Developing methods for developmental modeling: Learning reduced stochastic dynamics and Algebras of dynamic structures

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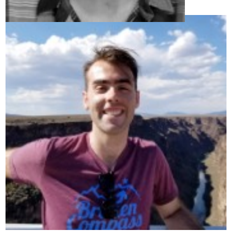
  - Oliver Ernst (UCSD), Tom Bartol (Salk), Terry Sejnowski (Salk)



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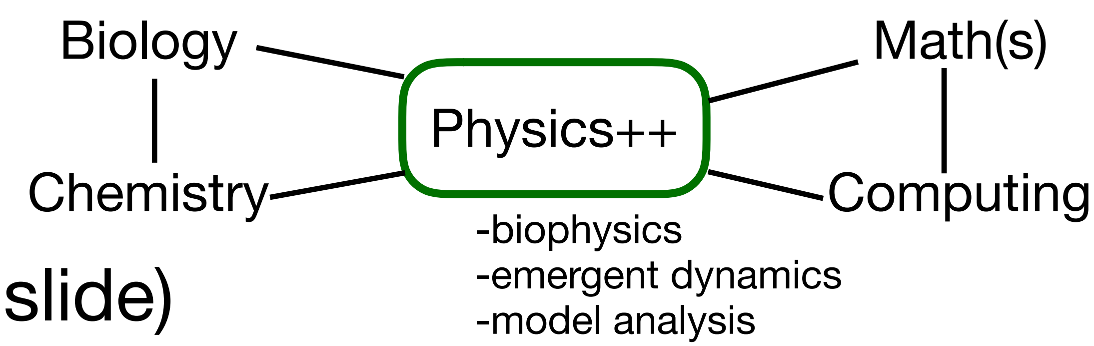
- Visits: KITP, CNLS, … SLCU

Outline

- This is a talk about methods - computational and mathematical



- Preamble: "Principles in biology" (1 slide)

- Machine learning for model reduction: Dynamic Boltzmann Distributions

- Algebra of dynamic spatially embedded graphs (structures), as semantics for languages sufficient for bio model reduction

- Epilogue: A conceptual architecture for model stacks (3 slides)

Mappings:

Semantics	Ψ
Reduction of models	$\mathscr{R}$
Analysis of models	$\mathscr{A}$
Implementation of models	$\mathscr{I}$

Preamble:
Some candidate bio “principles”

- Biophysical
  - scarce resources: Follow the … energy, elements/small molecules; information, proximity/access
  - specific feedback inhibition in biosynthesis [Umbarger 1950]
  - co-option of emergent properties (biomechanics, self-organization, phase separation, …)
  - regeneration of ~modular subunits => robustness
  - dynamic structures (~spatially embedded graphs) recur at all scales
- Informational
  - Information bottlenecks are key (e.g. genome; cell-cell signaling; spatial info flow in cell & dev …)
  - regulation, replication, … are catalysis by information. Other processes produce/consume information.
  - internal representations (of world, self) are highly functional as reduced models. (E.g. positional info~charts)
  - meta-evolution works (evo of evo; evo of sub-evolutions)
- Methodological
  - We’re not smart enough to just think it all through *(but we should try anyway; then use cyborg mode …)*
  - mathematical/computational **models**, simulations, & analyses are essential tools for understanding …
  - *but also **automated multiscale model stacks*** ⇒ numeric (ML) plus symbolic AI needed !

(Somewhat standard) Reduced model examples

- Well-mixed mass action concentration models of biochemical networks
- PDE mass action reaction-diffusion models
- Cell-centered biomechanical models of SAM
- Vertex biomechanical models of animal epithelia
- FEM multi-compartmental biomechanical models
- Mean field theory approaches to X
- Analyses:
  - topology of biomech models
  - phase diagram; bifurcation diagram

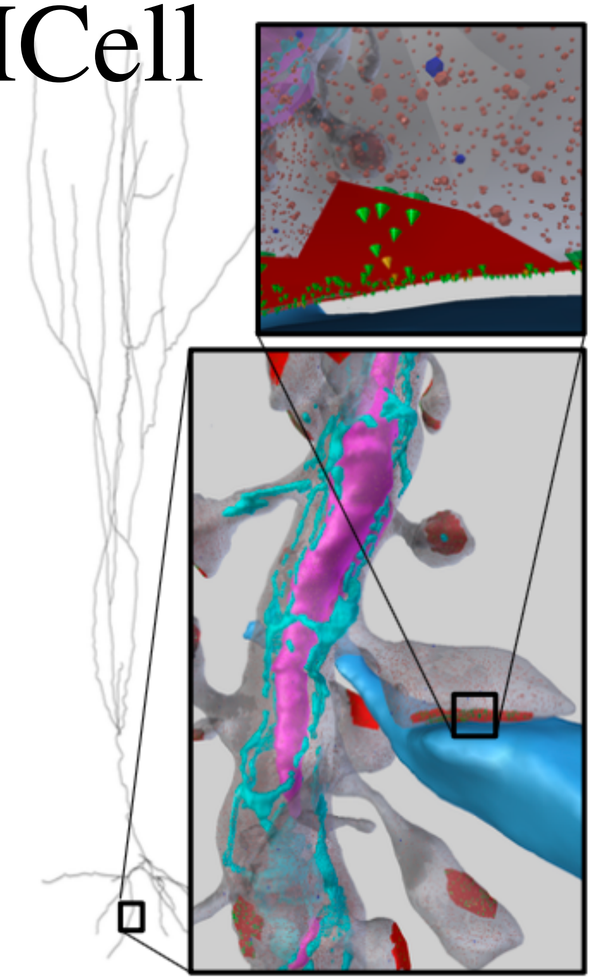
Learning reduced stochastic dynamics

Multiple Scales of Synapse

- multiscale modeling of synapse in MCell
- methods vs. problem scale

Particle Distribution

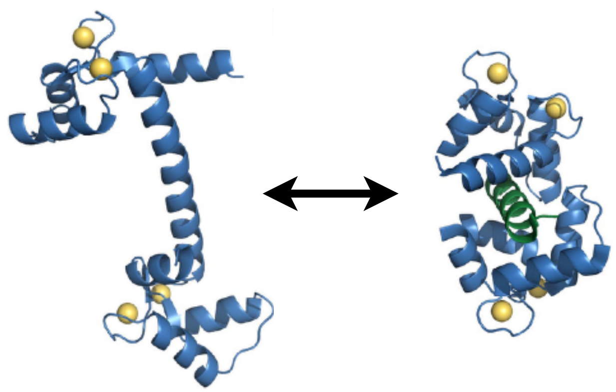
Particle Number	Uniform	Non-uniform
Low ↑	Gridless SSA (Stochastic Sim. Algorithm)	Particle-Based (MCell)
	Gridless SSA	Gridded SSA
	Stochastic ODEs	Stochastic PDEs
↓ Infinite	ODEs (Mass action)	PDEs (Finite elements)



[O. Ernst / UCSD]

E.g.: 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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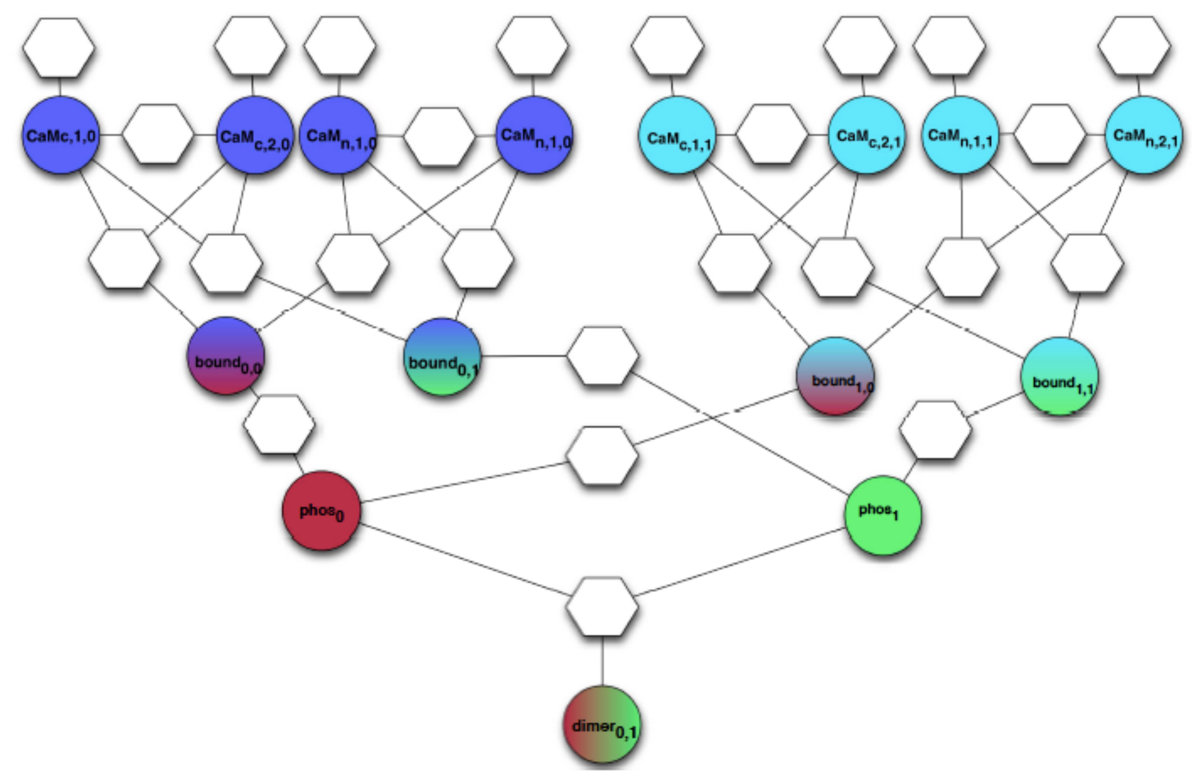


Figure 7.1: An MRF model of calcium binding, CaM/CaMKII interaction, and CaMKII dimerization.

[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

$$\frac{dp}{dt} = W \cdot p \qquad i.e. \qquad \frac{d\ p([n_i])}{d\,t} \simeq \sum_r \rho^{(r)} \left(\prod_j (n_j - S_j^{(r)})_{\tilde{m}_j^{(r)}} \right) p([n_i - S_i^{(r)}]) - \sum_r \rho^{(r)} \left(\prod_j (n_j)_{\tilde{m}_j^{(r)}} \right) p([n_i])$$

- Approximation: Boltzmann/MRF + parameter ODEs

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

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

- Error criterion: L1-regularized sum squared error

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

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

ℛ

GCCD eg. Synapse model spike train

- Fine scale: rule-based particle methods
- Coarse scale: time-varying Boltzmann distribution

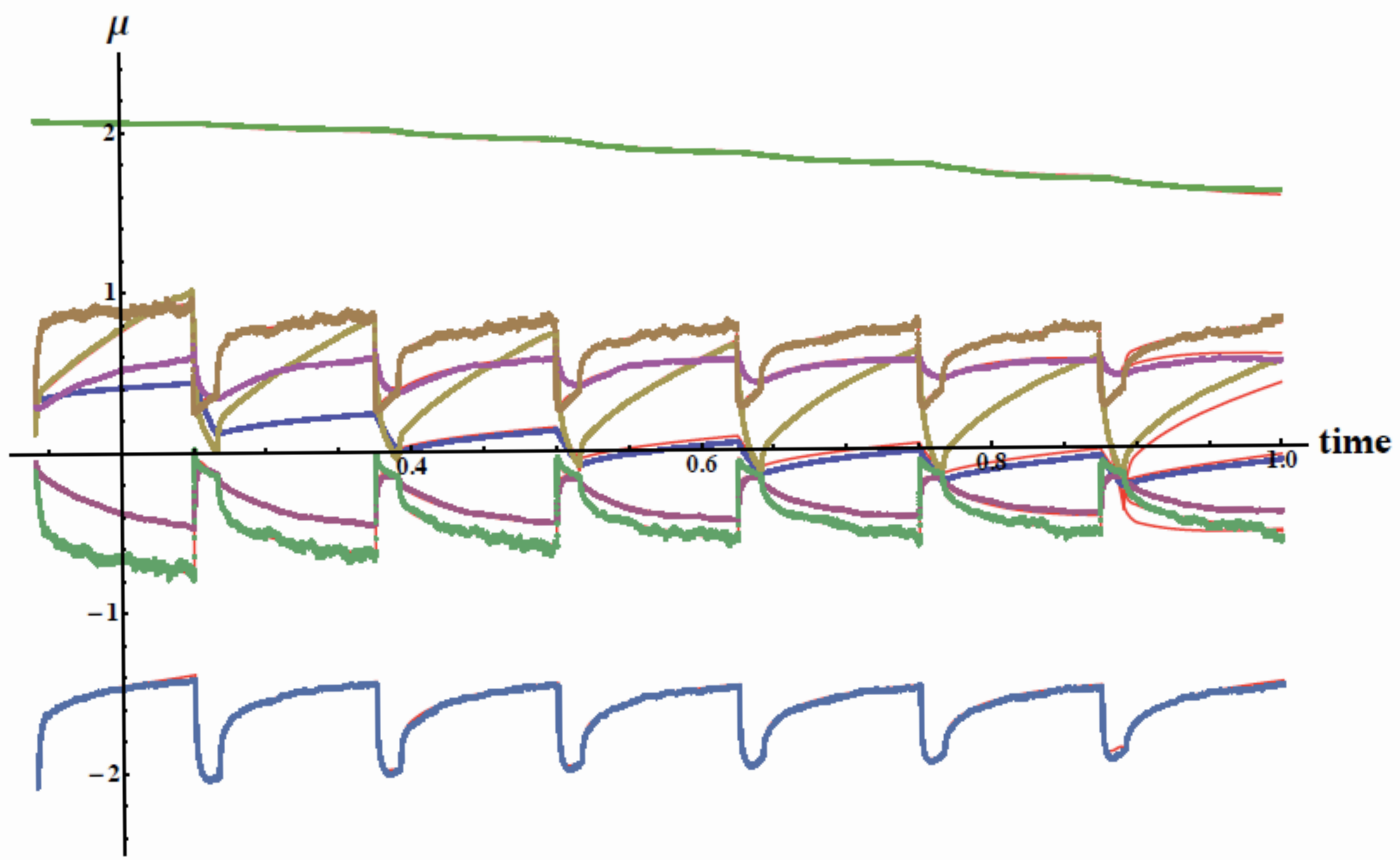
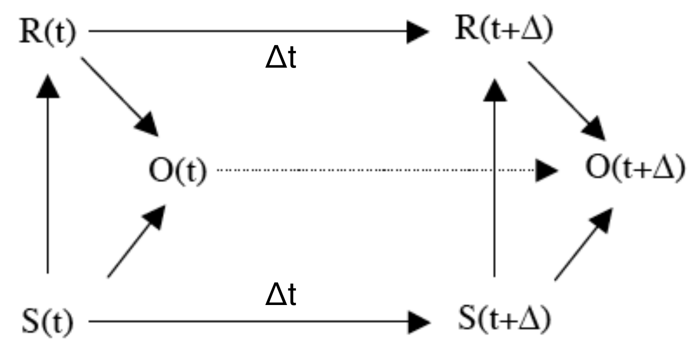


Figure 7.12: Set of ordinary differential equations with learned coefficients (red lines) versus time series of eight MRF parameter values (colored lines) (MCell), spike train.

[Johnson et al., Physical Biology 2015]

Mapping: Model reduction



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

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

- 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

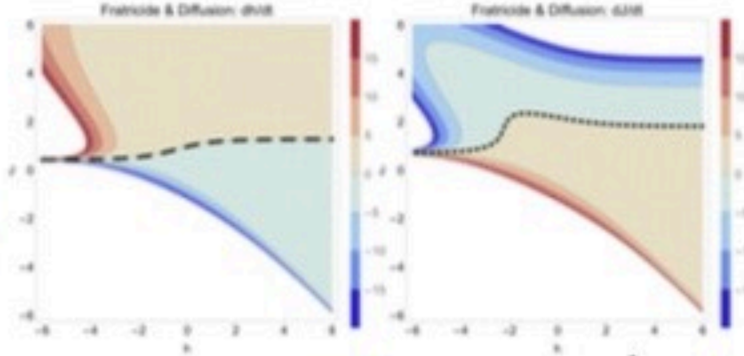
Approximating Statistical Systems by Dynamic Boltzmann Distributions

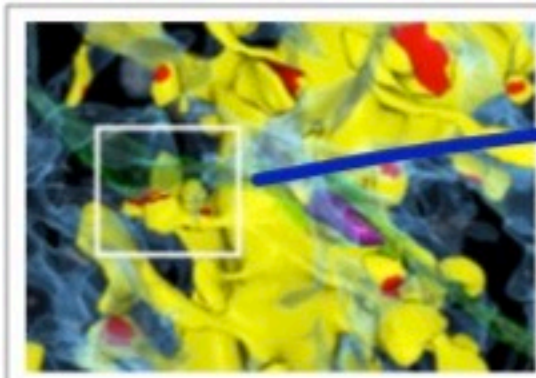
$$\dot{p} = Wp \to \tilde{p} \sim \exp(-E)/Z$$

Analytically construct MaxEnt approx. to MEs describing simple systems

Identify **basis functions**

Time evolution of approximating probability dist.





$$F(\boldsymbol{\nu}) = \alpha_{\mathrm{Diff}}(t) F_{\mathrm{Diff}}(\boldsymbol{\nu}) + \alpha_{A\to\varnothing}(t) F_{A\to\varnothing}(\boldsymbol{\nu}) + \dots$$

ML projections from true systems into reduced space

Reduced model is ***linear*** in fine-scale model sum over processes
⇒ $\mathscr{R}$ respects model structure

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

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

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

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

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

… Higher-order calculus!

Slides: Oliver Ernst, Salk

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Variational Problem: Spatial systems

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

①

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

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

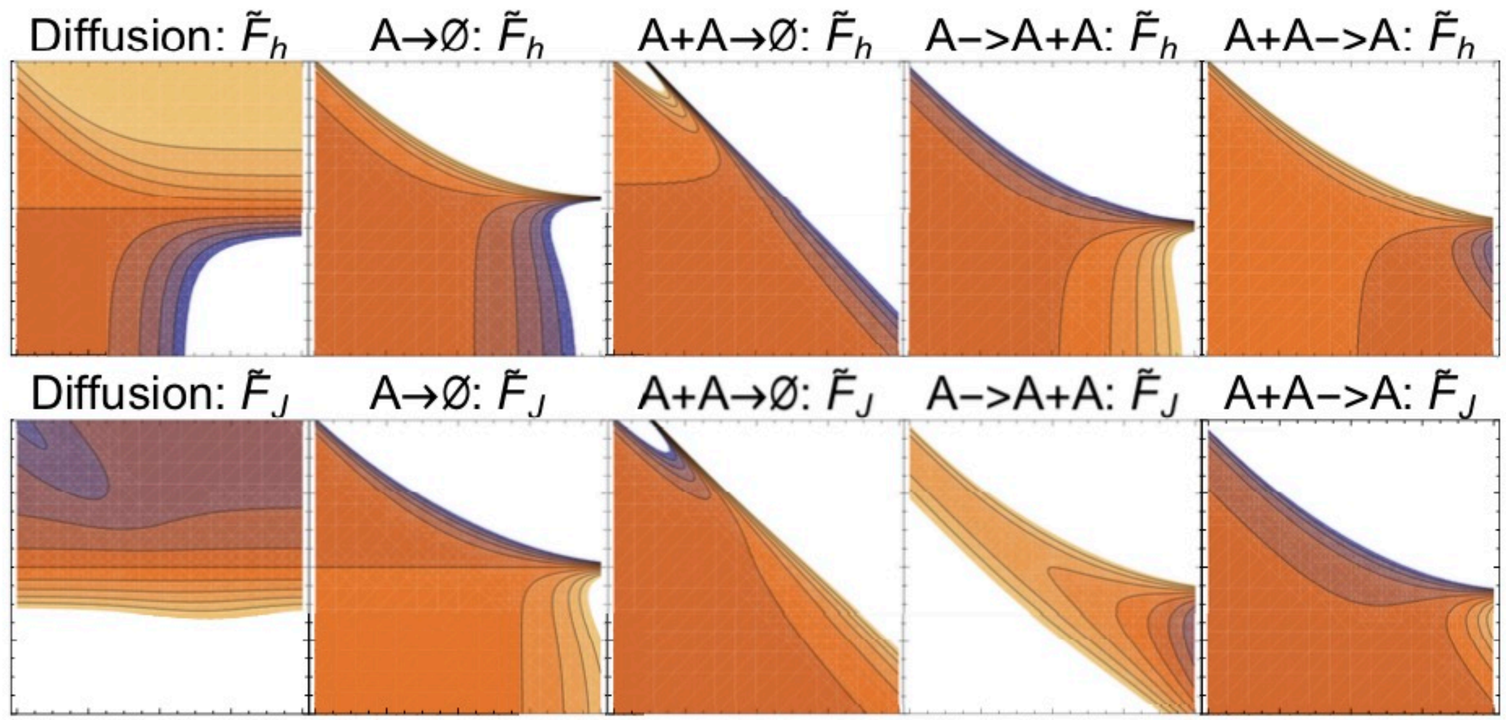
$$\text{Minimize} \sum_{k'=1}^{K} \int_0^\infty dt \left(\left\langle \sum_{\langle i \rangle_{k'}^n} \delta(\boldsymbol{x}' - \boldsymbol{x}_{\langle i \rangle_{k'}^n}) \right\rangle_p - \left\langle \sum_{\langle i \rangle_{k'}^n} \delta(\boldsymbol{x}' - \boldsymbol{x}_{\langle i \rangle_{k'}^n})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

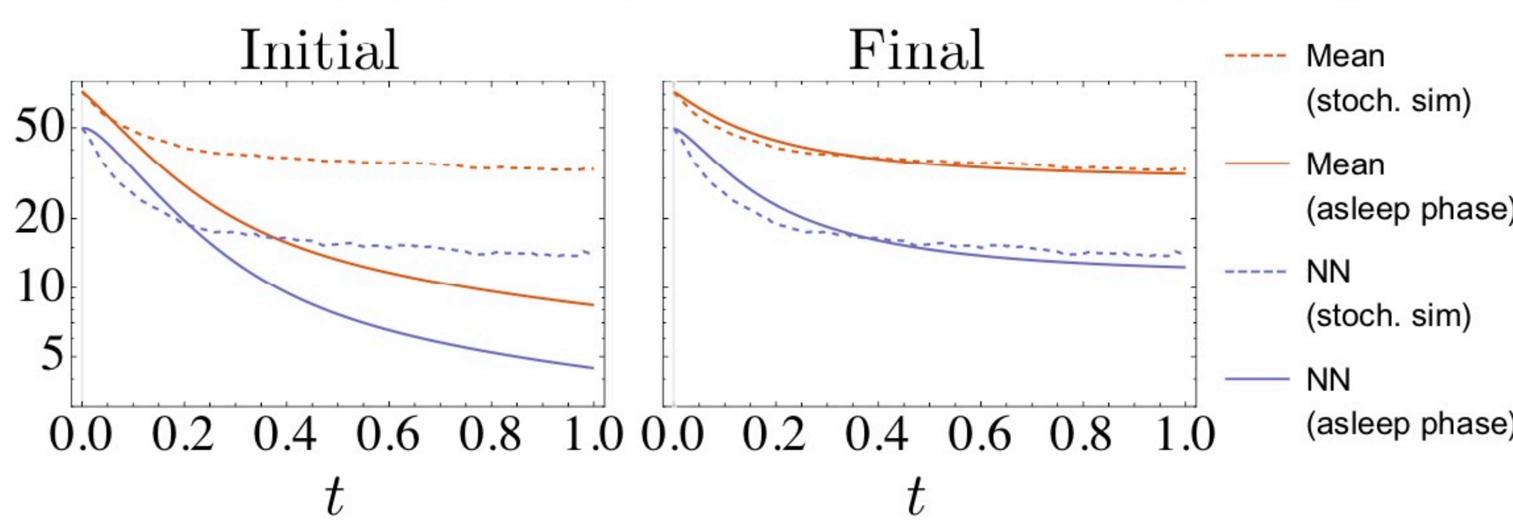
subject to PDE constraints for $\delta \nu_{k'}(t)/\delta F$.

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

Spatial Dynamic Boltzmann Distributions

$$\mathcal{Z} = \sum_{\{s\}} \sum_{\{\alpha\}} \exp\left[\sum_{i=1} h_{\alpha_i}(t) s_i + \sum_{i=1} J_{\alpha_i, \alpha_{i+1}}(t) s_i s_{i+1} \right]$$





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

BMLA-like Learning Algorithm

Algorithm 2. Boltzmann machine-style learning of dynamics.

Initialize
  Initial $\theta^{(r)}$ for all r.
  Max. integration time T.
  A formula for the learning rate λ.
  Time-series of lattice spins $\{s\}(t)$ from stochastic simulations from some known IC h_0, J_0.
  Fully visible MRF with NN connections and as many units as lattice sites N.
while not converged **do**
  ▹*Generate trajectory in reduced space:*
  Solve the PDE constraint (52) with IC h_0, J_0 for $0 \leq t \leq T$.
  ▹*Awake phase:*
  Evaluate true moments $\mu(t)$, $\Delta(t)$ from the Stochastic simulation data $\{s\}(t)$.
  ▹*Asleep phase:*
  Evaluate moments $\tilde{\mu}(t)$, $\tilde{\Delta}(t)$ of the Boltzmann distribution by Gibbs sampling.
  ▹*Update to decrease objective function:*
  Solve (54) for derivative terms.
  Update $\theta^{(s)}$ to decrease the objective function for all s by taking: $\theta^{(s)} \rightarrow \theta^{(s)} - \lambda \times (53)$.

$$\frac{dh}{dt} = F_h(h, J) = \sum_r \theta^{(r)} \tilde{F}_h^{(r)},$$

$$\frac{dJ}{dt} = F_J(h, J) = \sum_r \theta^{(r)} \tilde{F}_J^{(r)}.$$

$$\frac{\partial}{\partial t'}\left(\frac{\partial h(t')}{\partial \theta^{(s)}}\right) = \tilde{F}_h^{(s)} + \frac{\partial h(t')}{\partial \theta^{(s)}} \sum_r \theta^{(r)} \frac{\partial \tilde{F}_h^{(r)}}{\partial h} + \frac{\partial J(t')}{\partial \theta^{(s)}} \sum_r \theta^{(r)} \frac{\partial \tilde{F}_h^{(r)}}{\partial J},$$

$$\frac{\partial}{\partial t'}\left(\frac{\partial J(t')}{\partial \theta^{(s)}}\right) = \tilde{F}_J^{(s)} + \frac{\partial h(t')}{\partial \theta^{(s)}} \sum_r \theta^{(r)} \frac{\partial \tilde{F}_J^{(r)}}{\partial h} + \frac{\partial J(t')}{\partial \theta^{(s)}} \sum_r \theta^{(r)} \frac{\partial \tilde{F}_J^{(r)}}{\partial J},$$

$$\int_0^\infty dt' \, \left(\tilde{\mu}(t') - \mu(t')\right) \frac{\partial h(t')}{\partial \theta^{(s)}} + \int_0^\infty dt' \, \left(\tilde{\Delta}(t') - \Delta(t')\right) \frac{\partial J(t')}{\partial \theta^{(s)}} = 0,$$

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 $\boldsymbol{u}_k$ controlling the functions $F_k(\boldsymbol{\theta}; \boldsymbol{u}_k)$ for all $k = 1, \dots, K$.
  Time interval $[t_0, t_f]$, a formula for the learning rate λ.
while not converged **do**
  Initialize $\Delta F_{k,i} = 0$ for all $k = 1, \dots, K$ and parameters $i = 1, \dots, M_k$.
  for sample in batch **do**
    ▷ *Generate trajectory in reduced space* $\boldsymbol{\theta}$*:*
    Solve the PDE constraint (27) for $\theta_k(t)$ with a given IC $\theta_{k,0}$ over $t_0 \le t \le t_f$, for all k.
    ▷ *Wake phase:*
    Evaluate moments $\mu_k(t)$ of the data for all k, t.
    ▷ *Sleep phase:*
    Evaluate moments $\tilde{\mu}_k(t)$ of the Boltzmann distribution.
    ▷ *Solve the adjoint system:*
    Solve the adjoint system (31) for $\phi_k(t)$ for all k, t.
    ▷ *Evaluate the objective function:*
    Update $\Delta F_{k,i}$ as the cumulative moving average of the sensitivity equation (30) over the batch.
  ▷ *Update to decrease objective function:*
  $u_{k,i} \to u_{k,i} - \lambda \Delta F_{k,i}$ for all k, i.

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

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

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

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

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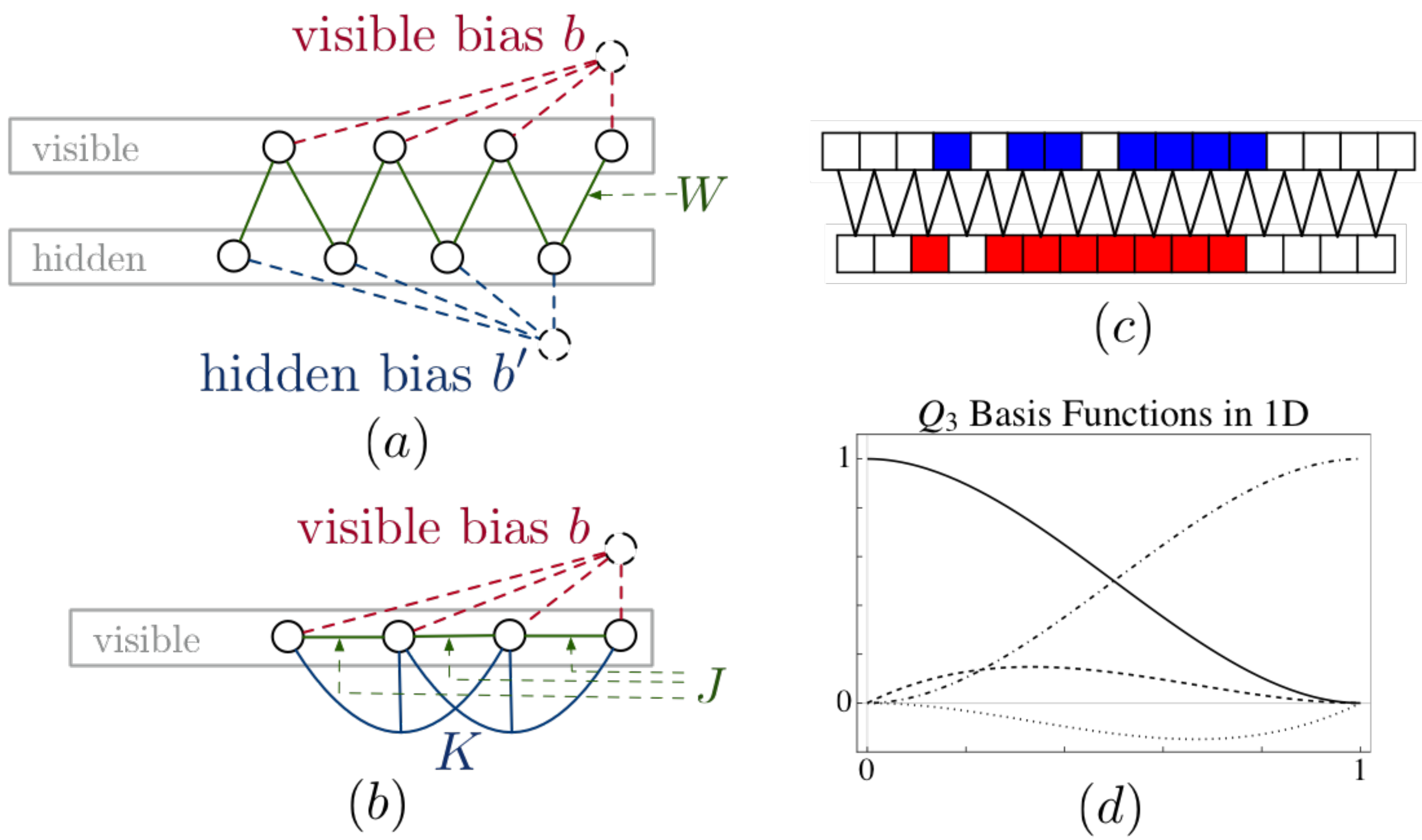
Benefit of Hidden Units

Network: fratricide + lattice diffusion



$$E(\boldsymbol{v}, \boldsymbol{h}, b(t), W(t), b'(t)) = -b(t)\sum_{i=1}^{N} v_i - b'(t)\sum_{j=1}^{N-1} h_j - W(t)\sum_{i=1}^{N}\sum_{j=i-1,i} v_i h_j,$$
$$\frac{d}{dt}\gamma = F_\gamma(b, b', W; \boldsymbol{u}_\gamma) \quad \text{for} \quad \gamma = b, b', W.$$

$$E(\boldsymbol{v}, b(t), J(t), K(t)) = -b(t)\sum_{i=1}^{N} v_i - J(t)\sum_{i=1}^{N-1} v_i v_{i+1} - K(t)\sum_{i=1}^{N-2} v_i v_{i+1} v_{i+2},$$
$$\frac{d}{dt}\gamma = F_\gamma(b, J, K; \boldsymbol{u}_\gamma) \quad \text{for} \quad \gamma = b, J, K.$$

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

Benefit of Hidden Units

Network: fratricide + lattice diffusion

- Learned DBD ODE RHS, without and with hidden units

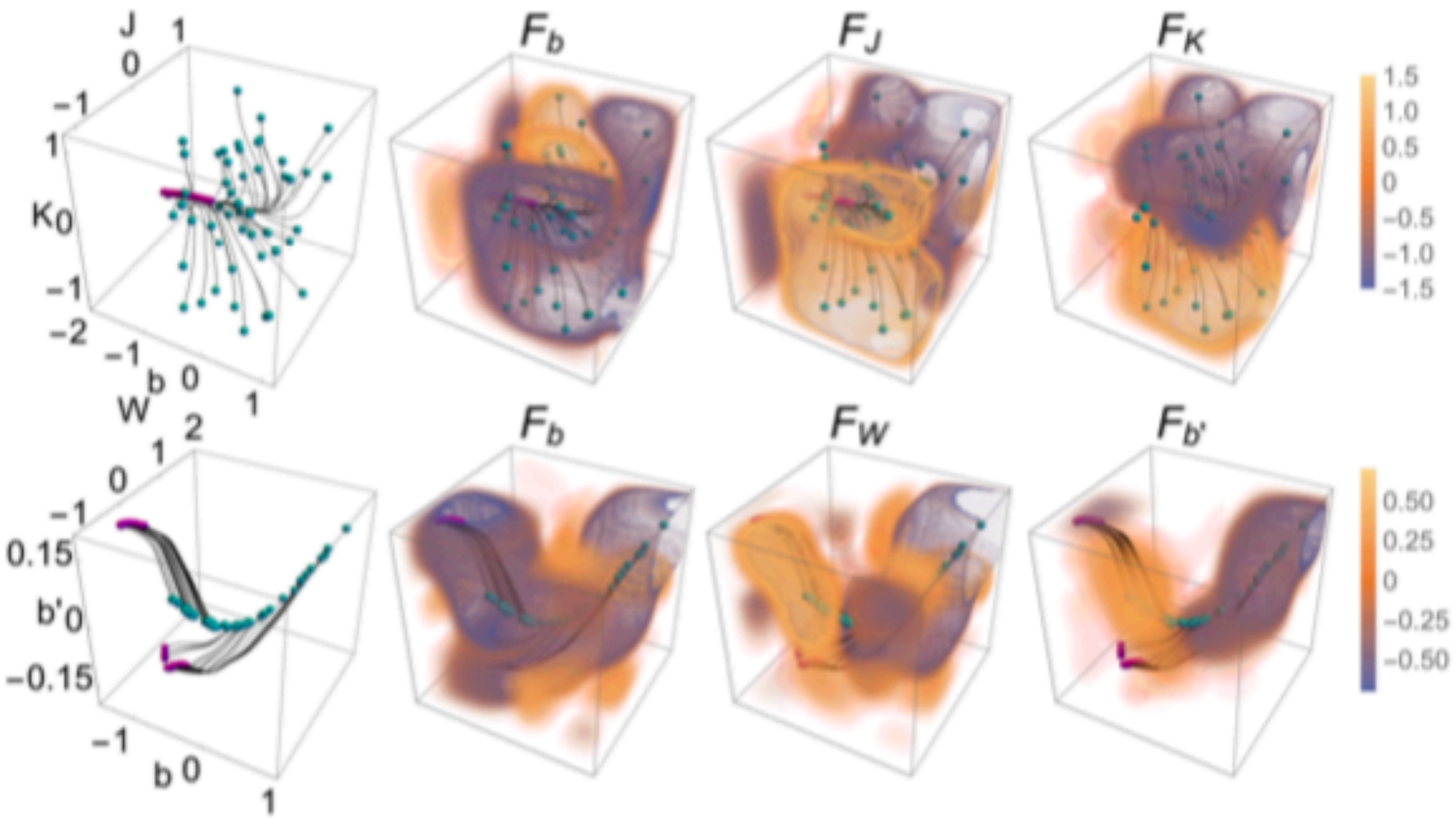
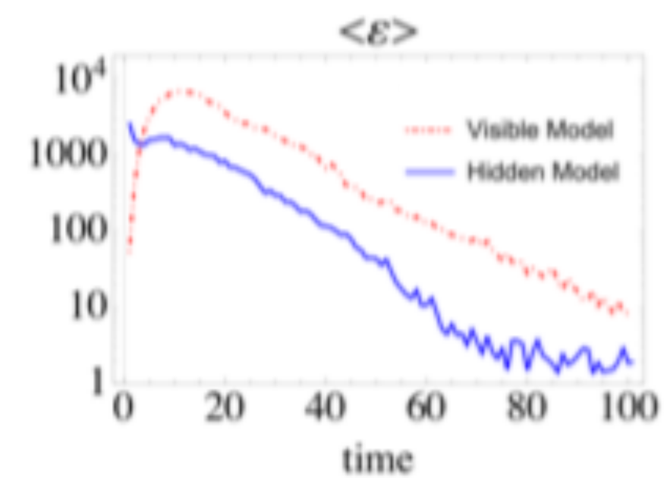


FIG. 2. *Top row:* Learned time-evolution functions for the fully visible model (19), using the Q_3, C_1 finite element parameterization (21) with $5 \times 5 \times 5$ evenly spaced cubic cells. Left: Training set of initial points (b, J, K) (cyan) sampled evenly in $[-1, 1]$. Stochastic simulations 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.

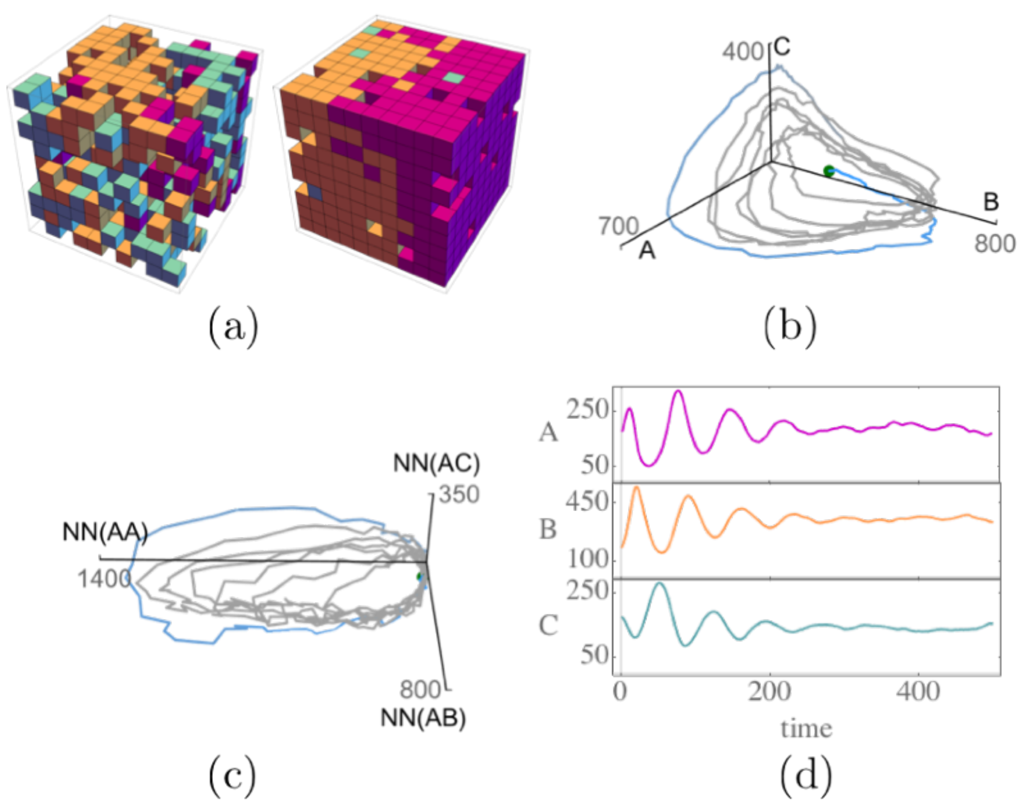


MSE of 4th order stats

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

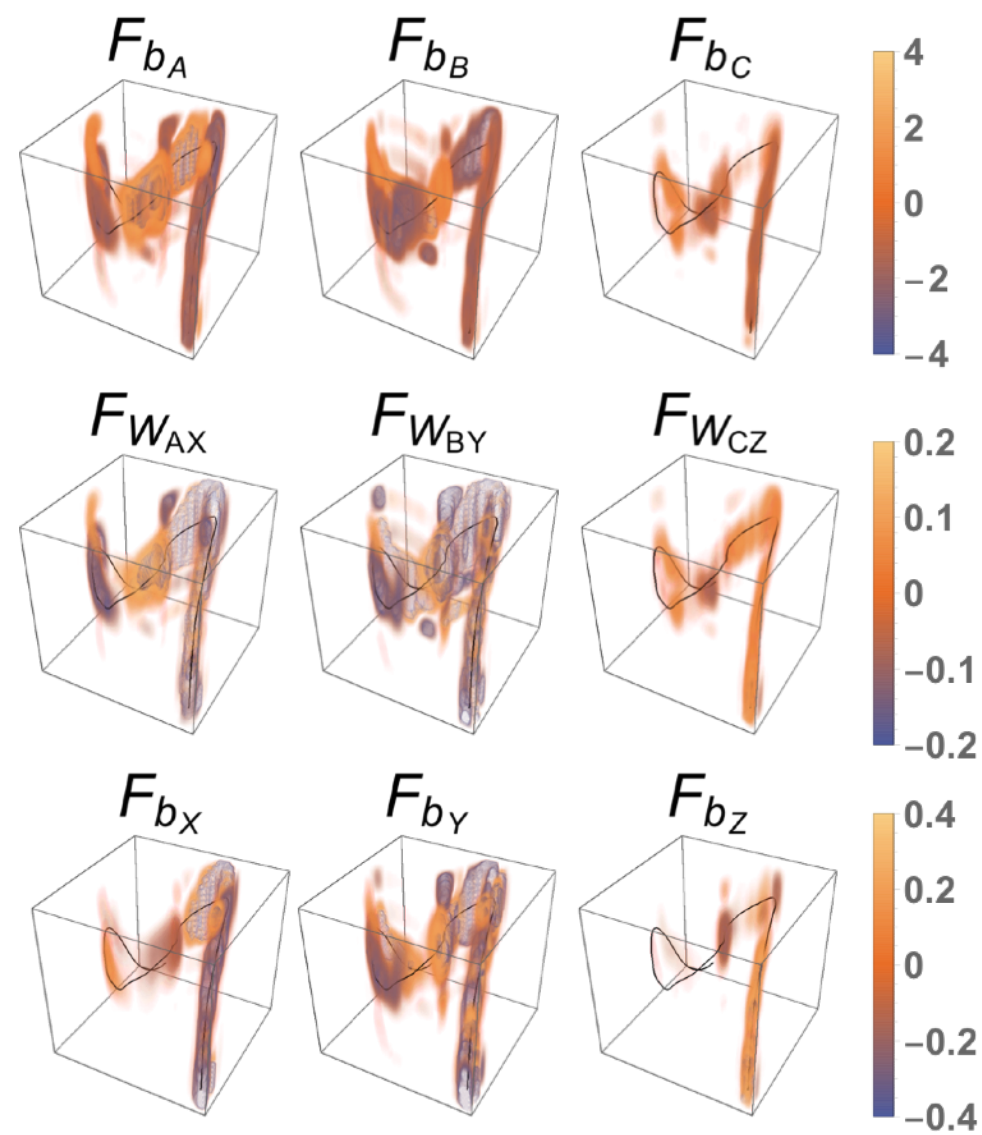
Rössler Oscillator in 3D

- Function:



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

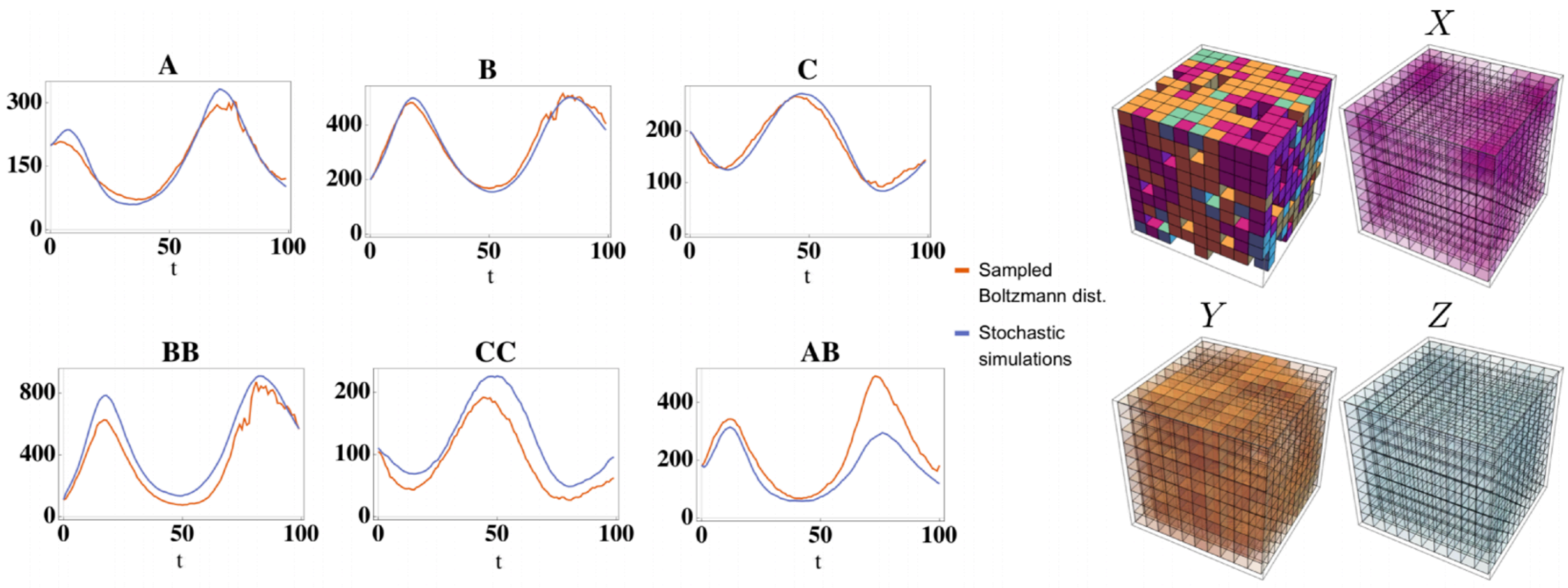
- Learned DBD ODE RHS:



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

Rössler Oscillator in 3D

- Learned correlations:
- Learned Configuration



(a) (b)

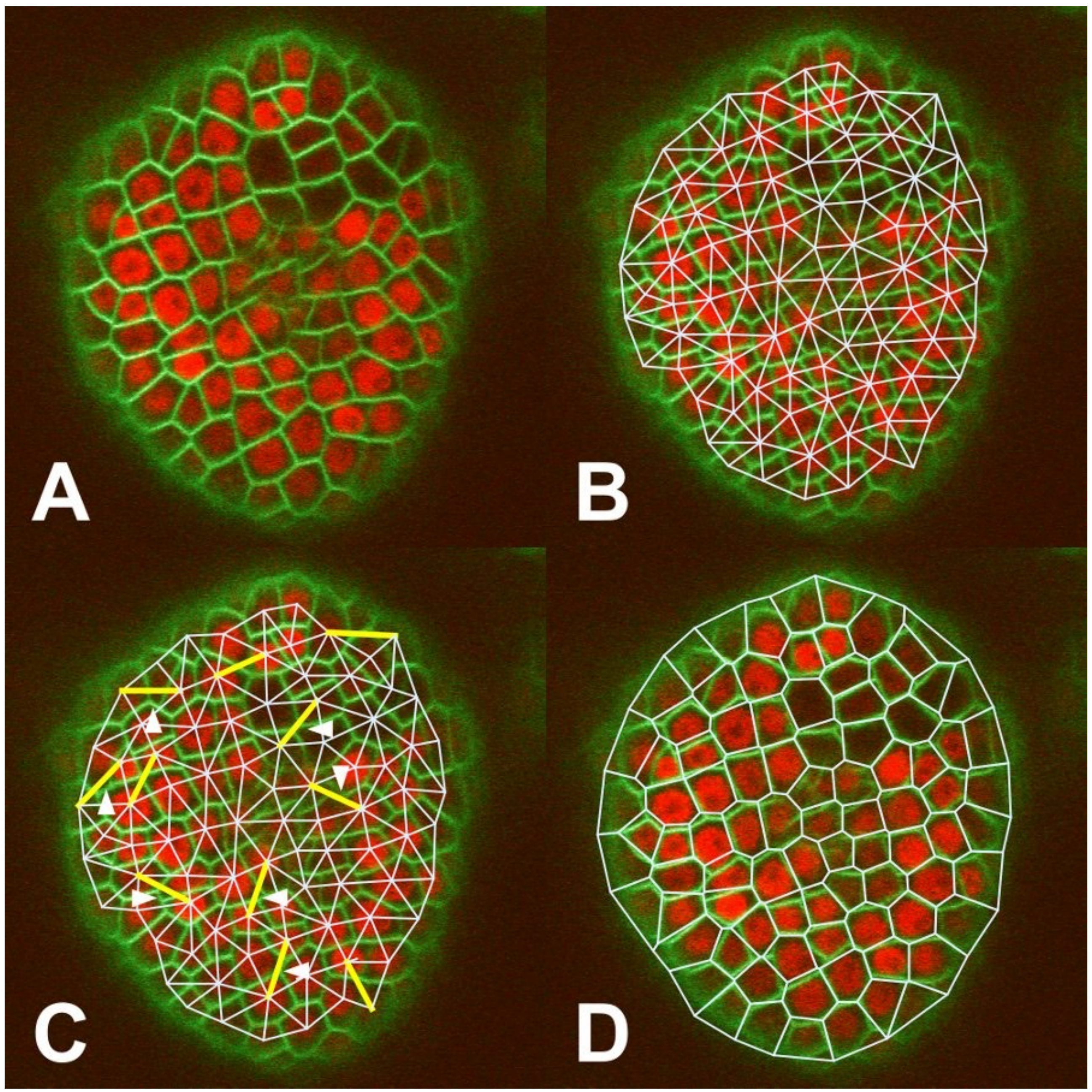
[Ernst, Bartol, Sejnowski, Mjolsness, Phys Rev E 99 063315, 2019]

Learned model reduction maps: Implications

- We can and should seek not models, but ***model stacks***
- simulation = $\text{model}_0 \hookrightarrow \text{model}_1 \hookrightarrow \ldots \hookrightarrow \text{model}_n$ = analysis
- each reduction is conditional
- great computing resources required at all levels - but becoming available

Algebras of dynamic structures

Living matter:
Tissues at cellular scale



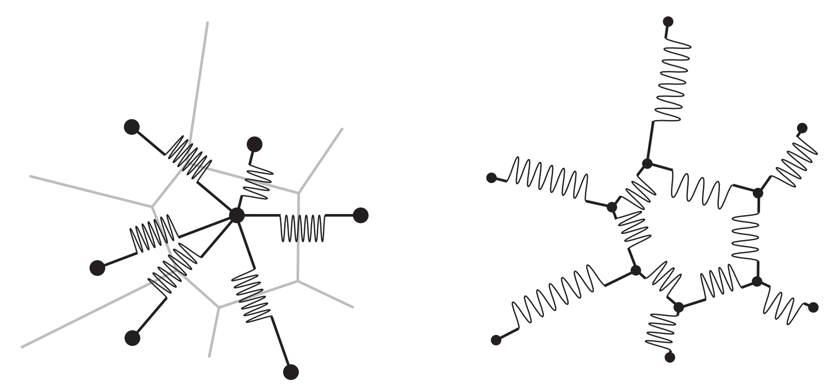
arXiv.org > q-bio > arXiv:1209.2937

Quantitative Biology > Cell Behavior

Tessellations and Pattern Formation in Plant Growth and Development

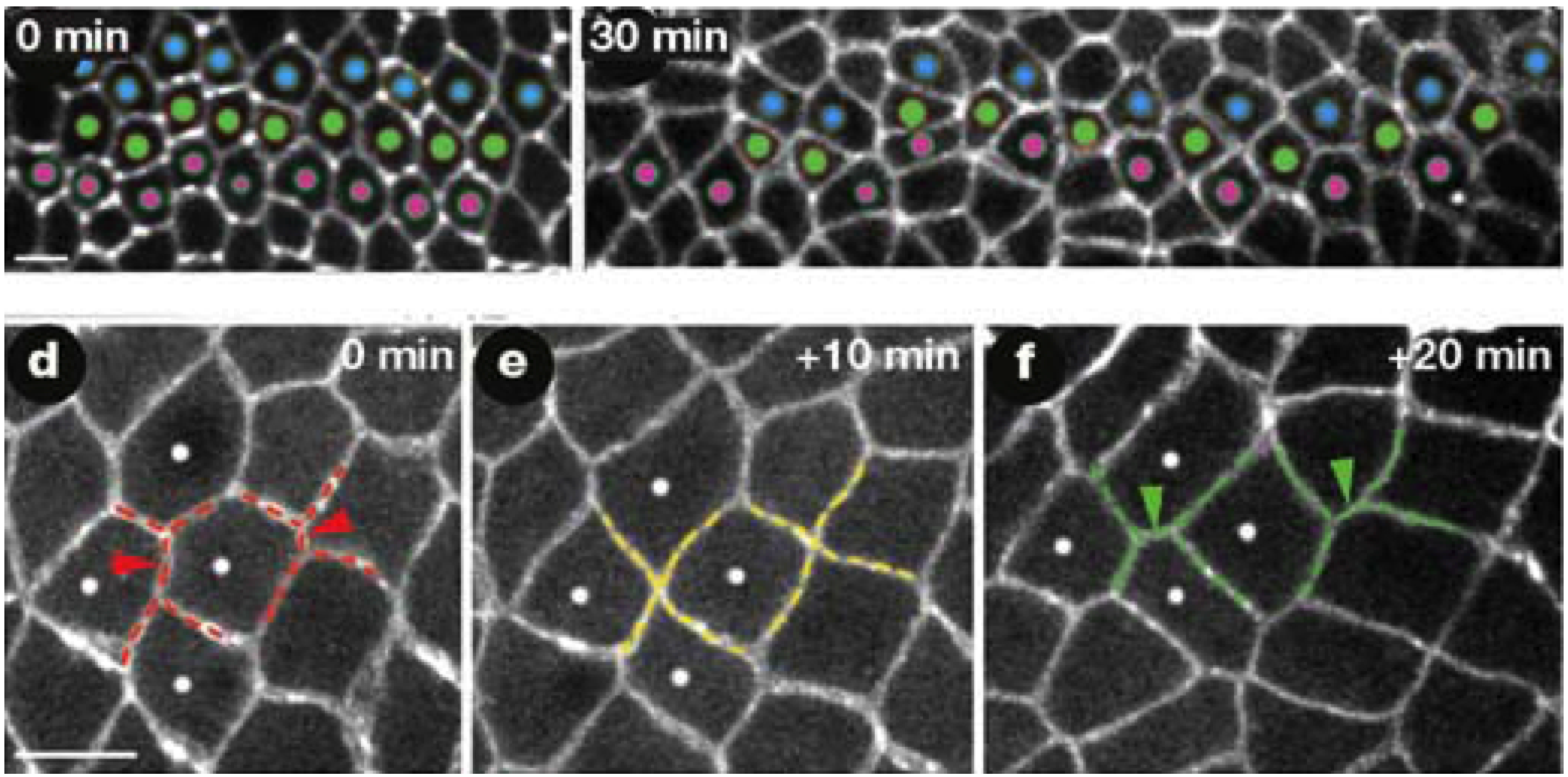
Bruce E Shapiro, Henrik Jonsson, Patrick Sahlin, Marcus Heisler, Adrienne Roeder, Michael Burl, Elliot M Meyerowitz, Eric D Mjolsness

Spring biomechanics:



Voronoi (or power) diagrams
fit SAM geometry

Dynamic cell structures in *Drosophila* embryo

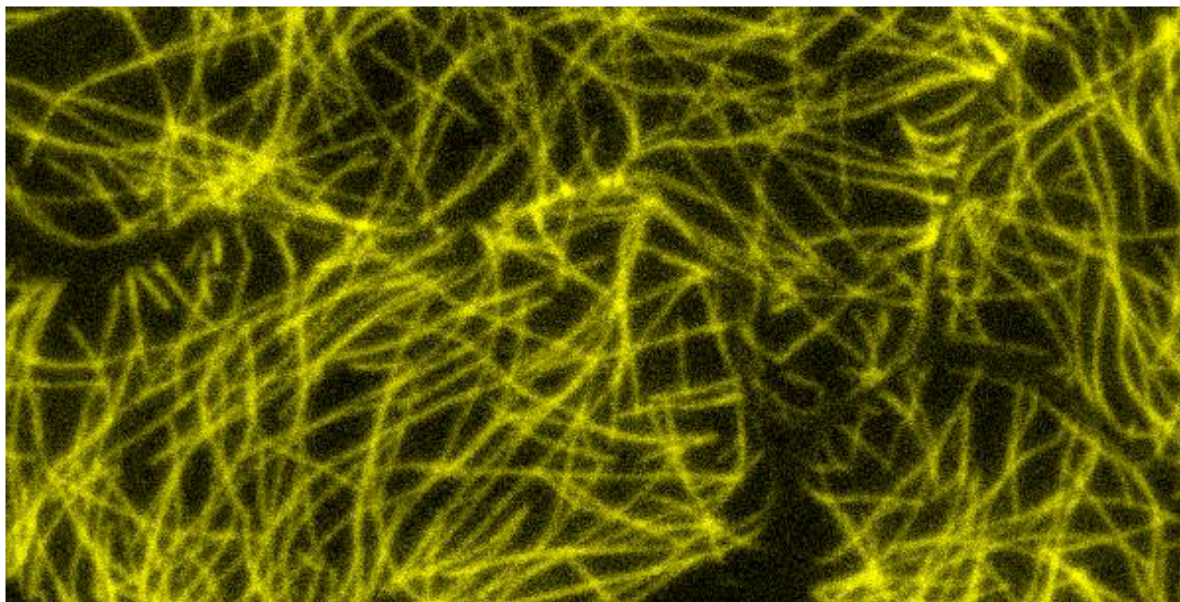


Intercalation and convergent extension observed during germ band elongation in Drosophila embryo. Note topological rearrangements. [Bertet et al. 2004]

Dynamic bio structures

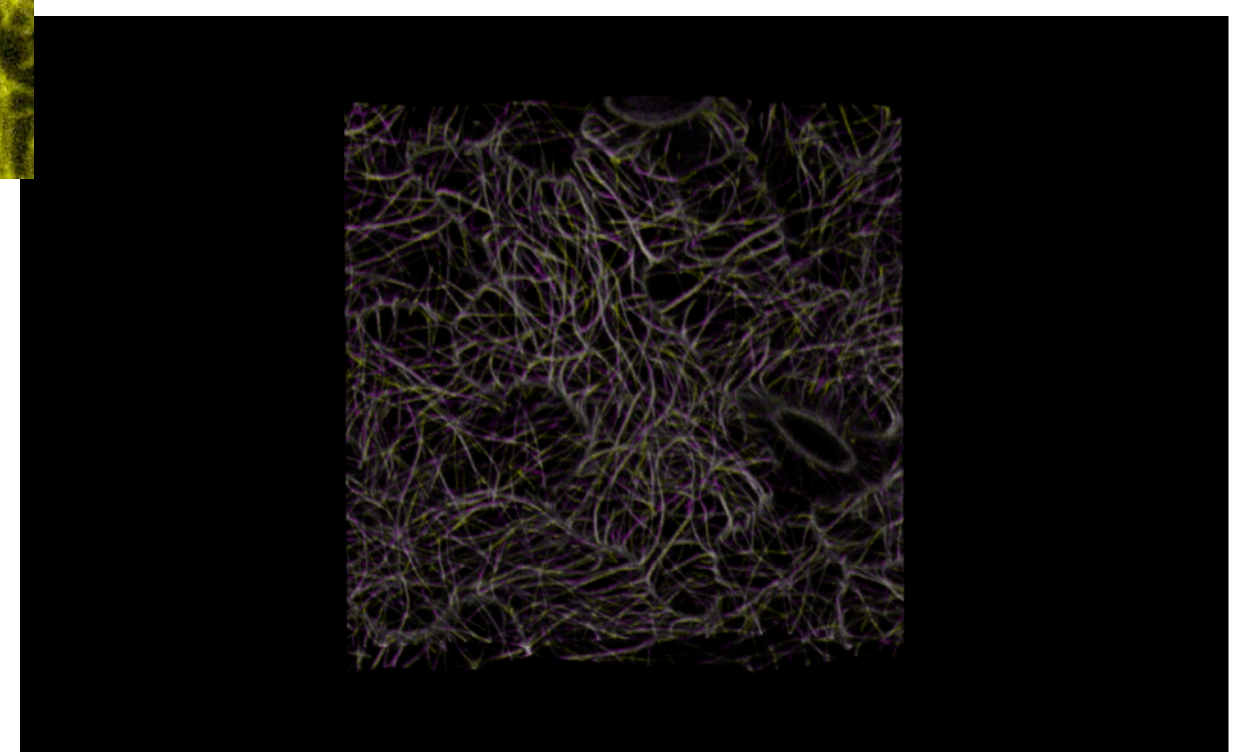
- ✓ geo-cell complexes of bio-cells in tissues
- cytoskeleton
- supercellular cables
- axons & dendrites
- cytonemes
- ...
- ✓ cell-centered and vertex biomechanical models
- PDE adaptive meshes and grids

Microtubule dynamics



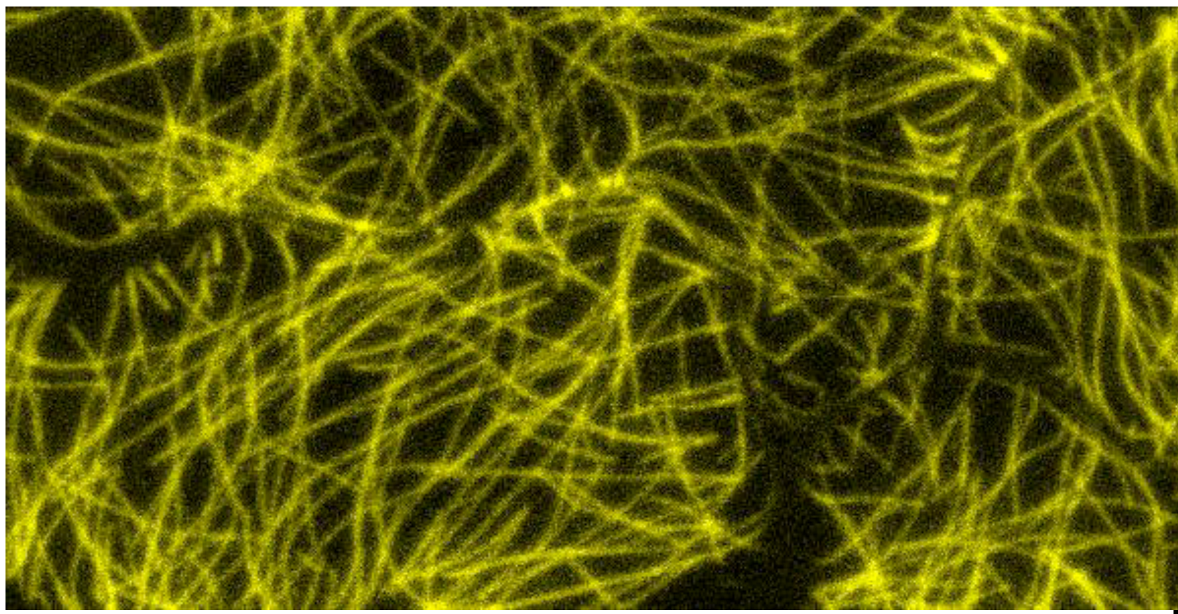
Cortical microtubules in *Arabidopsis* petiole cells.
Movie with Ray Wightman SLCU May 2015

WT data.
Also have mutants: *spiral2* and *botero*



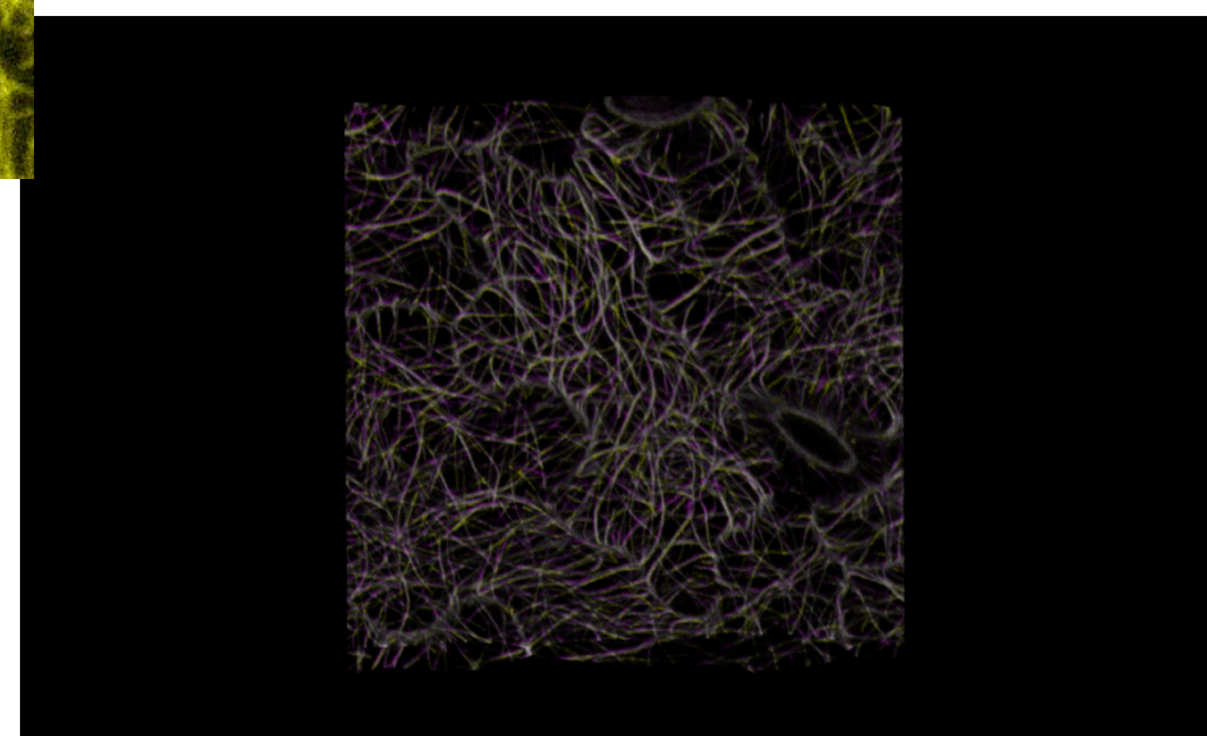
More cortical microtubules, color coded by growth vs shrinkage, in 3D.
From Ray Wightman SLCU 2015.

Microtubule dynamics



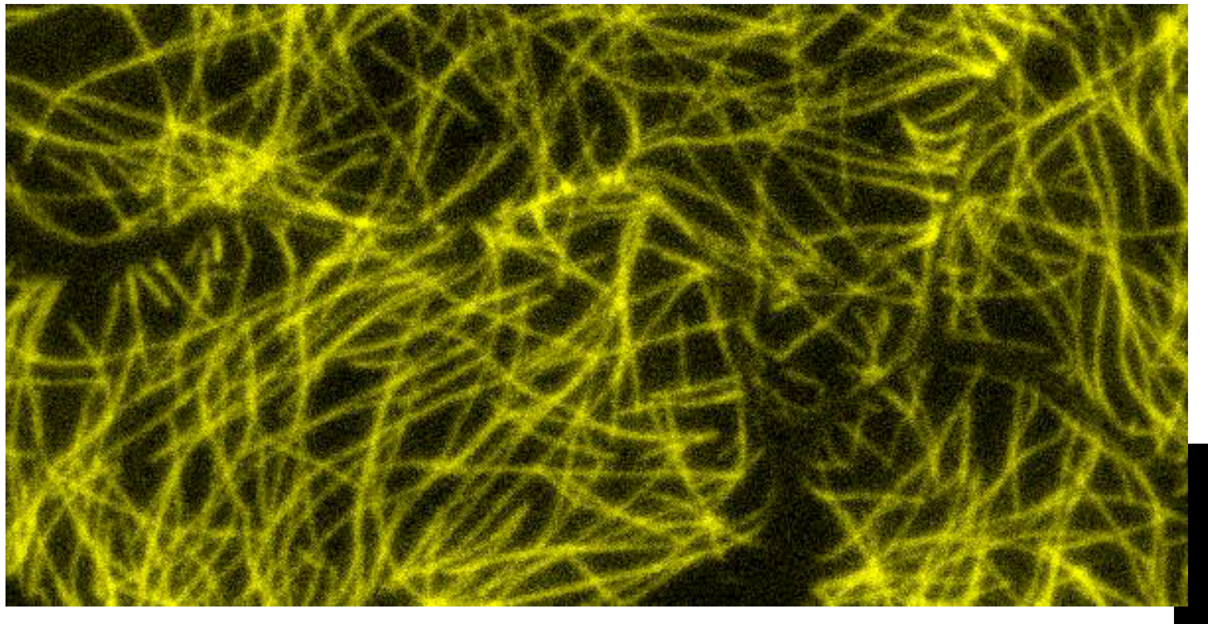
Cortical microtubules in *Arabidopsis* petiole cells.
Movie with Ray Wightman SLCU May 2015

WT data.
Also have mutants: *spiral2* and *botero*



More cortical microtubules, color coded by growth vs shrinkage, in 3D.
From Ray Wightman SLCU 2015.

Microtubule dynamics



Cortical microtubules in *Arabidopsis* petiole cells.
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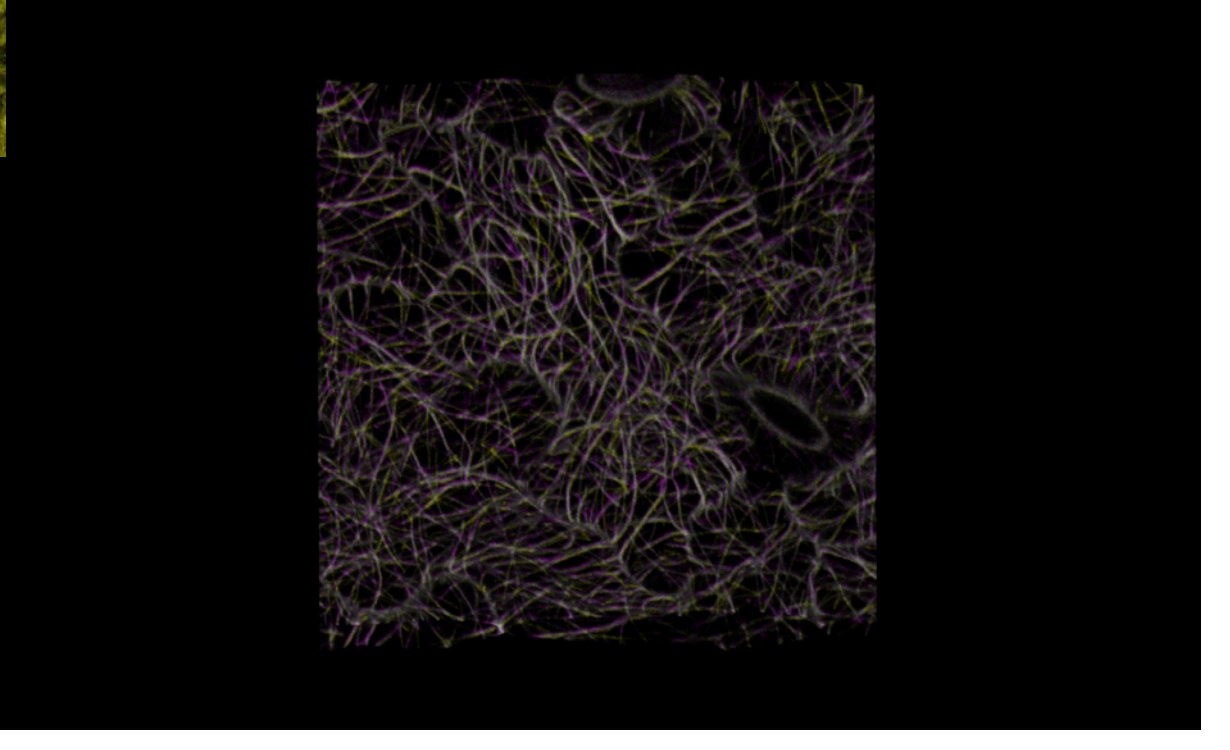
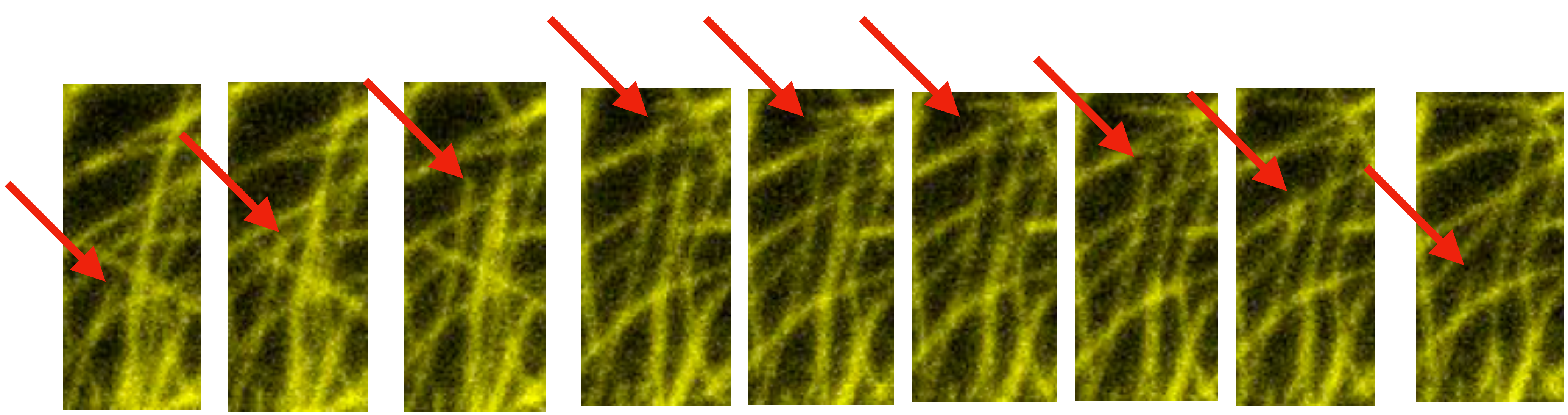


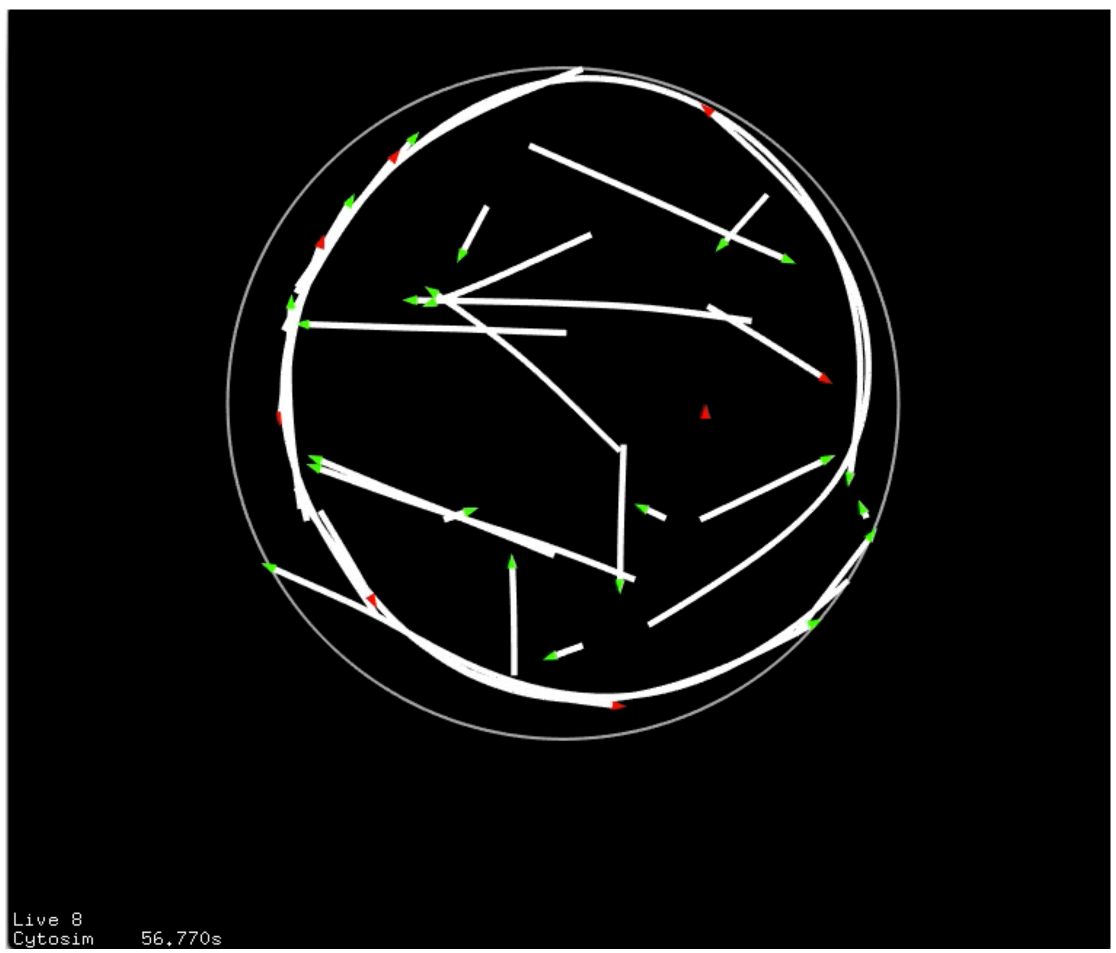
More cortical microtubules, color coded by growth vs shrinkage, in 3D.
From Ray Wightman SLCU 2015.

Bundling or Zippering

Collision catastrophe

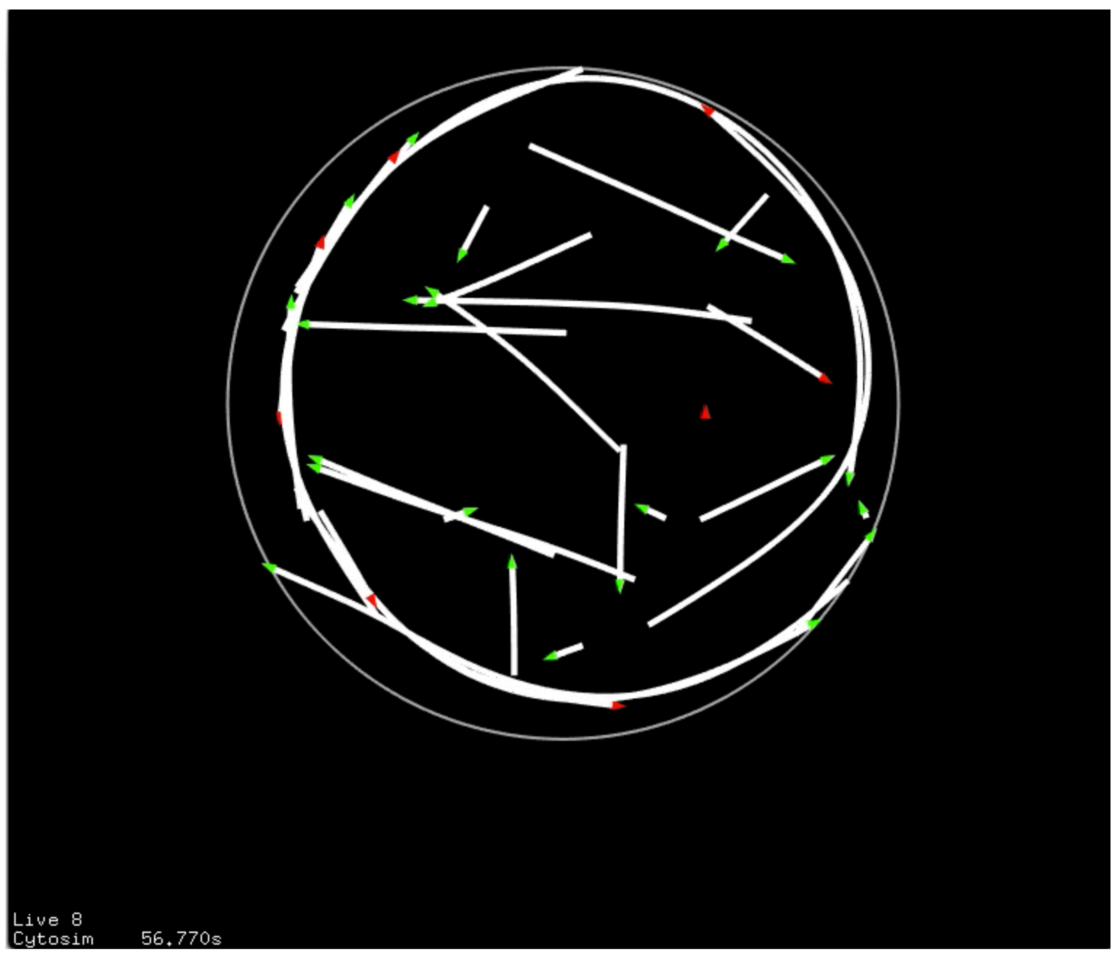


Simulated bundling, catastrophe



Dustin Maurer + Francois Nedelec

Simulated bundling, catastrophe



Dustin Maurer + Francois Nedelec

MT fiber
Stochastic Parametrized Graph Grammar

$$(\bullet_1)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1)\rangle\!\rangle \longrightarrow (\circ_1 \longrightarrow \bullet_2)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle$$
$$\quad \textbf{with} \quad \hat{\rho}_{\text{grow}}([\text{tubulin}])\mathcal{N}(\boldsymbol{x}_1-\boldsymbol{x}_2; L\boldsymbol{u}_1,\sigma)\mathcal{N}(\boldsymbol{u}_2;\boldsymbol{u}_1/(|\boldsymbol{u}_1|+\epsilon),\epsilon),$$

$$(\blacksquare_1 \longrightarrow \circ_2)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle \longrightarrow (\blacksquare_2)\langle\!\langle(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle$$
$$\quad \textbf{with} \quad \hat{\rho}_{\text{retract}}$$

$$\begin{pmatrix} \circ_1 \longrightarrow \circ_2 \longrightarrow \circ_3 \\ \bullet_4 \end{pmatrix}\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2),(\boldsymbol{x}_3,\boldsymbol{u}_3),(\boldsymbol{x}_4,\boldsymbol{u}_4)\rangle\!\rangle$$
$$\longrightarrow \begin{pmatrix} \circ_1 \longrightarrow \blacktriangle_2 \longrightarrow \circ_3 \\ \nearrow \\ \circ_4 \end{pmatrix}\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2),(\boldsymbol{x}_3,\boldsymbol{u}_3),(\boldsymbol{x}_4,\boldsymbol{u}_4)\rangle\!\rangle$$
$$\quad \textbf{with} \quad \hat{\rho}_{\text{bundle}}(|\boldsymbol{u}_2\cdot\boldsymbol{u}_4|/|\cos\theta_{\text{crit}}|)\exp(-|\boldsymbol{x}_2-\boldsymbol{x}_4|^2/2L^2)$$

$$(\blacksquare_1 \longrightarrow \bullet_2)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1),(\boldsymbol{x}_2,\boldsymbol{u}_2)\rangle\!\rangle \longleftrightarrow \varnothing \qquad \textbf{with} \quad \Big(\hat{\rho}_{\text{retract}},$$
$$\hat{\rho}_{\text{nucleate}}([\text{tubulin}])\mathcal{N}(\boldsymbol{x};\mathbf{0},\sigma_{\text{broad}})\delta_{\text{Dirac}}(|\boldsymbol{u}_1|-1)\delta_{\text{Dirac}}(\boldsymbol{u}_1-\boldsymbol{u}_2)\Big)$$

$$(\bullet_1)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1)\rangle\!\rangle \longleftrightarrow (\blacksquare_1)\langle\!\langle(\boldsymbol{x}_1,\boldsymbol{u}_1)\rangle\!\rangle$$
$$\quad \textbf{with} \quad (\hat{\rho}_{\text{retract}\leftarrow\text{growth}},\hat{\rho}_{\text{growth}\leftarrow\text{retract}})$$

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

MT fiber
Stochastic Parametrized Graph Grammar

$$(\bullet_1)\langle\!\langle(x_1,u_1)\rangle\!\rangle \longrightarrow (\circ_1 \longrightarrow \bullet_2)\langle\!\langle(x_1,u_1),(x_2,u_2)\rangle\!\rangle$$

$$\textbf{with}\ \hat\rho_{\text{grow}}([\text{Y}_g])\mathcal{N}(x_1-x_2;Lu_1,\sigma)\mathcal{N}(u_2;u_1/(|u_1|+\epsilon),\epsilon),$$

$$(\blacksquare_1 \longrightarrow \circ_2)\langle\!\langle(x_1,u_1),(x_2,u_2)\rangle\!\rangle \longrightarrow (\blacksquare_2)\langle\!\langle(x_2,u_2)\rangle\!\rangle$$

$$\textbf{with}\ \hat\rho_{\text{retract}}([\text{Y}_r])$$

$$\begin{pmatrix} \circ_1 \longrightarrow \circ_2 \longrightarrow \circ_3 \\ \bullet_4 \end{pmatrix}\langle\!\langle(x_1,u_1),(x_2,u_2),(x_3,u_3),(x_4,u_4)\rangle\!\rangle$$

$$\longrightarrow \begin{pmatrix} \circ_1 \longrightarrow \blacktriangle_2 \longrightarrow \circ_3 \\ \nearrow \\ \circ_4 \end{pmatrix}\langle\!\langle(x_1,u_1),(x_2,u_2),(x_3,u_3),(x_4,u_4)\rangle\!\rangle$$

$$\textbf{with}\ \hat\rho_{\text{bundle}}(|u_2\cdot u_4|/|\cos\theta_{\text{crit}}|)\exp\left(-|x_2-x_4|^2/2L^2\right)$$

$$\longrightarrow \begin{pmatrix} \circ_1 - \circ_2 - \circ_3 \\ \circ_4 - \blacksquare_5 \end{pmatrix}\langle\!\langle(x_1,u_1),(x_2,u_2),(x_3,u_3),(x_4,u_4)\rangle\!\rangle$$

$$\textbf{with}\ \hat\rho'_{\text{bundle}}(|u_2\cdot u_4|/|\cos\theta_{\text{crit}}|)\exp\left(-|x_2-x_5|^2/2L^2\right)$$

$$\longrightarrow \begin{pmatrix} & & \bullet_5 \\ & \circ_6 & \\ \circ_1 - \blacklozenge_2 - \circ_3 & & \\ \circ_4 & & \end{pmatrix}\langle\!\langle(x_1,u_1),(x_2,u_2),(x_3,u_3),(x_4,u_4),(x_5,u_5),(x_6,u_6)\rangle\!\rangle$$

$$\textbf{with}\ \hat\rho''_{\text{bundle}}(|u_2\cdot u_4|/|\cos\theta_{\text{crit}}|)\exp\left(-|x_2-x_5|^2/2L^2\right)$$

$$(\blacksquare_1 \longrightarrow \bullet_2)\langle\!\langle(x_1,u_1),(x_2,u_2)\rangle\!\rangle \longleftrightarrow \varnothing$$

$$\textbf{with}\ (\hat\rho_{\text{retract}}([\text{Y}_r]),\hat\rho_{\text{nucleate}}([\text{Y}_g])\mathcal{N}(x;\mathbf{0},\sigma_{\text{broad}})\delta_{\text{Dirac}}(|u_1|-1)\delta_{\text{Dirac}}(u_1-u_2))$$

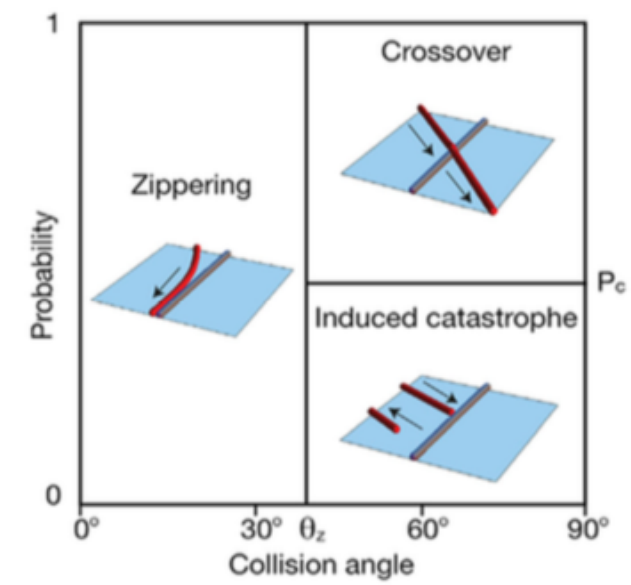
$$(\bullet_1)\langle\!\langle(x_1,u_1)\rangle\!\rangle \longleftrightarrow (\blacksquare_1)\langle\!\langle(x_1,u_1)\rangle\!\rangle$$

$$\textbf{with}\ (\hat\rho_{\text{retract}\leftarrow\text{growth}},\hat\rho_{\text{growth}\leftarrow\text{retract}})$$

$$(\circ_1 \longrightarrow \circ_2 \longrightarrow \circ_3)\langle\!\langle(x_1,u_1),(x_2,u_2),(x_3,u_3)\rangle\!\rangle$$

$$\longrightarrow (\circ_1 \longrightarrow \bullet_2 \quad \blacksquare_4 \longrightarrow \circ_3)\langle\!\langle(x_1,u_1),(x_2,u_2),(x_3,u_3),(x_4,u_4)\rangle\!\rangle$$

$$\textbf{with}\ \hat\rho_{\text{sever}}([\text{katanin}])\mathcal{N}(x;\mathbf{0},\sigma_{\text{broad}})\delta_{\text{Dirac}}(|u|-1))$$



[Chakrabortty et al. Current Biology 2018]

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

MT fiber
Dynamical Graph Grammar
(hand-transformed from stochastic G.G.)

5.2 MT dynamical graph grammar

// Treadmilling (growth end):

$$(\circ_1 \text{ --- } \bullet_2)\langle\!\langle (l,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle \longrightarrow (\circ_1 \text{ --- } \bullet_2)\langle\!\langle (l,\boldsymbol{u}), (\boldsymbol{x}_+ + d\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$

solving $d\boldsymbol{x}_+/dt = \hat{\rho}_{\text{grow}}([\mathrm{Y}_g])(1 - l/l_{\max})\boldsymbol{u}_+$

// Treadmilling (retracting end):

$$(\blacksquare_1 \text{ --- } \circ_2)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l,\boldsymbol{u})\rangle\!\rangle \longrightarrow (\blacksquare_1 \text{ --- } \circ_2)\langle\!\langle (\boldsymbol{x}_- + d\boldsymbol{x}_-, \boldsymbol{u}_-), (l,\boldsymbol{u})\rangle\!\rangle$$

solving $d\boldsymbol{x}_-/dt = \hat{\rho}_{\text{retract}}([\mathrm{Y}_r])(l/l_{\max})\boldsymbol{u}$

// Treadmilling (interior node):

$$(\blacksquare_1 \text{ --- } \circ_2 \text{ --- } \bullet_3)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$
$$\longrightarrow (\blacksquare_1 \text{ --- } \circ_2 \text{ --- } \bullet_3)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l + dl,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$

solving $dl/dt = |d\boldsymbol{x}_+/dt| - |d\boldsymbol{x}_-/dt| = \hat{\rho}_{\text{grow}}([\mathrm{Y}_g]) - \Big(\hat{\rho}_{\text{grow}}([\mathrm{Y}_g]) + \hat{\rho}_{\text{retract}}([\mathrm{Y}_r])\Big)(l/l_{\max})$

// Treadmilling (interior node):

$$(\bullet_1 \text{ --- } \circ_2 \text{ --- } \bullet_3)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$
$$\longrightarrow (\bullet_1 \text{ --- } \circ_2 \text{ --- } \bullet_3)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l + dl,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$

solving $dl/dt = |d\boldsymbol{x}_+/dt| - |d\boldsymbol{x}_-/dt| = 2\hat{\rho}_{\text{grow}}([\mathrm{Y}_g])(1 - l/l_{\max})\boldsymbol{u}_+$

// Treadmilling (interior node):

$$(\blacksquare_1 \text{ --- } \circ_2 \text{ --- } \blacksquare_3)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$
$$\longrightarrow (\blacksquare_1 \text{ --- } \circ_2 \text{ --- } \blacksquare_3)\langle\!\langle (\boldsymbol{x}_-, \boldsymbol{u}_-), (l + dl,\boldsymbol{u}), (\boldsymbol{x}_+, \boldsymbol{u}_+)\rangle\!\rangle$$

solving $dl/dt = |d\boldsymbol{x}_+/dt| - |d\boldsymbol{x}_-/dt| = 2\hat{\rho}_{\text{retract}}([\mathrm{Y}_r])(l/l_{\max})\boldsymbol{u}_-$

// Fiber collision, exerting continuous force:

$$\begin{pmatrix} & \star_1 \text{ --- } \circ_2 \text{ --- } \star_3 \\ \circ_4 \text{ --- } \bullet_5 & \end{pmatrix} \begin{array}{l} \langle\!\langle (\boldsymbol{x}_1, \boldsymbol{u}_1), (l_2, \boldsymbol{u}_2), (\boldsymbol{x}_3, \boldsymbol{u}_3), (l_4, \boldsymbol{u}_4), (\boldsymbol{x}_5, \boldsymbol{u}_5)\rangle\!\rangle \\ \to \langle\!\langle (\boldsymbol{x}_1, \boldsymbol{u}_1), (l_2, \boldsymbol{u}_2), (\boldsymbol{x}_3, \boldsymbol{u}_3), (l_4 + dl_4, \boldsymbol{u}_4), (\boldsymbol{x}_5 + d\boldsymbol{x}_5, \boldsymbol{u}_5)\rangle\!\rangle \end{array}$$

$$\textbf{solving} \begin{cases} d\boldsymbol{x}_5/dt = \kappa \boldsymbol{u}_5[\partial_\gamma \exp\big(-\gamma^2/2\epsilon^2\big)]\Theta(\epsilon \leqslant \alpha \leqslant 1 - \epsilon) \\ dl_4/dt = \boldsymbol{u}_5 \cdot d\boldsymbol{x}_+/dt = \kappa[\partial_\gamma \exp\big(-\gamma^2/2\epsilon^2\big)]\Theta(\epsilon \leqslant \alpha \leqslant 1 - \epsilon) \end{cases}$$

$$\textbf{where} \begin{cases} \gamma = -[(\boldsymbol{x}_3 - \boldsymbol{x}_1) \times (\boldsymbol{x}_1 - \boldsymbol{x}_5)]_z / [(\boldsymbol{x}_3 - \boldsymbol{x}_1) \times \boldsymbol{u}_5]_z & \text{// rel. distance to intersection along } \boldsymbol{u}_5 \\ \alpha = -[(\boldsymbol{x}_1 - \boldsymbol{x}_4) \times \boldsymbol{u}_5]_z / [(\boldsymbol{x}_3 - \boldsymbol{x}_1) \times \boldsymbol{u}_5]_z & \text{// fractional location of intersection along } \boldsymbol{u}_2 \end{cases}$$

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

MT fiber Dynamical Graph Grammar

(hand-transformed from stochastic G.G.)

// (continued)

// Fiber collision, with several alternative discrete outcomes:

$$\begin{pmatrix} \star_1 - \circ_2 - \star_3 \\ \circ_4 - \bullet_5 \end{pmatrix} \langle\langle (x_1,u_1),(l_2,u_2),(x_3,u_3),(l_4,u_4),(x_5,u_5) \rangle\rangle$$

$$\longrightarrow \begin{pmatrix} \star_1 - \circ_6 - \blacktriangle_2 - \circ_7 - \star_3 \\ \circ_4 \,/\, \blacktriangle_2 \end{pmatrix} \langle\langle (x_1,u_1),(x_2,u_2),(x_3,u_3),(l_4,u_4),\varnothing,(\alpha l_4,u_2),((1-\alpha)l_4,u_2$$

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

$$\longrightarrow \begin{pmatrix} \star_1 - \circ_2 - \star_3 \\ \circ_4 - \blacksquare_5 \end{pmatrix} \langle\langle (x_1,u_1),(l_2,u_2),(x_3,u_3),(l_4,u_4),(x_5,u_5) \rangle\rangle$$

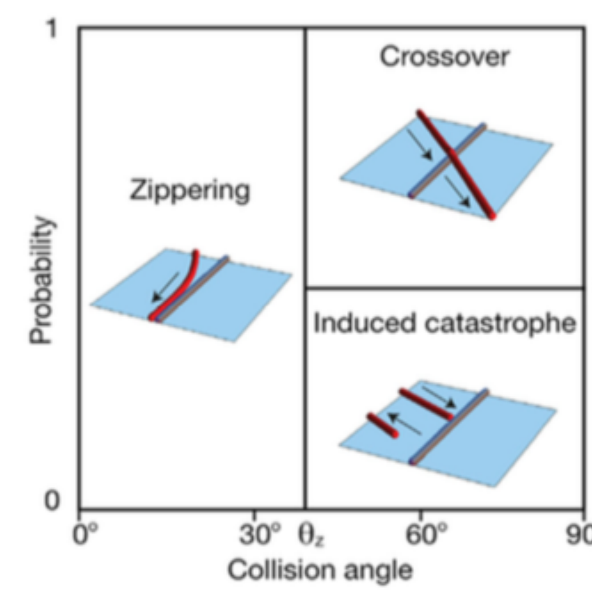
with $\hat{\rho}'_{\text{bundle}}(|u_2\cdot u_4|/|\cos\theta_{\text{crit}}|)\exp\left(-\gamma^2/2\epsilon^2\right)\Theta(\epsilon\leqslant\alpha\leqslant 1-\epsilon)$

$$\longrightarrow \begin{pmatrix} \blacklozenge_2 - \circ_8 - \bullet_9 \\ \star_1 - \circ_6 - \blacklozenge_2 - \circ_7 - \star_3 \\ \circ_4 \,/\, \blacklozenge_2 \end{pmatrix} \left\langle\left\langle \begin{matrix} (x_1,u_1),((1-\alpha)x_1+\alpha x_3,u_2),(x_3,u_3),(l_4,u_4),\varnothing, \\ (\alpha l_2,u_2),((1-\alpha)l_2,u_2),(\epsilon l_4,u_4),(x_2+\epsilon l_4 u_4),u_4) \end{matrix} \right\rangle\right\rangle$$

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

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



[Chakrabortty et al. Current Biology 2018]

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

Ψ

Operator algebra for Pure stochastic chemical reactions

- For reaction/rule r:

$$\hat{W}_{\{m_i^{(r)}\}\to\{n_i^{(r)}\}} = k^{(r)}\prod_i (\hat{a}_i)^{n_i^{(r)}}(a_i)^{m_i^{(r)}}$$

$n_\alpha \in \mathbb{N}$: $[a_\alpha, \hat{a}_\beta] = \delta_{\alpha\beta} I$, i.e.

$$a_\alpha \hat{a}_\beta = \hat{a}_\beta a_\alpha + \delta_{\alpha\beta} I_\alpha$$

$n_\alpha \in \{0,1\}$: $a_\alpha \hat{a}_\beta = (1-\delta_{\alpha\beta})\hat{a}_\beta a_\alpha + \delta_{\alpha\beta} Z_\alpha$

- For reaction/rules r_1 and r_2:

where $(n)_l \equiv \begin{cases} n!/(n-l)! & \text{for } l \le n; \\ 0 & \text{otherwise}. \end{cases}$

$$\hat{W}_{\{m_i^{(r_2)}\}\to\{n_i^{(r_2)}\}}\hat{W}_{\{m_i^{(r_1)}\}\to\{n_i^{(r_1)}\}} = k^{(r_2)}k^{(r_1)} \sum_{\{l_i=0\ldots\min(m_i^{(r_2)},n_i^{(r_1)})\}} \left(\prod_i \frac{(m_i^{(r_2)})_l (n_i^{(r_1)})_l}{l_i!}\right) \times \hat{W}_{\{(m_i^{(r_1)}+m_i^{(r_2)}-l_i)\}\to\{(n_i^{(r_1)}+n_i^{(r_2)}-l_i)\}}$$

Why: $\partial_x^m(x^n f(x)) =$ binomial sum

Ψ

Lie Algebra for Pure stochastic chemical reactions

- Rotation group: $[X, Y] = Z \ + \ \text{cyclic}$
  - Curvature in a Lie group w invariant metric:

$$R(X,Y)Z = \frac{1}{4}[[X,Y],Z]$$

- For reaction/rule *r*: $[a_\alpha, \hat{a}_\beta] = \delta_{\alpha\beta} I$

$$\hat{W}_{\{m_i^{(r)}\} \to \{n_i^{(r)}\}} = k^{(r)} \prod_i (\hat{a}_i)^{n_i^{(r)}} (a_i)^{m_i^{(r)}}$$

- For reaction/rules r_1 and r_2: where $(n)_l \equiv \begin{cases} n!/(n-l)! & \text{for } l \leq n; \\ 0 & \text{otherwise}. \end{cases}$

$$[\hat{W}_{\{m_i^{(r_2)}\} \to \{n_i^{(r_2)}\}}, \hat{W}_{\{m_i^{(r_1)}\} \to \{n_i^{(r_1)}\}}] = k^{(r_2)} k^{(r_1)} \sum_{\substack{\{l_i = 0 \ldots \min(m_i^{(r_2)}, n_i^{(r_1)})\} \\ \vec{l} \neq \vec{0}}} \left[\left(\prod_i \frac{(m_i^{(r_2)})_l (n_i^{(r_1)})_l}{l_i!} \right) - \left(\prod_i \frac{(m_i^{(r_1)})_l (n_i^{(r_2)})_l}{l_i!} \right) \right] \times \hat{W}_{\{(m_i^{(r_1)} + m_i^{(r_2)} - l_i)\} \to \{(n_i^{(r_1)} + n_i^{(r_2)} - l_i)\}}$$

Ψ

Particle to Structure Dynamics

- ***Particle*** reactions/transitions, with params

$$A_1(x_1),\ A_2(x_2),\ \ldots,\ A_n(x_n) \rightarrow B_1(y_1),\ B_2(y_2),\ \ldots,\ B_m(y_m)\ \textbf{with}\ \rho(\{x_i\},\{y_j\})$$

$$\tilde{O}_r = \rho_r \sum_{\{x'_i, x_j\}} \prod_{i \in \mathrm{rhs}(r)} \hat{a}(\tau_i, x_i) \prod_{j \in \mathrm{lhs}(r)} a(\tau_j, x_j)\, \Pr(\{x_i\} \mid \{x_j\})$$

$$[a_{ab}, \hat{a}_{cd}] = I\, \delta_{(ab),(cd)}$$
$$[a, a] = [\hat{a}, \hat{a}] = 0$$

(and can integrate ODE rules too)

Particle to Structure Dynamics

- ***Particle*** reactions/transitions, with params

$$A_1(x_1),\ A_2(x_2),\ \ldots,\ A_n(x_n) \rightarrow B_1(y_1),\ B_2(y_2),\ \ldots,\ B_m(y_m)\ \textbf{with}\ \rho(\{x_i\}, \{y_j\})$$

$$\tilde{O}_r = \rho_r \sum_{\{x'_i, x_j\}} \prod_{i \in \mathrm{rhs}(r)} \hat{a}(\tau_i, x_i) \prod_{j \in \mathrm{lhs}(r)} a(\tau_j, x_j)\, \Pr(\{x_i\} \mid \{x_j\})$$

(and can integrate ODE rules too)

$$[a_{ab}, \hat{a}_{cd}] = I\ \delta_{(ab),(cd)}$$
$$[a, a] = [\hat{a}, \hat{a}] = 0$$

- ***Labelled graph*** (structure) transitions

$$\begin{aligned} \hat{a}_\alpha^2 &= 0 = a_\alpha^2 \\ a_\alpha \hat{a}_\beta &= (1 - \delta_{\alpha\beta})\hat{a}_\beta a_\alpha + \delta_{\alpha\beta} Z_\alpha \\ Z_\alpha &\equiv I_\alpha - N_\alpha \\ N_\alpha &\equiv \hat{a}_\alpha a_\alpha \end{aligned}$$

$$\hat{W}_r \propto \int d\boldsymbol{\lambda} d\boldsymbol{\lambda}'\ \rho_r(\boldsymbol{\lambda}, \boldsymbol{\lambda}') \sum_{\langle i_1, \ldots i_k \rangle_{\neq}} \hat{a}_{i_1,\ldots i_k}(G^{r\ \mathrm{out}}) a_{i_1,\ldots i_k}(G^{r\ \mathrm{in}})$$

(and can integrate ODE rules too)

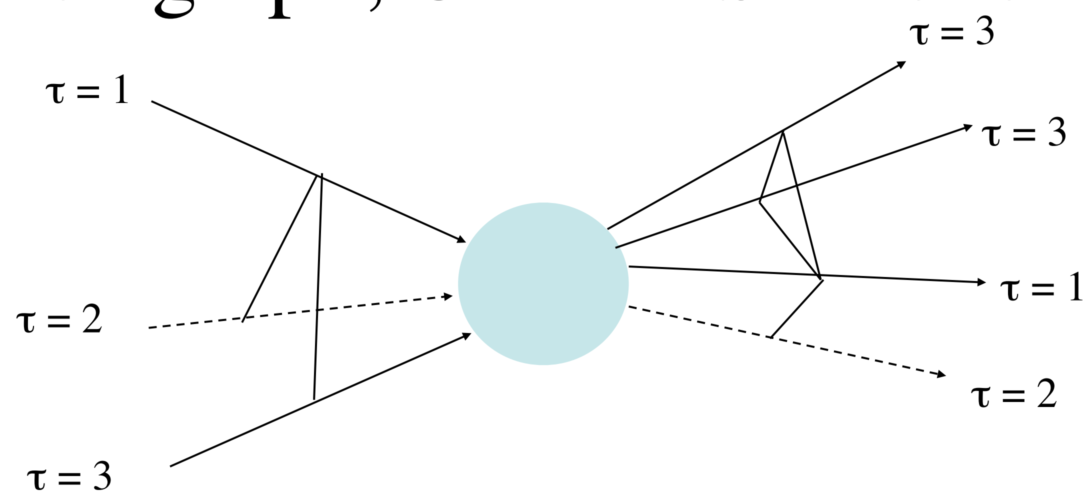
$$\begin{aligned} \hat{a}_{i_1,\ldots i_k}(G') &= \hat{a}_{i_1,\ldots i_k}(G'_{\mathrm{links}}) \hat{a}_{i_1,\ldots i_k}(G'_{\mathrm{nodes}}) \\ &= \left[\prod_{s', t' \in \mathrm{rhs}(r)} \left(\hat{a}_{i_{s'} i_{t'}} \right)^{g'_{s'\, t'}} \right] \left[\prod_{v' \in \mathrm{rhs}(r)} \hat{a}_{i_{v'} \lambda'_{v'}} \right] \\ a_{i_1,\ldots i_k}(G) &= a_{i_1,\ldots i_k}(G_{\mathrm{links}}) a_{i_1,\ldots i_k}(G_{\mathrm{nodes}}) \\ &= \left[\prod_{s, t \in \mathrm{lhs}(r)} \left(a_{i_s i_t} \right)^{g_{s\, t}} \right] \left[\prod_{v \in \mathrm{lhs}(r)} a_{i_v \lambda_v} \right]. \end{aligned}$$

[EM, MFPS Proc., ENTCS 2010]

Ψ

Graph rewrite rule operators

- G = LHS labelled graph, G' = RHS labelled graph



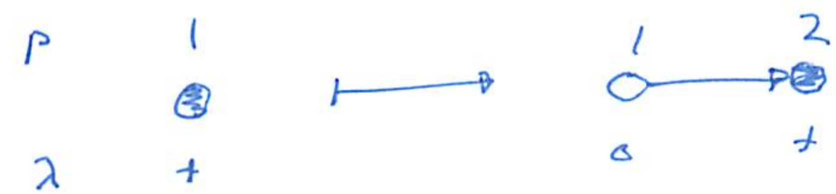
$$\hat{O}_r = \frac{1}{k!} \sum_{\{i_1,\ldots i_k\}} [\prod_{c,d\in \mathrm{rhs}(r)} (\hat{a}_{i_c i_d})^{g'cd}][\prod_{c\in \mathrm{rhs}(r)} \hat{a}_{i_c \lambda' c}][\prod_{a,b\in \mathrm{lhs}(r)} (a_{i_a i_b})^{g_{ab}}][\prod_{a\in \mathrm{lhs}(r)} a_{i_a \lambda_a}]$$

[EM, MFPS Proc. 2010]

$$\begin{aligned}
\hat{a}_\alpha^2 &= 0 = a_\alpha^2 \\
a_\alpha \hat{a}_\beta &= (1-\delta_{\alpha\beta})\hat{a}_\beta a_\alpha + \delta_{\alpha\beta} Z_\alpha \\
Z_\alpha &\equiv I_\alpha - N_\alpha \\
N_\alpha &\equiv \hat{a}_\alpha a_\alpha
\end{aligned}$$

MT Treadmilling Rules

Rule 1: + end extension



$$\hat{w}_1 = \sum_{ij} \hat{a}_{i,o}\, \hat{a}_{j,+}\, \hat{a}_{ji}\, a_{i,+}$$

Rule 2: − end retraction

$$\hat{w}_2 = \sum_{i'j'} \hat{a}_{j',-}\, a_{i',-}\, a_{j',o}\, a_{j'i'}$$

$$[\hat{w}_2, \hat{w}_1] = \hat{w}_2 \hat{w}_1 - \hat{w}_1 \hat{w}_2 \propto \sum_{iji'} \hat{a}_{j,+}\, \hat{a}_{i,-}\, \hat{a}_{ji}\, a_{i',-}\, a_{i+}\, a_{ii'}$$

(diagram:

)

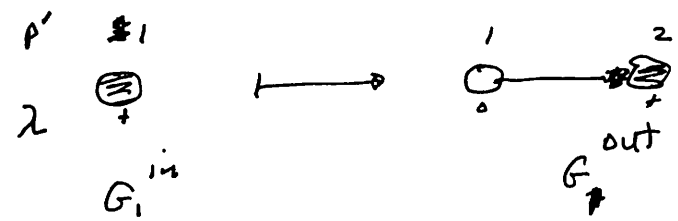
$\simeq I$

(*if* dangling edges are removed)

Growth vs. Bundling

+ end growth

$\hat{W}_1$:



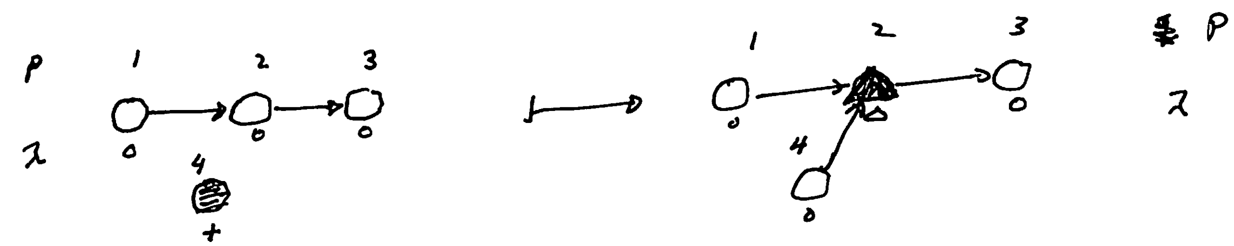
$$a(G_1^{in}) = a_{i_1,+}$$

$$\hat{a}(G_1^{out}) = \hat{a}_{i_2 i_1}\left(\hat{a}_{i_2,+}\,\hat{a}_{i_1,0}\right)$$

$$\Rightarrow \boxed{\hat{W}_1 \propto \sum_{\langle i_1, i_2\rangle_{\neq}} \left(\hat{a}_{i_2 i_1}\,\hat{a}_{i_2,+}\,\hat{a}_{i_1,0}\right) a_{i_1,+}}$$

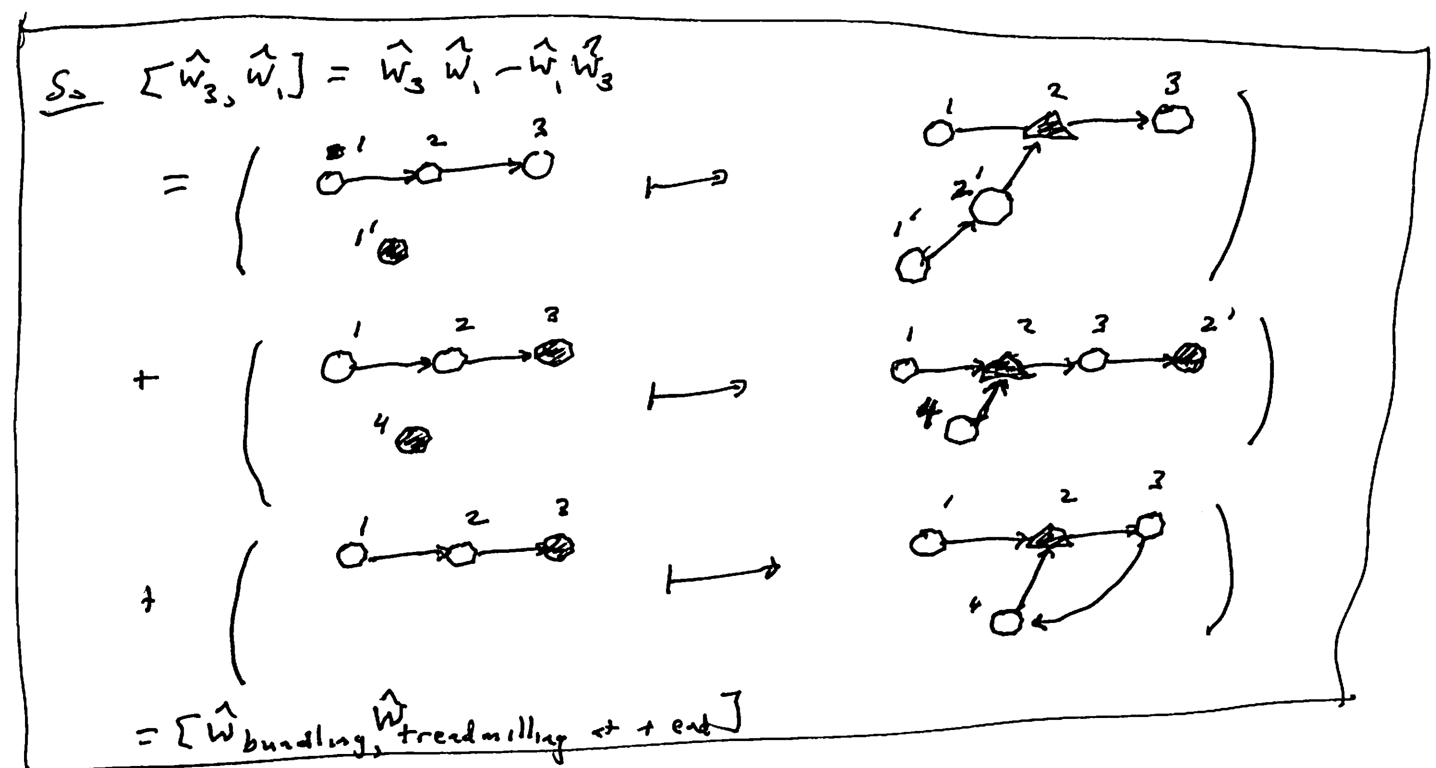
bundling

$\hat{W}_3$:



$$\hat{W}_3 \propto \sum_{\langle j_1 j_2 j_3 j_4\rangle_{\neq}} \left(\hat{a}_{j_2 j_4}\,\hat{a}_{j_3 j_2}\,\hat{a}_{j_2 j_1}\,\hat{a}_{j_4,0}\,\hat{a}_{j_3,0}\,\hat{a}_{j_2,\Delta}\,\hat{a}_{j_1,0}\right)\left(a_{j_3 j_2}\,a_{j_2 j_1}\,a_{j_4,+}\,a_{j_3,0}\,a_{j_2,0}\,a_{j_1,0}\right)$$

Growth vs. Bundling



expected

rare

energetically disfavored

$\mathcal{J}$

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]

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

  - weighted SSA (wSSA) possible too

Generation of valid algorithms, continued

Approximate algorithms from Operator Exponentials

t/n small:

$$e^{t(A+B)} = e^{tA} e^{tB + \frac{t^2}{2}[B,A] + \frac{t^3}{12}(2[A,[A,B]] - [B,[B,A]]) + O(t^4)}$$

[Campbell-Baker-Hausorff]

$$= e^{tA} e^{tB} + O(t^2)$$

$$e^{t(A+B)} = e^{tA/2} e^{tB} e^{tA/2} e^{D_3' t^3} + O(t^4)$$

$$= e^{tA} e^{tB} e^{-\frac{t^2}{2}[A,B]} e^{D_3 t^3} + O(t^4)$$

[Zassenhaus]

$$D_3' = \frac{1}{24}[A,[A,B]] - \frac{1}{12}[B,[B,A]]$$

$$D_3 = \frac{1}{6}[A,[A,B]] - \frac{1}{3}[B,[B,A]]$$

So commutators are key to analysing errors & minimizing it beyond $O(t^2)$.

Product Theorems

- Semantics:
  (compositional)

$$\hat{W}_r \propto \int d\boldsymbol{\lambda} d\boldsymbol{\lambda}' \, \rho_r(\boldsymbol{\lambda}, \boldsymbol{\lambda}') \sum_{\langle i_1,\ldots i_k \rangle_{\neq}} \hat{a}_{i_1,\ldots i_k}(G^{r\ \mathrm{out}}) a_{i_1,\ldots i_k}(G^{r\ \mathrm{in}})$$

- Calculate product …

$$\begin{aligned}
\hat{W}_{r_2}\hat{W}_{r_1} \propto & \sum_{\bar{S} \subseteq G^{r_1\ \mathrm{out}}_{\mathrm{links}}} \sum_{\bar{h}:\bar{S} \overset{1\text{-}1}{\hookrightarrow} G^{r_2\ \mathrm{in}}_{\mathrm{links}}} \sum_{S \subseteq G^{r_1\ \mathrm{out}}_{\mathrm{nodes}}} \sum_{h:S \overset{1\text{-}1}{\hookrightarrow} G^{r_2\ \mathrm{in}}_{\mathrm{nodes}} | h=\bar{h}_{1,2} \text{ on } S \cap (\bar{S}_1 \cup \bar{S}_2)} \\
& \sum_{U \subseteq G^{r_1\ \mathrm{out}}_{\mathrm{nodes}} \setminus S} \sum_{\chi:U \overset{1\text{-}1}{\hookrightarrow} G^{r_2\ \mathrm{in}}_{\mathrm{nodes}} \setminus h(S)} \sum_{T \subseteq G^{r_1\ \mathrm{in}}_{\mathrm{nodes}} \setminus G^{r_1\ \mathrm{out}}_{\mathrm{nodes}}} \sum_{\pi:T \overset{1\text{-}1}{\hookrightarrow} G^{r_2\ \mathrm{out}}_{\mathrm{nodes}} \setminus G^{r_2\ \mathrm{in}}_{\mathrm{nodes}}} \\
& \times \Bigg\{ \int d\boldsymbol{\lambda}_1 d\boldsymbol{\lambda}_1' d\boldsymbol{\lambda}_2 d\boldsymbol{\lambda}_2' \ \rho_{r_1}(\boldsymbol{\lambda}_1, \boldsymbol{\lambda}_1') \rho_{r_2}(\boldsymbol{\lambda}_2, \boldsymbol{\lambda}_2') \underbrace{\sum_{\langle i_1,\ldots i_{k_1} \rangle_{\neq}} \sum_{\substack{\langle j_a \rangle_{\neq} \\ a \notin (\pi(T) \dot{\cup} (h(S) \cup \bar{h}_1(\bar{S}) \cup \bar{h}_2(\bar{S})))}}}_{\text{to replace with } \sum_{\langle I \rangle_{\neq}}} \\
& \prod_{v''' \in G^{r_1\ \mathrm{in}}_{\mathrm{nodes}} \setminus G^{r_1\ \mathrm{out}}_{\mathrm{nodes}}} (1 - \delta_{j_k i_{v''}}) \sum_{\substack{\langle j_b \rangle_{\neq},\ \forall j_b \neq \forall j_a \\ b \in \pi(T)}} \underbrace{\prod_{b \in \pi(T)} \delta_{j_b i_{\pi^{-1}(b)}}}_{\text{eliminates } j_b} \sum_{\substack{\langle j_c \rangle_{\neq},\ \forall j_c \neq \forall j_a, j_b \\ c \in (h(S) \cup \bar{h}_1(\bar{S}) \cup \bar{h}_2(\bar{S}))}} \\
& \underbrace{\Bigg[\prod_{v' \in S} \prod_{(s',t') \in \bar{S}} \delta_{j_{h(v')}, i_{v'}} \delta_{j_{\bar{h}_1(s',t')}, i_{s'}} \delta_{j_{\bar{h}_2(s',t')}, i_{t'}} \Bigg]}_{\text{eliminates } j_c} \underbrace{\Bigg[\prod_{v' \in S} \delta_{\lambda_{2,h(v')}, \lambda'_{1,v'}} \Bigg]}_{\iff \text{ label compatibility for } h} \\
& \times \prod_{\tilde{v} \in G^{r_2\ \mathrm{in}}_{\mathrm{nodes}} \setminus h(S)} \prod_{\tilde{v}' \in G^{r_1\ \mathrm{out}}_{\mathrm{nodes}} \setminus S} \prod_{(\tilde{s},\tilde{t}) \in G^{r_2\ \mathrm{in}}_{\mathrm{links}} \setminus \bar{h}(\bar{S})} \prod_{(\tilde{s}',\tilde{t}') \in G^{r_1\ \mathrm{out}}_{\mathrm{links}} \setminus \bar{S}} \prod_{v \in G^{r_2\ \mathrm{out}}_{\mathrm{nodes}}} \prod_{v'' \in G^{r_1\ \mathrm{in}}_{\mathrm{nodes}}} \prod_{(s,t) \in G^{r_2\ \mathrm{out}}_{\mathrm{links}}} \prod_{(s'',t'') \in G^{r_1\ \mathrm{in}}_{\mathrm{links}}} \\
& \times \underbrace{\Bigg[\prod_{\hat{v} \in \chi(U)} \delta_{j_{\hat{v}}, i_{\chi^{-1}(\hat{v})}} (1 - \delta_{\lambda_{2,\hat{v}}, \lambda'_{1,\chi^{-1}(\hat{v})}}) \Bigg] \Bigg[\prod_{\check{v} \in G^{r_2\ \mathrm{in}}_{\mathrm{nodes}} \setminus h(S) \setminus \chi(U)} (1 - \delta_{j_{\check{v}}, i_{\tilde{v}'}}) \Bigg] (1 - \delta_{j_{\tilde{s}}, i_{\tilde{s}'}} \delta_{j_{\tilde{t}}, i_{\tilde{t}'}})}_{\text{expanded using subperm } \chi\text{; commutator miss}} \\
& \times \underbrace{(1 - \delta_{j_v, i_{\tilde{v}'}})(1 - \delta_{j_{\tilde{v}}, i_{v''}})(1 - \delta_{j_s i_{\tilde{s}'}} \delta_{j_t i_{\tilde{t}'}})(1 - \delta_{j_{\tilde{s}} i_{s''}} \delta_{j_{\tilde{t}} i_{t''}})}_{\text{can be reabsorbed into } \hat{a}, a \text{ operators below}} \\
& \times \Big(\hat{a}_{j_v, \lambda'_{2,v}} \hat{a}_{i_{\tilde{v}'}, \lambda'_{1,\tilde{v}'}} \hat{a}_{j_s j_t} \hat{a}_{i_{\tilde{s}'} i_{\tilde{t}'}} \Big) \Big(a_{j_{\tilde{v}}, \lambda_{2,\tilde{v}}} a_{i_{v''}, \lambda_{1,v''}} a_{j_{\tilde{s}} j_{\tilde{t}}} a_{i_{s''} i_{t''}} \Big) \\
& \times \Bigg[\prod_{v' \in S} \prod_{(s',t') \in \bar{S}} \underbrace{\delta_{j_{h(v')}, i_{v'}} \delta_{j_{\bar{h}_1(s',t')}, i_{s'}} \delta_{j_{\bar{h}_2(s',t')}, i_{t'}}}_{\implies h \text{ compatible with } \bar{h} \text{ on } S \cap (\bar{S}_1 \cup \bar{S}_2)} \underbrace{(Z_{i_{v'} \lambda'_{1,v'}})^{\mathrm{Churn}_{v'}(S,h)} (Z_{i_{s'} i_{t'}})^{\overline{\mathrm{Churn}}_{s',t'}(\bar{S},\bar{h})}}_{\text{equivalent to identity operator in infinite memory limit}} \Bigg] \Bigg\}
\end{aligned}$$

Product Theorems

- Semantics:
  (compositional)

$$\hat{W}_r \propto \rho_r(\boldsymbol{\lambda},\boldsymbol{\lambda}') \sum_{\{i_1,\ldots i_k\}} \left[\prod_{p',q'\in \mathrm{rhs}(r)} \left(\hat{a}_{i_{p'} i_{q'}}\right)^{g'_{p'\,q'}} \right] \left[\prod_{p'\in \mathrm{rhs}(r)} (\hat{a}_{i_{p'} \lambda'_{p'}})^{h'_{p'}} \right] \times \left[\prod_{p,q\in \mathrm{lhs}(r)} (a_{i_p i_q})^{g_{p\,q}} \right] \left[\prod_{p\in \mathrm{lhs}(r)} (a_{i_p \lambda_p})^{h_p} \right]. \quad (*)$$

- Product:

$$\hat{W}_{r_2}\hat{W}_{r_1} \propto \left(\rho_{r_1}(\boldsymbol{\lambda}_1,\boldsymbol{\lambda}'_1)\rho_{r_2}(\boldsymbol{\lambda}_2,\boldsymbol{\lambda}'_2)\right) \sum_{\{i_1,\ldots i_{k_1}\}} \sum_{\{j_1,\ldots j_{k_2}\}} \left[\prod_{p',q'\in \mathrm{rhs}(r_2)} \left(\hat{a}_{i_{p'} i_{q'}}\right)^{g'_{2,p'\,q'}} \right] \left[\prod_{p'\in \mathrm{rhs}(r_2)} (\hat{a}_{i_{p'} \lambda'_{2,p'}})^{h'_{2,p'}} \right]$$
$$\times \left[\prod_{p,q\in \mathrm{lhs}(r_2)} (a_{i_p i_q})^{g_{2,p\,q}} \right] \left[\prod_{p\in \mathrm{lhs}(r_2)} (a_{i_p \lambda_{2,p}})^{h_{2,p}} \right]$$
$$\times \left[\prod_{p',q'\in \mathrm{rhs}(r_1)} \left(\hat{a}_{j_{p'} j_{q'}}\right)^{g'_{1,p'\,q'}} \right] \left[\prod_{p'\in \mathrm{rhs}(r_1)} (\hat{a}_{j_{p'} \lambda'_{1,p'}})^{h_{1,p'}} \right]$$
$$\times \left[\prod_{p,q\in \mathrm{lhs}(r_1)} (a_{j_p j_q})^{g_{1,p\,q}} \right] \left[\prod_{p\in \mathrm{lhs}(r_1)} (a_{j_p \lambda_{1,p}})^{h_{1,p}} \right],$$

+ a variant which eliminates dangling edges

Proposition 1 *The product of two operators taking the form of Equation (*) can be rewritten as an signed-integer-weighted sum of expressions taking the same form. The product and the sum are equal, and graph-equivalent, and each is subpermutation-invariant with respect to indexing.*

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

Computed Products and Commutators

- Computation must yield the form:

$$\hat{\sigma}_{r_1} \circ \hat{\sigma}_{r_2} = \sum_{\alpha} (w_\alpha : \mathbb{Z})\, \hat{\sigma}_{G^{(\alpha)} \to G^{(\alpha)\prime}}$$

$$[\hat{\sigma}_{r_1}, \hat{\sigma}_{r_2}] = \sum_{\alpha} (w_\alpha : \mathbb{Z})\, \hat{\sigma}_{G^{(\alpha)} \to G^{(\alpha)\prime}}$$

  - Cf. Heisenberg & rotation-group Lie algebras

- Particular cases simplify further
  - eg. polymerization, dendromers, etc..
  - analysis for *compilation*?

Algebra of Labelled-Graph Rewrite Rules

Ψ

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

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

Ψ

Algebra of Labelled-Graph Rewrite Rules

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

$$G^{1;2\ \mathrm{in}}_{\mathrm{nodes}} = G^{r_1\ \mathrm{in}}_{\mathrm{nodes}} \,\dot{\cup}\, (G^{r_2\ \mathrm{in}}_{\mathrm{nodes}} \setminus \tilde{H}_{\mathrm{nodes}}) \qquad G^{1;2\ \mathrm{out}}_{\mathrm{nodes}} = G^{r_2\ \mathrm{out}}_{\mathrm{nodes}} \,\dot{\cup}\, (G^{r_1\ \mathrm{out}}_{\mathrm{nodes}} \setminus H_{\mathrm{nodes}})$$

$$G^{1;2\ \mathrm{in}}_{\mathrm{links}} = G^{r_1\ \mathrm{in}}_{\mathrm{links}} \cup h^{-1\star}(G^{r_2\ \mathrm{in}}_{\mathrm{links}} \setminus \tilde{H}_{\mathrm{links}}) \qquad G^{1;2\ \mathrm{out}}_{\mathrm{links}} = G^{r_2\ \mathrm{out}}_{\mathrm{links}} \cup h^{\star}(G^{r_1\ \mathrm{out}}_{\mathrm{links}} \setminus H_{\mathrm{links}})$$

$$K_a = G^{r_a\ \mathrm{in}}_{\mathrm{nodes}} \cap G^{r_a\ \mathrm{out}}_{\mathrm{nodes}}$$

$$K_{1;2} = (K_1 \setminus H_{\mathrm{nodes}} \ \cup\ h^{-1}(K_2 \setminus \tilde{H}_{\mathrm{nodes}}) \ \cup\ (K_1 \cap h^{-1\star}(K_2))$$

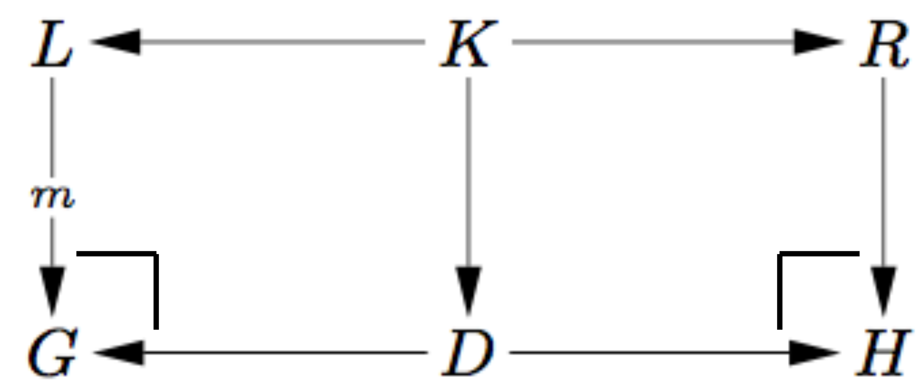
[EM, http://arxiv.org/abs/1909.04118]

Product Theorems

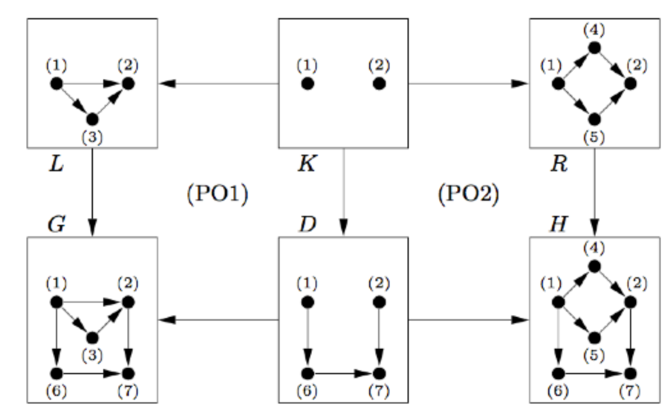
- Double pushout semantics:

  in the category of graphs

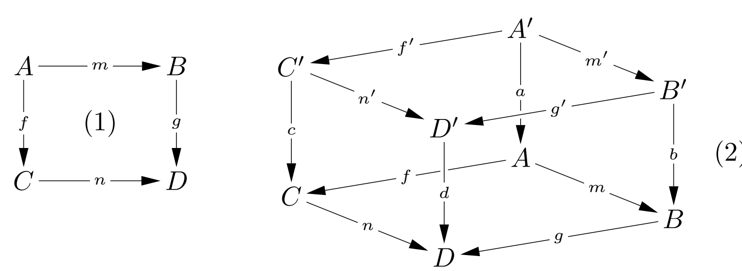
- Commutator=0 condition



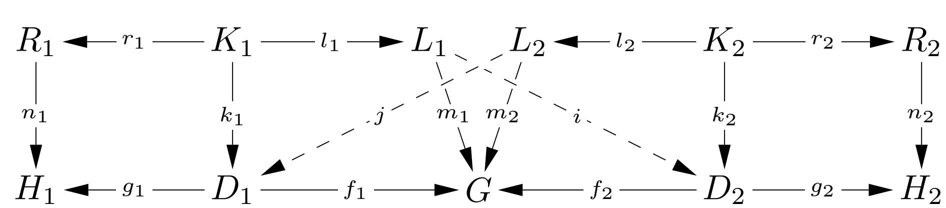
- L, R = Left, Right graphs;
- K = shared graph;
- G = input, H = output
- Eg:



Definition 4.1 (van Kampen square). *A pushout (1) is a* van Kampen square *if, for any commutative cube (2) with (1) in the bottom and where the back faces are pullbacks, the following statement holds: the top face is a pushout iff the front faces are pullbacks:*



Fact 3.18 (characterization of parallel and sequential independence). *Two direct (typed) graph transformations $G \stackrel{p_1,m_1}{\Longrightarrow} H_1$ and $G \stackrel{p_2,m_2}{\Longrightarrow} H_2$ are parallel independent iff there exist morphisms $i : L_1 \to D_2$ and $j : L_2 \to D_1$ such that $f_2 \circ i = m_1$ and $f_1 \circ j = m_2$:*



H. Ehrig · K. Ehrig
U. Prange · G. Taentzer

Fundamentals of Algebraic Graph Transformation

Meta-graph grammar for scalable implementation

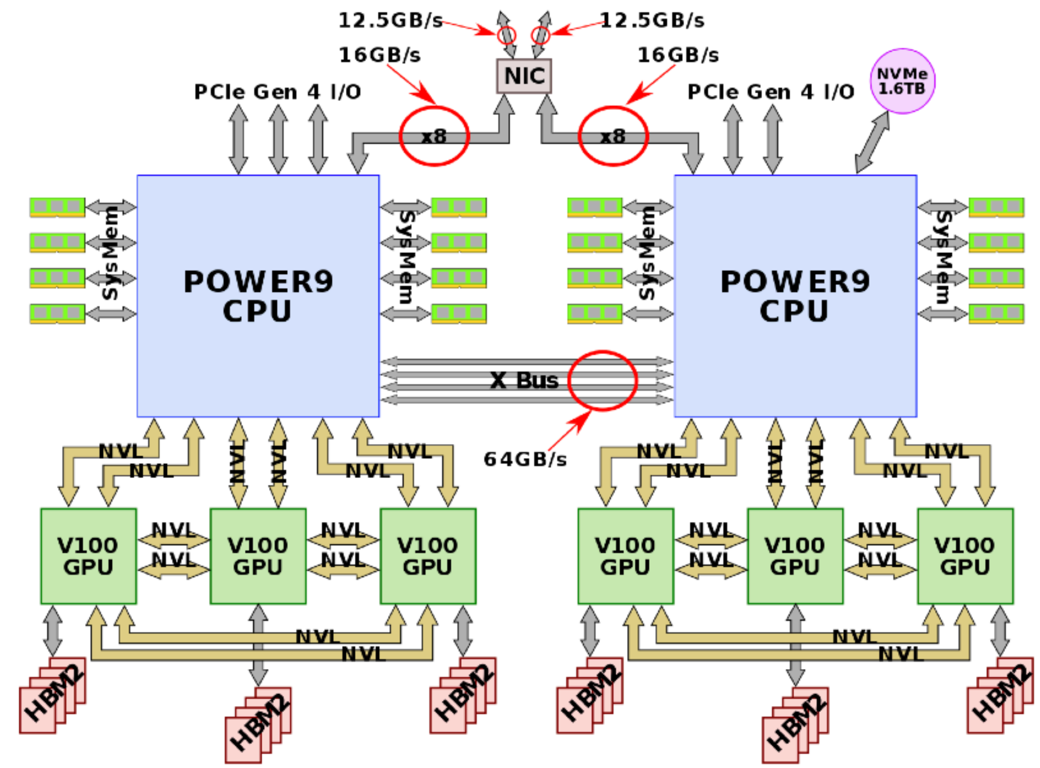
- Transformation target for spatially embedded labeled graph rewrite dynamics
- For computational reduction to scalable particle codes?

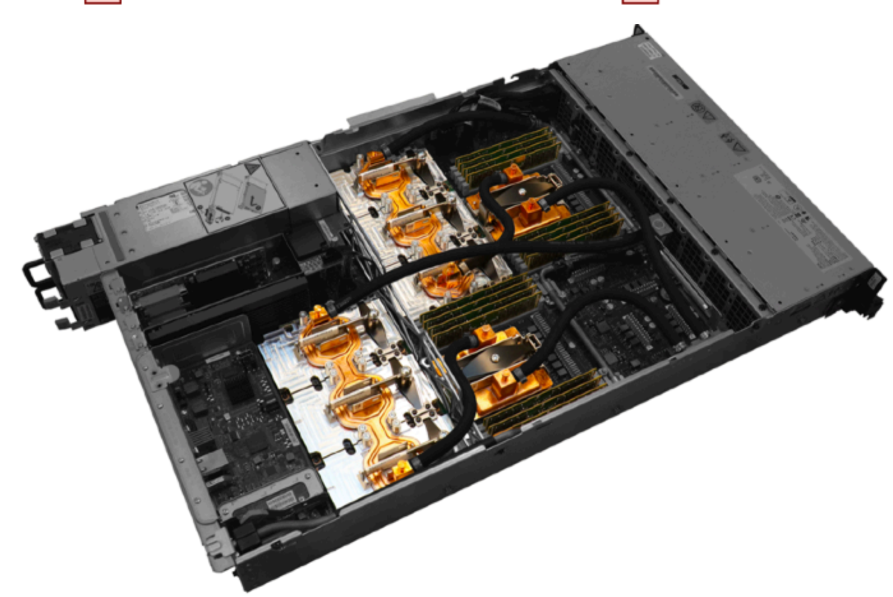
```
x,y,z: real-valued params
a,b,c: discete-valued params
A,B,C: OIDs

particle(A,a,x) --> itself under an ODE |a

particle(A, a, x), particle(B, b, y) --> themselves under an ODE |a,b for x

particle(A, a, x), particle(B, b, y), link(A,B)
    --> themselves under an ODE |a,b for x

particle(A, a, x) <--> particle(A, a, x), particle(B, b, y)
        with a propensity depending on x-y, a, b

particle(A, a, x)  <--> null  with a propensity depending on x
        (null is non-modeled stuff - but violates conservation)

particle(A, a, x), particle((B, b, y)
    <--> particle(A, a, x), particle((B, b, y), link(A,B)
        with a propensity depending on x-y, a, b

particle(A, a, x), particle((B, b, y), link(A,B)
    <--> particle(A, a, x, particle(B,y), link(A,B), link(B,A)

particle(A, a, x), particle((B, b, y), link(A,B), particle(C,z), link(B,C)
    <--> particle(A, a, x), particle(B, b, y), link(A,B), particle(C, c, z),
                link(B,C), link(C,A)  with a propensity(x-y,y-z,z-x | a,b,c)

other local graph grammar rules
```

Summit Architecture

(#1 in 2018-9)

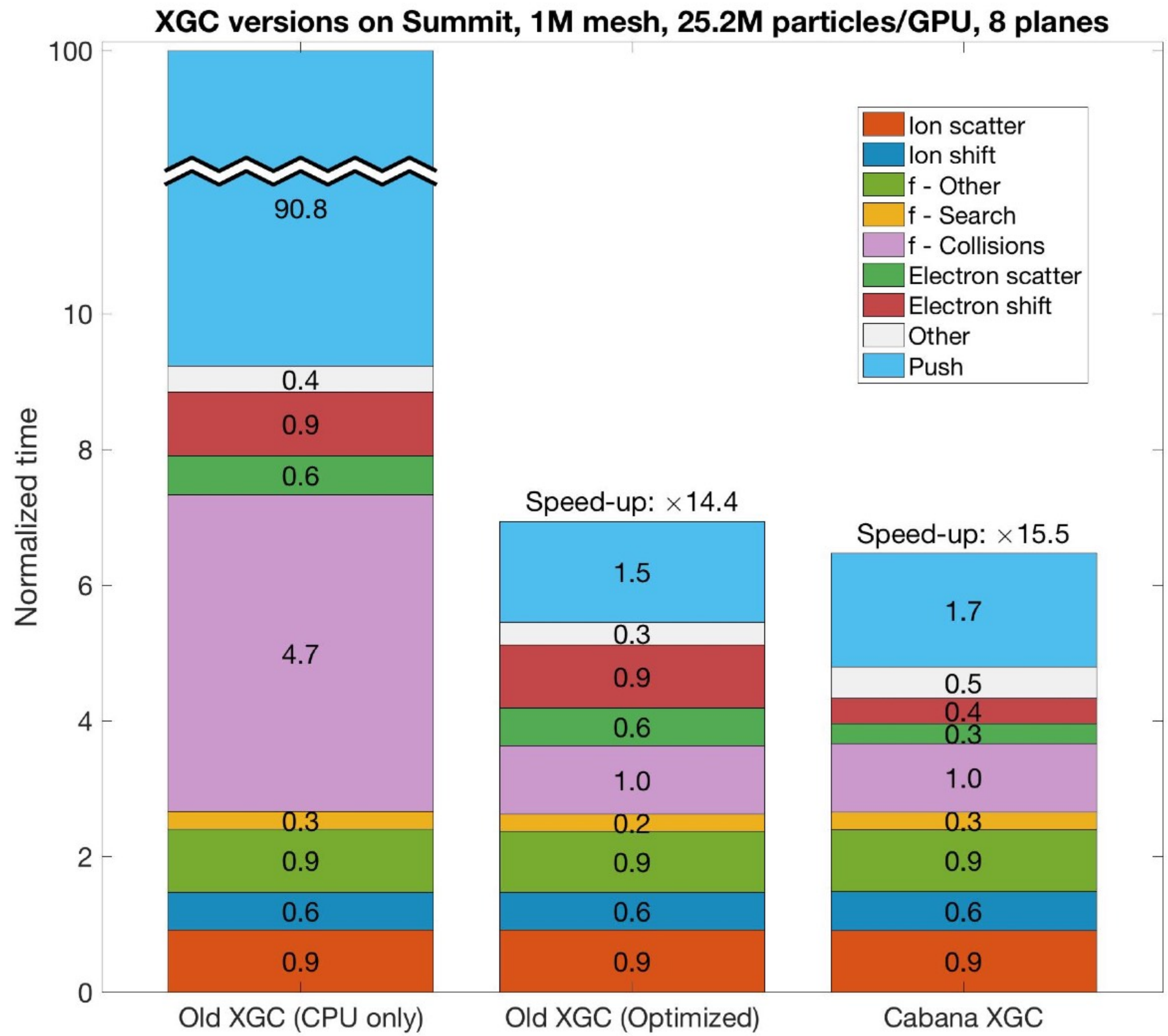
- Each node:
  - 2 x 22 cores/CPU ~1 TFlops
  - 6xV100 GPU ~47 TFlops
- 4608 nodes
  - ~200 PFlops
  - ~340 tons





https://en.wikichip.org/wiki/supercomputers/summit

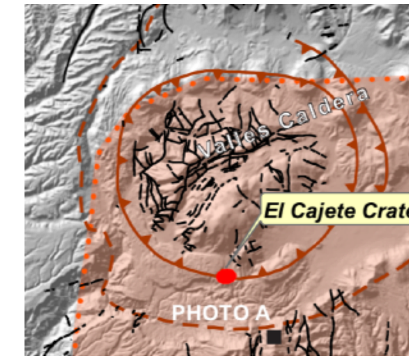
“Cabana” particle sim can be fast



Aaron Scheinberg and XGC team

Cabana-friendly pseudocode: “Cajete” MT prototype

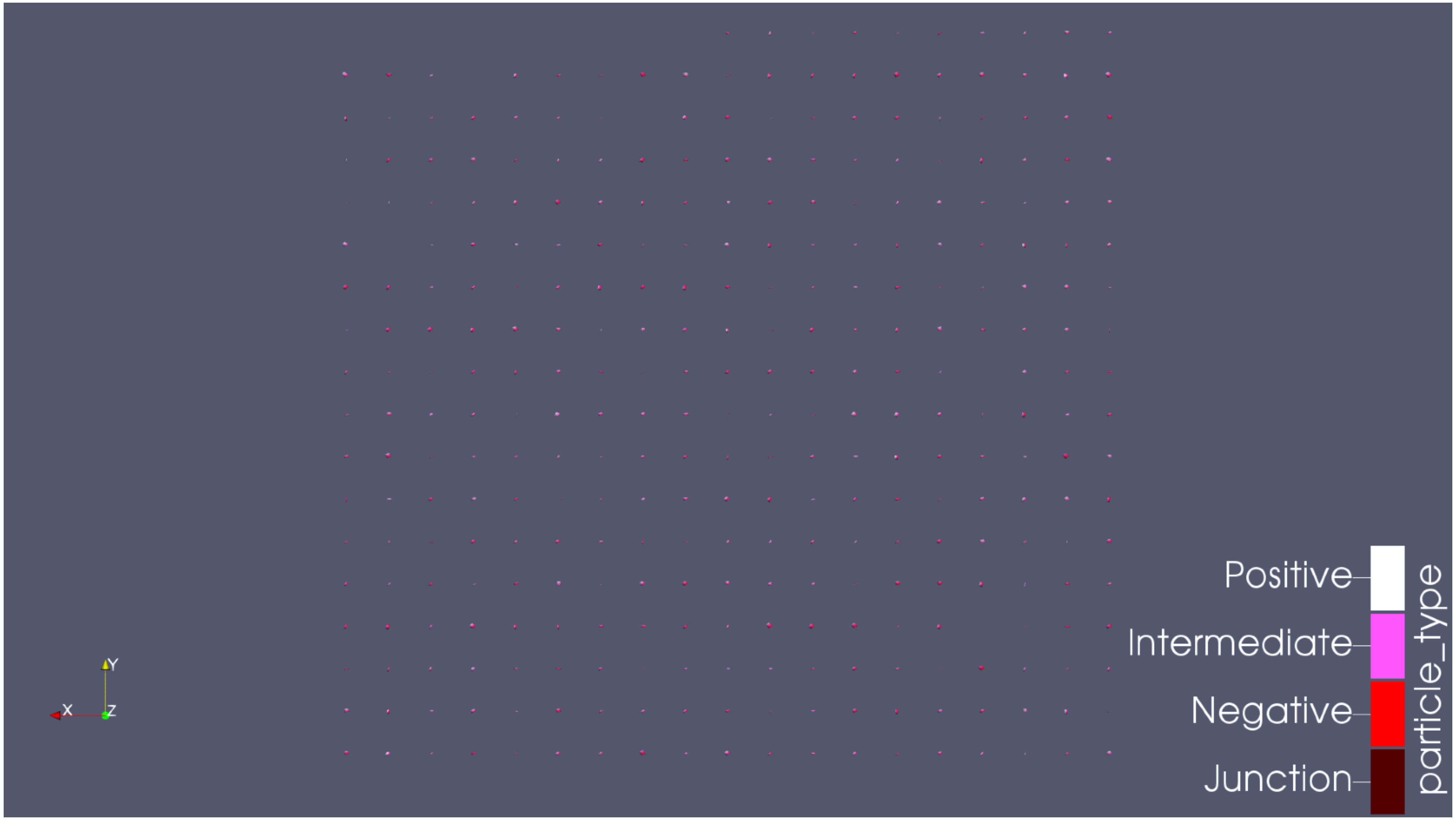
w. Bob Bird, LANL



WoldeGabriel et al., NM Geology 5/16

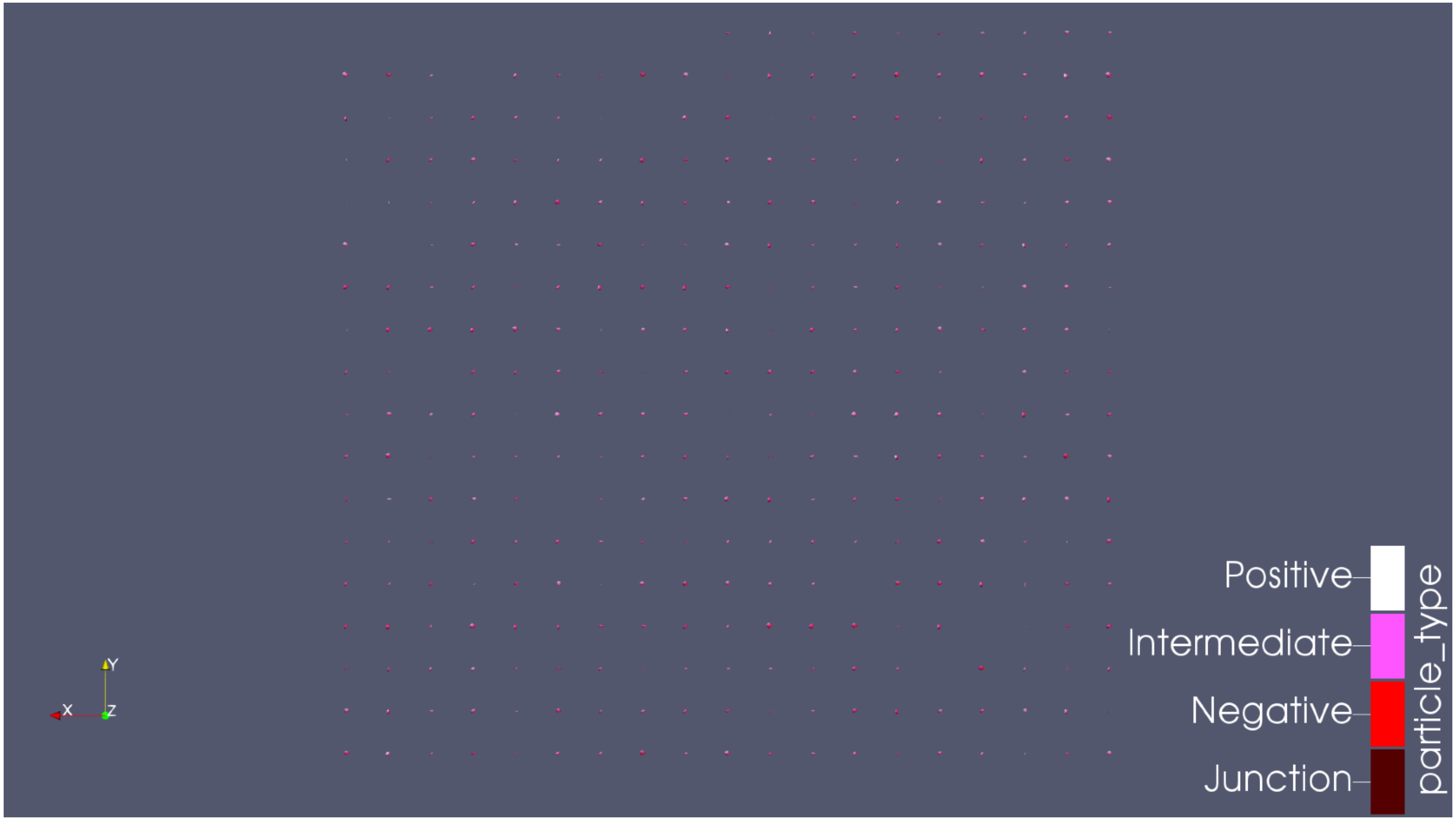
```
void evolve_particle_damped(particle_list_t& particles, size_t i)

{

   auto type = particles.slice<Type>();

   auto force_type_A = particles.slice<Type>()(i);

   auto velocity = particles.slice<Velocity>();

   auto position = particles.slice<Position>();

   auto length = particles.slice<Length>();



   if ( force_type_A == positive )

   {

      // ith particle, property j (0..2)

            i_1 = nbr_interior.i; j_1 = nbr_interior.j;
            velocity(i,j) = v_plus * (1-length(i_1)/length_max) * u(i,j);

      position(i, j) += velocity(i, j) * delta; //?? + length(i);

            for all nearby other fibers k {
                        alpha = - 2dcross((...), (...))/2dcross((...), (...)) ; // 2d cross product
                        gamma = - 2dcross((...), (...))/2dcross((...), (...)) ; // 2d cross product

                        // directional derivative of  kappa * exp(- gamma^2/(2*epsilon^2)):
                        velocity(i,j) += kappa * u(i,j)*(-gamma/epsilon^2) * exp(- gamma^2/(2*epsilon^2));
                        elongation_speed(i_) += v_plus (v_plus + v_minus)*(length(i)/length_max) ;
            }

      position(i, j) += velocity(i, j) * delta; //?? + length(i);
   }

else if ( force_type_A == negative )

{
         i_1 = nbr_interior.i;
         velocity(i,j) = v_minus * (length(i_1)/length_max) * u(i,j);

   position(i, j) += velocity(i, j) * delta; //?? + length(i);

}


else if ( force_type_A == intermediate )

{

         // i_1 = nbr1.i; j_1 = nbr2.j; i_2 = nbr2.i; j_2 = nbr2.j;
         ftype1 = nbr1.force_type_A;
         ftype2 = nbr2.force_type_A;
         if ((ftype1 == positive && ftype2==negative)||(ftype1 == negative && ftype2==positive))
                     elongation_speed(i) += v_plus (v_plus + v_minus)*(length(i)/length_max) ;
         else if (ftype1 == positive && ftype2==positive) elongation_speed(i) += 2*v_plus* (1-length(i)/length_max);
         else if (ftype1 == negative && ftype2==negative) elongation_speed(i) += 2* v_minus * (length(i_1)/length_m

         length(i) += elongation_speed(i)*delta;

}


else if ( force_type_A == junction )

{

}

else {

   std::cout << " ??? " << std::endl;

}


}
```

Cajete MT: First Light



Eric Medwedeff, UCI

Cajete MT: First Light



Eric Medwedeff, UCI

Eg: Plant gene expression model

Declarative, with cell growth & division

$$\{\{\emptyset \to \mathtt{U}, \mathtt{k_1TIP[t]}\}, \{\mathtt{U} \to \emptyset, \mathtt{k_2}\}, \{\mathtt{U} \longrightarrow \mathtt{U}, \mathtt{Diffusion[D_U]}\},$$

$$\{\emptyset \to \mathtt{V}, \mathtt{k_3L1[t]}\}, \{\mathtt{V} \to \emptyset, \mathtt{k_4}\}, \{\mathtt{V} \longrightarrow \mathtt{V}, \mathtt{Diffusion[D_V]}\},$$

$$\{\emptyset \rightleftarrows \mathtt{Z}, \mathtt{k_7}, \mathtt{k_8U[t]}\}, \{\mathtt{X} \mapsto \mathtt{V}, \mathtt{GRN[v_V, T_{WV}, 1, h_V]}\},$$

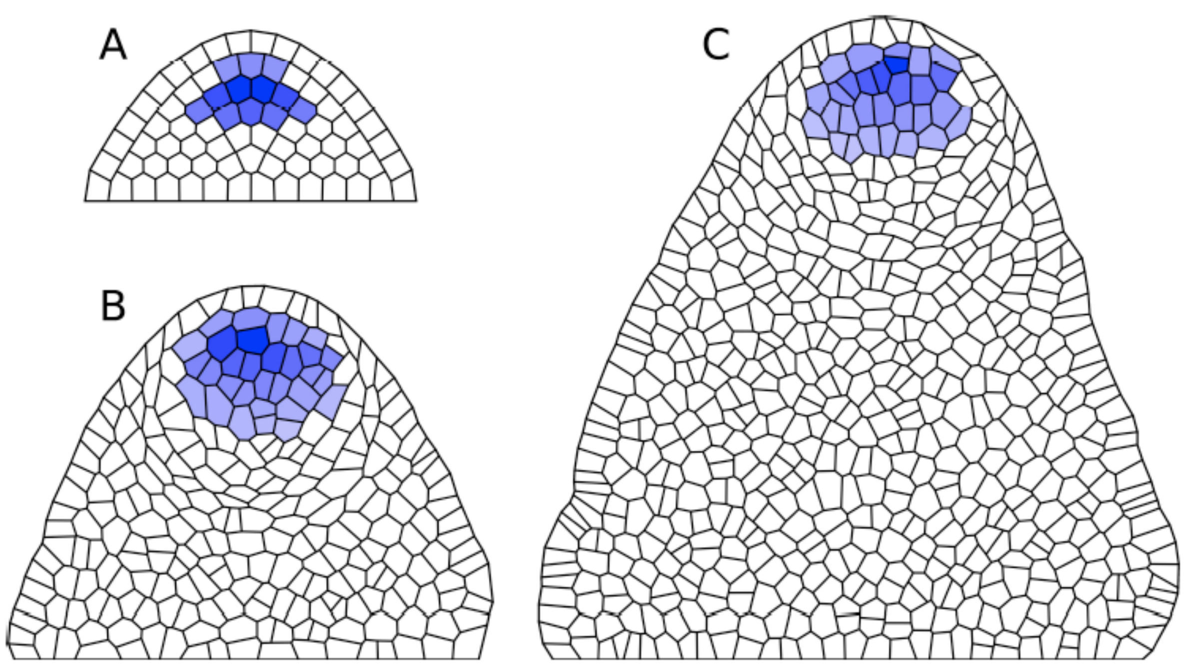
$$\{\{\mathtt{U}, \mathtt{V}, \mathtt{W}\} \mapsto \mathtt{W}, \mathtt{GRN[v_W, \{T_{UW}, T_{VW}, T_{WW}\}, 1, h_W]}\}, \{\mathtt{W} \to \emptyset, \mathtt{k_6Z[t]} + \mathtt{k_9L2[t]}\}$$

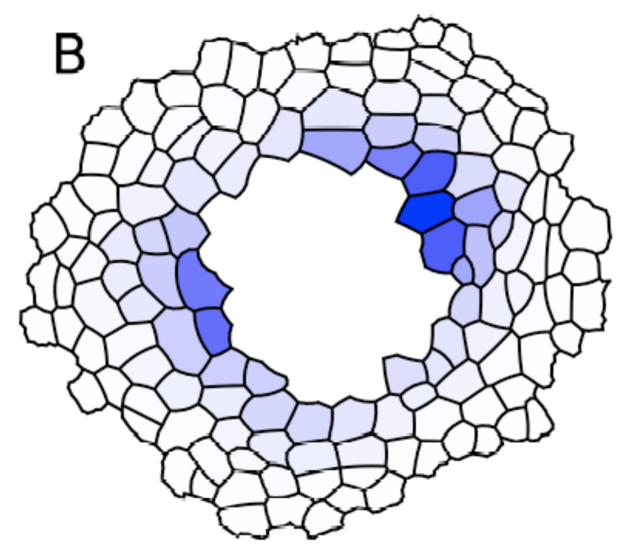
$$\{\mathtt{W} \mapsto \mathtt{X}, \mathtt{GRN[v_X, T_{WX}, 1, h_X]}\}, \{\mathtt{X} \to \emptyset, \mathtt{k_5}\}, \{\mathtt{X} \longrightarrow \mathtt{X}, \mathtt{Diffusion[D_X]}\},$$

$$\{\mathtt{cell} \longrightarrow \mathtt{cell}, \mathtt{Grow[GrowthRate[}\mu, \mathtt{f}_\mu\mathtt{]}, \mathtt{Pressure[P, f_P]}, \mathtt{Spring[k, f_k]}\},$$

Cf. L-systems:

$$\{\mathtt{cell} \longrightarrow \mathtt{cell} + \mathtt{cell}, \mathtt{Errera[cell}, \mu, \sigma\mathtt{]}\}\}$$





[Shapiro et al Frontiers in Plant Science 2013]

Dynamical Grammar example: Root growth

Cell division

$$\{Cell(x_i, r_i, m_i = 2, a_i, y_i)\} \rightarrow \left\{ \begin{array}{l} Cell(x_l, \frac{r_l}{2}, m_l = 1, a_l, y_l),\ Cell(x_{l+1}, \frac{r_{l+1}}{2}, m_{l+1} = 1, a_{l+1}, y_{l+1}) \\ s_{l,l+1} = spring(c_l, c_{l+1})\} \rightarrow \{c_l, c_{l+1}, s_{l,l+1}\} \end{array} \right\}$$

$$\text{with } \rho_{div}(y_i) = \left(\frac{y_i}{k_{div,1}}\right)^{h_{div,1}} \Bigg/ \left(1 + \left(\frac{y_i}{k_{div,2}}\right)^{h_{div,2}}\right)$$

Active auxin transport

$$\{c_i = Cell(x_i, r_i, m_i, a_i, y_i),\quad c_{i+1} = Cell(x_{i+1}, r_{i+1}, m_{i+1}, a_{i+1}, y_{i+1}),\quad s_{i,i+1} = spring(c_i, c_{i+1})\} \rightarrow \{c_i, c_{i+1}, s_{i,i+1}\}$$

$$\text{solving}\left\{\frac{da_{i+1}}{dt} = -K_0 a_{i+1} b(a_{i+1}), \frac{da_i}{dt} = K_0 a_{i+1} b(a_{i+1})\right\}$$

Auxin flow from the shoot

$$\{c_N = Cell(x_N, r_N, m_N, a_N, y_N)\} \rightarrow \{c_N\}$$

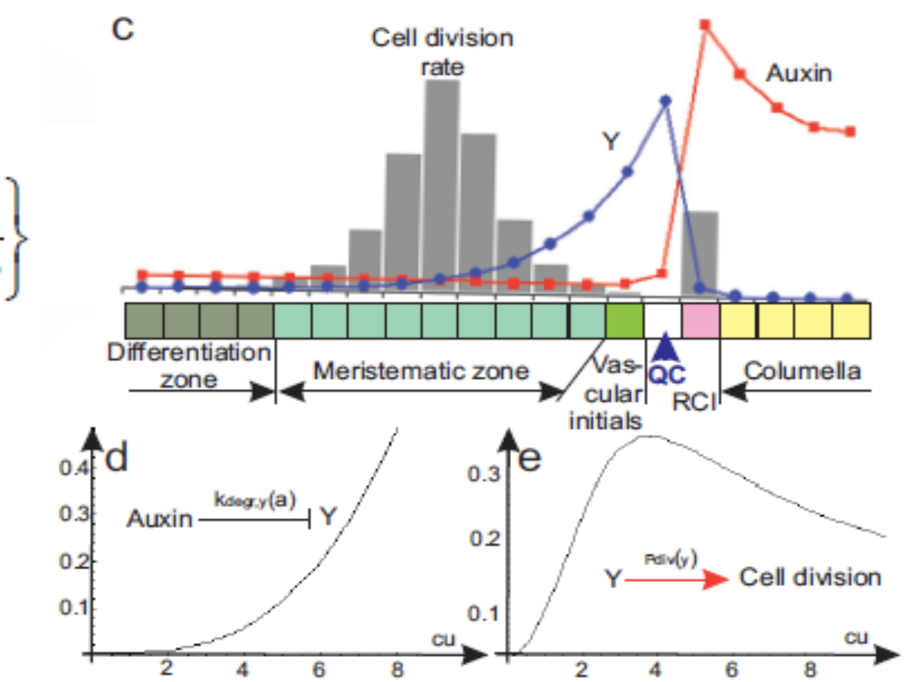
$$\text{solving}\left\{\frac{da_N}{dt} = \alpha_{init} + \frac{0.17t}{CellCycleTime}\right\}$$

Hypothetical substance Y

$$\{c_i = Cell(x_i, r_i, m_i, a_i, y_i)\} \rightarrow \{c_i\}$$

$$\text{solving}\left\{\frac{dy_i}{dt} = -y_i(K_{d,y}(a_i) + \frac{v(r_i)}{r_i}), \frac{dr_i}{dt} = v(r_i)\right\}$$

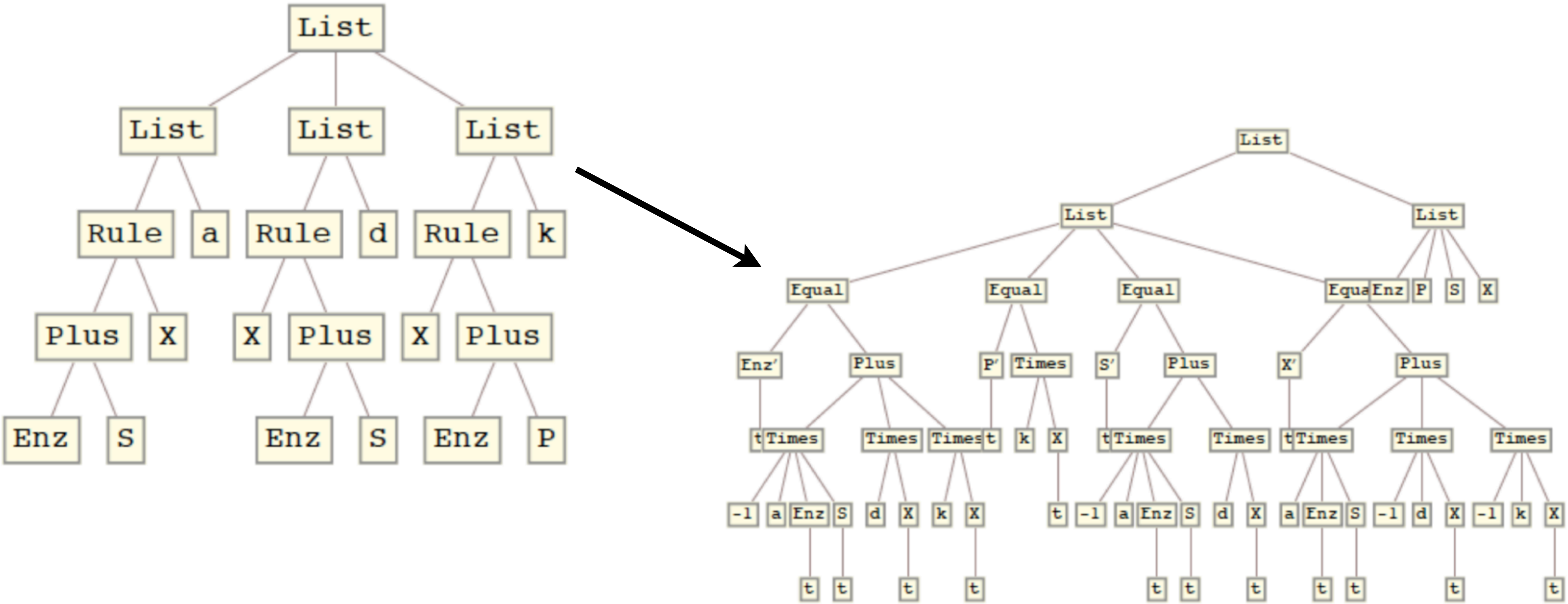
$$K_{d,y}(a_i) = k^0_{d,y}\left(1 + \left(\frac{a_i}{k^1_{d,y}}\right)^{h_{y,1}} \Bigg/ \left(1 + \left(\frac{a_i}{k^2_{d,y}}\right)^{h_{y,2}}\right)\right)$$



[Mironova et al., BMC Systems Biology 2010]

Dynamical Grammars:
[EM and Yosiphon, Ann. Math. AI 2006], [EM, Phys. Bio. 2013]

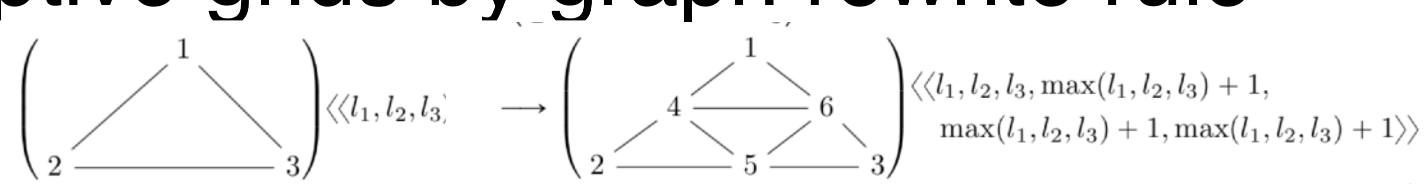
Symbolic transformation: {Reaction} --> {ODE}



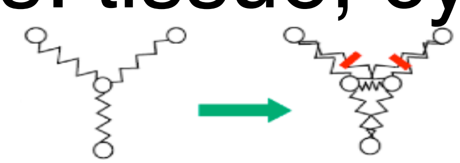
- This can be done by meta-rules, in a meta-grammar
- As can many modeling-language extensions & translations

Symbolic model transformations: endless possibilities

- Meta-rules for transforming dynamics rules
  - e.g. Reactions → ~ODEs
  - e.g. detailed balance by arrow reversal
  - generation of ML algorithms from models, > autodiff
- ~Model reduction by ML (linear combination)
  - structural discovery of fast modes
- ~Reduction to spatial graph dynamics
  - e.g. adaptive grids by graph rewrite rule



  - emergent dynamical structures: tissue, cytoskeleton, …

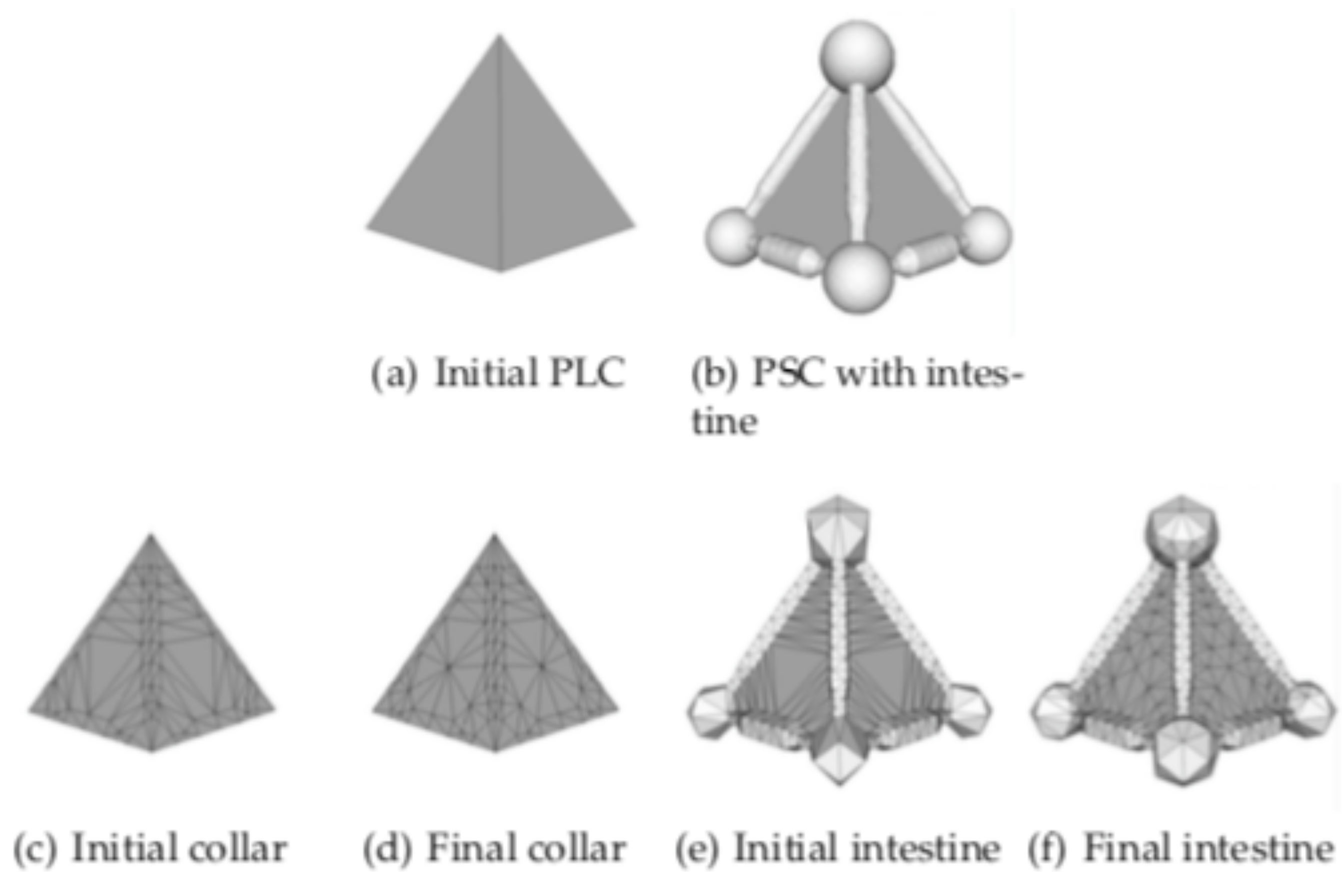


$\Psi, \mathscr{I}$

Fields to Structures

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

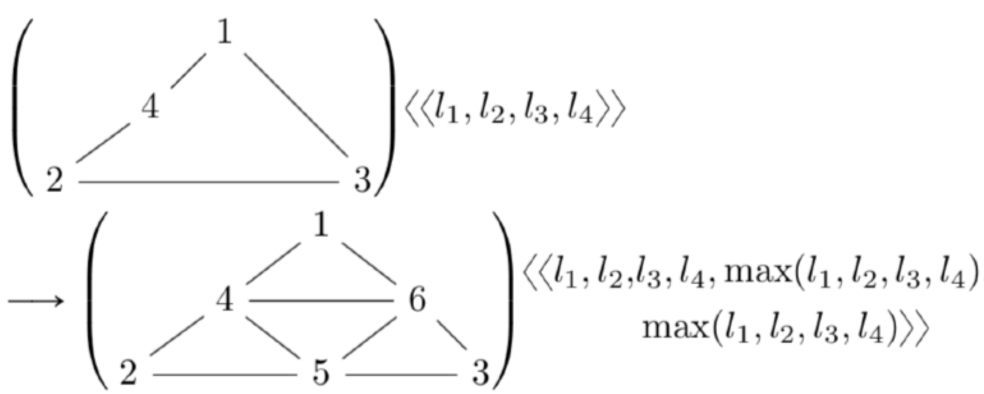
Geometric meshing: protective manifolds

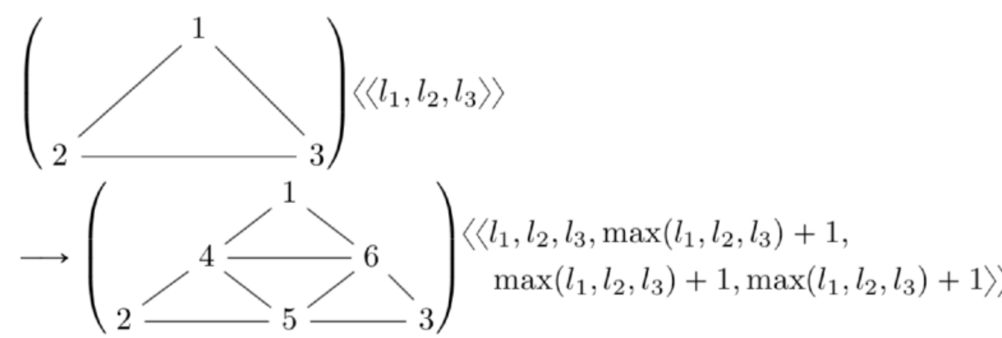


[Rand and Walkington 2009]
Cf. [Murphy, Mount, & Gable 2001;
Engwirda 2016]

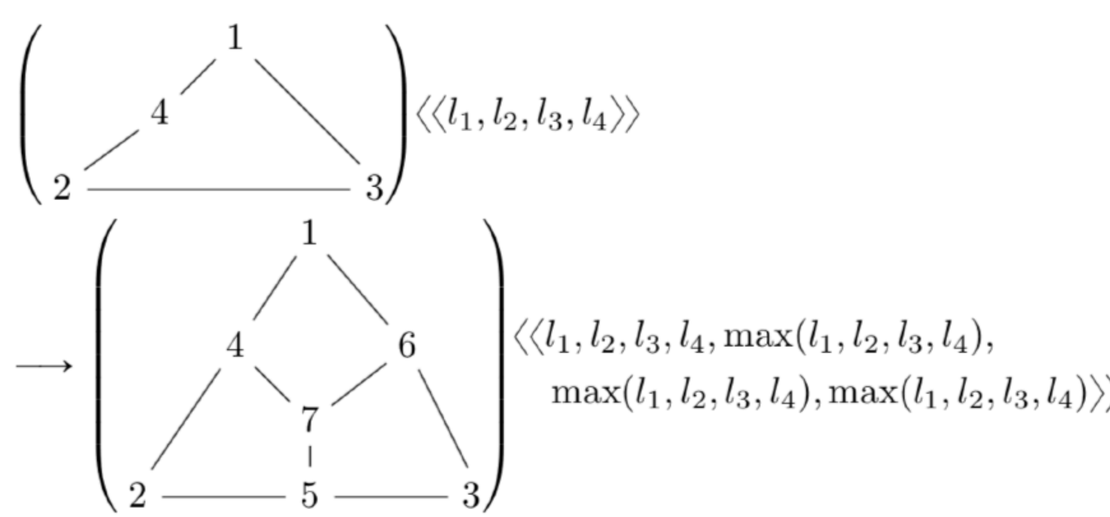
Graph Grammars for 2D meshes

- Triangular:





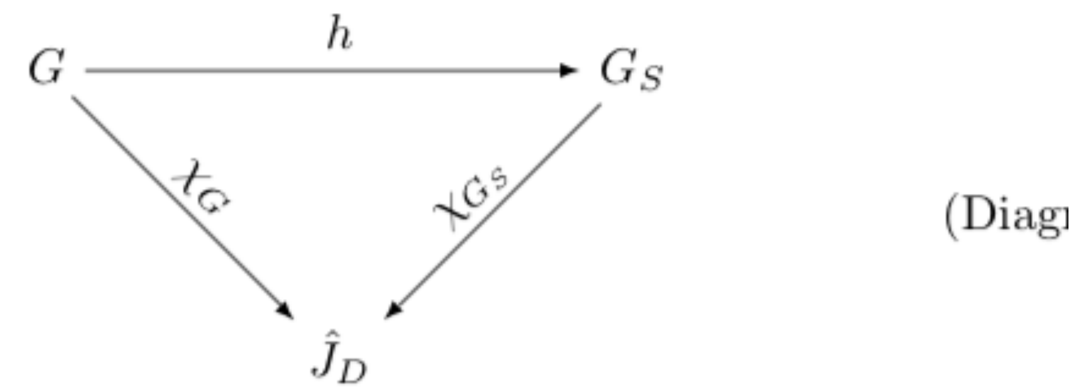
- Cuboid:



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

Higher level rewrite rules

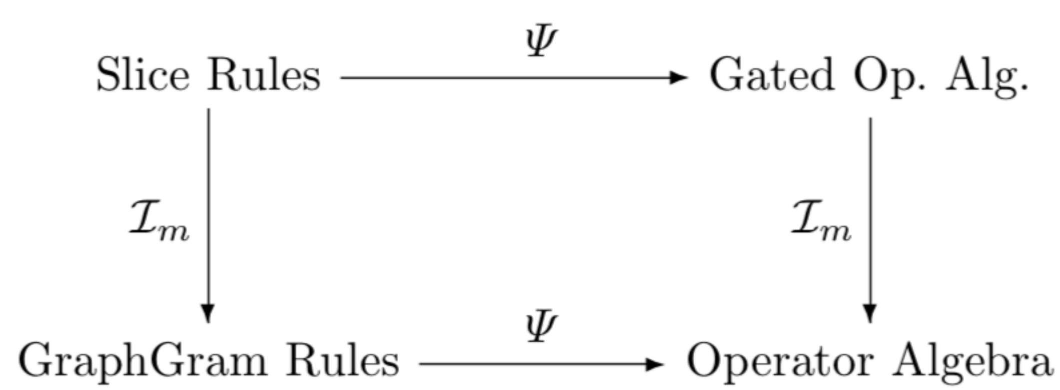
- Identify strata



each inverse image $(\chi_{G_S}^{-1})(d)$ must be a fully disconnected

- Operator algebra semantics for strata and other slices

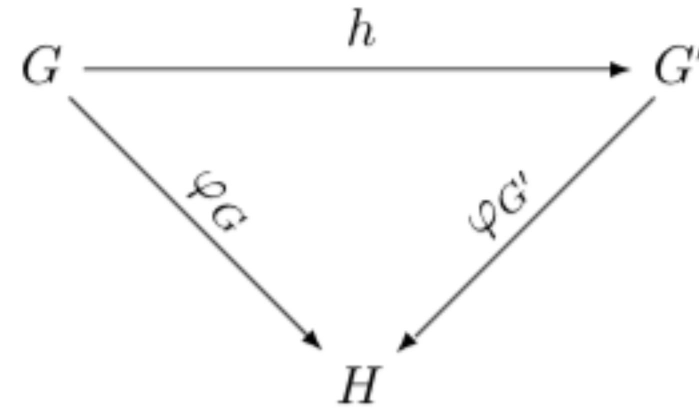
$$\rho_{\text{graph }r}((\boldsymbol{\kappa},\boldsymbol{\lambda}),(\boldsymbol{\kappa}',\boldsymbol{\lambda}')) = \Theta(P_H(\boldsymbol{\kappa})) \times \Theta(P_H(\boldsymbol{\kappa}')) \times \rho_{\text{slice }H,\ r}(\boldsymbol{\lambda},\boldsymbol{\lambda}')$$



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

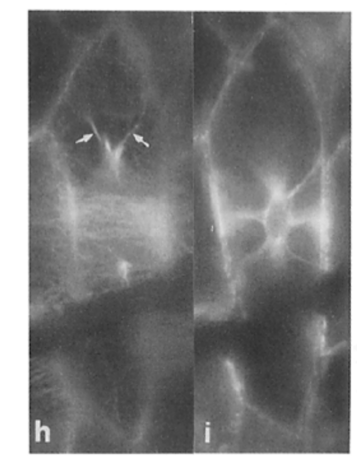
Extended objects via slices

using graph homomorphisms



$$H = \hat{\mathbb{N}},\ \ \hat{J}_D,\ \ \hat{\mathbb{N}}^{\mathrm{op}}_D,\ \ C_D,\ \ \text{or}\ \ \tilde{C}_D.$$

Stratified space of MTs:



Antitubulin labelling in premitotic epidermal cells *Datura stramonium* [Flanders et al., J. Cell Bio. 110, 1990].

$$\begin{aligned}\hat{\mathbb{N}} \equiv &(\mathbb{N}, \text{Successor})\\ &= \text{ nonnegative integers } \{0,1,\ldots\} \text{ as vertices,}\\ &\text{with (possibly directed) edges from each}\\ &\text{integer } i \text{ to its immediate successor } i+1 \text{ and to itself;}\end{aligned}$$

$$\hat{J}_D \equiv \begin{cases} (\mathbb{N}_D \equiv \{0,\ldots D \geqslant 0\}, \geqslant) & \text{directed graphs;}\\ \quad = \text{ integers } \{0,\ldots D\} \text{ with } (i,j) \text{ edge iff } i \geqslant j; & \\ \hat{K}_{\mathbb{N}_D} = \hat{K}_{\{0,\ldots D\}} \text{ (fully connected w. self-edges)} & \text{undirected graphs}\end{cases}$$

$$\hat{\mathbb{N}}^{\mathrm{op}}_D \equiv \begin{cases} \text{integers } \{0,\ldots D\} \text{ with } (i,j) \text{ edge iff } i=j+1 \text{ or } i=j & \text{directed graphs;}\\ \text{integers } \{0,\ldots D\} \text{ with } (i,j) \text{ edge iff } |i-j| \leqslant 1 & \text{undirected graphs}\end{cases}$$

$$C_D \equiv \hat{\mathbb{N}} \square \hat{J}_D$$

$$\tilde{C}_D \equiv \hat{\mathbb{N}} \square \hat{\mathbb{N}}^{\mathrm{op}}_D$$

Graded graph

Stratified graph

Abstract cell complex

Graded stratified graph

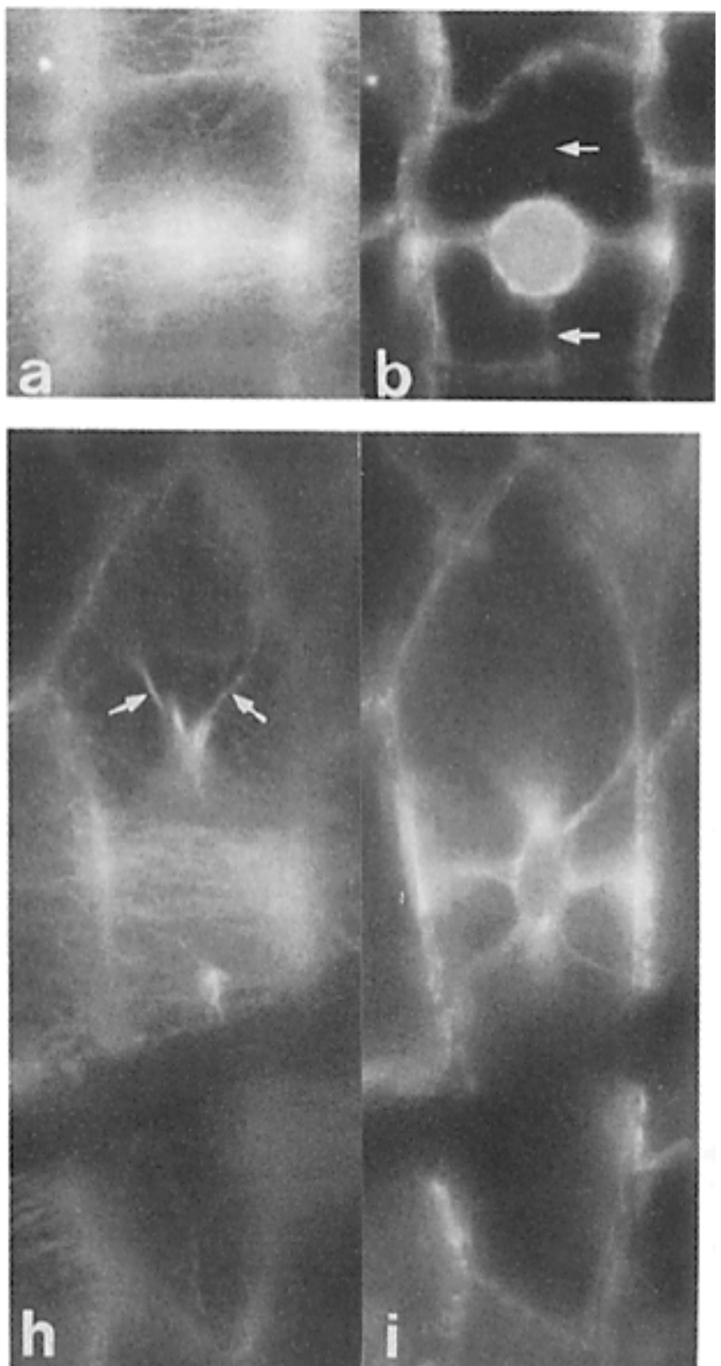
Graded abstract cell complex

Operator Algebra variants:

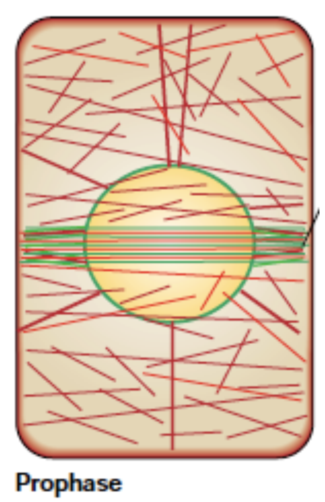
$$\rho_{\mathrm{graph}\ r}((\boldsymbol{\kappa}, \boldsymbol{\lambda}), (\boldsymbol{\kappa}', \boldsymbol{\lambda}')) = \Theta(P_H(\boldsymbol{\kappa})) \times \Theta(P_H(\boldsymbol{\kappa}')) \times \rho_{\mathrm{slice}\ H,\ r}(\boldsymbol{\lambda}, \boldsymbol{\lambda}')$$

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

Stratified spaces, not cell complexes, are necessary for cytoskeleton



Left: Antitubulin labelling in premitotic epidermal cells *Datura stramonium* [Flanders et al., J. Cell Bio. 110, 1990].

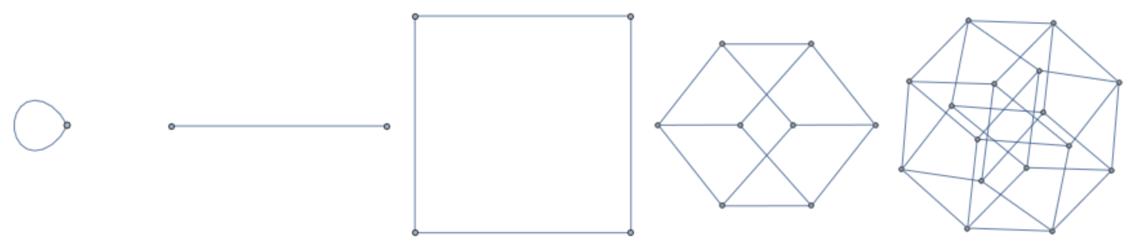


[Smith, Nat Rev MCB 2 2001]

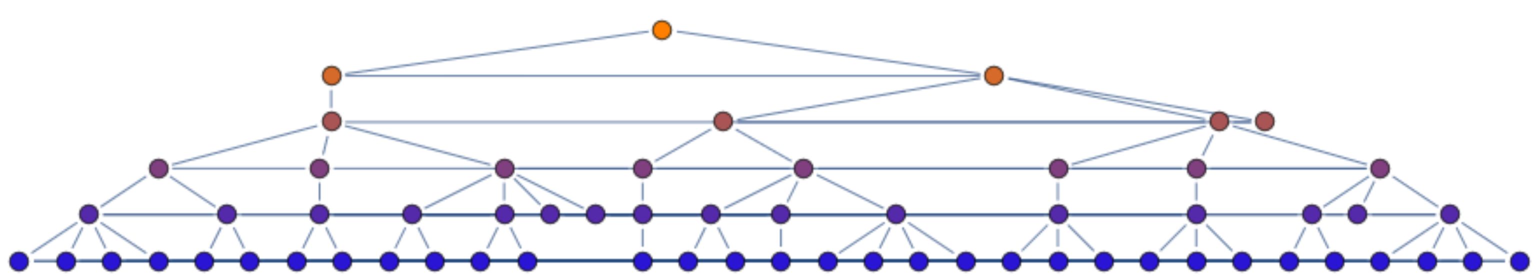
Above: Antitubulin labelling at intact cell cortex [DeBolt et al., PNAS 2007 supplementary info figure 8A.]

Graph Lineage Definitions

- *Hierarchical Graph Sequence:* a mapping from ℕ into some sequence of graphs which obeys the following:
  - G_0 is the graph with one vertex and one loop on that vertex
  - Edge and vertex cardinality of graphs in the sequence grow at most "exponentially" in some base, *b*: $O(b^{l^{1+\epsilon}})$



- *Graded Graph: G* is a graded graph if all of the vertices of *G* are labeled with non-negative integers such that if (v_1, v_2) is an edge, the labels of v_1 and v_2 differ by at most 1.

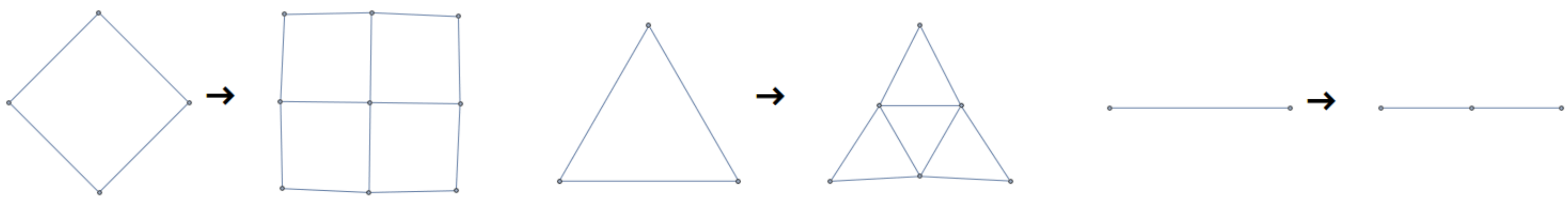


- *Graph Lineage:* a graded graph where the sequence of $\Delta L = 0$ subgraphs is a HGS and the subgraphs with $\Delta L = 1$ are a HGS of bipartite graphs. The above is a graph lineage of path graphs of length 2^n.

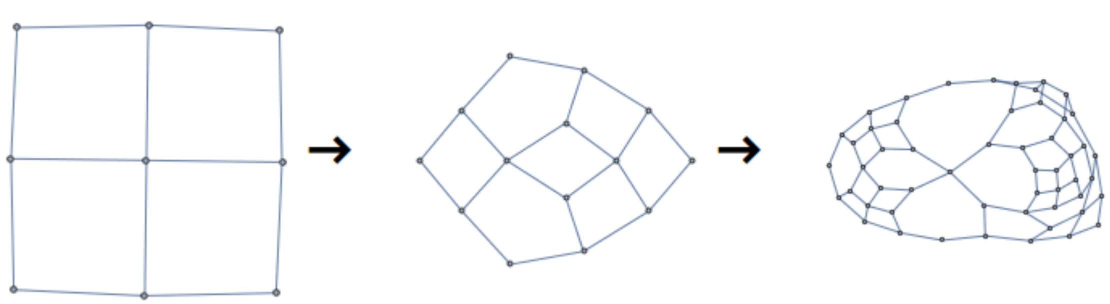
- *Hierarchitecture*: A graph lineage, used as a model architecture.

Generating Graph Lineages

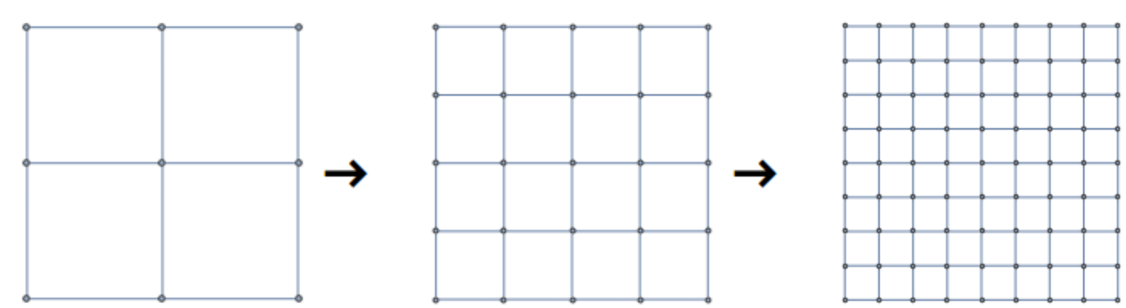
- One way to generate a graph lineage (or more generally, graded graphs) is via local graph rewrite rules.



- Rules can be applied locally, or to all cells in a graph simultaneously:

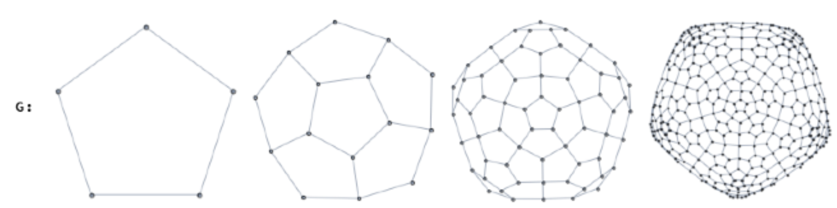


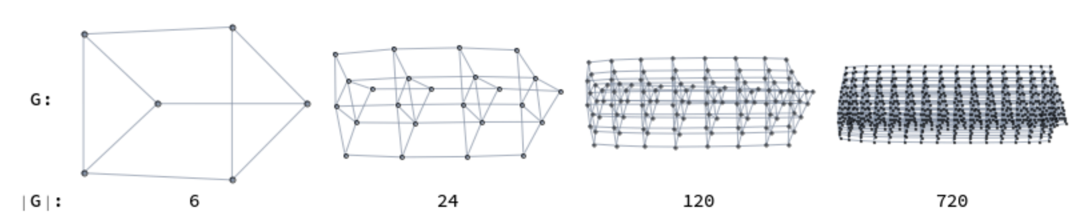
Local Firing



Global Firing

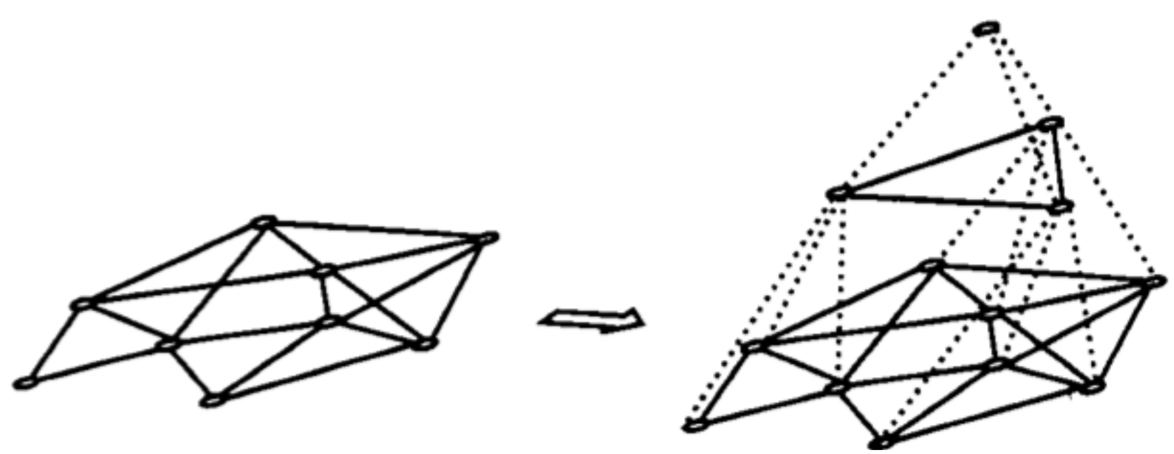
- Graph labels suppressed, but necessary
- More:





Multiscale numerics: Alg. Multigrid Methods for Graphs

$$G' \simeq P^T G P$$



Define Graph Process Directed "Distances"

- Definition requires constrained opt of diffusion operator:

$$D(G_1, G_2|R, \alpha > 0, t) = \inf_{P|C(P)} ||P\exp(\alpha^{-1/2} t W_1^{(R)}) - \exp(\alpha^{1/2} t W_2^{(R)}) P||_F$$
$$D(G_1, G_2|R, t) = \inf_{\alpha > 0} D(G_1, G_2|R, \alpha, t)$$

- Constraints: orthogonality; sparsity?

$C(P)$: $\underbrace{P^T P}_{\text{restriction.prolongation}} = I$; $\max \text{fanout}(P) \leq (n_{P\text{fine}}/n_{P\text{course}})^s$

- Optimize time & time dilation due to graph size:

$$\tilde{D}(G_1, G_2|R) = \sup_{t>0} \inf_{\alpha>0} D(G_1, G_2|R, \alpha, t)$$

- Can obtain *P* at early times ("rigid" vs "flexible" def of *D*):

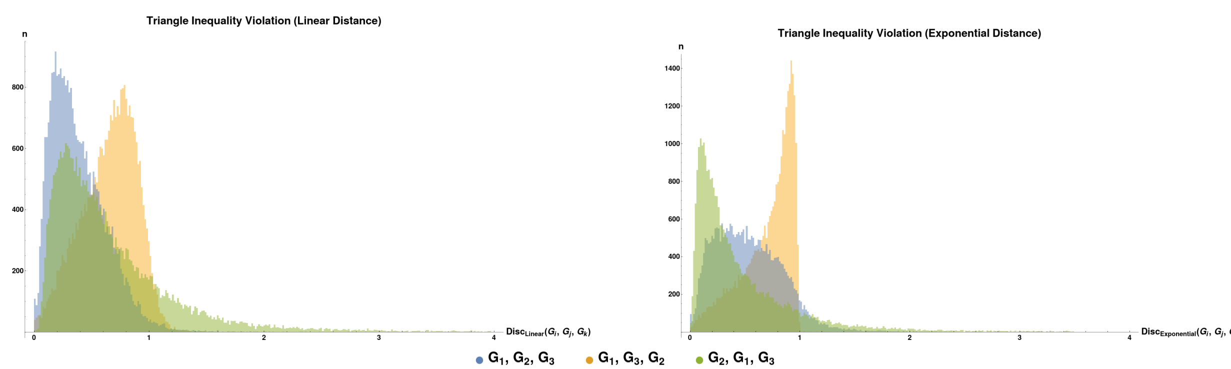
$$D_{\text{rigid}}(G_1, G_2|R, t) = \inf_{P|C(P)} ||P^* \exp(\alpha^{*\,-1/2} t W_1^{(R)}) - \exp(\alpha^{*\,1/2} t W_2^{(R)}) P^*||_F \text{ , where}$$
$$(\alpha^*, P^*) = \text{argmin}_{\alpha>0, P|C(P)} ||\alpha^{-1/2} P W_1^{(R)} - \alpha^{1/2} W_2^{(R)} P||_F$$

- $\triangle\leq$ provable with weaker α : $\alpha = \left(\frac{n_1}{n_2}\right)^r$

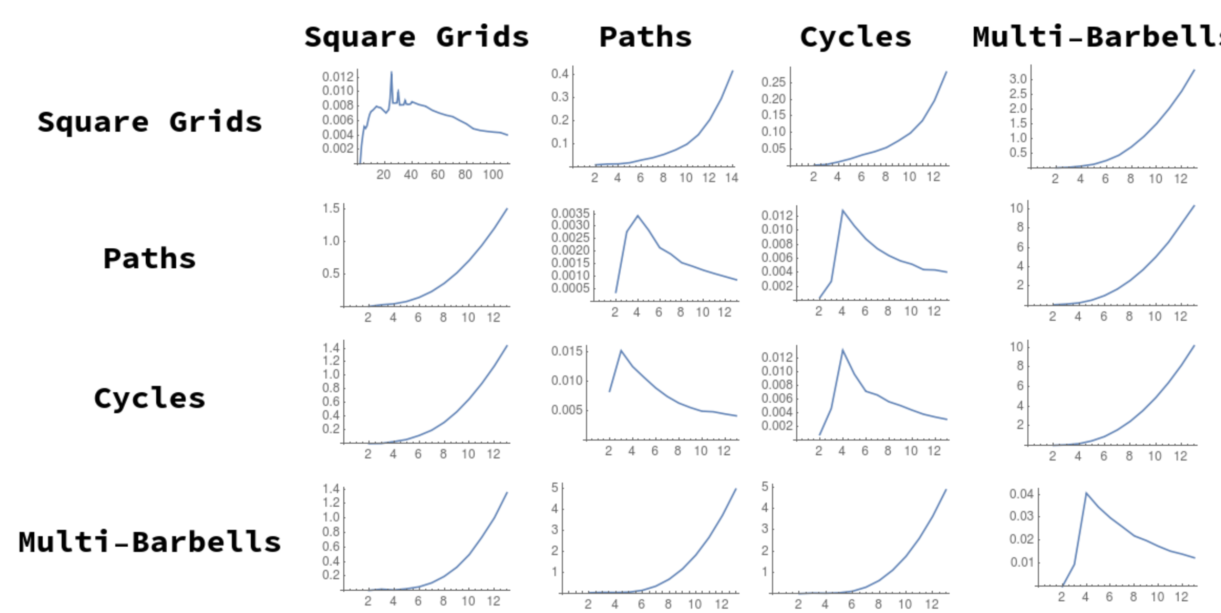
[C. Scott and EM, http://arxiv.org/abs/1909.04203]

Graph Distance Experiments

- Triangle inequality



- Graph limits



[C. Scott and EM, http://arxiv.org/abs/1909.04203]

with Cory Scott
MS in prep

Key data type:
Stack of models

w. conditional reductions, each model on the spectrum:

- pure chemical reactions
- parameterized object rewrite rules
  - propensity functions
  - differential equations (ordinary, stochastic, delay)
- graph grammar rewrite rules
- graph-limit rewrite rules
  - support PDEs on R^n, manifolds, CCs, SSs
- sub-grammar calls, macros, types/inheritance

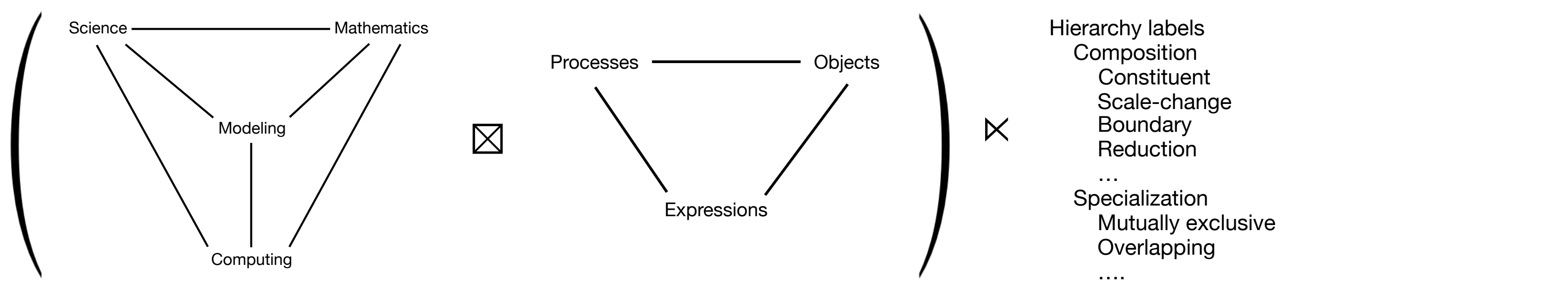
[EM, Bull. Math Biol. 81:8 Aug 2019
+arXiv:1804.11044]

Epilogue

- Interlevel mappings in “morphodynamics”/dev bio modeling are central to: AI for bio
- Such model reductions can be *specified*, *curated*, *optimized* and *learned* computationally
  - *optimized* and *learned*: Dynamic Boltzmann Distributions, GCCD, machine learning methods
  - *specified*: ~Dyn Graph Grammar high level languages + graph limits. Microtubule, cell tissue models as test cases.
  - *curated*: Tschicoma conceptual architecture; Cajete scalable prototype
- Comments? Want to help? emj@uci.edu .

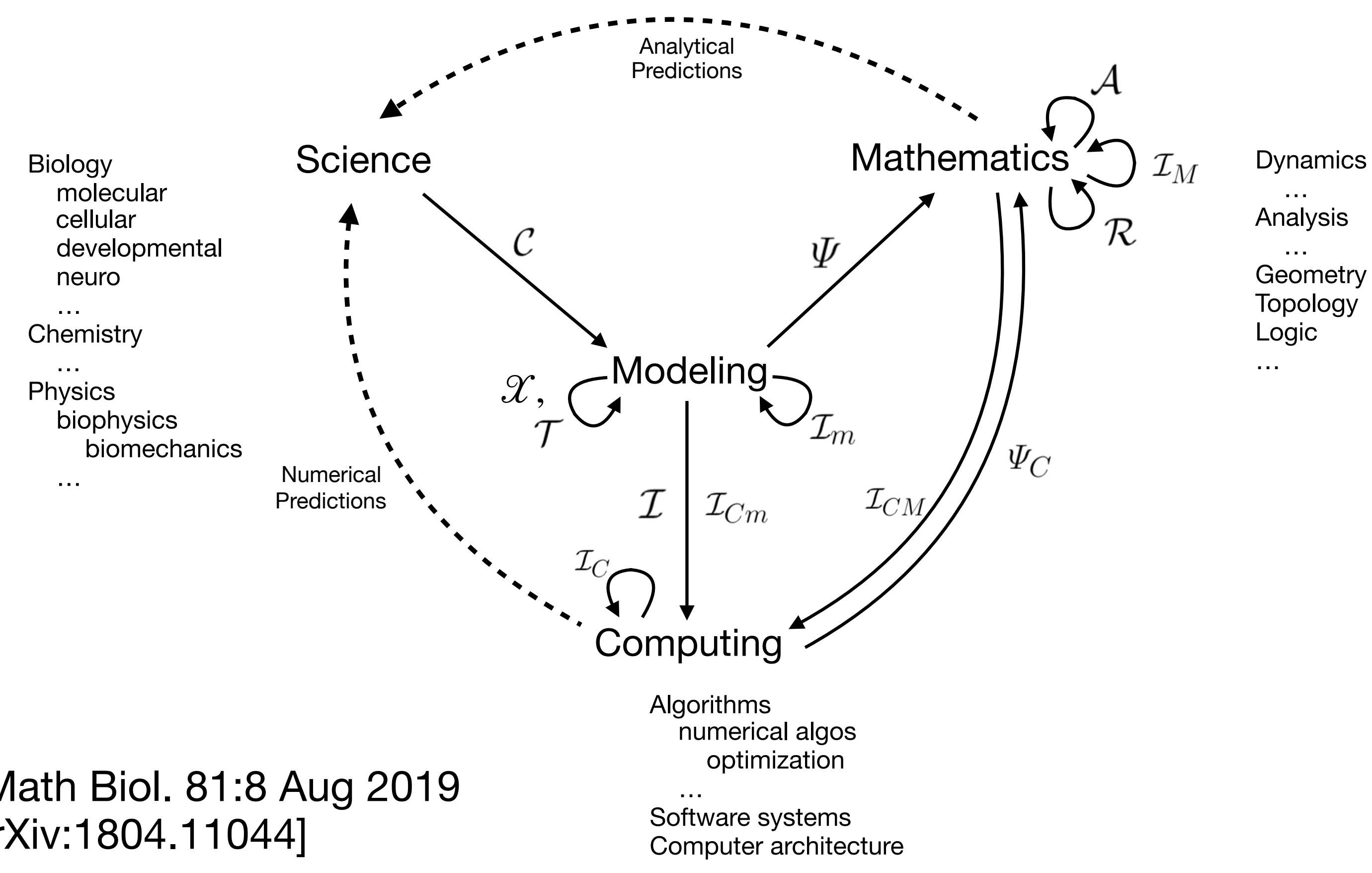
"Tchicoma" Architecture for Mathematical Modeling

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



- Mappings therein:

respecting compositional structure



Enables problem-solving via chaining, theorem-proving

Foments abstraction via commutation

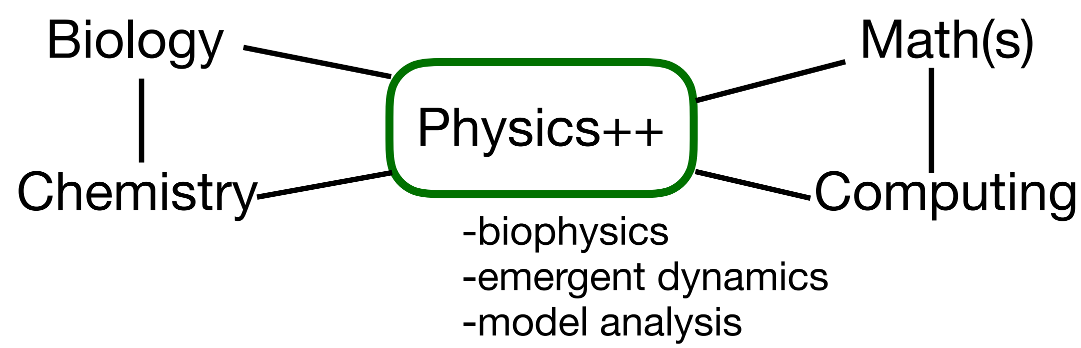
[EM, Bull. Math Biol. 81:8 Aug 2019 +arXiv:1804.11044]

Conclusions

- Biological model reduction can be achieved by machine learning, in spatial stochastic models (and easier ones). Reaction/diffusion examples.
- Morpho-dynamic spatial structures (and easier models) 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".
- Declarative modeling languages with operator algebra semantics can support generic model reduction, hence model stacks.
- In these ways, both symbolic and numeric AI can be brought to bear on understanding complex biological systems at their own scale.

A change of view

- Human, physics-centric viewpoint:



- Computer viewpoint: