Progress in modeling biological development as it bears on SBML

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representing

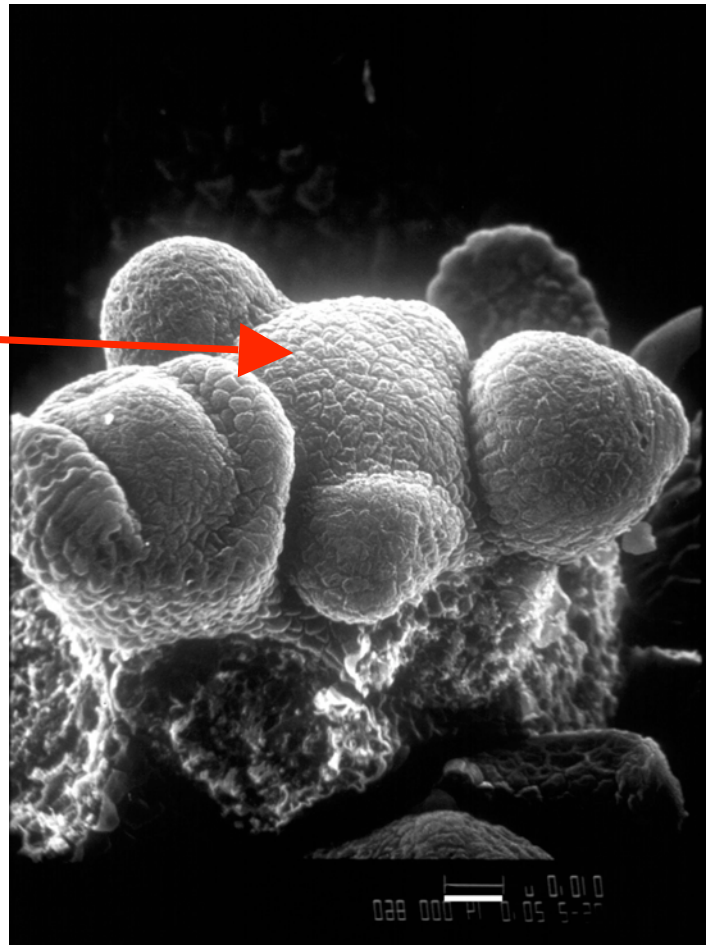
the Computable Plant project

www.computableplant.org

Three relevant examples

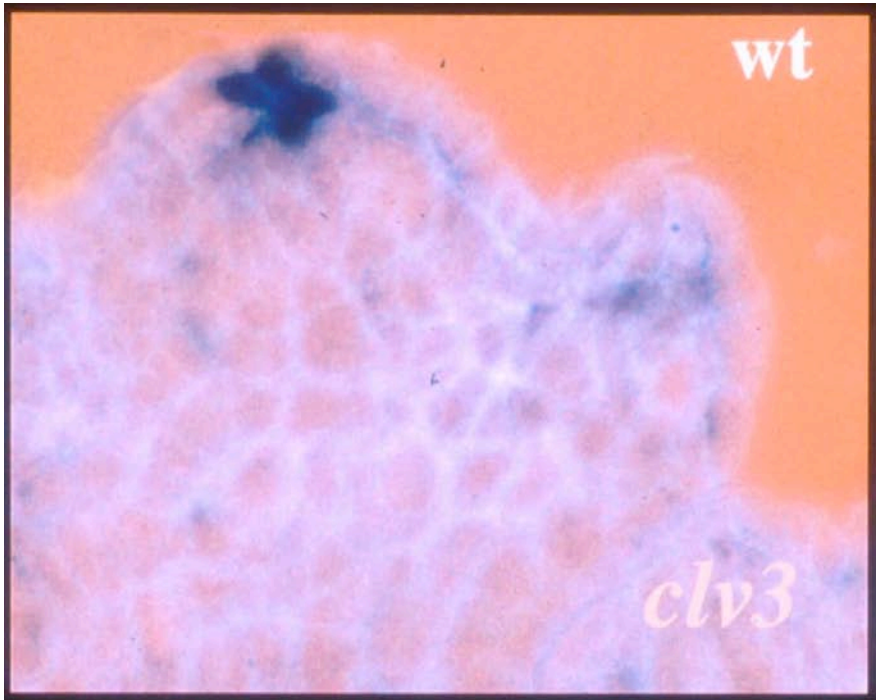
- Meristem maintenance by Wuschel
- Phyllotaxis mechanical network
- Molecular complexes

Example: *Arabidopsis* Shoot Apical Meristem (SAM)

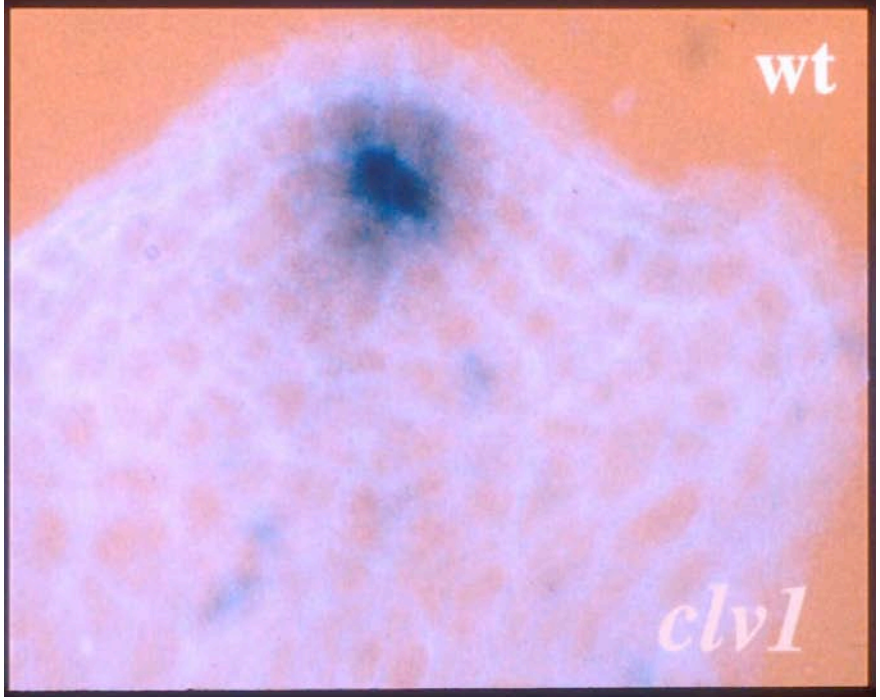


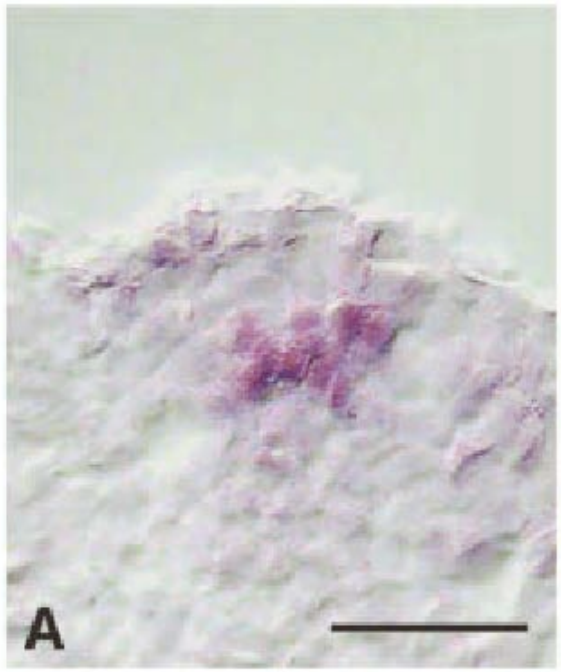
WILD TYPE

clavata3 mutant



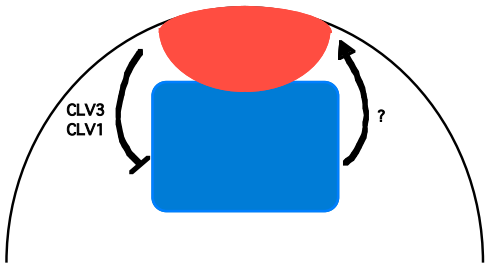
Fletcher et al., Science v. 283, 1999



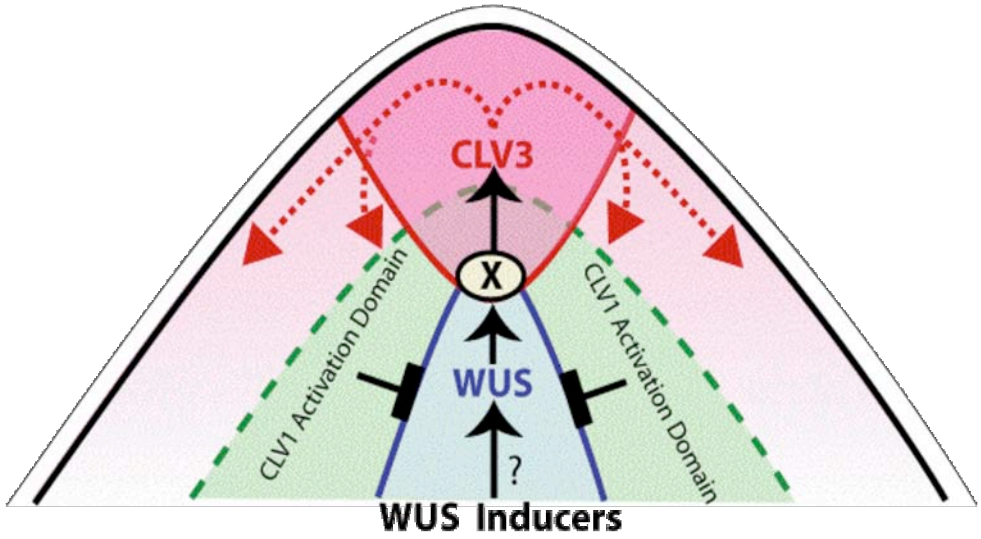


WUS

Brand et. al., Science **289**, 617-619, (2000)



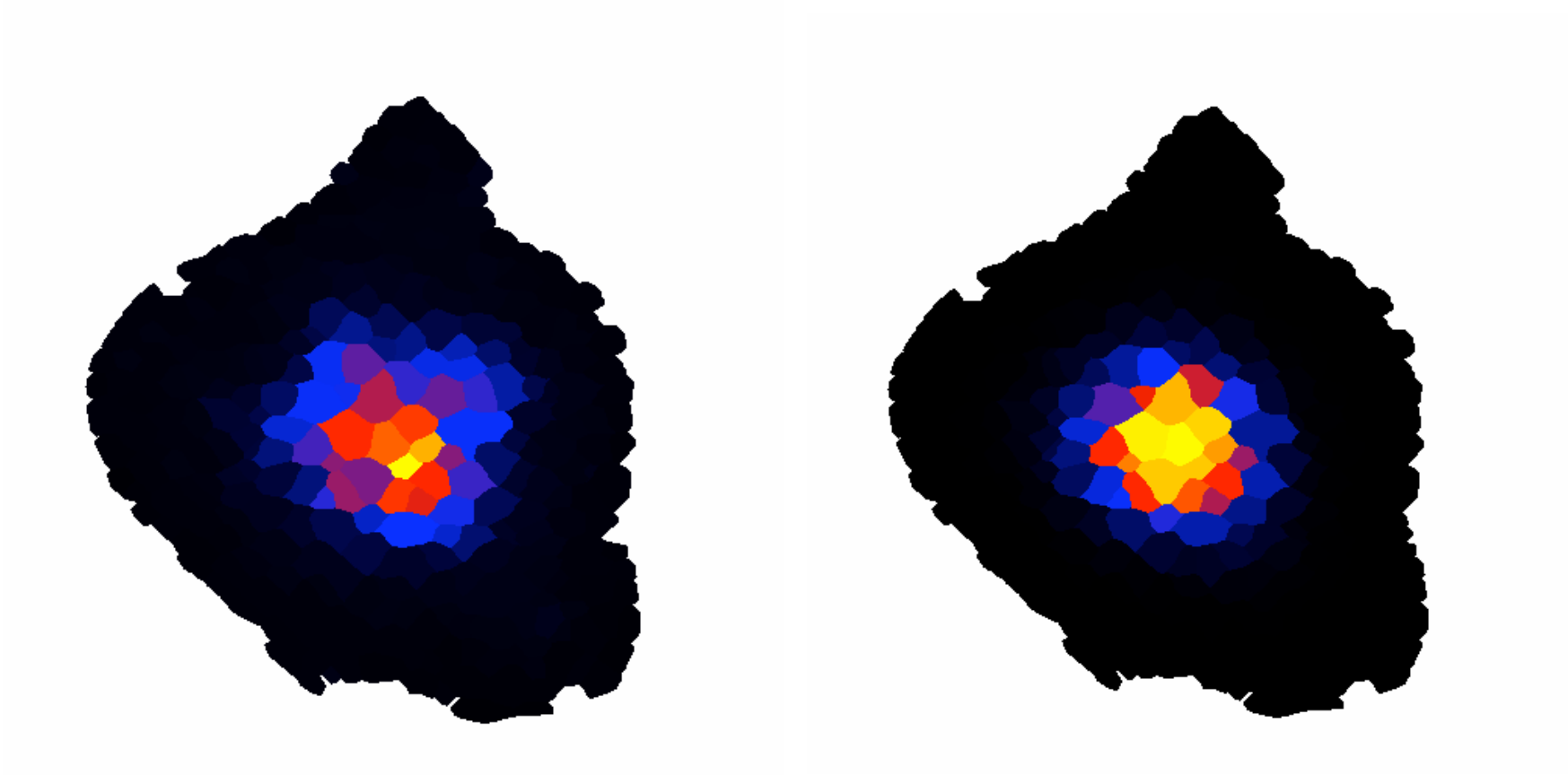
CLV3/WUS networks for meristem maintenance



Jönsson et al., Bioinformatics 21(Suppl. 1):i232-i240 June 2005.

WUS network simulation (2D template)

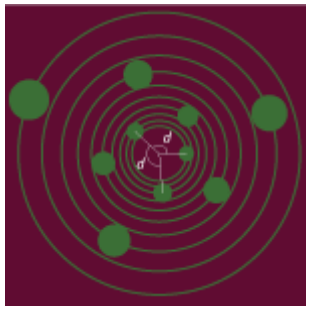
Cell volumes, wall areas, and neighbors from template

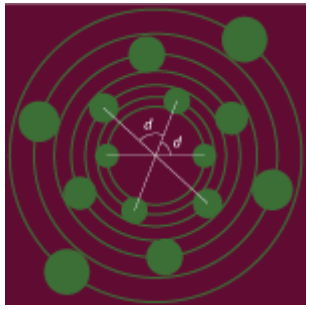


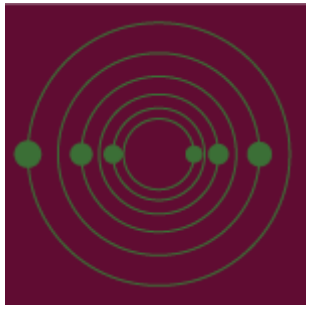
Template **Simulation**

Jönsson et al., Bioinformatics 21(Suppl. 1):i232-i240 June 2005.

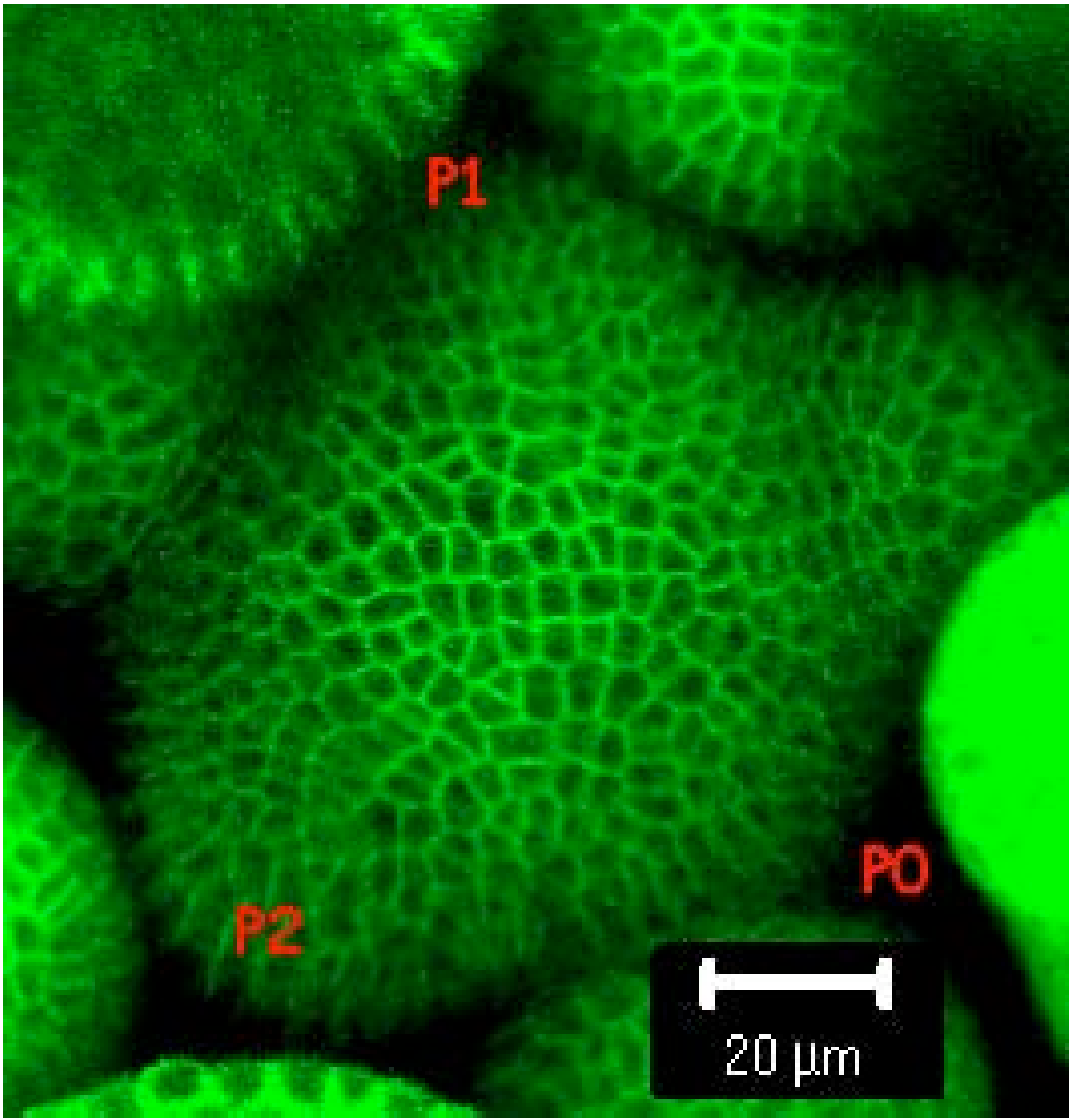
Phyllotaxis







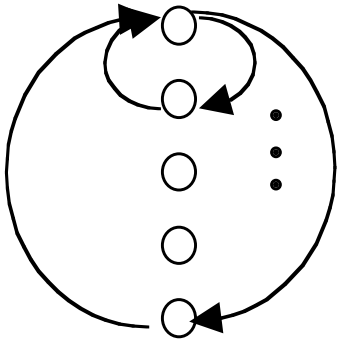
SAM growth imagery PIN1 cell walls



Venu Reddy,
Caltech

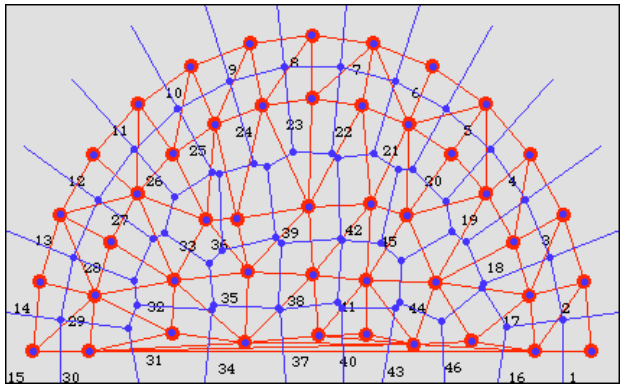
Regulatory and Mechanical Networks, Coupled

Regulated cell division, spring constants



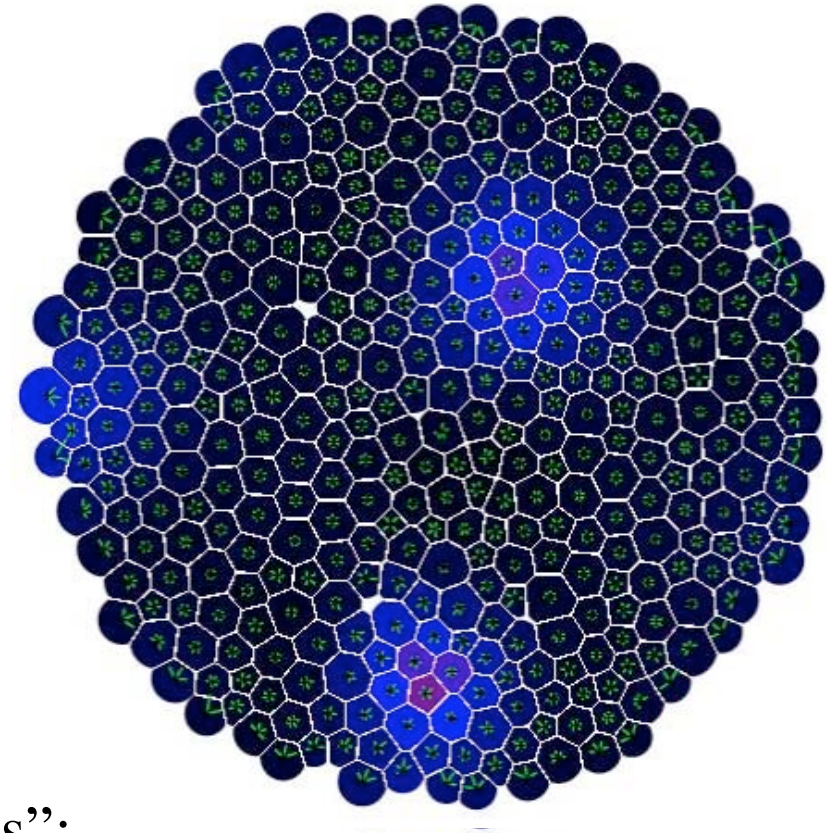
T_{ab}

Adjacency + cell signaling



Λ_{ij}

Dynamic Phyllotactic Model



Emergence of new extended, interacting *objects*: floral meristem primordia.

DG's at ≥ 3 scales:
- molecular;
- cellular;
- multicellular.

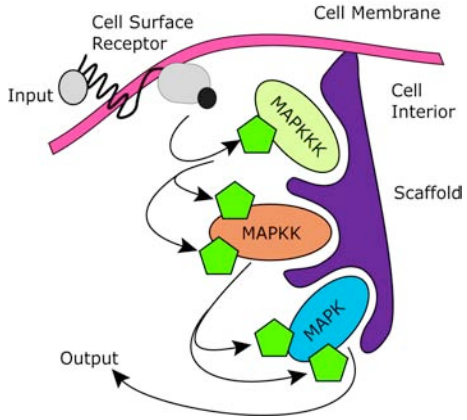
Reaction "rules":

$$\left\{\text{auxin}[i] \overset{\text{PIN1}[i,j]}{\Longrightarrow} \text{auxin}[j],\ \emptyset \overset{\text{auxin}[i]}{\Longrightarrow} \text{PIN1}[i],\right.$$

$$\left.\text{PIN1}[i] \overset{\text{auxin}[j]}{\Longrightarrow} \text{PIN1}[i, j],\ \text{PIN1}[i, j] \to \emptyset,\ \text{PIN1}[i, j] \to \text{PIN1}[i]\right\}$$

H. Jönnson, M. Heisler, B. Shapiro, E. Meyerowitz, E. Mjolsness - *Proc. Nat'l Acad. Sci.* 1/06

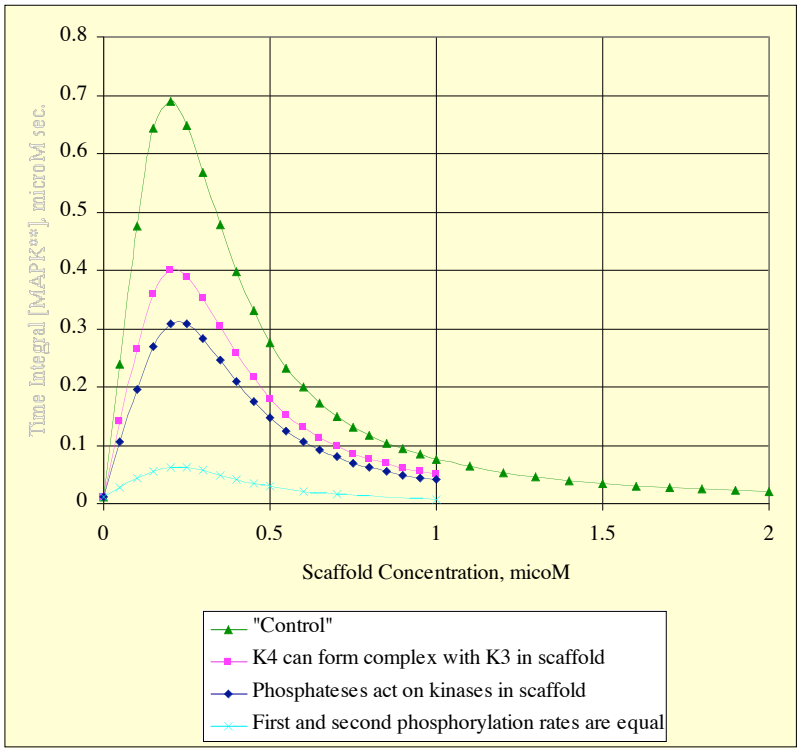
MAPK/Scaffold Modeling



(c) Phosphorylation in the Scaffold

```
phosphorylationReactions = genScafPhosReacts[S, {2, 2, 1, 1}, K]

{S[0, 2, -1] → S[1, 2, -1], S[0, 2, 0] → S[1, 2, 0], S[0, 2, 1] → S[1, 2, 1],
 S[1, 2, -1] → S[2, 2, -1], S[1, 2, 0] → S[2, 2, 0], S[1, 2, 1] → S[2, 2, 1],
 S[-1, 0, 1] → S[-1, 1, 1], S[-1, 1, 1] → S[-1, 2, 1], S[0, 0, 1] → S[0, 1, 1],
 S[0, 1, 1] → S[0, 2, 1], S[1, 0, 1] → S[1, 1, 1], S[1, 1, 1] → S[1, 2, 1],
                                                                  K[4,1]
 S[2, 0, 1] → S[2, 1, 1], S[2, 1, 1] → S[2, 2, 1], S[-1, -1, 0] ⇄ S[-1, -1, 1],
                K[4,1]                                K[4,1]                                K[4,1]
 S[-1, 0, 0] ⇄ S[-1, 0, 1], S[-1, 1, 0] ⇄ S[-1, 1, 1], S[-1, 2, 0] ⇄ S[-1, 2, 1],
                K[4,1]                                K[4,1]                                K[4,1]
 S[0, -1, 0] ⇄ S[0, -1, 1], S[0, 0, 0] ⇄ S[0, 0, 1], S[0, 1, 0] ⇄ S[0, 1, 1],
                K[4,1]                                K[4,1]                                K[4,1]
 S[0, 2, 0] ⇄ S[0, 2, 1], S[1, -1, 0] ⇄ S[1, -1, 1], S[1, 0, 0] ⇄ S[1, 0, 1],
                K[4,1]                                K[4,1]                                K[4,1]
 S[1, 1, 0] ⇄ S[1, 1, 1], S[1, 2, 0] ⇄ S[1, 2, 1], S[2, -1, 0] ⇄ S[2, -1, 1],
                K[4,1]                                K[4,1]                                K[4,1]
 S[2, 0, 0] ⇄ S[2, 0, 1], S[2, 1, 0] ⇄ S[2, 1, 1], S[2, 2, 0] ⇄ S[2, 2, 1]}
```



Shapiro et al., 1st Int. Conf. Systems Biology, 2000

Reactions in Scaffolded MAP Kinase Cascade

- Phosphorylation in Solution

$$\left\{ K_i^j \underset{Ph_i}{\overset{K_{i+1}^{a_{i+1}}}{\Leftrightarrow}} K_i^{j+1} \;\middle|\; i = 1,\ldots,n-1,\ j = 0,\ldots,a_j - 1 \right\}$$

- Binding to Scaffold

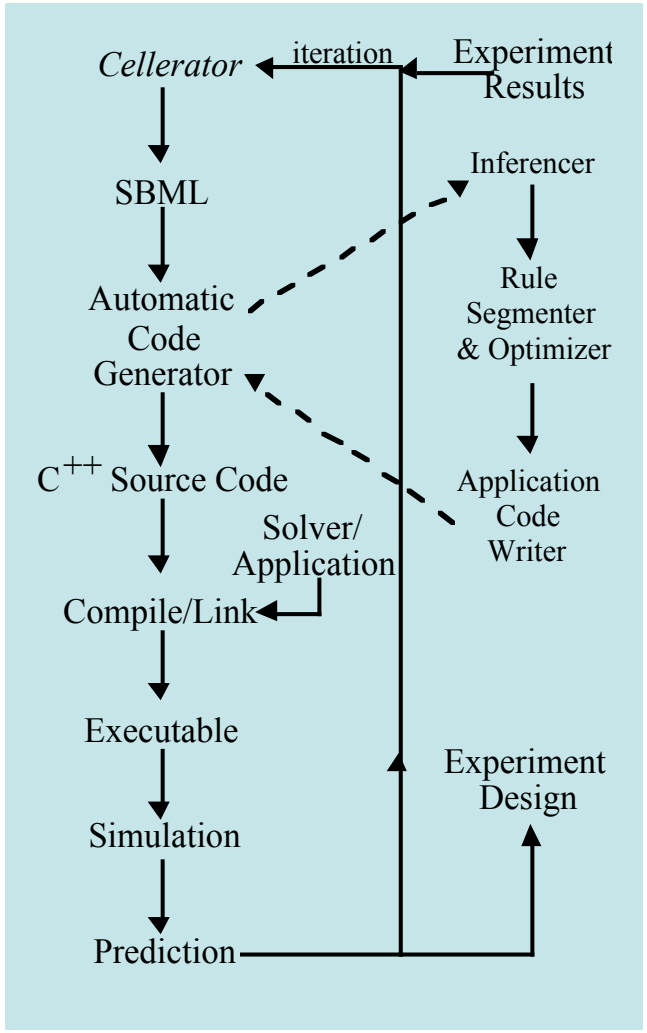
$$\left\{ S_{p_1,\cdots,p_i=\varepsilon,\cdots,p_n} + K_i^j \leftrightarrow S_{p_1,\cdots,p_i=j,\cdots,p_n} \right\}, \quad p_i = \begin{cases} \varepsilon, 0, 1, \ldots, a_i, & i \neq j \\ 0, 1, \ldots, a_i, & i = j \end{cases}$$

- Phosphorylation in Scaffold

$$\left\{ S_{p_1,\cdots,p_{i-1=j<a_i-1},p_i=a_i,\cdots,p_n} + K \Leftrightarrow S_{p_1,\cdots,p_{i-1=j+1},p_i=a_i,\cdots,p_n} \right\}$$

$$\left\{ S_{p_1,\cdots,p_{i-1=j<a_i-1},p_i=a_i,\cdots,p_n} \rightarrow S_{p_1,\cdots,p_{i-1=j+1},p_i=a_i,\cdots,p_n} \right\}$$

Code Autogeneration Data Flow



Fundamental modeling issues: How to specify…

- *Structure* of the existence and interactions of state variables
  - "Structure" meaning low Kolmogoroff complexity, via generative procedure
  - Eg. Wuschel; auxin/Pin1 multicellular reaction "rules"; Ste5 reaction "rules"
- *Dynamics* of the existence and interactions of state variables
  - Eg. auxin/Pin1 phyllotaxis model, weak spring mechanics
  - Eg. many rarely-occurring reactions

Relevant Theory:
Semantic Maps for …

- Dependency diagrams (DD's; prob. models)
- Graph automata (GAA's ?)
- Dynamical grammars (DG's)

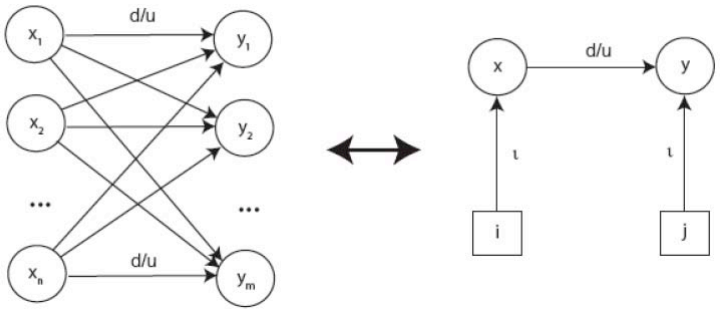
DD Link Types

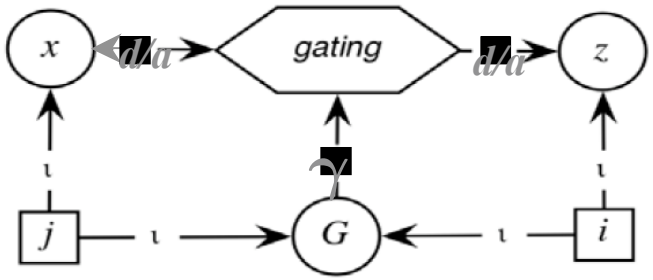
Link type

- BN and MRF links
- Index links ι (from index nodes)
- Interaction gating links γ
- Node existence, ε
- Constraint, δ

Purpose

- Probabilistic models
- Replicate variables and interactions
- Gate an interaction based on other variables
- Gate all interactions of a node; finish vbl-structure system definition. Eg: parse tree. [From γ]
- Impose constraints on random variables and index values
  - e.g. sphere; constraint nets





Graph Automata

Boltzmann distributions *E(G,x)* with detailed-balance dynamics.
Conjecture: a general form is:

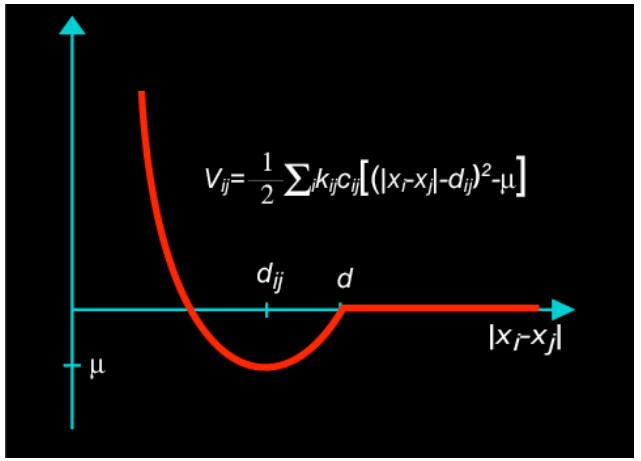
$$E(\boldsymbol{x}_i, G) = C_0 \sum_i F_1(\boldsymbol{x}_i) + C_1 \sum_{ij} G_{ij}\, F_2(\boldsymbol{x}_i, \boldsymbol{x}_j) + C_2 \sum_{ij} G_{ij}\, G_{ji} + C_3 \sum_{ijk} G_{ij}\, G_{jk}\, G_{ki}$$

optionally: $$+ \quad C_4 \sum_{i\, j\, i_n\, j_n} \sum_{a\, b} G^a_{i\, j}\, \Gamma^{a\, b}_{i_n\, j_n}\, G^b_{\lambda(i\, i_n)\, \lambda(j\, j_n)}$$

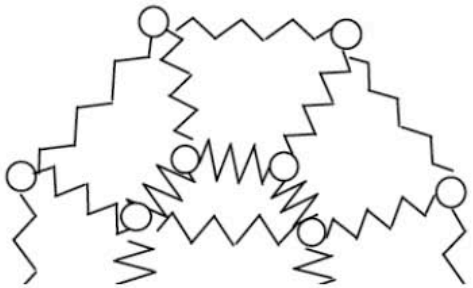
Example: weak spring model

Bhan and Mjolsness, Complexity 11(6), 2006

Weak spring mechanical model



(a)



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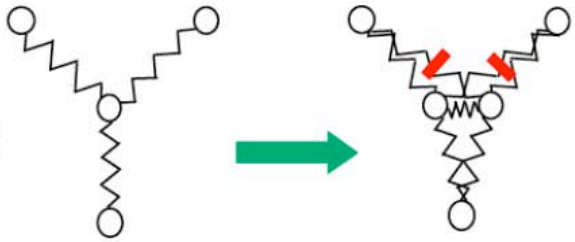
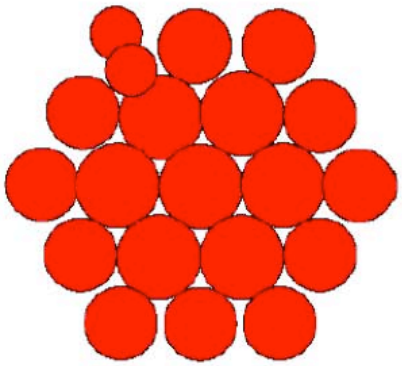


(c)



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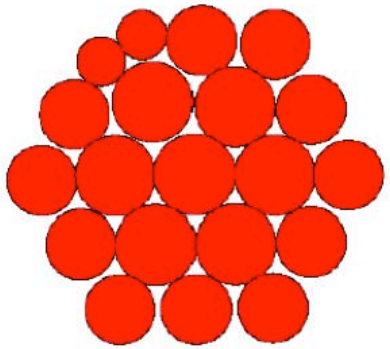
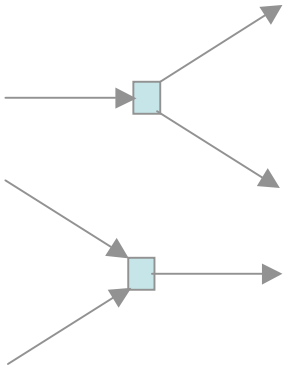


A Modeling Language for Biological Development



- "Dynamical Grammars" formal language, eg.:

  $A(x) \rightarrow B(y) + C(z)$ **with** $\rho_f(x, y, z)$

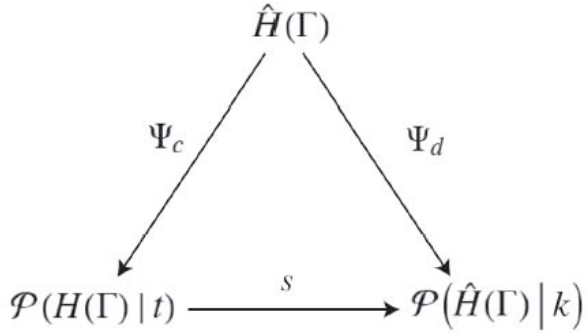
  $B(y) + C(z) \rightarrow A(x)$ **with** $\rho_r(y, z, x)$

  - *x,y,z* can be static indices *and/or* variables (new)
- Semantics: "events" & XDEs --> time evolution generators *H*; exp *tH*
- Implementation: "Plenum"

  [Mjolsness and Yosiphon 2006]
- Generalizes Cellerator to multiscale dynamics, via various hybrids

  (ICSB math tutorial notes)
- 1-page reimplementation of weak spring tissue model with cell division
- parameters can include indices

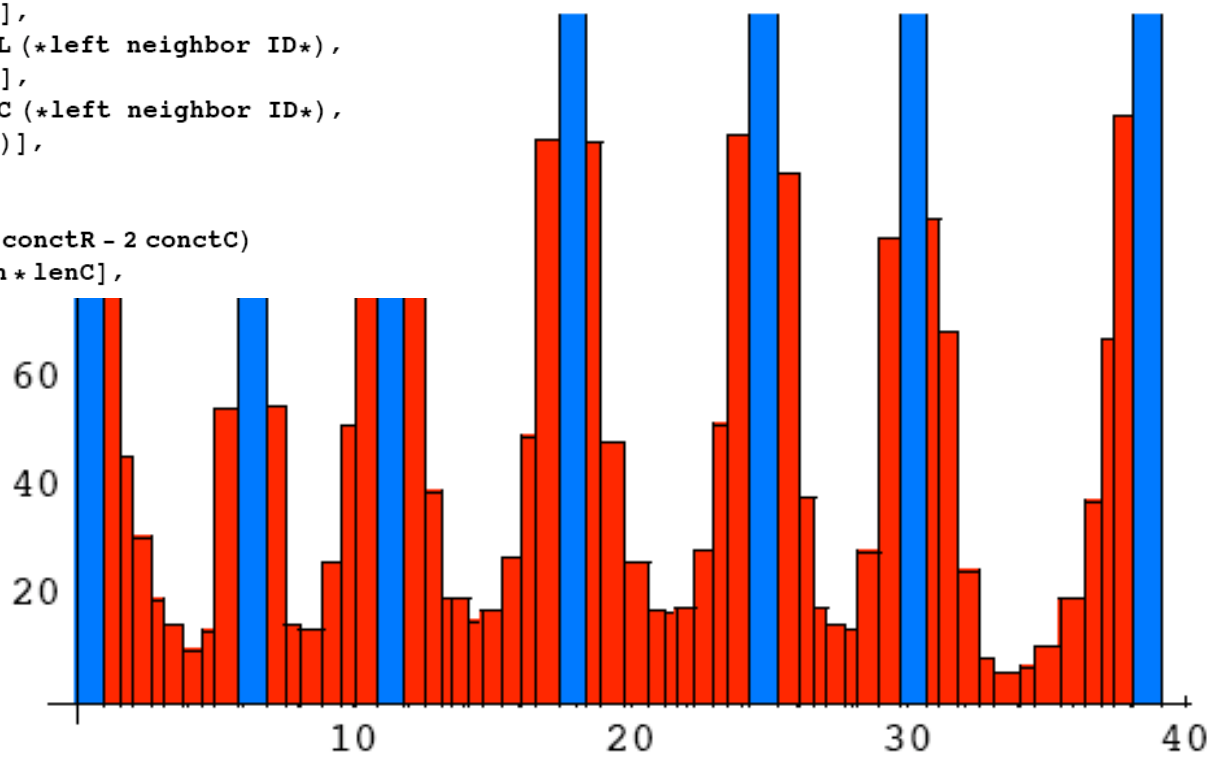
  => index-matching "rules"



Plenum Example: *Anabaena*

Prusinkiewicz et al. model

```
(*continuous change in vegetatice cell's concentartion and length*)
{cell[cellIDL, lenL, conctL, cellIDLL (*left neighbor ID*),
       cellIDC(*right neighbor ID*)],
  cell[cellIDC, lenC, conctC, cellIDL (*left neighbor ID*),
       cellIDR(*right neighbor ID*)],
  cell[cellIDR, lenR, conctR, cellIDC (*left neighbor ID*)
    cellIDRR(*right neighbor ID*)],
  cellTypeVeg[cellIDC]
 } → {cell[cellIDL, lenL, conctL, cellIDLL (*left neighbor ID*),
       cellIDC(*right neighbor ID*)],
  cell[cellIDC, lenC, conctC, cellIDL (*left neighbor ID*),
       cellIDR(*right neighbor ID*)],
  cell[cellIDR, lenR, conctR, cellIDC (*left neighbor ID*),
       cellIDRR(*right neighbor ID*)],
  cellTypeVeg[cellIDC]
 },
solving[conctC' == expConct1 (conctL + conctR - 2 conctC)
   - expConct2 * conctC, lenC' == expLen * lenC],
```



Summary

- Developmental examples
  - Meristem maintenance model
  - Phyllotaxis model (weak spring mechanics)
  - Molecular complex models
- Core modeling issues
  - Structure of state vbl existence & interaction
  - Dynamics of state vbl existence & interaction
- Theory: Semantics for …
  - DD links: indexing, gating, existence
  - Graph automata (no static indices)
  - Dynamical grammars (no static indices)