Learning PDE model reductions/ moment closures of stochastic reaction-diffusion dynamics

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NIH
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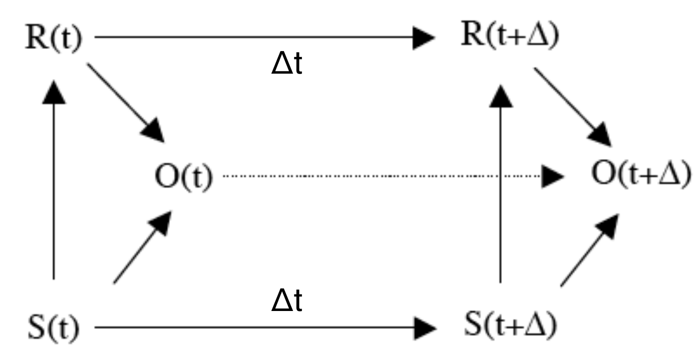
Mapping: Model reduction



[Johnson, Bartol, Sejnowski, and Mjolsness. Physical Biology 12:4, July 2015]

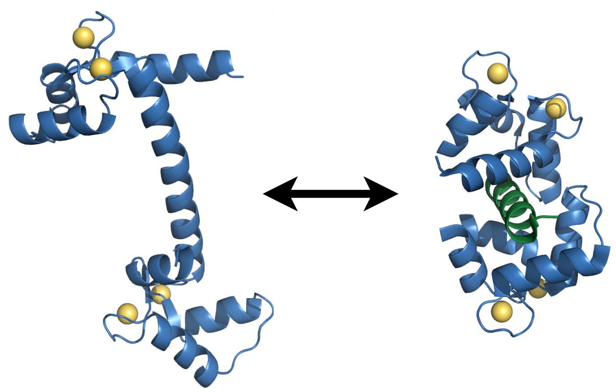
$$\Psi\mathscr{R} \simeq \mathscr{R}\Psi$$

$$\frac{dp}{dt} = W \cdot p$$

- Nonspatial: $\hat{p}(R,t) = \exp\left[-\sum_{\alpha}\mu_{\alpha}(t)V_{\alpha}(R)\right] / \hat{Z}(\mu(t))$
  - Graph-Constrained Correlation Dynamics
  - warmup case for …
- Spatial generalization: $\tilde{p}(n, \boldsymbol{x}, \boldsymbol{\alpha}, t) = \frac{1}{Z}\exp\left[-\sum_{k=1}^{K}\sum_{\langle j\rangle}\nu_k(\boldsymbol{x}_{\langle j\rangle}, \boldsymbol{\alpha}_{\langle j\rangle}, t)\right],$
  - Dynamic Boltzmann distributions

E.g.: Synapse CaMKII Signaling Model

interacting particles with dynamical state information



[Pepke et al., PLoS Comp Bio, 2010]

```
(* CaM binding/unbinding free CaMKII *)
{CaM[n,c], CaMKII[num]} -> {Kk[n,c,0], CaMKII[num-1]},
  with[num*kon2[n,c,p0]/timeMultiplier],
{Kk[a0,b0,0], CaMKII[num]} -> {CaM[a0,b0], CaMKII[num+1]},
  with[koff2[a0,b0,0]If[a0>=0&&b0>=0,1,0]/timeMultiplier],
```

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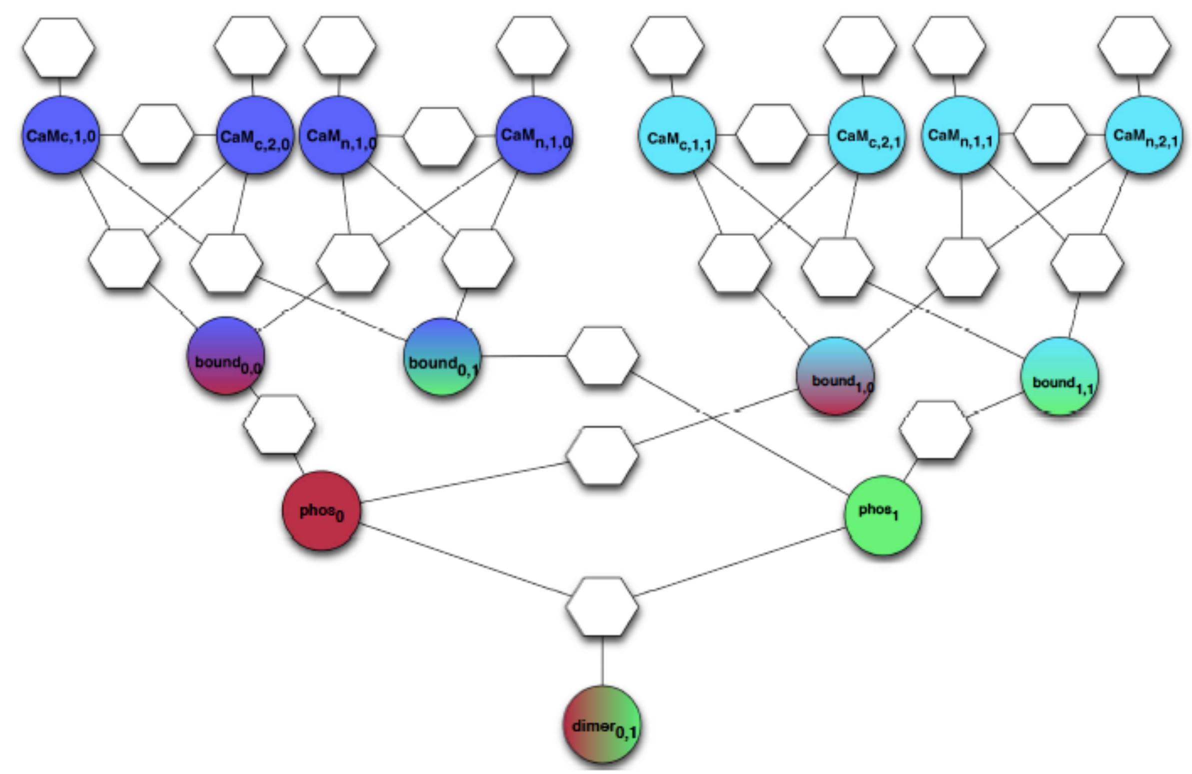


Figure 7.1: An MRF model of calcium binding, CaM/CaMKII interaction, and CaMKII dimerization.

[Phys Bio 2015] [Johnson PhD thesis 2012].
Original model: [Pepke et al. 2010]

GCCD: Target and Approximate Stochastic Dynamics

[Physical Biology 2015]

- Target stoch. dynamics: Chemical master equation

$$\boxed{\frac{dp}{dt} = W \cdot p}$$

i.e.

$$\frac{d\ p([n_i])}{d\,t} \simeq \sum_r \rho^{(r)} \left(\prod_j \left(n_j - S_j^{(r)}\right)_{\tilde{m}_j^{(r)}} \right) p([n_i - S_i^{(r)}]) - \sum_r \rho^{(r)} \left(\prod_j (n_j)_{\tilde{m}_j^{(r)}} \right) p([n_i])$$

- Approximation: Boltzmann/MRF + parameter ODEs

$$\boxed{\hat{p}(R,t) = \exp\left[-\sum_\alpha \mu_\alpha(t) V_\alpha(R) \right] / \hat{Z}(\mu(t))}$$

$$\boxed{\frac{d}{dt}\mu_\alpha = f_\alpha(\mu|\theta) = \sum_A \theta_A f_{\alpha A}(\mu)}$$

- Error criterion: L1-regularized sum squared error

$$\boxed{S([\theta_A]) = \sum_{\alpha, t_{discr}} \left\| \frac{d\mu_\alpha(t)}{dt}\bigg|_{fit} [\theta_{\alpha A}] - \frac{d\mu_\alpha(t)}{dt}\bigg|_{BMLA} \right\|^2 + \lambda \sum_A |\theta_A|}$$

- Name: Graph-Constrained Correlation Dynamics
  - "Graph" = assumed MRF structure graph; "Correlations" = $\mu_c V_c(X_c)$

Mapping: Model reduction

$$
\begin{tikzcd}
R(t) \arrow[rr, "\Delta t"] \arrow[dr] & & R(t+\Delta) \arrow[dr] & \\
 & O(t) \arrow[rr, dotted] & & O(t+\Delta) \\
S(t) \arrow[uu] \arrow[ur] \arrow[rr, "\Delta t"] & & S(t+\Delta) \arrow[uu] \arrow[ur] &
\end{tikzcd}
$$

[Johnson, Bartol, Sejnowski, and Mjolsness. Physical Biology 12:4, July 2015]

$$\Psi\mathscr{R} \simeq \mathscr{R}\Psi$$

$$\frac{dp}{dt} = W \cdot p$$

- Nonspatial: $\hat{p}(R,t) = \exp\left[-\sum_{\alpha} \mu_{\alpha}(t) V_{\alpha}(R)\right] / \hat{Z}(\mu(t))$
  - Graph-Constrained Correlation Dynamics
  - warmup case for …
- Spatial generalization: $\tilde{p}(n, \boldsymbol{x}, \boldsymbol{\alpha}, t) = \frac{1}{Z} \exp\left[-\sum_{k=1}^{K} \sum_{\langle j \rangle} \nu_k(\boldsymbol{x}_{\langle j \rangle}, \boldsymbol{\alpha}_{\langle j \rangle}, t)\right],$
  - Dynamic Boltzmann distributions

MaxEnt Problem

$$S = \int_0^\infty dt\, \mathcal{D}_{\mathcal{KL}}(p||\tilde{p})$$

$$\text{w/ } \mathcal{D}_{\mathcal{KL}}(p||\tilde{p}) = \sum_{n=0}^{\infty} \int d\boldsymbol{x}\, p \ln \frac{p}{\tilde{p}}$$

$$\tilde{p}(n, \boldsymbol{x}, \boldsymbol{\alpha}, t) = \frac{1}{Z} \exp\left[-\sum_{k=1}^{K} \sum_{\langle j \rangle} \nu_k(\boldsymbol{x}_{\langle j \rangle}, \boldsymbol{\alpha}_{\langle j \rangle}, t) \right],$$

Variational problem

$$\frac{\delta S}{\delta F_k[\{\nu_k(\boldsymbol{x})\}_{k=1}^K]} = 0 \text{ for } k = 1, \ldots, K \text{ at all } \boldsymbol{x} \quad (12)$$

where the variation is with respect to a set of **functionals**

$$\boxed{\dot{\nu}_k(\mathbf{x}) = F_k[\{\nu_k\}_{k=1}^K]} \quad (13)$$

… Higher-order calculus!

Slides: Oliver Ernst, Salk

O. Ernst, T. Bartol, T. Sejnowksi, and E. Mjolsness , J of Chem Phys 149, 034107, July 2018. Also arXiv 1803.01063

Variational Problem: Spatial systems

$$\frac{\delta S}{\delta F_k[\boldsymbol{\nu}(\boldsymbol{x})]} = \sum_{k'=1}^{K} \int d\boldsymbol{x}' \int dt \, \frac{\delta S}{\delta \nu_{k'}(\boldsymbol{x}', t)} \frac{\delta \nu_{k'}(\boldsymbol{x}', t)}{\delta F_k[\boldsymbol{\nu}(\boldsymbol{x})]} = 0 \qquad (19)$$

1

$$\frac{\delta S}{\delta \nu_{k'}(\boldsymbol{x}', t)} = \left\langle \sum_{\langle i \rangle^n_{k'}} \delta(\boldsymbol{x}' - \boldsymbol{x}_{\langle i \rangle^n_{k'}}) \right\rangle_p - \left\langle \sum_{\langle i \rangle^n_{k'}} \delta(\boldsymbol{x}' - \boldsymbol{x}_{\langle i \rangle^n_{k'}}) \right\rangle_{\tilde{p}} \qquad (20)$$

e.g. $k' = 1 : \left\langle \sum_{i=1}^{n} \delta(x_i - x') \right\rangle$ for all x'

$k' = 2 : \left\langle \sum_{i=1}^{n} \sum_{j>i} \delta(x_i - x_1') \delta(x_j - x_2') \right\rangle$ for all x_1', x_2'

2

Need to choose a parametrization for functional!

O. Ernst, T. Bartol, T. Sejnowksi, and E. Mjolsness , J of Chem Phys 149, 034107, July 2018. Also arXiv 1803.01063

$\mathscr{R}$

Diffusion-inspired parametrization

$$p(x) \sim \exp\left[-\frac{(x-x_0)^2}{4Dt}\right] \to \exp[-\nu_1(x)]$$

$$\text{satisfies: } \frac{\partial \nu_1}{\partial t} = D\nabla^2 \nu_1(x) - D(\nabla \nu_1(x))^2$$

$$\therefore F_k[\boldsymbol{\nu}(\boldsymbol{x})] = F_k^{(0)} + \sum_{\lambda=1}^{k} F_{k\lambda}^{(1)} (\nabla \nu_\lambda)^2 + \sum_{\lambda=1}^{k} F_{k\lambda}^{(2)} (\nabla^2 \nu_\lambda) \qquad (20)$$

where: $F =$ some funcs of ν on LHS

$$\frac{\delta S}{\delta F_k^{(0)}} = 0, \frac{\delta S}{\delta F_{k\lambda}^{(1)}} = 0, \frac{\delta S}{\delta F_{k\lambda}^{(2)}} = 0$$

PDE-constrained Optimization Problem

$$\text{Minimize} \sum_{k'=1}^{K} \int_0^\infty dt \left(\left\langle \sum_{\langle i \rangle_{k'}^n} \delta(\boldsymbol{x}' - \boldsymbol{x}_{\langle i \rangle_{k'}^n}) \right\rangle_p - \left\langle \sum_{\langle i \rangle_{k'}^n} \delta(\boldsymbol{x}' - \boldsymbol{x}_{\langle i \rangle_{k'}^n}) \right\rangle_{\tilde{p}} \right) \frac{\delta \nu_{k'}(t)}{\delta F} \quad (23)$$

subject to PDE constraints for $\delta\nu_{k'}(t)/\delta F$.

O. Ernst, T. Bartol, T. Sejnowksi, and E. Mjolsness , J of Chem Phys 149, 034107, July 2018. Also arXiv 1803.01063

Adjoint method BMLA-like learning algorithm

Algorithm 1 Stochastic Gradient Descent for Learning Restricted Boltzmann Machine Dynamics

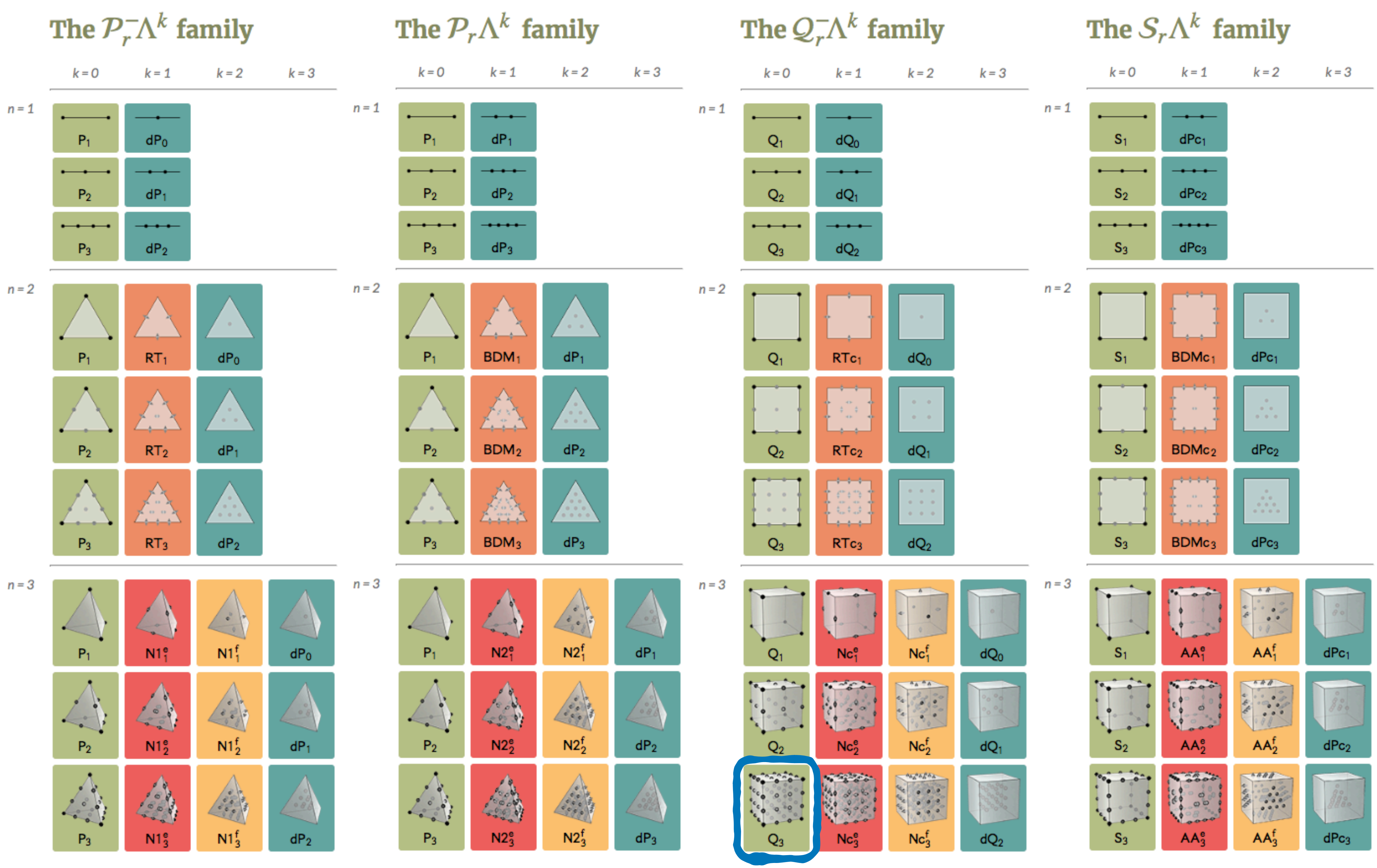
```
Initialize
    Parameters u_k controlling the functions F_k(θ; u_k) for all k = 1, ..., K.
    Time interval [t_0, t_f], a formula for the learning rate λ.
while not converged do
    Initialize ΔF_{k,i} = 0 for all k = 1, ..., K and parameters i = 1, ..., M_k.
    for sample in batch do
        ▷ Generate trajectory in reduced space θ:
        Solve the PDE constraint (27) for θ_k(t) with a given IC θ_{k,0} over t_0 ≤ t ≤ t_f, for all k.
        ▷ Wake phase:
        Evaluate moments μ_k(t) of the data for all k, t.
        ▷ Sleep phase:
        Evaluate moments μ̃_k(t) of the Boltzmann distribution.
        ▷ Solve the adjoint system:
        Solve the adjoint system (31) for φ_k(t) for all k, t.
        ▷ Evaluate the objective function:
        Update ΔF_{k,i} as the cumulative moving average of the sensitivity equation (30) over the batch.
    ▷ Update to decrease objective function:
    u_{k,i} → u_{k,i} − λΔF_{k,i} for all k, i.
```

$$\frac{d}{dt}\theta_k(t) = F_k(\boldsymbol{\theta}(t); \boldsymbol{u}_k)$$

$$\frac{d}{dt}\phi_k(t) = \tilde{\mu}_k(t) - \mu_k(t) - \sum_{l=1}^{K} \frac{\partial F_l(\boldsymbol{\theta}(t); \boldsymbol{u}_l)}{\partial \theta_k(t)} \phi_l(t),$$

$$\frac{dS}{du_{k,i}} = -\int_{t_0}^{t_f} dt \, \frac{\partial F_k(\boldsymbol{\theta}(t); \boldsymbol{u}_k)}{\partial u_{k,i}} \phi_k(t).$$

Periodic Table of the Finite Elements



Benefit of Hidden Units $\mathscr{R}$

Network: fratricide + lattice diffusion

- Learned DBD ODE RHS, without and with hidden units

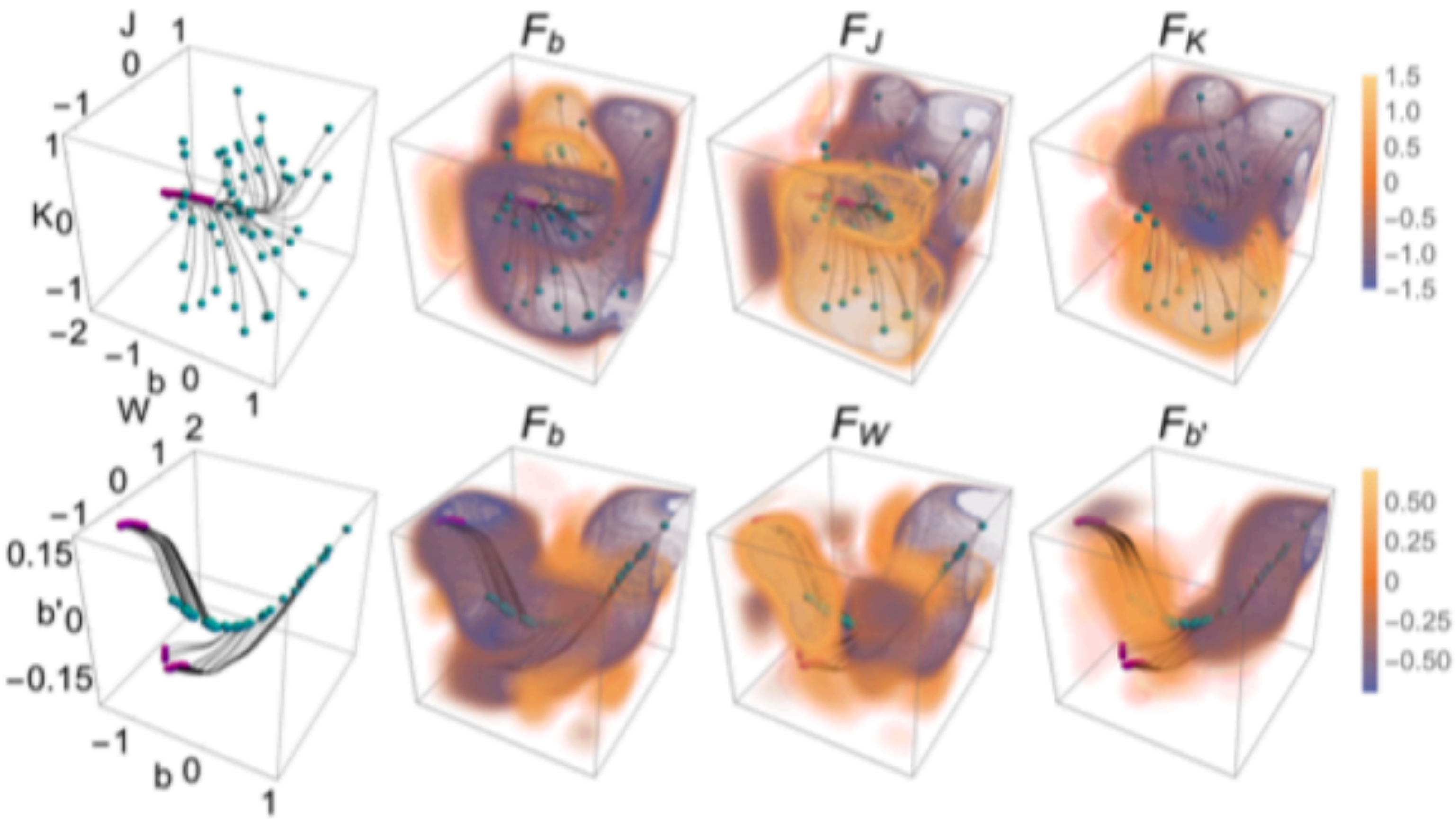
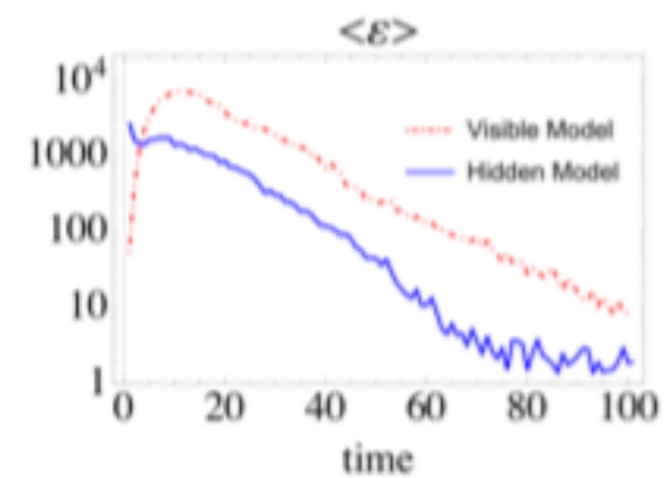


FIG. 2. *Top row:* Learned time-evolution functions for the fully visible model (19), using the Q_3, C_1 finite element parameterization (21) with $5 \times 5 \times 5$ evenly spaced cubic cells. Left: Training set of initial points (b, J, K) (cyan) sampled evenly in $[-1, 1]$. Stochastic simulations for each initial point are used as training data (learned trajectories shown in black, endpoints in magenta). Other panels: the time evolution functions learned. *Bottom row:* Hidden layer model (20) and parameterization (21) with the same number of cells as the visible model. Initial points are generated by BM learning the points of the visible model.

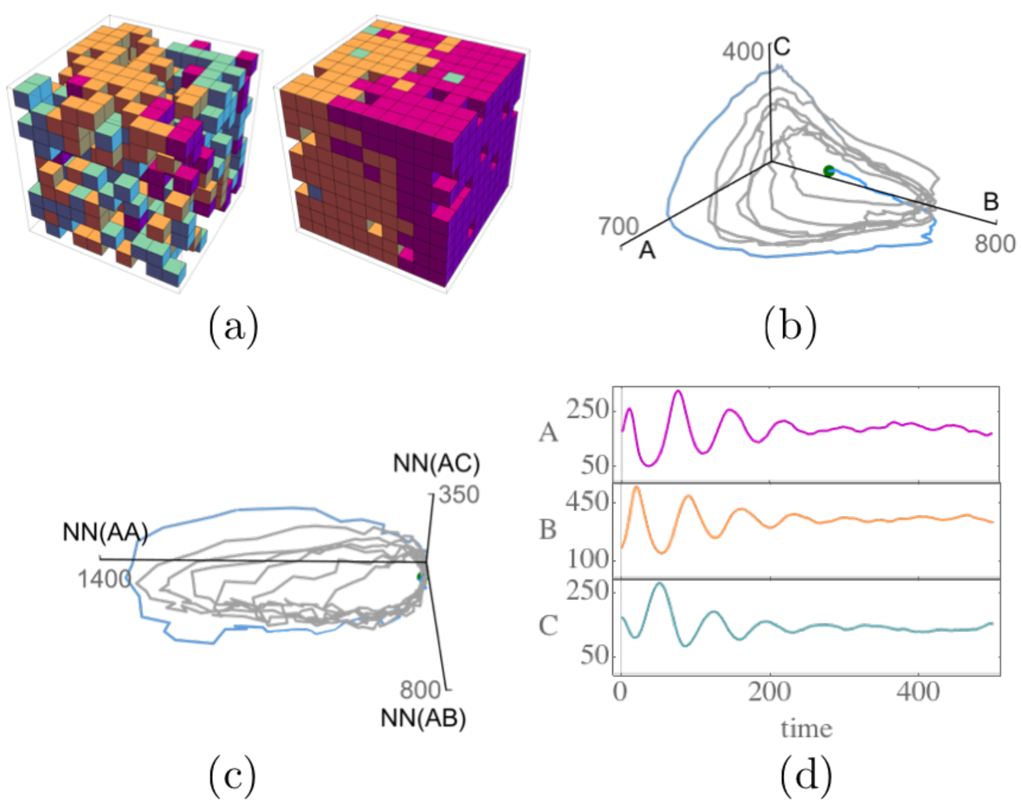


MSE of 4th order stats

[Ernst, Bartol, Sejnowski, Mjolsness, Phys Rev E 99 063315, 2019]

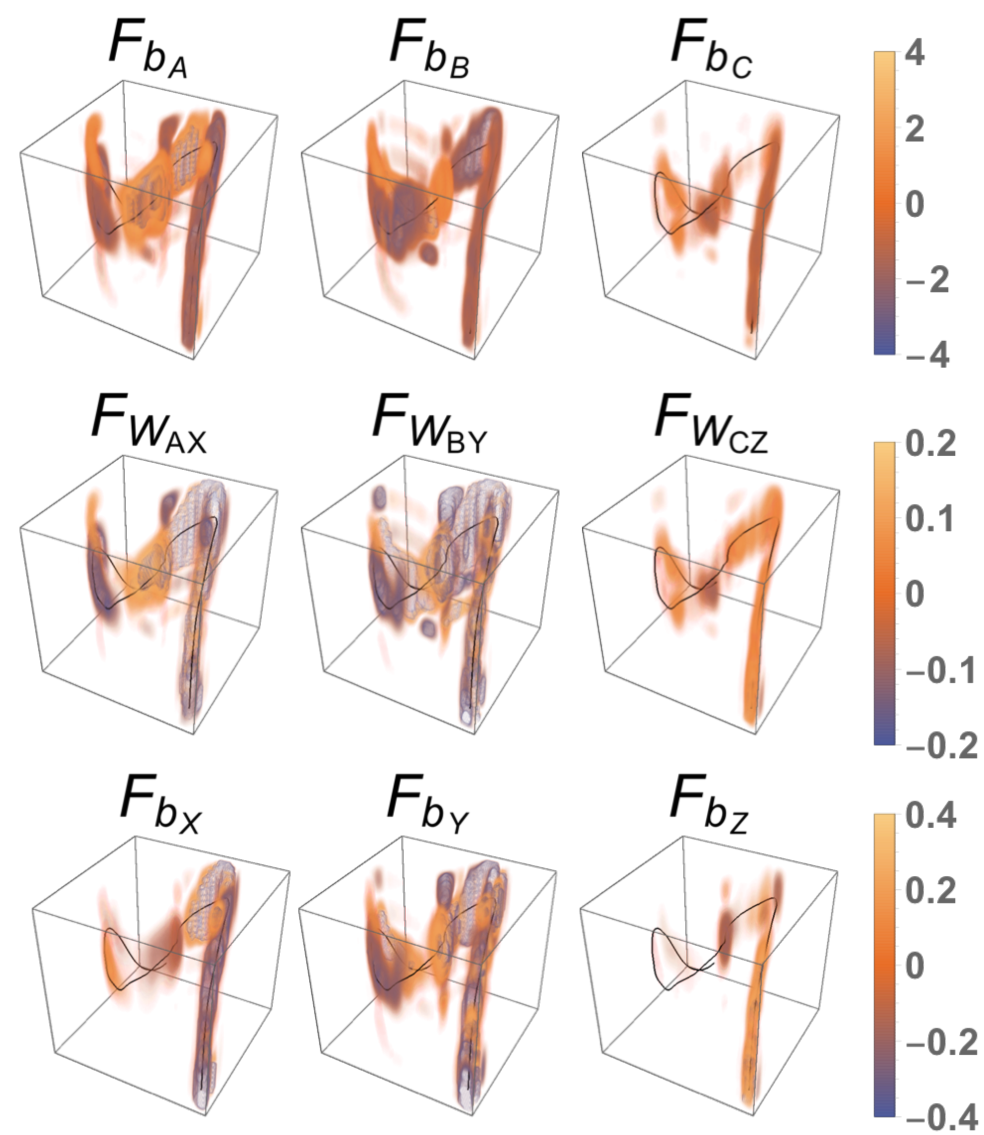
Rössler Oscillator in 3D

- Function:



(a) (b) (c) (d)

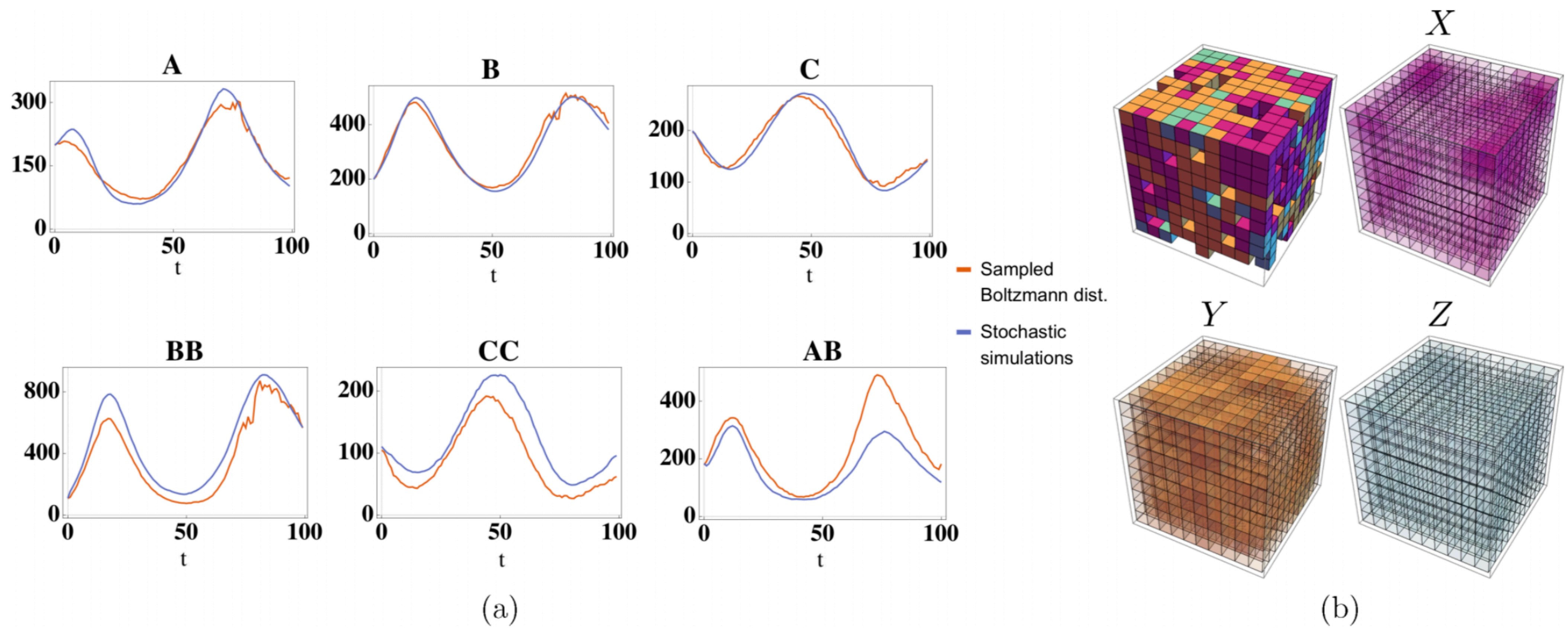
- Learned DBD ODE RHS:



[Ernst, Bartol, Sejnowski, Mjolsness, Phys Rev E 99 063315, 2019]

Rössler Oscillator in 3D

- Learned correlations:
- Learned Configuration



[Ernst, Bartol, Sejnowski, Mjolsness, Phys Rev E 99 063315, 2019]

$\Psi, \mathcal{I}$

Fields to Structures

$$\frac{dp}{dt} = W \cdot p$$

- Fields: PDE differential operator dynamics in W
- Dynamical Graph Grammars (DGGs):
  - operator addition of reactions, GGs, ODEs;
  - but what about PDEs?
- Approximately eliminate fields by:
  - Cell complexes in PDE (adaptive) meshing / FEMs, FVMs

MT fiber
Stochastic Parametrized Graph Grammar

$$
(\bullet_1)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1)\rangle\!\rangle \longrightarrow (\circ_1 \longrightarrow \bullet_2)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle
$$
$$
\textbf{with}\quad \hat{\rho}_{\text{grow}}([\text{tubulin}])\mathcal{N}(\boldsymbol{x}_1-\boldsymbol{x}_2;L\boldsymbol{u}_1,\sigma)\mathcal{N}(\boldsymbol{u}_2;\boldsymbol{u}_1/(|\boldsymbol{u}_1|+\epsilon),\epsilon),
$$
$$
(\blacksquare_1 \longrightarrow \circ_2)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle \longrightarrow (\blacksquare_2)\langle\!\langle(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle
$$
$$
\textbf{with}\quad \hat{\rho}_{\text{retract}}
$$
$$
\begin{pmatrix} \circ_1 \longrightarrow \circ_2 \longrightarrow \circ_3 \\ \bullet_4 \end{pmatrix}\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2),(\boldsymbol{x}_3,\boldsymbol{u}_3),(\boldsymbol{x}_4,\boldsymbol{u}_4)\rangle\!\rangle
$$
$$
\longrightarrow \begin{pmatrix} \circ_1 \longrightarrow \blacktriangle_2 \longrightarrow \circ_3 \\ \circ_4 \nearrow \end{pmatrix}\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2),(\boldsymbol{x}_3,\boldsymbol{u}_3),(\boldsymbol{x}_4,\boldsymbol{u}_4)\rangle\!\rangle
$$
$$
\textbf{with}\quad \hat{\rho}_{\text{bundle}}(|\boldsymbol{u}_2\cdot\boldsymbol{u}_4|/|\cos\theta_{\text{crit}}|)\exp(-|\boldsymbol{x}_2-\boldsymbol{x}_4|^2/2L^2)
$$
$$
(\blacksquare_1 \longrightarrow \bullet_2)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle \longleftrightarrow \varnothing \qquad \textbf{with}\ \Big(\hat{\rho}_{\text{retract}},
$$
$$
\hat{\rho}_{\text{nucleate}}([\text{tubulin}])\mathcal{N}(\boldsymbol{x};\mathbf{0},\sigma_{\text{broad}})\delta_{\text{Dirac}}(|\boldsymbol{u}_1|-1)\delta_{\text{Dirac}}(\boldsymbol{u}_1-\boldsymbol{u}_2)\Big)
$$
$$
(\bullet_1)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1)\rangle\!\rangle \longleftrightarrow (\blacksquare_1)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1)\rangle\!\rangle
$$
$$
\textbf{with}\quad (\hat{\rho}_{\text{retract}\leftarrow\text{growth}},\hat{\rho}_{\text{growth}\leftarrow\text{retract}})
$$

[EM, Bull. Math Biol. 81:8 Aug 2019
+arXiv:1804.11044]

$\mathscr{X}$

MT fiber
Stochastic Parametrized Graph Grammar

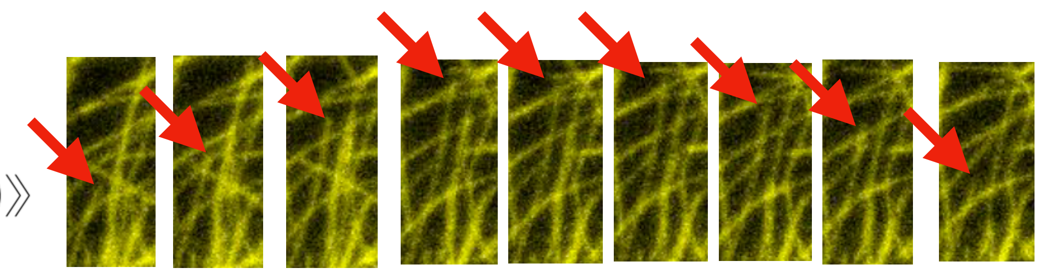
// (continued)

// Fiber collision, with several alternative discrete outcomes:

$$\left(\begin{array}{ccc} & \bigstar_1 \text{ —— } \bigcirc_2 \text{ — } \bigstar_3 \\ \bigcirc_4 \text{ —— } \bullet_5 & \end{array}\right) \langle\!\langle (x_1, u_1), (l_2, u_2), (x_3, u_3), (l_4, u_4), (x_5, u_5) \rangle\!\rangle$$

$$\longrightarrow \left(\begin{array}{c} \bigstar_1 \text{ — } \bigcirc_6 \text{ —— } \blacktriangle_2 \text{ — } \bigcirc_7 \text{ — } \bigstar_3 \\ \diagup \\ \bigcirc_4 \end{array}\right) \langle\!\langle (x_1, u_1), (x_2, u_2), (x_3, u_3), (l_4, u_4), \varnothing, (\alpha l_4, u_2), ((1-\alpha) l_4, u_2$$

with $\hat{\rho}_{\text{bundle}}(|u_2 \cdot u_4| / |\cos\theta_{\text{crit}}|) \exp\left(-\gamma^2/2\epsilon^2\right) \Theta(\epsilon \leqslant \alpha \leqslant 1-\epsilon)$

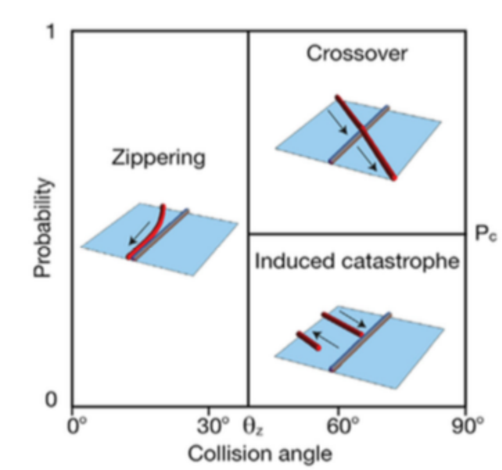


$$\longrightarrow \left(\begin{array}{ccc} & \bigstar_1 \text{ —— } \bigcirc_2 \text{ — } \bigstar_3 \\ \bigcirc_4 \text{ —— } \blacksquare_5 & \end{array}\right) \langle\!\langle (x_1, u_1), (l_2, u_2), (x_3, u_3), (l_4, u_4), (x_5, u_5) \rangle\!\rangle$$

with $\hat{\rho}'_{\text{bundle}}(|u_2 \cdot u_4| / |\cos\theta_{\text{crit}}|) \exp\left(-\gamma^2/2\epsilon^2\right) \Theta(\epsilon \leqslant \alpha \leqslant 1-\epsilon)$

$$\longrightarrow \left(\begin{array}{c} \bullet_9 \\ \diagup \\ \bigcirc_8 \\ \diagup \\ \bigstar_1 \text{ — } \bigcirc_6 \text{ —— } \blacklozenge_2 \text{ — } \bigcirc_7 \text{ — } \bigstar_3 \\ \diagup \\ \bigcirc_4 \end{array}\right) \left\langle\!\!\left\langle \begin{array}{c} (x_1, u_1), ((1-\alpha)x_1 + \alpha x_3, u_2), (x_3, u_3), (l_4, u_4), \varnothing, \\ (\alpha l_2, u_2), ((1-\alpha) l_2, u_2), (\epsilon l_4, u_4), (x_2 + \epsilon l_4 u_4), u_4) \end{array} \right\rangle\!\!\right\rangle$$

with $\hat{\rho}''_{\text{bundle}}(|u_2 \cdot u_4| / |\cos\theta_{\text{crit}}|) \exp\left(-\gamma^2/2\epsilon^2\right) \Theta(\epsilon \leqslant \alpha \leqslant 1-\epsilon)$



[Chakrabortty et al.
Current Biology

where $\gamma = -[(x_3 - x_1) \times (x_1 - x_5)]_z / [(x_3 - x_1) \times u_5]_z$ // rel. distance to intersection along u_5

$\alpha = -[(x_1 - x_5) \times u_5]_z / [(x_3 - x_1) \times u_5]_z$ // fractional location of intersection along u_2

[EM, Bull. Math Biol. 81:8 Aug 2019
+arXiv:1804.11044]

Cajete MT: First Light

Eric Medwedeff, UCI

$\mathcal{J}$

Why operator algebra yields algorithms

- Baker Campbell Hausdorff theorem
  - => operator splitting algorithms e.g. Trotter Product Formula …

$$\lim_{n\to\infty}\left[e^{(t/n)H_0}\;e^{(t/n)H_1}\right]^n$$

- Time-ordered product expansions => Stochastic Simulation Algorithm (SSA)
  – [EMj, Phys Bio 2013]

$$\boxed{\begin{aligned}\exp(t\,(W_0+W_1)) &= \exp(t\,W_0)\left(\exp\left(\int_0^t \exp(-\tau\,W_0)\,W_1\,\exp(\tau\,W_0)\,d\tau\right)\right)_+\\ &\equiv \exp(t\,W_0)\left(\exp\left(\int_0^t W_1\,(\tau)\,d\tau\right)\right)_+\end{aligned}}$$

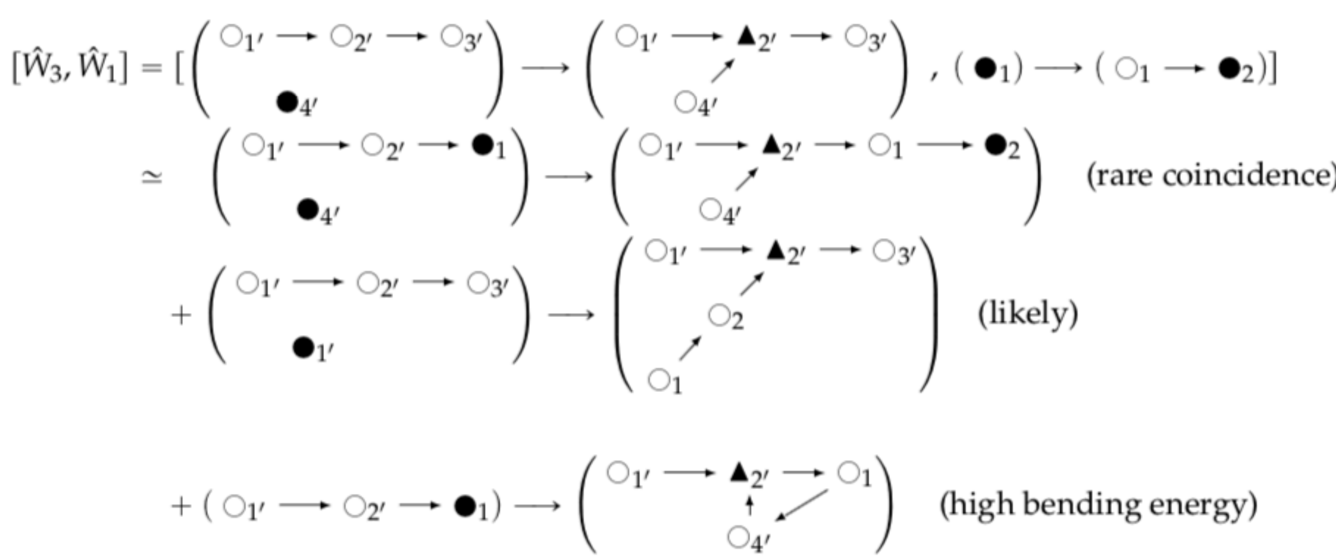
  – weighted SSA (wSSA) possible too

Algebra of Labelled-Graph Rewrite Rules

$$\hat{W}_{G^{r_2\,\text{in}} \to G^{r_2\,\text{out}}} \hat{W}_{G^{r_1\,\text{in}} \to G^{r_1\,\text{out}}} \simeq \sum_{\substack{H \subseteq G^{r_1\,\text{out}} \simeq \tilde{H} \subseteq G^{r_2\,\text{in}} \\ |\ \text{edge-maximal}}} \sum_{h: H \overset{1\text{-}1}{\hookrightarrow} \tilde{H}} \hat{W}_{G^{r_1\,\text{in}} \cup (G^{r_2\,\text{in}} \setminus \tilde{H}) \underset{h}{\to} G^{r_2\,\text{out}} \cup (G^{r_1\,\text{out}} \setminus H)}$$

E.g.:

$$[\hat{W}_2, \hat{W}_1] = [(\blacksquare_{1'} \longrightarrow \bigcirc_{2'}) \longrightarrow (\blacksquare_{2'}) \,,\ (\bullet_1) \longrightarrow (\bigcirc_1 \longrightarrow \bullet_2)]$$
$$\simeq \quad (\blacksquare_{1'} \longrightarrow \bullet_1) \longrightarrow (\blacksquare_1 \longrightarrow \bullet_2)$$

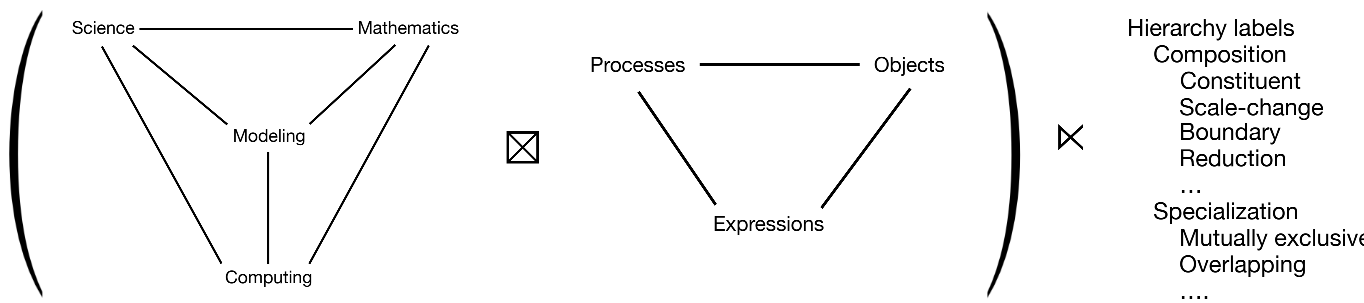


+ (3 terms whose LHS rely on MT syntax violations - omitted)

[EM, http://arxiv.org/abs/1909.04118]

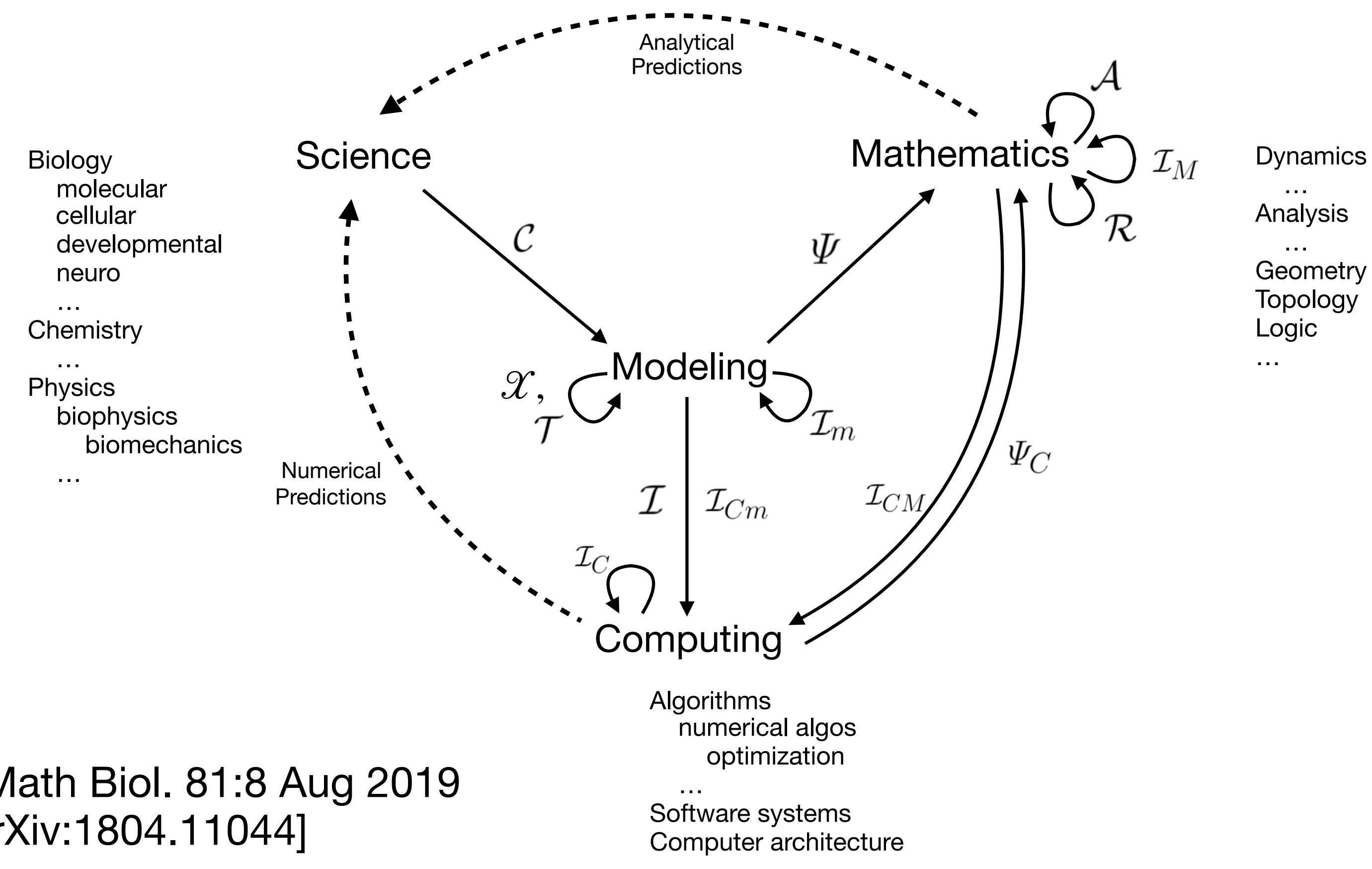
"Tchicoma" Architecture for Mathematical Modeling

- Language meta-hierarchy: *(a DAG with edge labels in a tree)*



- Mappings therein:

respecting compositional structure



Features:
Enables problem-solving
via chaining, theorem-proving
Foments abstraction
via commutation
Decoupled, yet can be efficient

[EM, Bull. Math Biol. 81:8 Aug 2019
+arXiv:1804.11044]

Conclusions

- Model reduction can be achieved by machine learning, in spatial stochastic models. Reaction/diffusion examples.
- Declarative modeling languages with operator algebra semantics can support generic model reduction.
- Morpho-dynamic spatial structures can be modeled by dynamical graph grammars with operator semantics. Bio-universal; scalability is in progress. MT examples.
- Model stacks are the key data structure for understanding complex bio systems.
    - They require model reduction and bio-universal modeling languages (perhaps as above).
    - They can intersect productively, and could be curated in a proposed conceptual architecture “Tchicoma”.
    - “Intelligent Formal Methods for Stacks of Models - InformCosm”
- In these ways, both symbolic and numeric AI can (and should!) be brought to bear on understanding complex biological systems.