf{x} e_n(\mathbf{x}) e_m(\mathbf{x}) = \delta_{nm}$$

Stochastic Brownian dynamics:

$$d\mathbf{x} = a(\mathbf{x})dt + \sigma d\mathbf{w}, \; u(t, \mathbf{x})dx = \mathbb{E}(1_{[\mathbf{x}, dx]}(\mathbf{x}(t)))$$



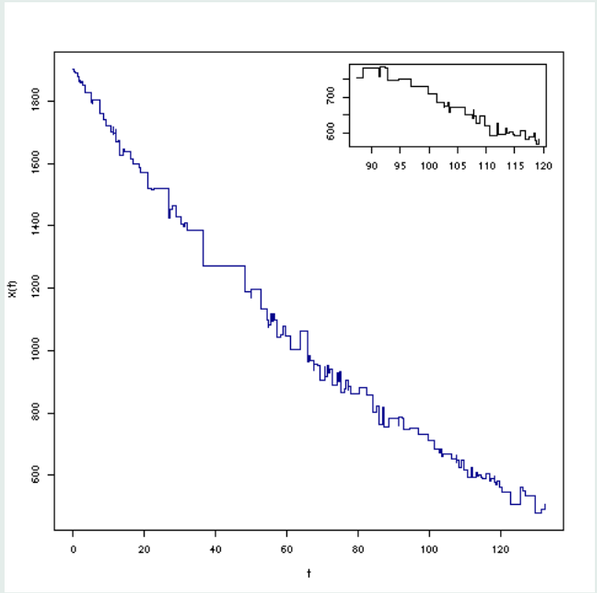
- Allows to trace motion of individual particles
- Fixed time step, no mesh generation
- Boundary conditions may be tricky to deal with
- Collision detection-> small time step in general ($10^{-3}\frac{r_\sigma^2}{D}$)

7. Two poles of the (computational) world(contd.)

7.1. Reaction events

SSA/KMC:

- Construction of $N(t)$ by (SSA/KMC) is *exact*
- Intensive when close to deterministic case



8. Bringing two poles together. . .

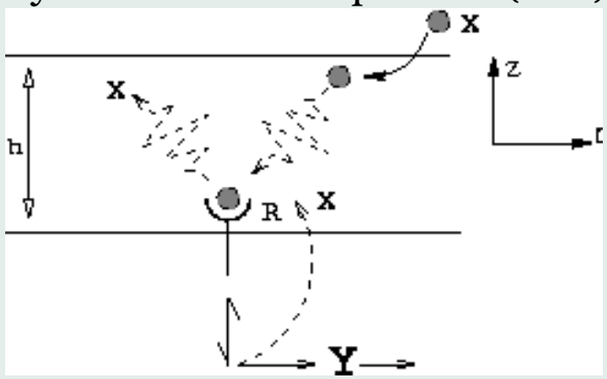
...is a hard problem

- Sub-volume method (divide the reaction volume into small "well-mixed" sub-volumes) [Gardiner,Stundzia&Lumsden96, Mesord2005,...]
- Smoluchowski dynamics (discrete time-step)[AndrewsBray2004]
- Smoluchowski dynamics (random-time step): Green Function RD [tenWolde2005]. Method uses analytical results to perform large time steps.

Separation of time scales plays a crucial role.

9. Signalling Example

System includes species X(diff.), R, XR and Y.



$$r = 1, 2 : \mathsf{X} + \mathsf{R} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathsf{XR}, \qquad (7a)$$

$$r = 3 : \mathsf{XR} \overset{k_3}{\rightarrow} \mathsf{X} + \mathsf{R} + \mathsf{Y}, \qquad (7b)$$

$$r = 4 : \mathsf{Y} \overset{k_4}{\rightarrow} (\dots) \qquad (7c)$$

$$\#X = n_0,\ \#R = n_1,\ \#XR = n_2,\ \#Y = n_3,\ n_1 + n_2 = 1$$

Typical parameters:
$k_1 = 3 \times 10^8 M^{-1}s^{-1}$, $k_2 = 0.05s^{-1}$, $D = 0.1\mu\mathrm{m}^2/\mathrm{s}$, $h = 1\mu\mathrm{m}$, $R = 50\ \mu\mathrm{m}$, κ-"stickiness" of the walls

10. Questions

- Is spatial nature of signalling important?
- Are there any delays in signal transmission due to the diffusion?
- What can we gain adding randomness of diffusion into the picture? (Distribution of signal arrival times)
- Discuss the place of well mixed assumption in this picture

11. Spectral decomposition

Time scales of diffusion can be characterized via *spectral approach* and collection of *modes*:

$$\Delta e_{nm}(r,z) = -(k_n^2 + k_m^2) e_{nm}(r,z), \tag{8a}$$

$$\text{subject to } : \frac{\partial e_{nm}(r,z)}{\partial z}|_{z=0,h} = \frac{\kappa}{D} e_{nm}(r,z)|_{z=0,h}, \quad n,m = 1,2,\ldots, \tag{8b}$$

$$\lambda_{nm} = D(k_n^2 + k_m^2) \tag{8c}$$

- Can be found analytically for a given geometry
- numerically otherwise

12. Yet another attempt to bring R& D together: Stochastic PDEs

- It is hard if not impossible to represent the stochastic RD processes in term of the smooth concentration field $u(t, \mathbf{x})$
- Discrete noise sources $\Theta(t, \mathbf{x})$ are localized in space (near receptor: $\theta(\mathbf{x}) \propto 1_{|\mathbf{x}<r_\sigma|}$):

$$\Theta(t, \mathbf{x}) = \theta(\mathbf{x}) \sum_{r=1}^{4} \nu_{0r} \underbrace{N_r(t)}_{state\ depend.} \tag{9}$$

- *Weak solution* of SPDE [KullinapurXiong98]; $\forall f$

$$\langle f, du(t, \mathbf{x}) \rangle = \langle f, \mathcal{A}u(t, \mathbf{x}) \rangle + \langle f, d\Theta(t, \mathbf{x}) \rangle \tag{10}$$

If $\{e_{nm}\}$ are orthogonal then we define projected dynamics:

$$\langle e_{nm}, u \rangle = u_{nm}(t), \tag{11}$$

$$\langle e_{nm}, \theta \rangle = \theta_{nm} \tag{12}$$

13. Some Technical details: Spectral Finite Elements

- Choose not to model spatial dynamics in details, instead approximate it by the *finite* subset of the base functions ($n = 1 \dots N_r, m = 1 \dots N_z$).
- Result (jump-SDE system $N_r \times N_z + 3$)

$$du_{nm} = \underbrace{-\lambda_{nm} u_{nm}(t) dt}_{diff.} + \theta_{nm} \sum_{r=1}^{4} \nu_{0r} dN_r(t | u_{nm}(t_-), n_i(t_-)), \tag{13}$$

$$dn_i(t) = \sum_{r=1}^{4} \nu_{ir} dN_r(t | u_{nm}(t_-), n_i(t_-)), \ i = 1 \dots 3 \tag{14}$$

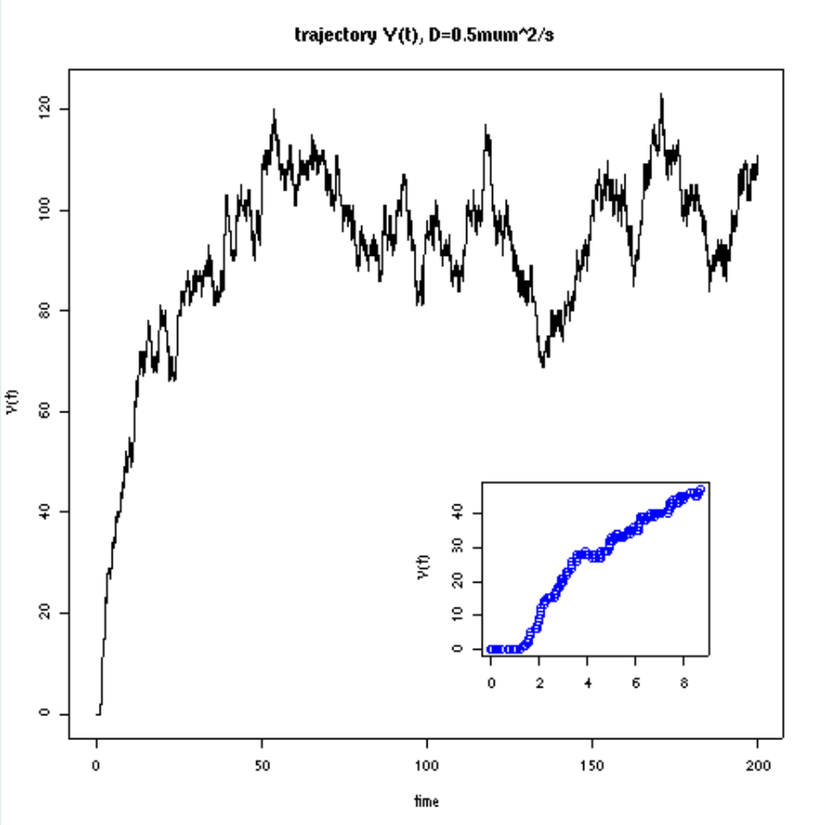
- Diffusion modes $\{u_{nm}(t)\}$ and discrete states n_{1-3} a coupled through reaction counters $N_r(t)$ (their intensities).
- System is stiff (λ_{nm} grow fast) but simulation can be performed via modofied Direct SSA (i.e. generate jump time, propagate diffusion modes)
- Error: depends mostly on N_r, N_z

14. Well-mixed assumption and Spectral Finite Elements

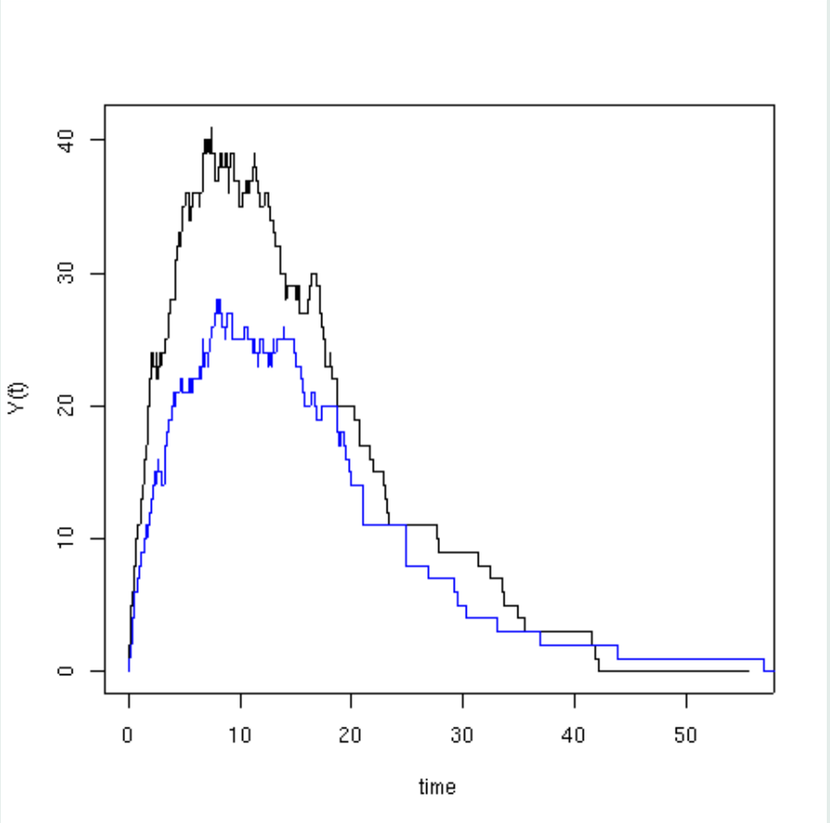
- As diffusion goes up ($D \to \infty, \kappa \approx 0$) only low level mode survives: $\lambda_{00} \approx 0,\ \theta_{00} \propto 1/V$
- One recovers "well-mixed" situation in a singular limit

15. Influence of diffusion and environment

$(N_r = N_z = 10)$

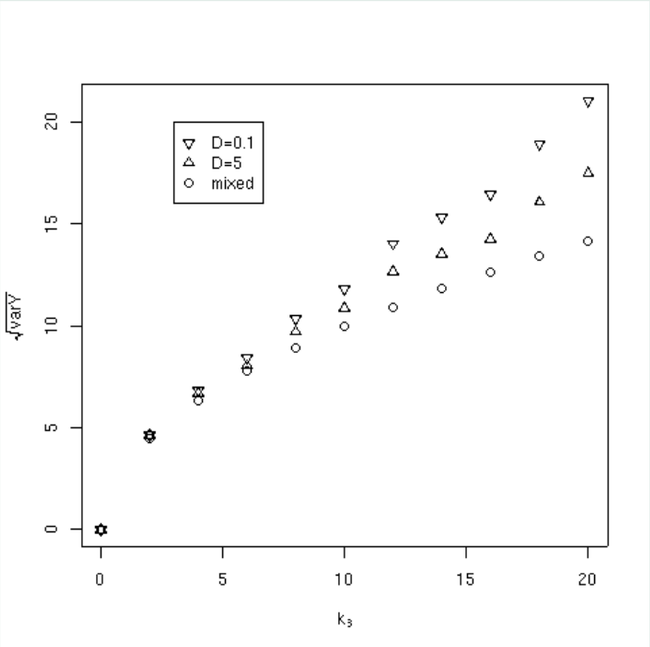


Delays in signal transduction
$(h^2/D \geq (k_3 + k_1 N_X/V)^{-1})$



Role of the κ

16. Variance of a signal



Increse of the noise at finite rates of diffusion at increased k_3

17. Conclusions

- Biochemical networks process signals in time via distributed / ”wireless” units
- Use of CME is limited for biochemcial networks
- Hybrid simulation can serve as a tool for exploring the sources and nature of the stochastic behavior

18. Acknowledgments

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