An alternative modeling of biological signaling networks

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The facts

Goal: Understanding how cells manage to respond properly to noisy signals from its environment

- Extra-cellular information is transmitted through cell-membrane receptors
- The receptors are activated or repressed by *ligands* —hormones, neurotransmitters, growth factors...
- Receptors trigger complex time-dependent cascades of internal cellular biochemical transformations
- These transformations lead to different cellular responses —cell-cycle, cell arrest, cellular suicide, etc.

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- Signaling pathway: components linked by activation/repression actions
- They must contain sophisticated control mechanisms preventing inappropriate responses leading to diseases, like cancer.
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- Several signaling pathways databases are available
- Information is usually presented as an oriented graph:
  - nodes: pathway components or group of components
  - (oriented) edges: interaction like activation or repression
- Usually no detailed information about biochemical mechanisms behind the interactions
- Each oriented edge may involve several different processes (regulations of gene transcription/translation, protein transformations, transport,...)

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The models

The qualitative continuous-time behavior of signaling networks is well grasped by differential equations

These differential equations provide a general framework —based on dynamical systems ideas— to analyze cellular behavior

Key issue: derive these equations starting from models of cellular processes.

The usual modeling approach —based in chemical kinetics— involves too many assumptions impossible to check at present

We seek an alternative approach

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Our models

- Cellular biochemical network with k types of molecules
- Each type is in one of two states, ex. *active* or *inactive*
- There is a large number N of molecules of each type
- The collective state of the kN molecules evolves like a continuous-time Markov process
- *Asymmetric* interactions between types (type A may be triggered by type B but not conversely)
- Because of this asymetry the resulting spin-flip process is not an usual finite-volume stochastic spin model
- Any molecule may interact with any other (consistent with the biochemical motivation; "mean-field" character)

These are the *type-dependent interaction models*

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Main result

We focus on the (k-dimensional) density of active molecules

Its dynamics defines the so-called *density-profile process*:

- Random walk jump-processes in $\mathbb{R}^k$
- Jumps of size $1/N$
- Expected drift velocity $V(x)$ does not depend on N

Main theorem:
The paths of such a process converge almost surely to the trajectories of the dynamical system with velocity field V

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Spin configurations

- Discrete set Λ of *sites*; $|\Lambda| = N$
- Finite set $\mathcal{T} = \{1, \ldots, k\}$ of *types*

Configuration space

Each type $i \in \mathcal{T}$ present at each *site* $\ell \in \Lambda$

$$\Sigma = \{-1, +1\}^{\mathcal{T} \times \Lambda}$$

If $\eta \in \Sigma$,

$$\eta(i, \ell) = \left\{ \begin{array}{c} +1 \\ -1 \end{array} \right\} \text{ if particle of type } i \text{ at site } \ell \text{ is } \left\{ \begin{array}{c} \text{active} \\ \text{inactive} \end{array} \right\}$$

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Spin-flip rates

Only single spin flips are allowed

Rate for $\eta \to \eta^{(i,\ell)}$ (type i flipped at site ℓ)

$$c(i,\ell,\eta) = \exp\Big\{-\Big[H_i(\eta^{(i,\ell)}) - H_i(\eta)\Big]\Big\}$$

with

$$H_i(\eta) = -\sum_{\ell\in\Lambda}\left(\sum_{(j,n)\in\mathcal{T}\times\Lambda}\frac{\alpha_{ji}}{|\Lambda|}\,\eta(j,n)\,\eta(i,\ell) + a_i\,\eta(i,\ell)\right).$$

- *Mean-field* interaction
- α_{ji} = strength of the influence of type j on type i
- a_i = type-dependent external field
- Most interesting phenomena: α not symmetric

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Density profiles

Let $x = (x_1, \ldots, x_k)$ be the vector of *empirical densities*

$$x_i(\eta) = \frac{|\{\ell \in \Lambda : \eta(i,\ell) = +1\}|}{N}$$

Rate of activation of type i at an inhibited site

$$\lambda_i(x) = \exp\left\{2\left(\sum_{j\in\mathcal{I}} \alpha_{ji}\, x_j + a_i\, x_i\right)\right\}$$

Rate of inhibition of type i at an active site

$$\mu_i(x) = \exp\left\{-2\left(\sum_{j\in\mathcal{I}} \alpha_{ji}\, x_j + a_i\, x_i\right)\right\}$$

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Density profile process $\{m_t^{x^0 N}\}_{t\geq 0}$

Process followed by the empirical densities

Continuous-time jump-process in the hypercube $\mathcal{D}_N = (-\frac{1}{N}, 1+\frac{1}{N})^k$.

At each jump, a point x changes its i-th coordinate by $1/N$ or $-1/N$ with respective rates $N f_i(x)$, $N g_i(x)$:

$$\begin{aligned} f_i(x) &= (1-x_i)\,\lambda_i(x) \\ g_i(x) &= x_i\,\mu_i(x) \end{aligned}$$

for $0 \leq x_i \leq 1$

$\{m_t^{x^0 N}\}_{t\geq 0}$ = process starting at x^0

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Dynamical system $\{x_t^{x^0}\}_{t\geq 0}$

Let $V : \mathbb{R}^k \longrightarrow \mathbb{R}_+^k$ be the *velocity field* associated to $\{m_t^{x^0 N}\}_{t\geq 0}$:

$$V(x) = \lim_{t\downarrow 0} \frac{\mathbf{E}(m_t^{xN} - x)}{t} = f(x) - g(x) \ ,$$

Let $\{x_t^{x^0}\}_{t\geq 0}$ be the solution of the dynamical system

$$\dot{x}_t = V(x_t)$$

starting at $x^0 \in (0,1)^k$

[The global trajectory exists by the smoothness of the field V and the flow does not leave $(0,1)^k$ because $V_i(0^+) > 0$ and $V_i(1^-) < 0$ for $i = 1, \ldots k$]

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Main result

Convergence of the sequence of density profile processes $(m_t^{x^0 N})_N$ to the trajectory $x_t^{x^0}$

For $\epsilon > 0$ let τ_ϵ^N be the stopping time

$$\tau_\epsilon^N = \inf\left\{ t \geq 0 : |m_t^{x^0,N} - x_t^{x^0}| > \frac{1}{N^{\frac{1}{2}-\epsilon}} \right\}$$

Write $\mathcal{A}_{N\epsilon}^T = \{\tau_\epsilon^N < T\}$

Theorem

For any finite T, initial position x^0 and $\epsilon > 0$,

$$P\left(\overline{\lim_N} \mathcal{A}_{N\epsilon}^T\right) = 0$$

[For typical realizations there exists $N_{\epsilon,T}$ s.t. for $N > N_{\epsilon,T}$ every $\{m_t^{x^0 N}\}_{t\geq 0}$ stays up to time T within $N^{-1/2+\epsilon}$ of the deterministic path $\{x_t^{x^0}\}_{t\geq 0}$]

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Example: Cyclic-interaction model

Ingredients

- Think $\{1, \ldots, k\}$ as points on the circle
- $c(i) =$ counter-clockwise nearest-neighbor of i
- $\alpha_{ji} = s_i J$ if $j = c(i)$, 0 otherwise
- $s_i \in \{-1, +1\}$ represents the signals, and $J > 0$
- $a_i = -J/2$

Features

- For fixed $\{s_i\}_{i=1}^k$ the only free parameter is J
- If $s_i = 1$, the rate for type i to flip from -1 to $+1$ increases with $x_{c(i)}$: Type $c(i)$ *activates* the production of type i
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Bifurcations on the cyclic-interaction model

Dynamical system:

$$\dot{x}_i = e^{s_i J(x_{c(i)} - \frac{1}{2})} - x_i \left(e^{s_i J(x_{c(i)} - \frac{1}{2})} + e^{-s_i J(x_{c(i)} - \frac{1}{2})} \right) \qquad (4.1)$$

- J small: single stable eq. point at $\mathbf{\frac{1}{2}} = (\frac{1}{2}, \ldots, \frac{1}{2}) \in \mathbb{R}^k$, $\forall s_i$
- J large: behavior depends on the sign of $s = \Pi_{i=1}^{k} s_i$
  - For $s = -1$ (*frustrated*): Hopf bifurcation for $J \geq J_c(k)$
  - For $s = +1$: behaves as the *Curie-Weiss* model

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Formal bifurcation result

Theorem

For the system (4.1) with $k \geq 3$

(a) *If* $s = 1$, *there is a bifurcation at* $J_c = 2$*: the fixed point* $\mathbf{\frac{1}{2}}$ *looses stability and two stable points appear for* $J > J_c$.

(b) *If* $s = -1$, *there is a Hopf bifurcation at* $J_c = 2/\cos(\pi/k)$.

For instance, if $k = 3$ and all interactions are antiferromagnetic ($s_i = -1$ for $i = 1, 2, 3$), the dynamical system has stable orbits for $J > J_c = 4$

The convergence result, implies that, within any finite time interval, the density-profile process evolves as close to this orbit as wished, for N sufficiently large.

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Main mathematical steps in the proof

(i) A coupled simultaneous construction of density-profile processes for different N.

(ii) An auxiliary process $\{\widehat{m}_t^{x^0,N}\}_{t\geq 0}$ with independent flips (but time-dependent rates) which shadows the deterministic dynamical system

(iii) A coupling between auxiliary and density-profile processes keeping both processes as close as possible:

- Instants where they move further apart define a process of *discrepancies*
- Bounds on the rate of these discrepancies yield the convergence theorem

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First step: Auxiliary process $\{\widehat{m}_t^{x^0,N}\}_{t\geq 0}$

Independent spins flips but *time-dependent rates*

Ingredients

- kN independent Markov chains with state space $\{-1,+1\}$
- Each type of a spin at i flips

$$\begin{matrix} -1 \to +1 \\ +1 \to -1 \end{matrix} \quad \text{with rate} \quad \begin{matrix} \lambda_i(x_t^{x^0}) \\ \mu_i(x_t^{x^0}) \end{matrix}$$

- Chains initialized with the uniform distribution on configurations with profile $m(\eta_0) = x^0$
- $\{\widehat{m}_t^{x^0,N}\}_{t\geq 0}$ is the corresponding density-profile process

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$$\begin{matrix} -1 \to +1 \\ +1 \to -1 \end{matrix} \quad \text{with rate} \quad \begin{matrix} \lambda_i(x_t^{x^0}) \\ \mu_i(x_t^{x^0}) \end{matrix}$$

- Chains initialized with the uniform distribution on configurations with profile $m(\eta_0) = x^0$
- $\{\widehat{m}_t^{x^0,N}\}_{t\geq 0}$ is the corresponding density-profile process

Features

- Total number of spins of type i fixed and equal to x_i^0
- Independent initial densities $m_1(\eta_0), \ldots, m_k(\eta_0)$
- Each $p_t(i,n) = P(\eta_t(i,n) = +1)$ satisfies Kolmogorov's

$$\dot{p}_t(i,n) \;=\; [1 - p_t(i,n)]\,\lambda_i(x_t^{x^0}) - p_t(i,n)\,\mu_i(x_t^{x^0})$$

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Convergence of $\{\widehat{m}_t^{x^0,N}\}_{t\geq 0}$

We are interested in following the actual empirical densities

Lemma

For $\delta > 0$ there exists $c > 0$ such that, for $t \geq 0$

$$P\left(\left|\widehat{m}_t^{x^0,N} - x_t^{x^0}\right| > N^{\delta-1/2}\right) \;<\; \exp(-cN^{\delta})$$

[Proof uses another auxiliary process defined as $\{\widehat{m}_t^{x^0,N}\}_{t\geq 0}$ but initial spins chosen independently with $P(\eta_0(i,n) = +1) = (x^0)_i$]

To prove the theorem: show that $\widehat{m}_t^{x^0,N}$ and $m_t^{x^0,N}$ remain close

We couple both evolutions through a graphical construction

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Step II: Graphical construction

- At each site y: $2k$ independent Poisson processes

$$\begin{matrix} N_t^{i+}(y) \\ N_t^{i-}(y) \end{matrix} \quad \text{with rate} \quad \begin{matrix} f_i(y) \\ g_i(y) \end{matrix}$$

- Marks associated to $N_t^{i+}(y)$ ($N_t^{i-}(y)$) instruct jumps in the positive (negative) i coordinate direction
- Resulting open paths determine process $\{g_t^{x^0,N}\}_{t\geq 0}$
- As rates differ by N: $m_t^{x^0,N} = g_{Nt}^{x^0,N}$

  [*density-profile time* $t \leftrightarrow$ *graphical-construction time* Nt; graphical-construction time is *slower* by a factor N]

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Main coupling

We couple $m_t^{x^0,N}$ and $\widehat{m}_t^{x^0,N}$ through the graphical construction

Properties of the coupling

- The relative distance of processes kept whenever possible
- As rates are different, asynchronous moves take them apart
- Coupling designed so to minimize this asynchrony

Sketch of its construction

- Several Poissonian mark-processes at each site, updated at asynchronous moves
- Successive times of these moves: stopping times τ_n, $n \geq 1$
- Recursive definition within time intervals $[\tau_{n-1}, \tau_n)$
- Construction defines $g_t^{x^0,N}$ and $\widehat{g}_t^{x^0,N}$ $[= m_{t/N}^{x^0,N}$ and $\widehat{m}_{t/N}^{x^0,N}]$

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Initial stage of the coupling

For each site y and type i define six types of marks:

- For the transition $y \to y + \frac{e_i}{N}$,
  - With rate

$$\widehat{u}_t^{i,+}(y) \;=\; \min\big\{(1-y_i)\,\lambda_i(y)\,,\,(1-y_i)\,\lambda_i(x^{x^0}_{t/N})\big\}$$

    both $g_t^{x^0,N}$ and $\widehat{g}_t^{x^0,N}$ jump

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Initial stage of the trajectory

- Start with $g_0^{x^0} = \widehat{g}_0^{x^0} = x^0$
- Stop at the first discrepancy:

$$g_{\tau_1}^{x^0,N} = x^1 \quad , \quad \widehat{g}_{\tau_1}^{x^0,N} = x^1 + \Delta^1$$

(defines τ_1 and Δ_1)

Second stage of the coupling

New marks

- For the transition $y \to y + \frac{e_i}{N}$,
  - With rate

$$\widehat{u}_t^{i,+}(y, \Delta^1) \;=\; \min\left\{(1 - y_i)\,\lambda_i(y)\,,\,(1 - y_i - \Delta_i^l)\,\lambda(x^{x^0}_{t/N})\right\}$$

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$$g_{\tau_2}^{x^0,N} = x^2 \quad , \quad \widehat{g}_{\tau_2}^{x^0,N} = x^2 + \Delta^2$$

(defines τ_2 and Δ_2)

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(defines τ_2 and Δ_2)

Discrepancy process

The construction is continued, for each trajectory, until $t = NT$

This involves, almost surely a finite number of stages

The counting of discrepancies defines a *discrepancy process* $\overline{D}_t$:

$$\{\overline{D}_t \geq l\} = \{\tau_l \leq t\}$$

As each discrepancy brings an additional separation of $1/N$,

$$\left| m_t^{x^0,N} - \widehat{m}_t^{x^0,N} \right| \leq \frac{\overline{D}_{Nt}}{N}$$

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Conclusion of the proof

Technical part: It involves a bound on discrepancy rates

Lemma

Let R_t^l be the instantaneous rate of the level-l discrepancy process D_t^l, $t \in [\tau_l, \tau_{l+1}]$. Then, almost sure,

$$R_l \leq N^{\delta - 1/2} + \frac{A\, l}{N}$$

for N large

Finally

Lemma

For any $\varepsilon > 0$ and $0 \leq t \leq T$,

$$P\Big(\overline{\lim_N}\big\{\overline{D}_{NT} \geq N^{\varepsilon + 1/2}\big\}\Big) \;=\; 0\,.$$

Final (obvious) questions

- Application to actual signaling networks?
- Use as a simulation tool of differential equations?