Netherlands Consortium for
Systems Biology

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The Virtual Leaf

A generic tool for cell-based plant tissue modeling

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Amsterdam, The Netherlands

Work initiated at VIB - Dept. Plant Systems Biology, Ghent, Belgium

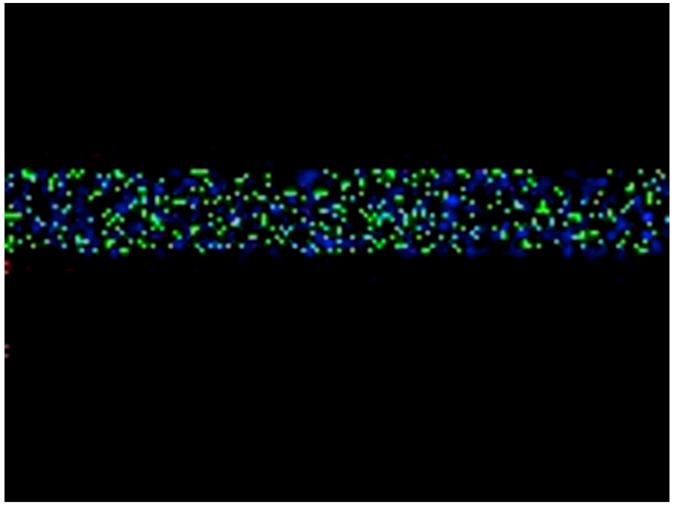
Biocomplexity X - Virtual Tissues
CBO Workshop
Bloomington, Indiana, 10/28/09-11/02/09

Plant Systems
Biology

VIB
FLANDERS INTERUNIVERSITY INSTITUTE
FOR BIOTECHNOLOGY

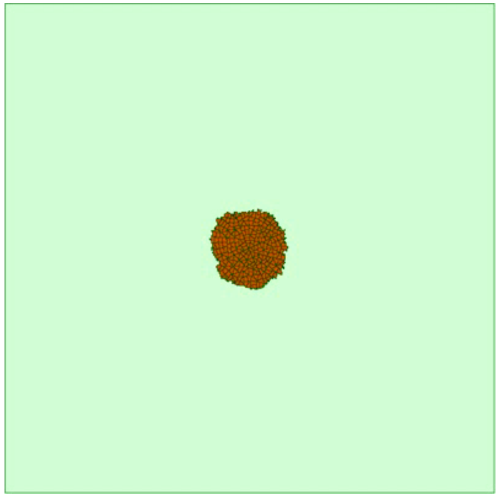
Biomodeling & Biosystems Analysis

- Core modeling group of Netherlands Consortium for Systems Biology



Metabolism of gut microbiota
(Milan van Hoek)
TIFN, KC

Plant development
VIB Ghent,
Wageningen University



Blood vessel growth
VUMC

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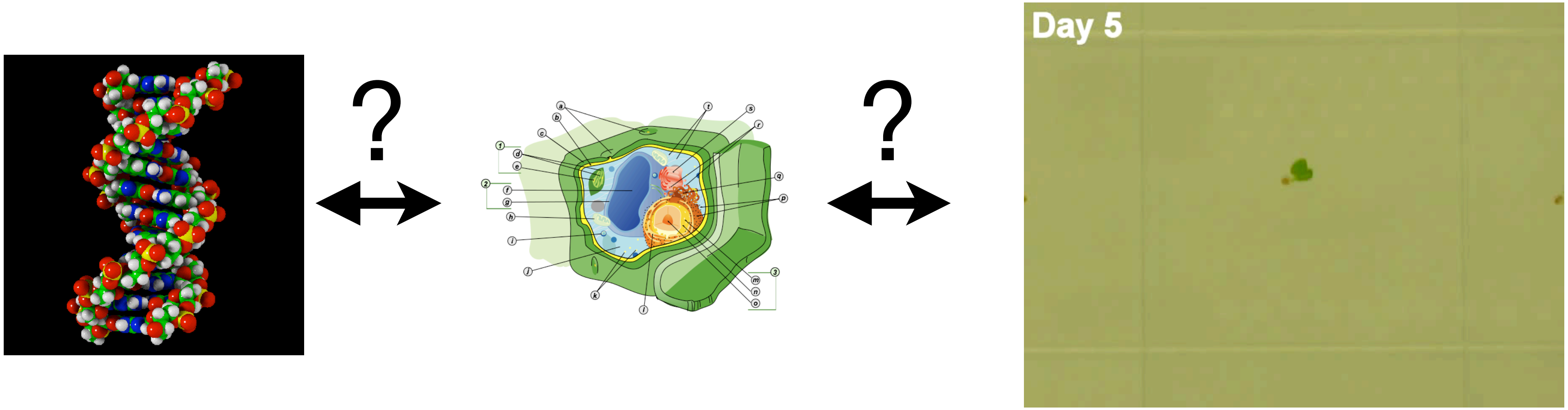
Cell-based plant growth models



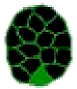
- How can the genome regulate plant growth and form, and *vice versa*?
- A cell-centered perspective:
  - DNA/regulatory networks regulate cell behavior (cell cycle time, cell expansion rates, etc.)
  - Cell behavior leads to tissue and plant growth
  - tissue architecture feeds back on regulatory networks
- Need to understand genetics in the context of the *physics* of collective cell behavior

Cell-based Modeling

See *e.g.* Merks and Glazier, *Phys. A* 2005

- Allows for more detailed descriptions of the cells
- Genetic and metabolic networks primarily regulate *individual cells*
  - Response to extracellular signals, secretion of signaling and extracellular matrix proteins, cell migration, cell adhesion, *etc.*
- To understand how genetics regulates multicellular phenomena, we must ask:
  - how genetics drives cell behavior (*i.e.* networks)
  - how cell behavior produces multicellular patterns
  - how the cells (and their regulatory networks) respond to the multicellular environment
- **"Middle-out approach" (Denis Noble 2006, *The Music of Life*)**
  - the cell in the middle

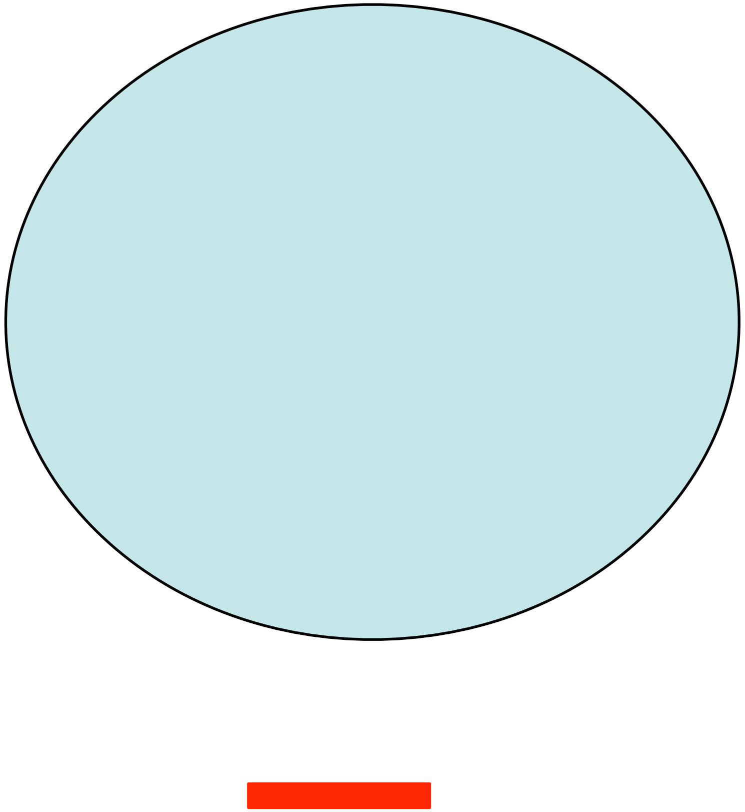
Plant tissue growth and patterning



Cell-based plant tissue model

- Phenomenological model of plant cells:
  - Representation of cell walls
  - Cell's relative position remains fixed
  - Cell wall and membrane properties (elasticity, yielding threshold, wall permeability, transporter density, *etc.*)
  - Cell properties: turgor, concentrations of intracellular chemicals, *etc.*
  - Cell behaviors: division, cell expansion, *etc.*
- Energy minimization philosophy
  - Calculate force balance between cell expansion and cell wall resistance using energy minimization

Plant tissue model

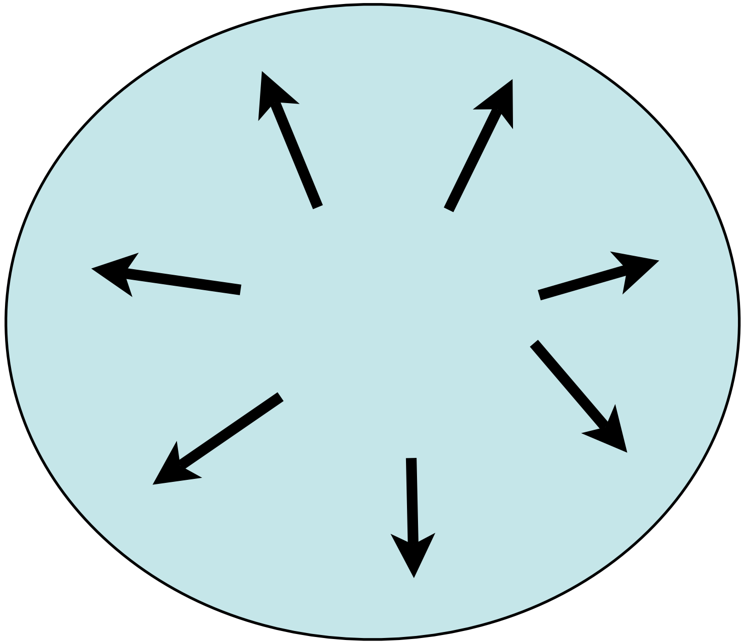


A cell

A cell wall

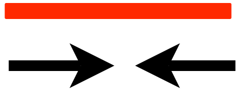
Plant tissue model

A cell expands



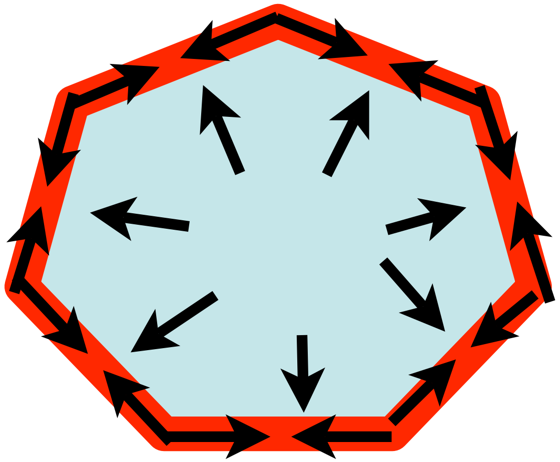
A cell wall is flexible

A cell wall contracts

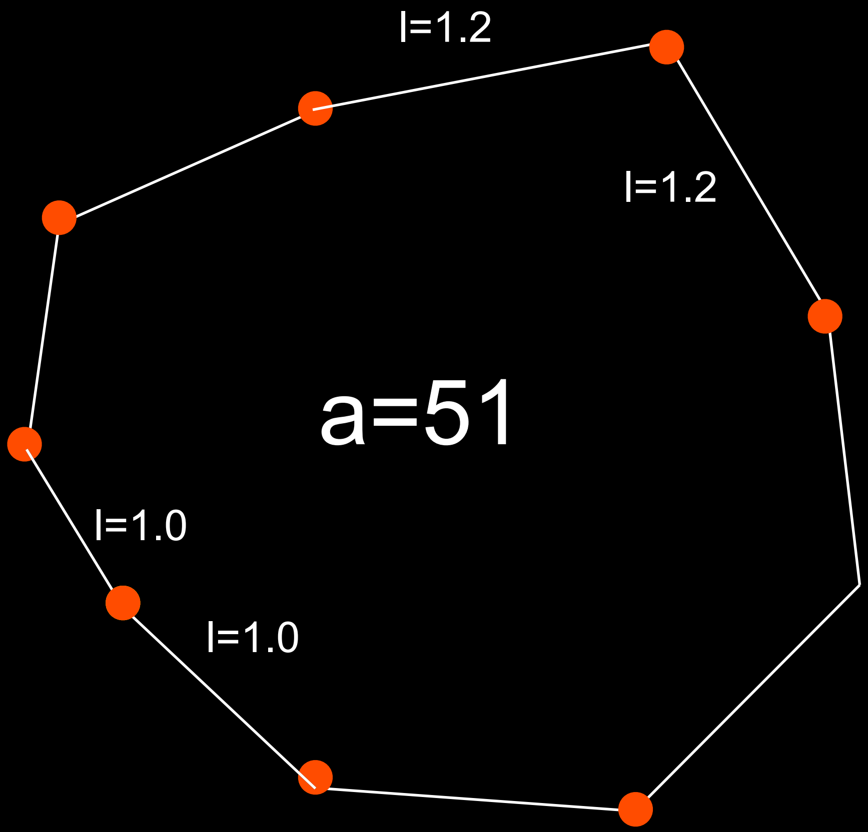


Plant tissue simulation

A plant cell



Symplastic tissue mechanics
Metropolis algorithm



$$A = 50$$

$$a = 51$$

$$(A - a)^2 = (-1)^2 = 1$$

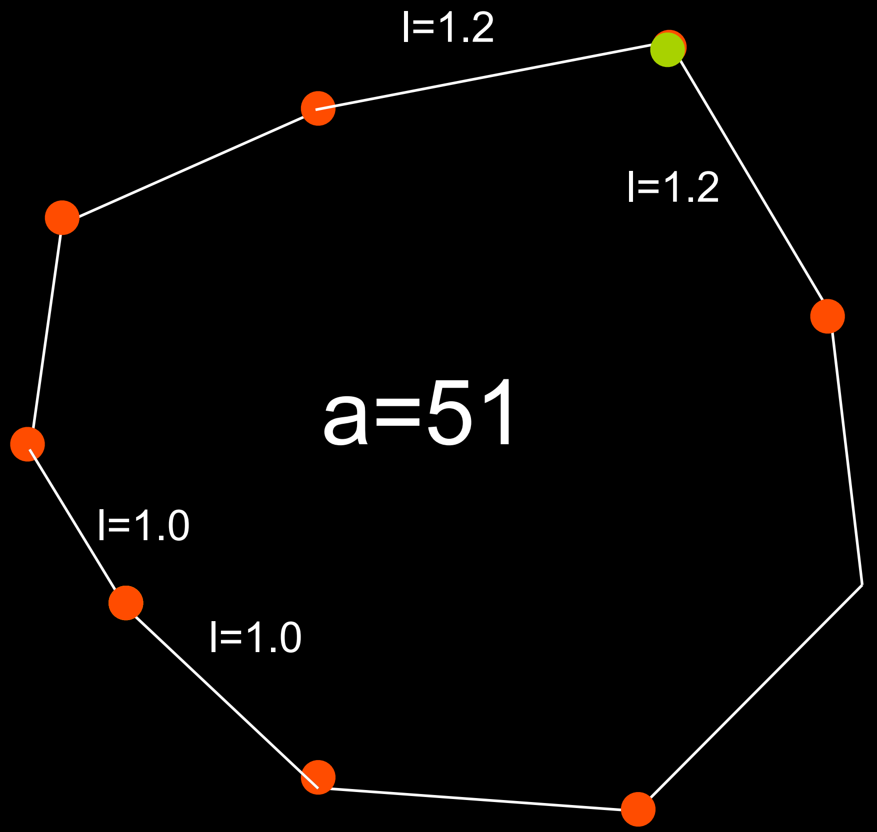
$$L = 1$$

$$\sum_j (L - l_j)^2 = 0.08$$

$$H = 1 + 100 * 0.08 = 9$$

$$H = \lambda_A \sum_j (A_j - a_j)^2 + \lambda_L \sum_i (L_i - l_i)^2$$

Symplastic tissue mechanics
Metropolis algorithm



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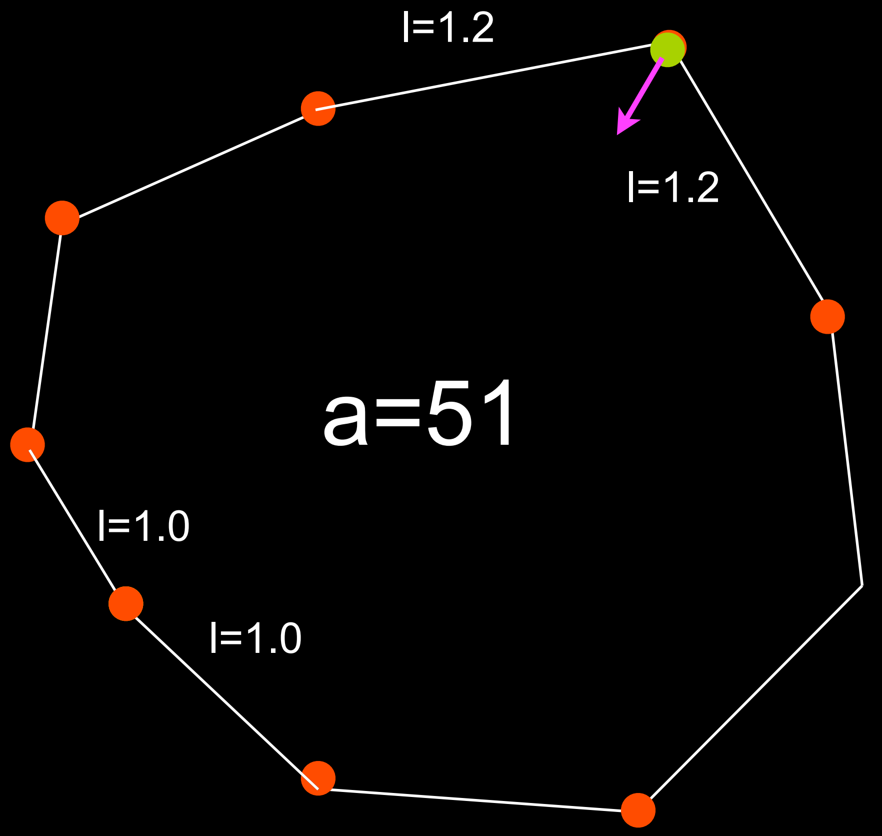

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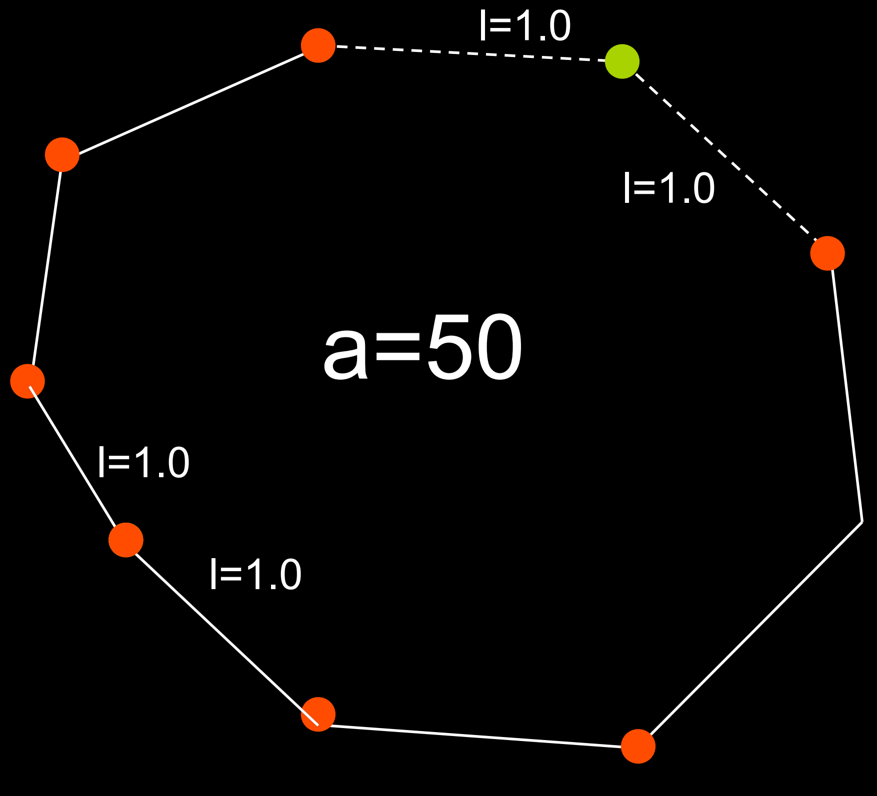

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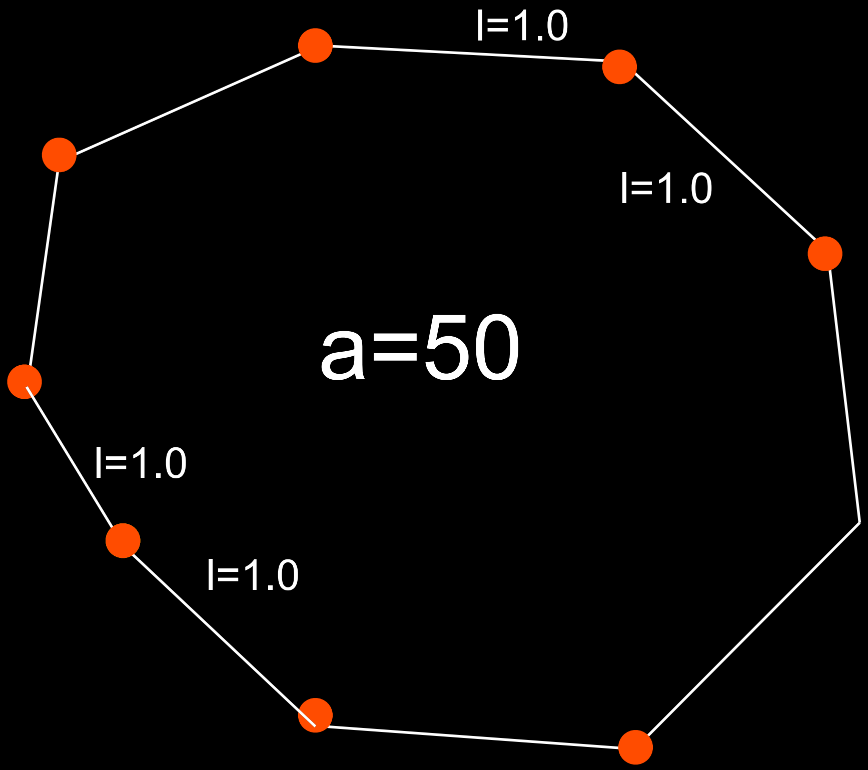
Symplastic tissue mechanics *Metropolis* algorithm



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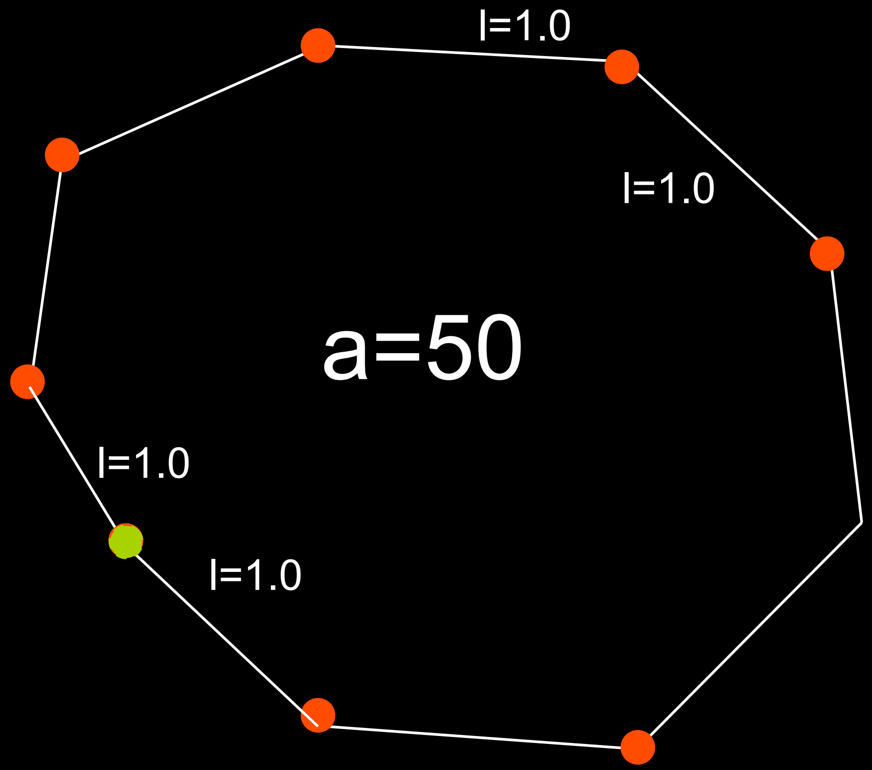
$$(A - a)^2 = 0$$

$$L = 1$$

$$\sum_j (L - l_j)^2 = 0$$

$$H = 0$$

Symplastic tissue mechanics *Metropolis* algorithm



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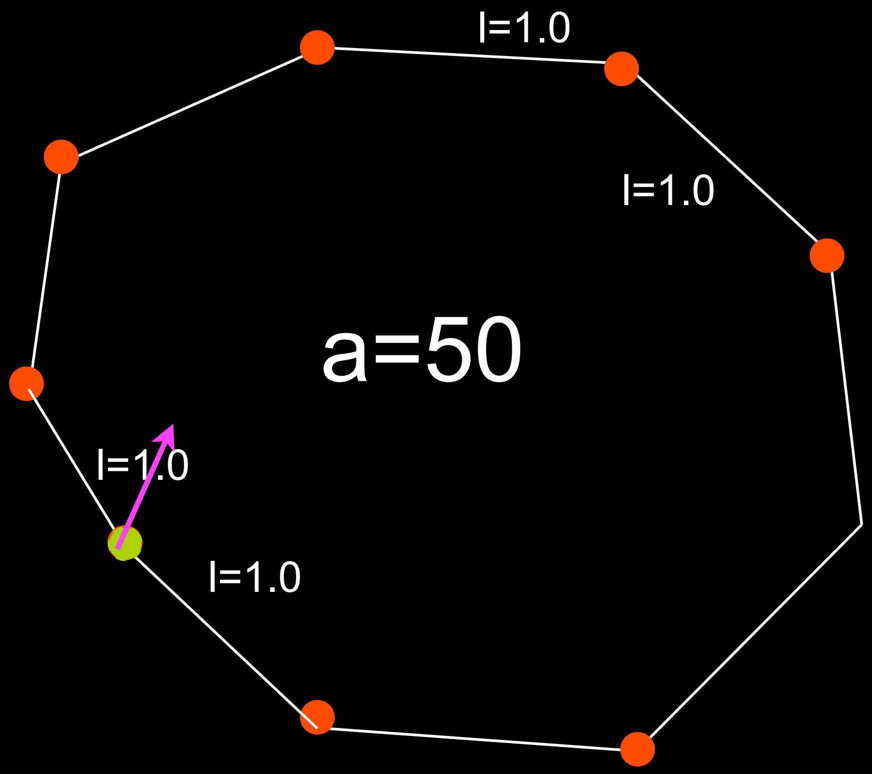
Symplastic tissue mechanics
Metropolis algorithm



$$A = 50$$

$$a = 50$$

$$(A - a)^2 = 0$$

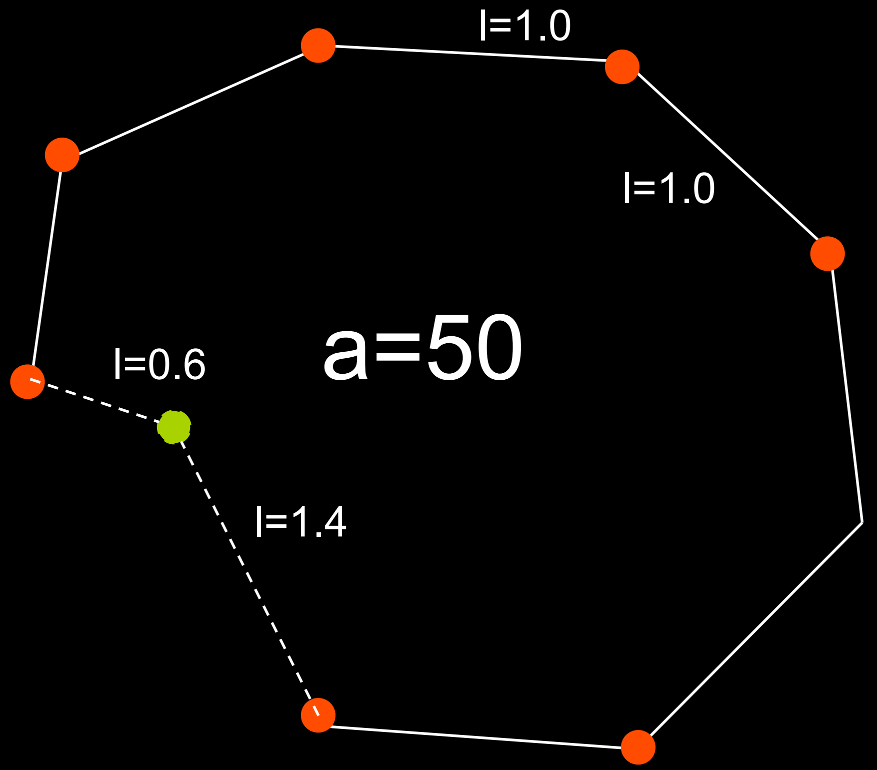
$$L = 1$$

$$\sum_j (L - l_j)^2 = 0$$

$$H = 0$$

$$H = \lambda_A \sum_j (A_j - a_j)^2 + \lambda_L \sum_i (L_i - l_i)^2$$

Symplastic tissue mechanics
Metropolis algorithm



$$A = 50$$

$$a = 49$$

$$(A - a)^2 = 1$$

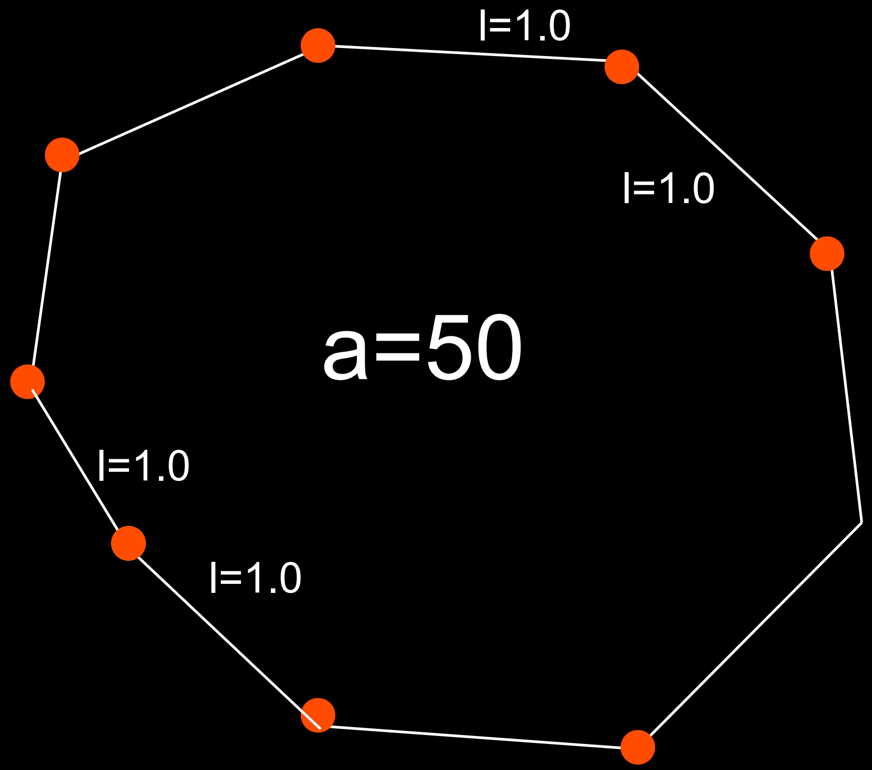
$$L = 1$$

$$\sum_j (L - l_j)^2 = 0.72$$

$$H = 1 + 100 * 0.72 = 73$$

$$H = \lambda_A \sum_j (A_j - a_j)^2 + \lambda_L \sum_i (L_i - l_i)^2$$

Symplastic tissue mechanics
Metropolis algorithm



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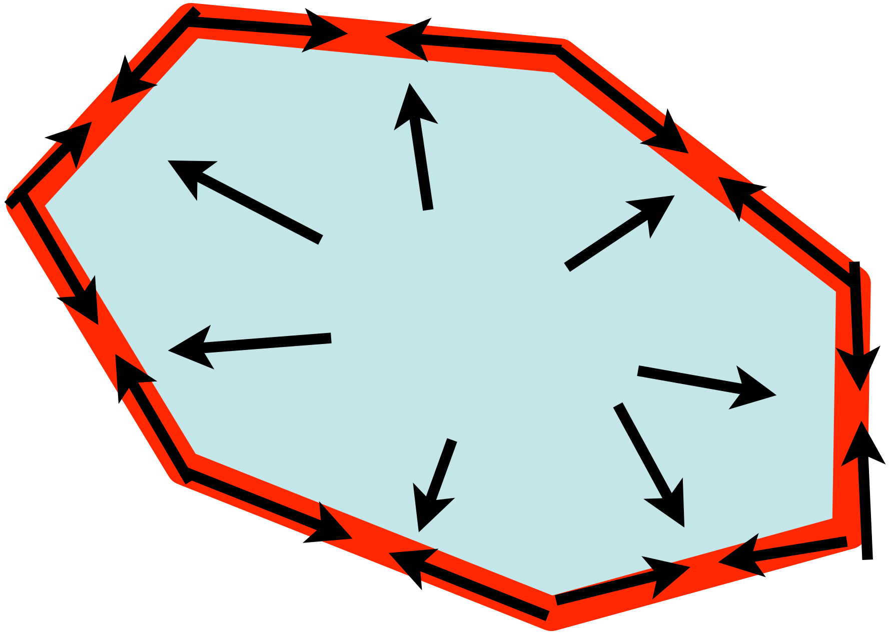
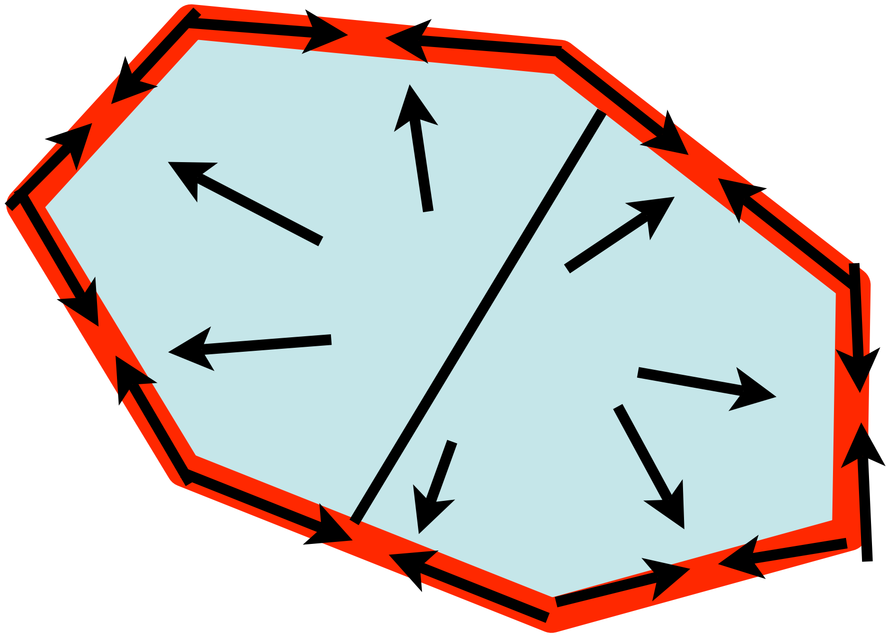
Plant tissue simulation



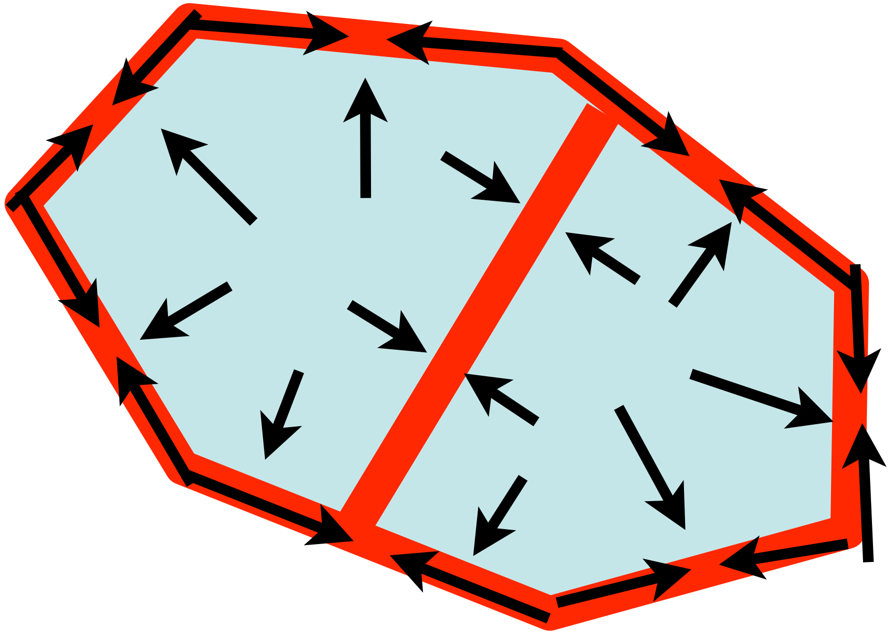
A plant cell increases turgor pressure

Plant tissue simulation



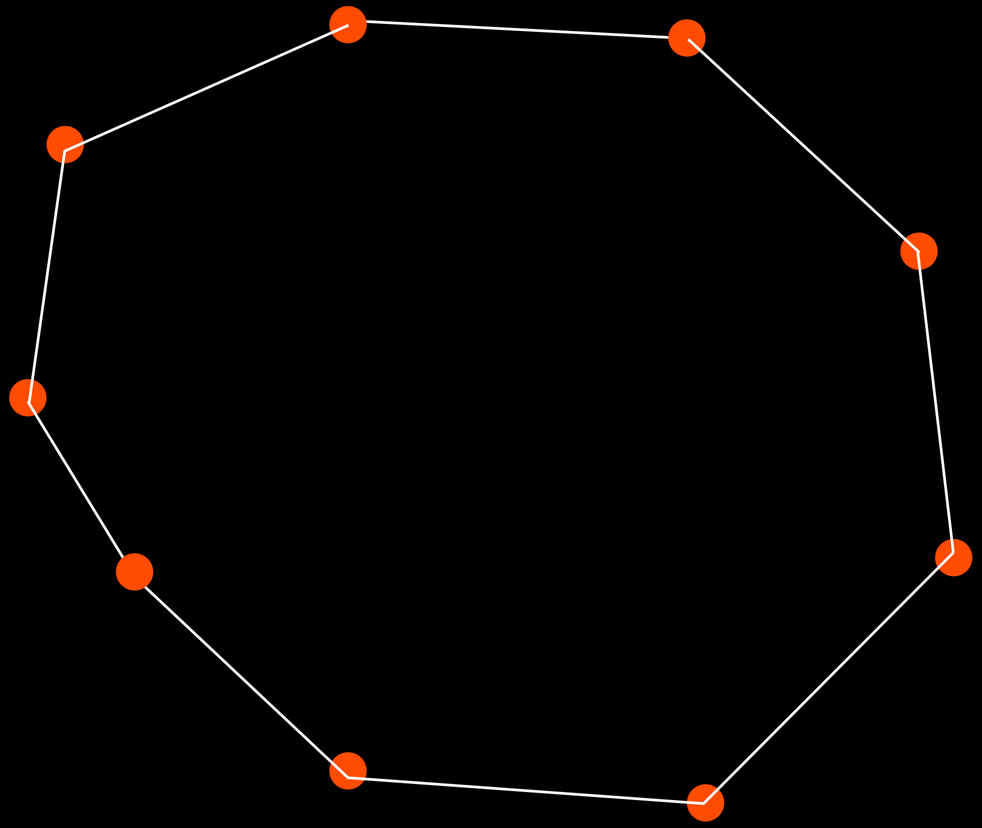
A plant cell divides

Plant tissue simulation



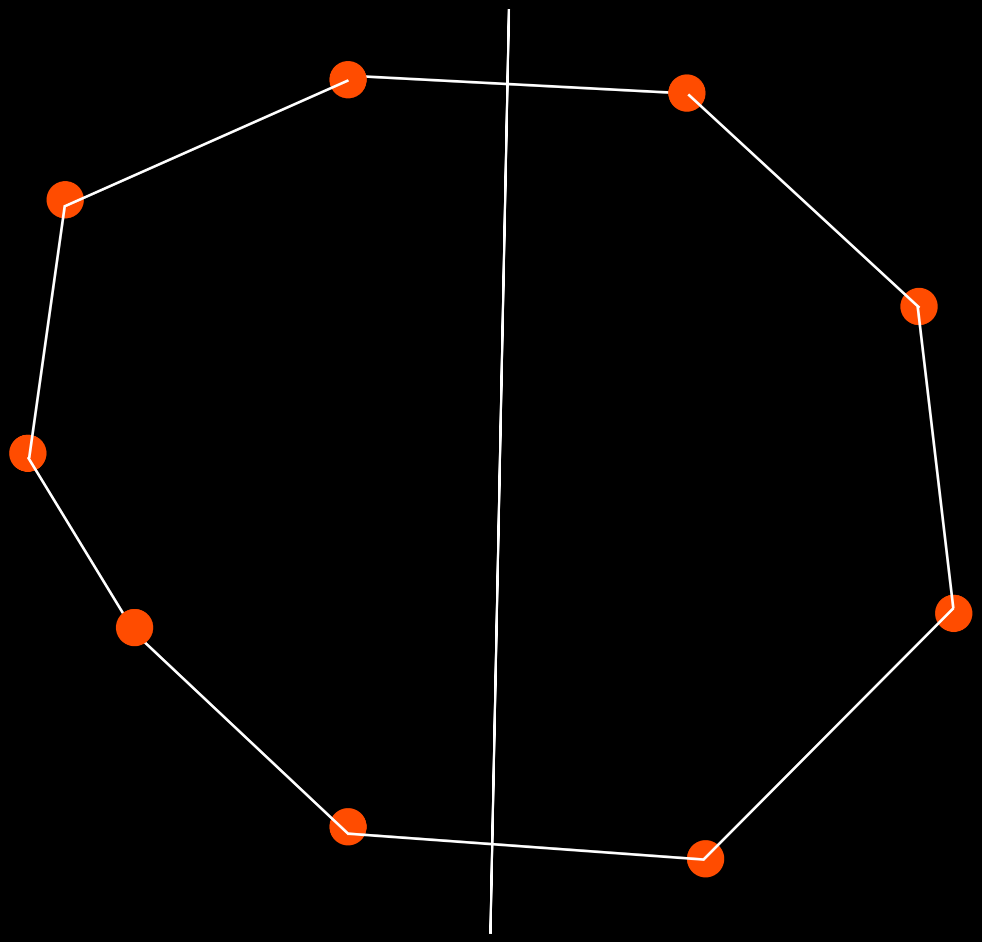
A plant cell forms a new wall

Cell division



- Set division axis
- Insert new nodes and add to neighboring cells
- Transfer nodes to daughter cell
- Insert cell wall
- Reset target areas

Cell division



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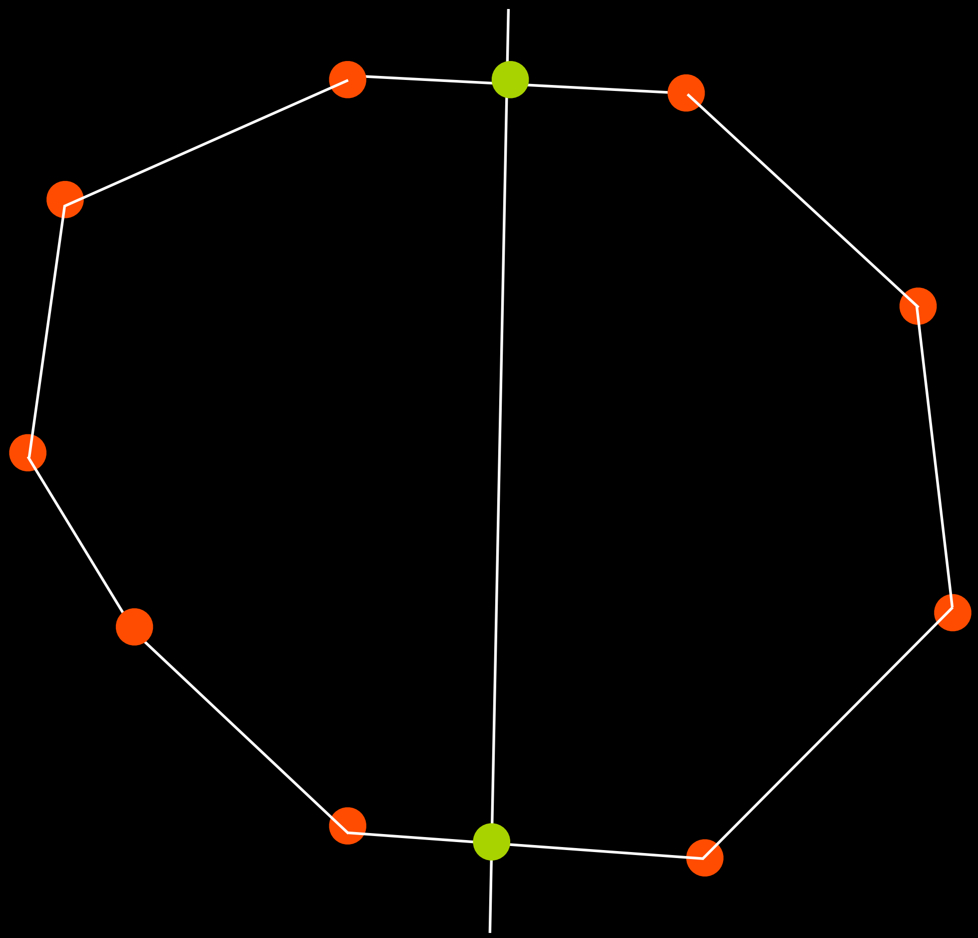

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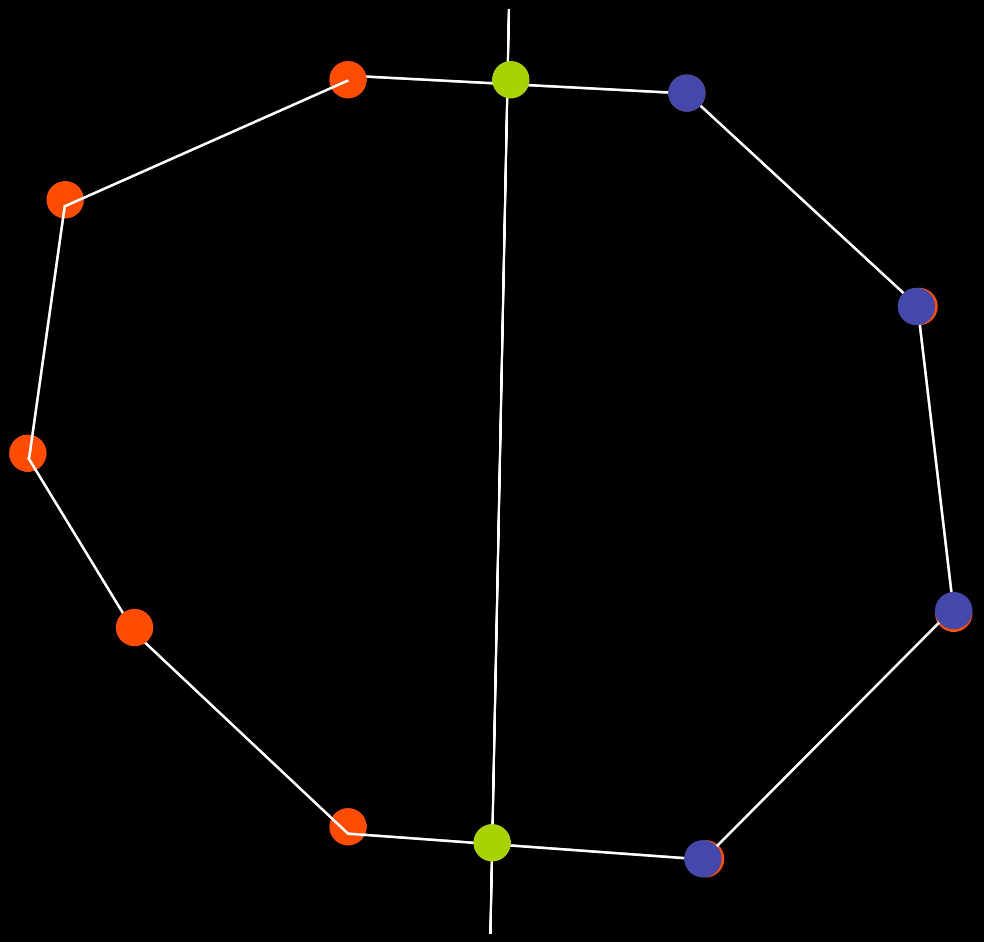

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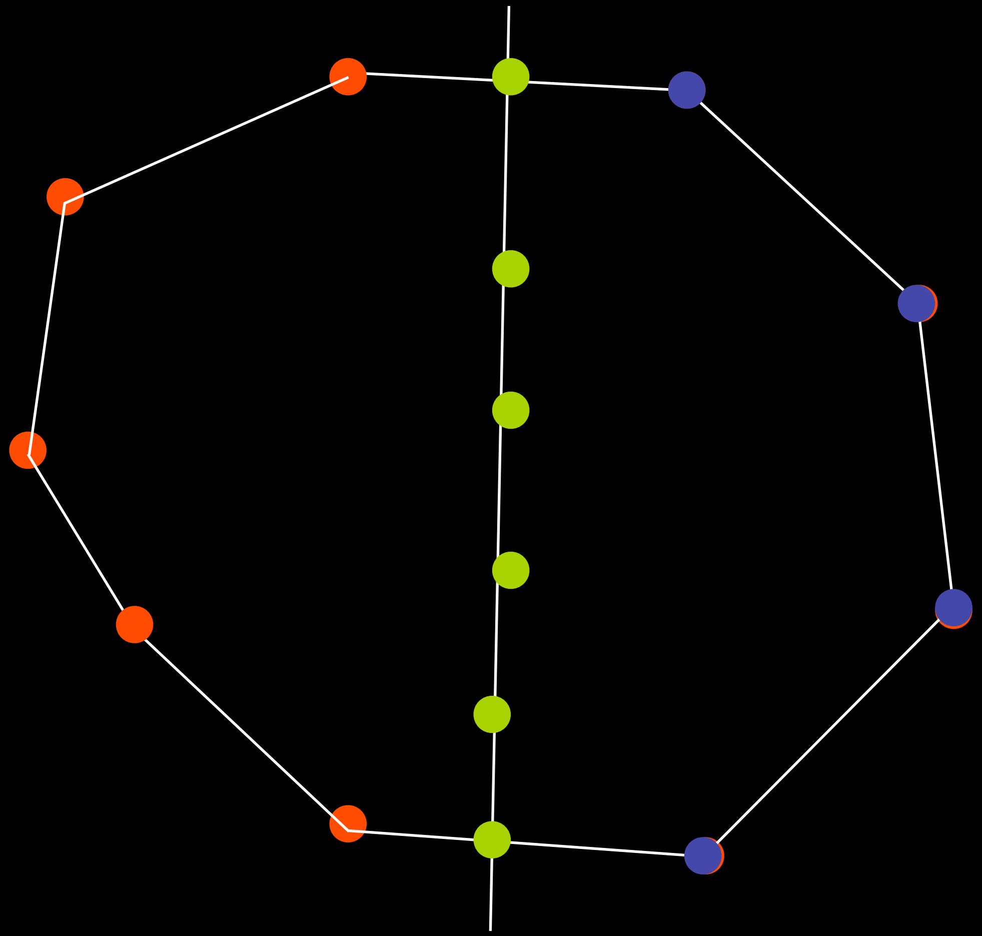

- Set division axis
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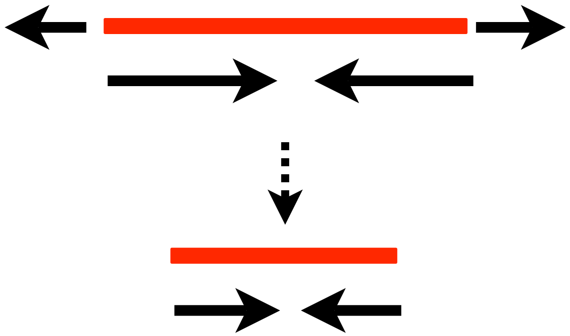
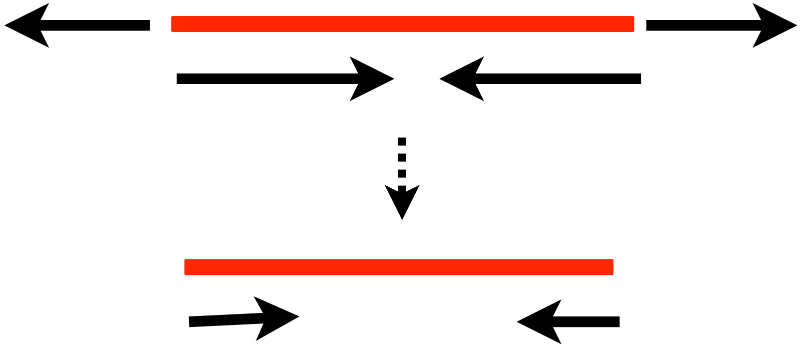
- Insert cell wall
- Reset target areas

Plant tissue model

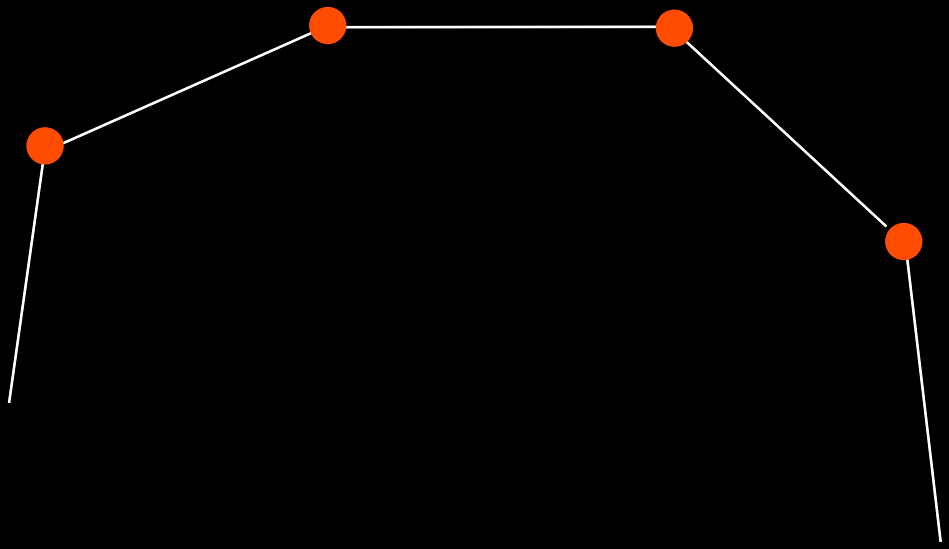
A cell wall is elastic



A cell wall yields

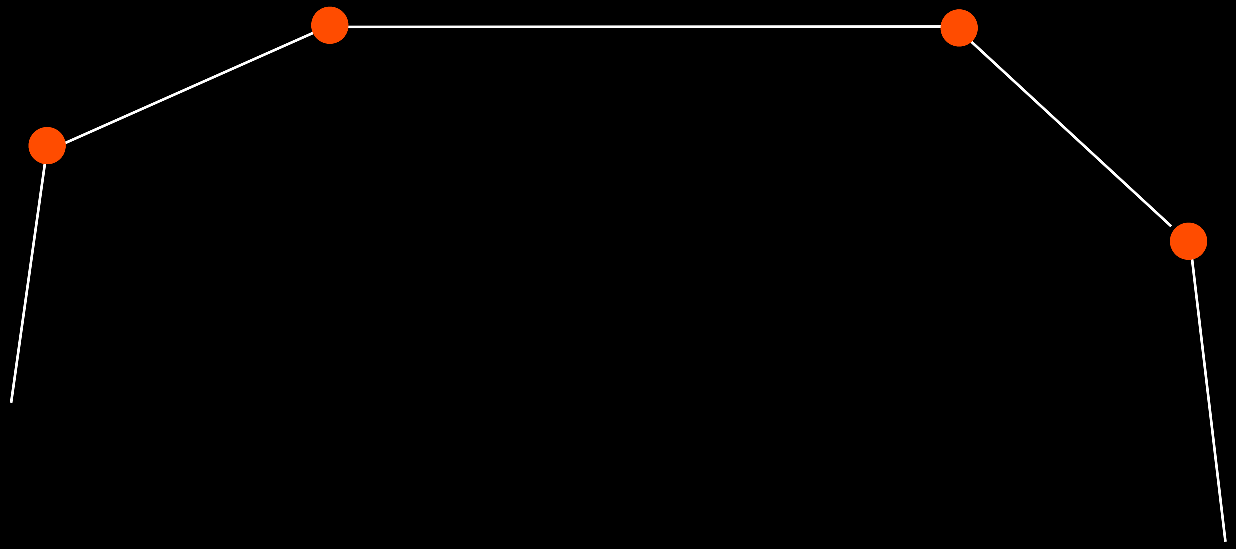


Cell wall yielding



Reduces wall strain if it exceeds a threshold

Cell wall yielding



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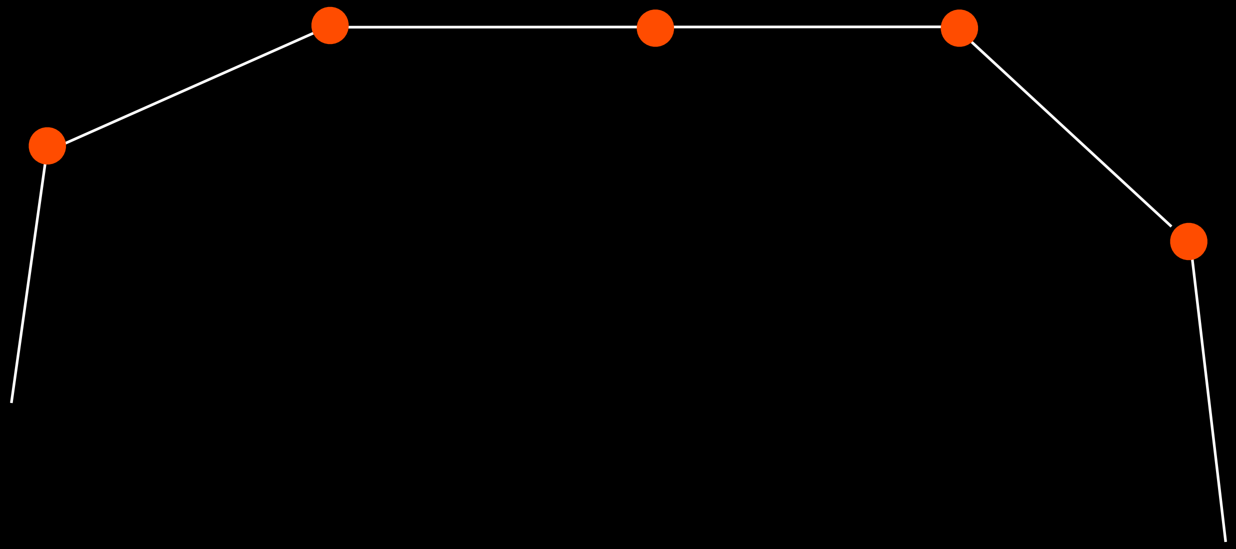
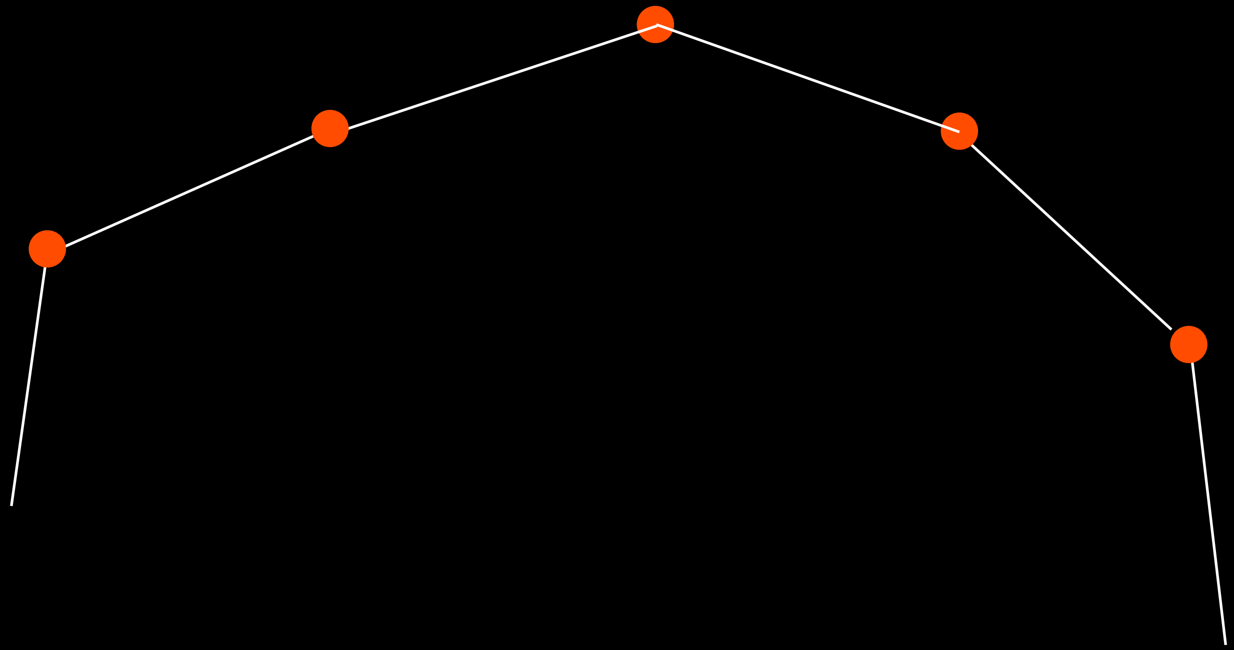
Cell wall yielding

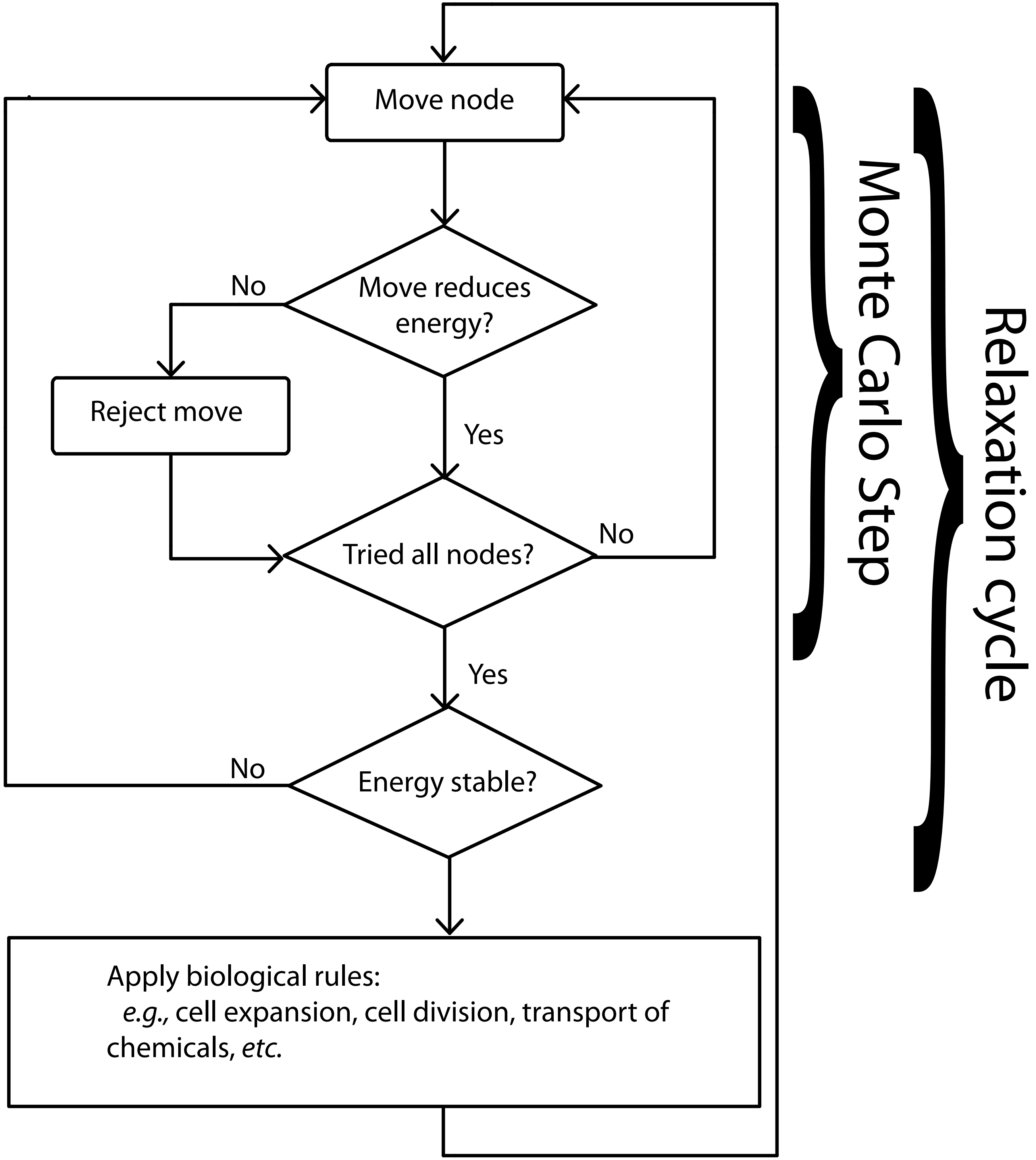


Reduces wall strain if it exceeds a threshold

Cell wall yielding



Reduces wall strain if it exceeds a threshold



Move node

Move reduces energy?

No

Reject move

Yes

Tried all nodes?

No

Yes

Energy stable?

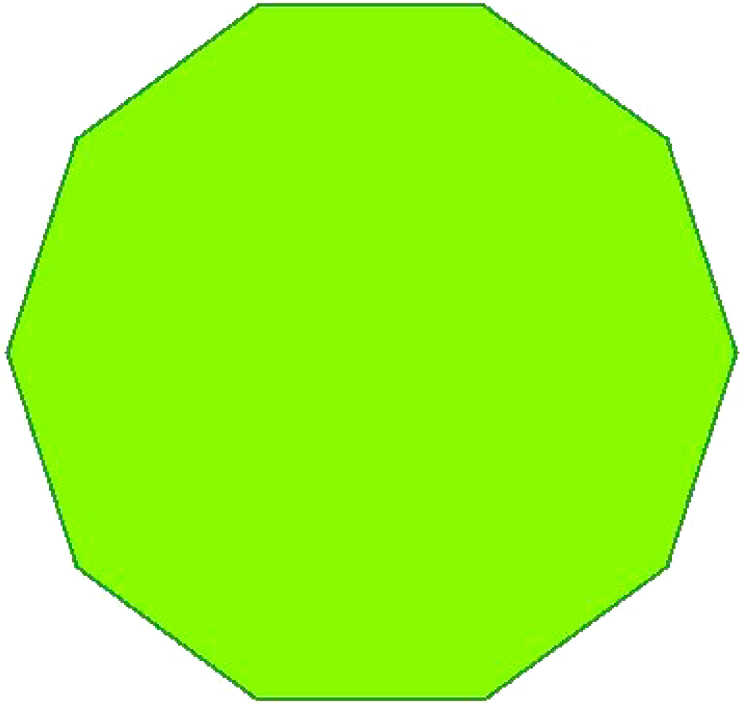
No

Apply biological rules:
e.g., cell expansion, cell division, transport of chemicals, *etc.*

Monte Carlo Step

Relaxation cycle

Callus growth: expansion and division



Tissue growth is exponential, due to cell division

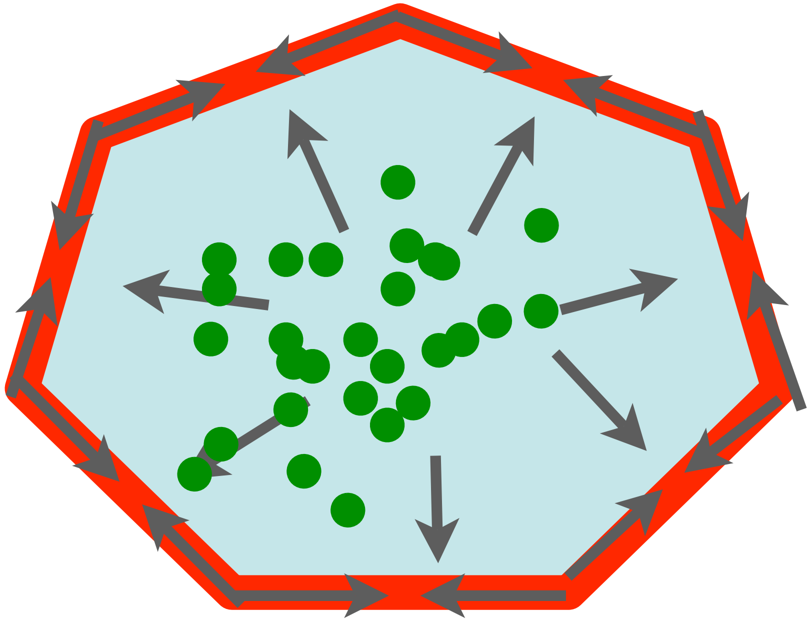
Tissue mechanics: margin cell stiffness may determine leaf shape

(with Andrew Fleming, University of Sheffield)

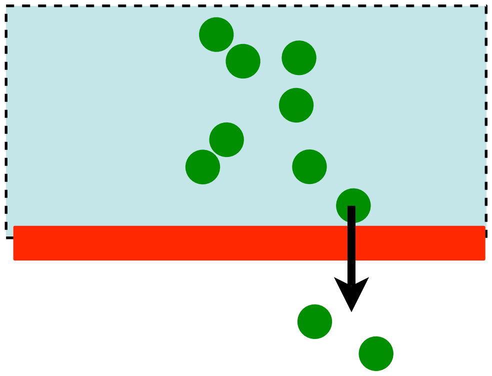
Stiff margin cells

Floppy margin cells

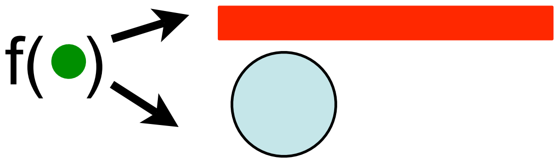
Cell-cell communication



A cell contains chemicals

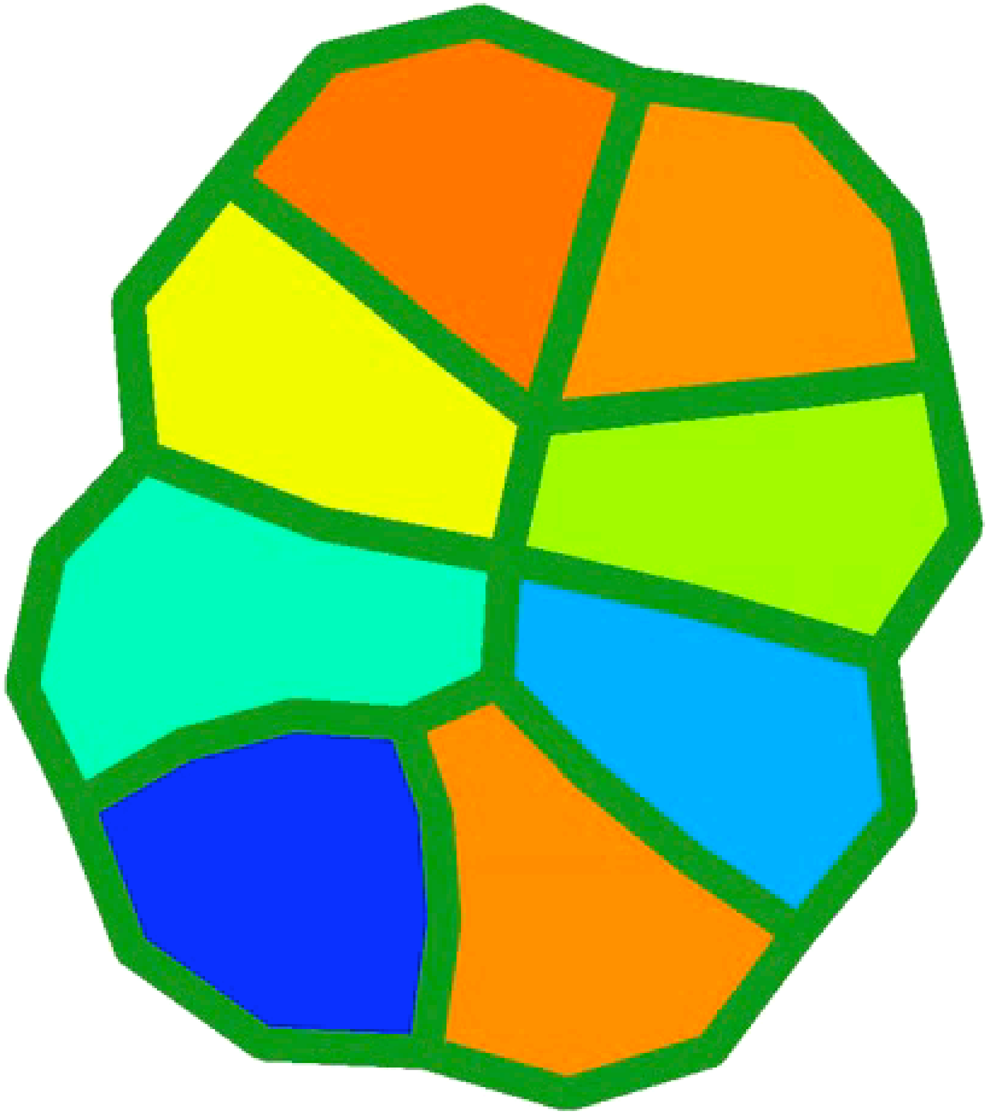


A cell wall is permeable



Cells and walls respond to chemicals

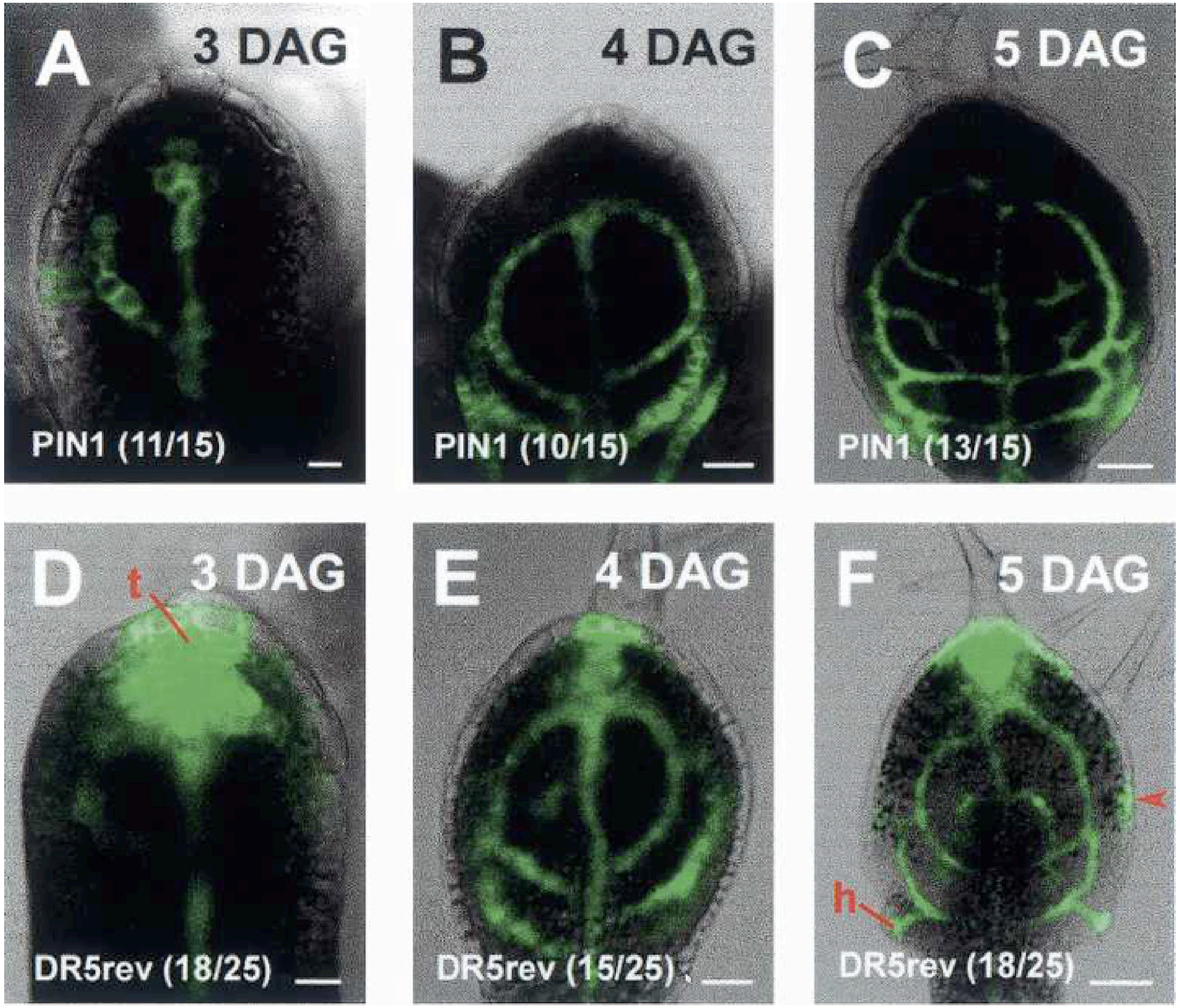
“Meristem growth”



1. Tip cell produces growth factor
2. Cells expand and divide for high concentrations
3. Cells expand for intermediate concentrations

How do leaf veins form?
Auxin and auxin efflux pumps (PIN1)

Scarpella *et al.* Genes Dev. 2006



PIN1::GFP
Auxin efflux
transporter

DR5::GPF
Marker for
auxin activity

Polar auxin transport

Could cross-talk between PIN1 and auxin also drive venation patterning? *A travelling-wave hypothesis*

- Leaf venation patterning according to mechanism proposed for phyllotaxis: *upstream pumping*
  - Is dominating view - positive feedback between auxin flux and PIN1 polarization - the most likely hypothesis?
- Formation of midvein
- Comparison with experiments, e.g. NPA treatment
- Adding additional components to fine-tune model
  - Influx carrier: AUX/LAX
  - Growth

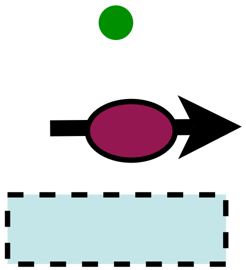
PINs polarize towards auxin maxima?

(*E.g.* Jönsson *et al.* 2006; Smith *et al.* 2006)

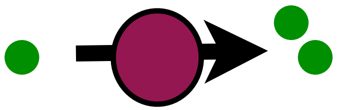
Auxin

PIN

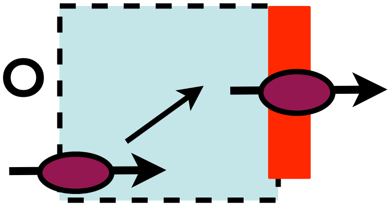
Cytoplasm



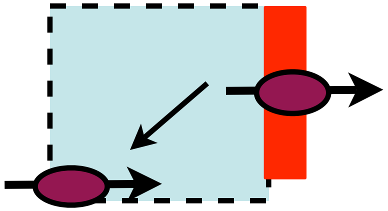
PIN pumps auxin



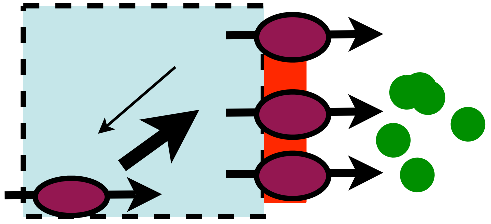
PIN sticks to "wall"



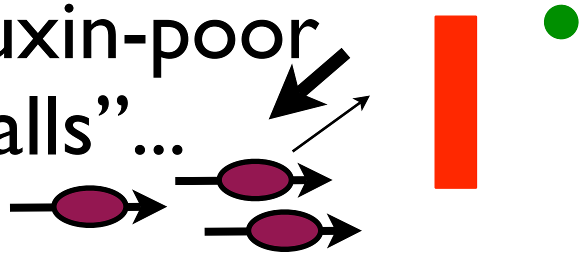
PIN drops from "wall"

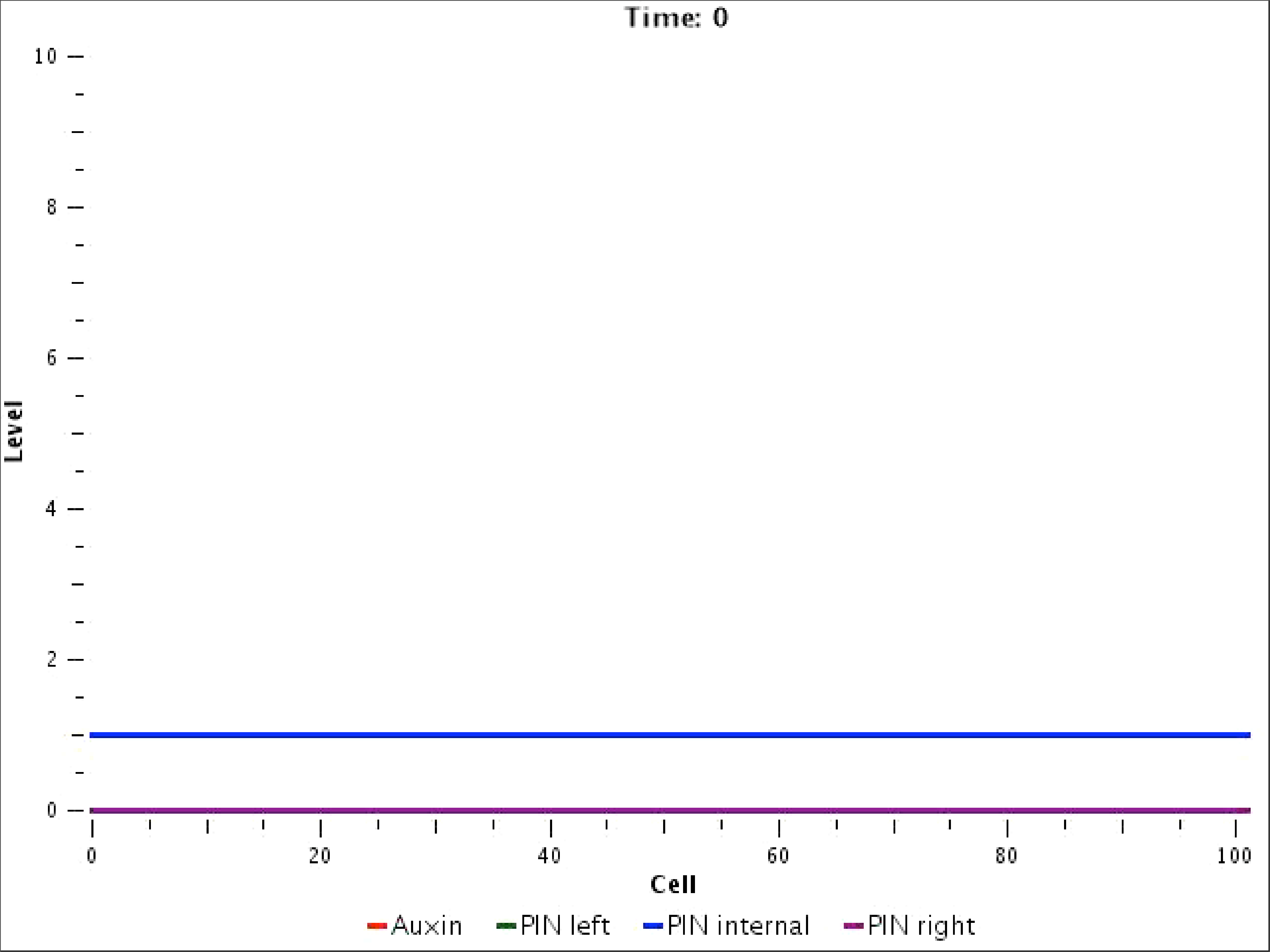


PIN prefers auxin-rich "walls"...

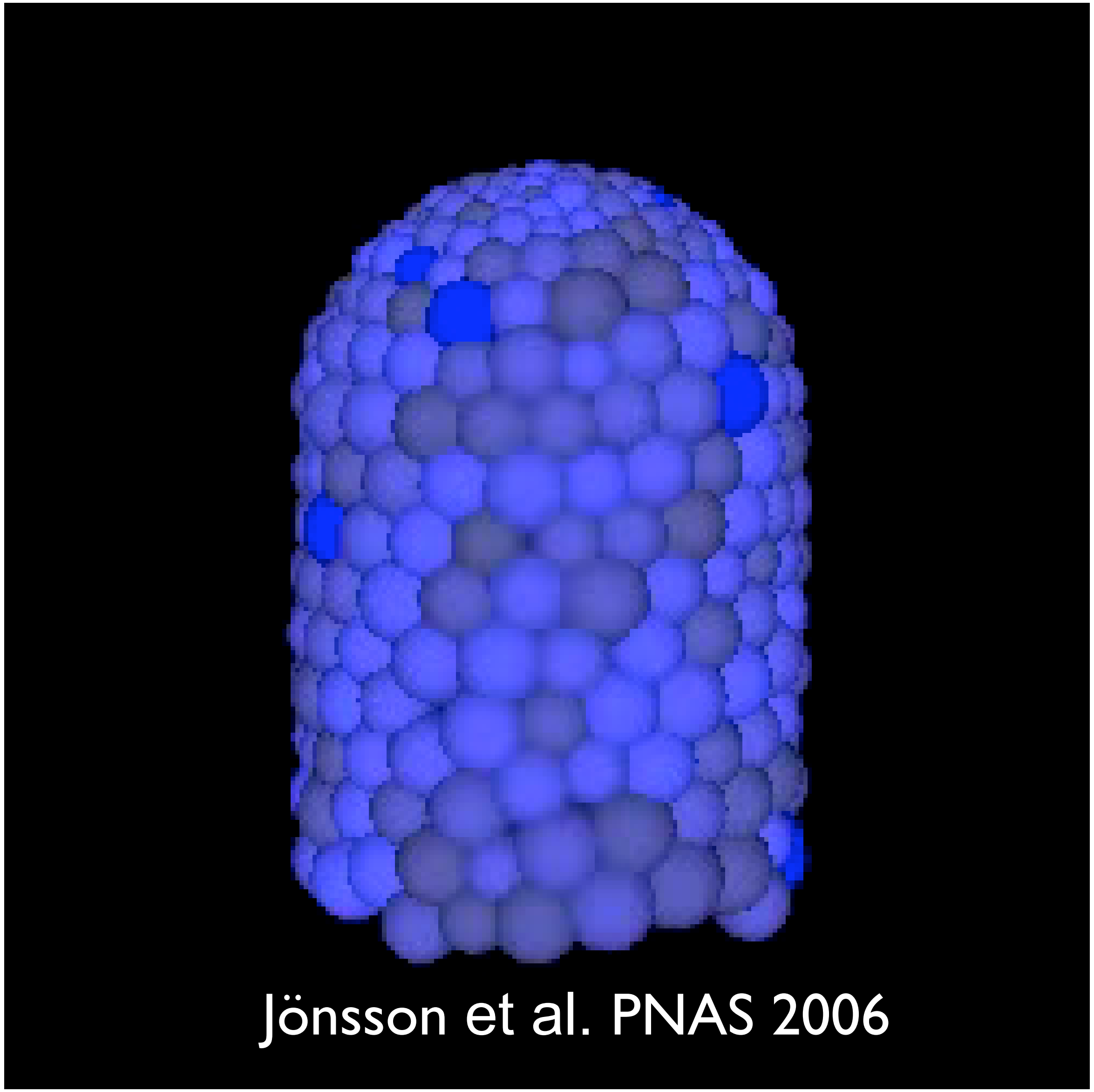


over auxin-poor "walls"...



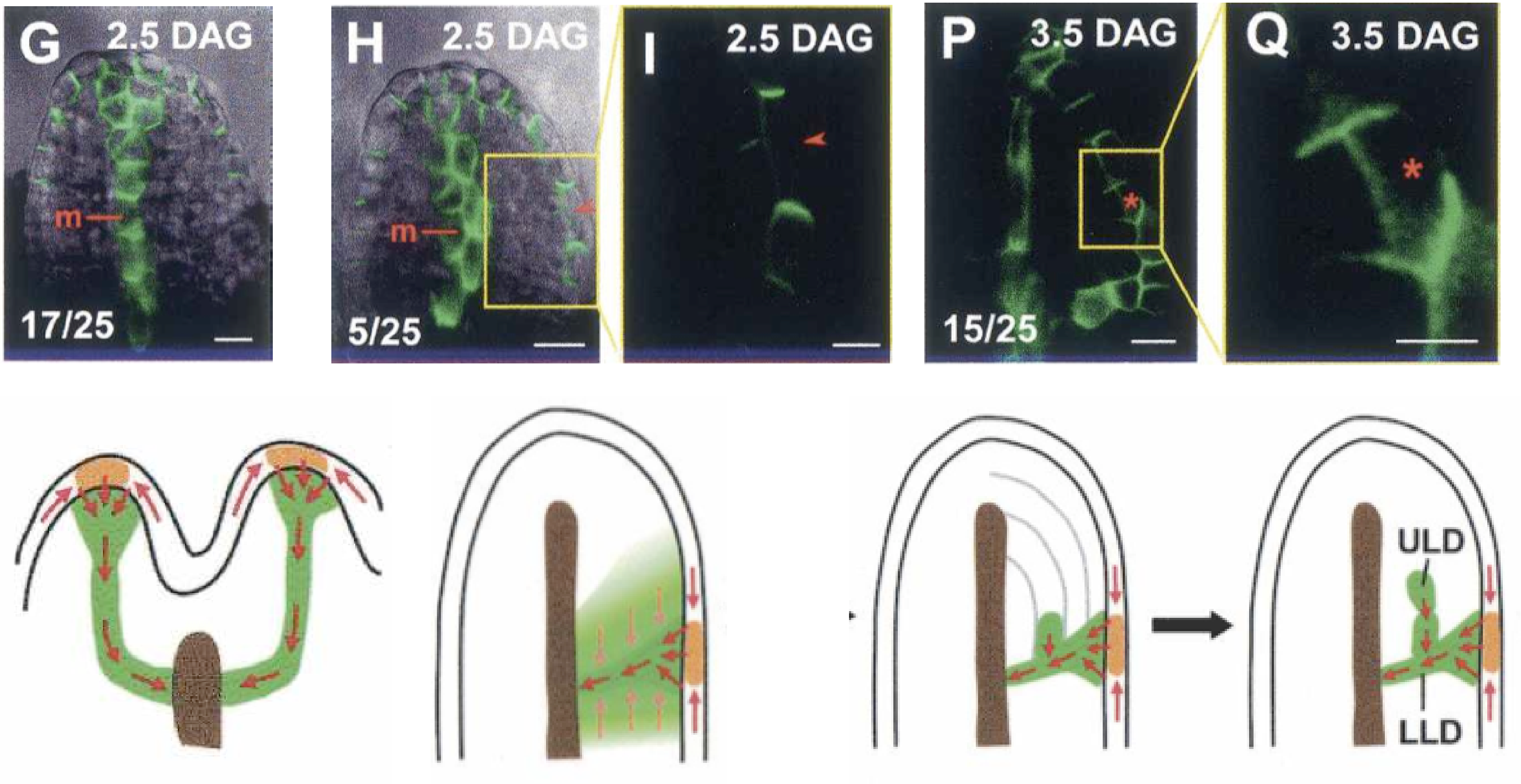

Time: 0
10
8
6
4
2
0
Level
0
20
40
60
80
100
Cell
Auxin
PIN left
PIN internal
PIN right

Phyllotaxis *via* auxin accumulation



Jönsson et al. PNAS 2006

PIN1 may also produce auxin maxima in leaf margin



Scarpella *et al. Genes Dev.* 2006

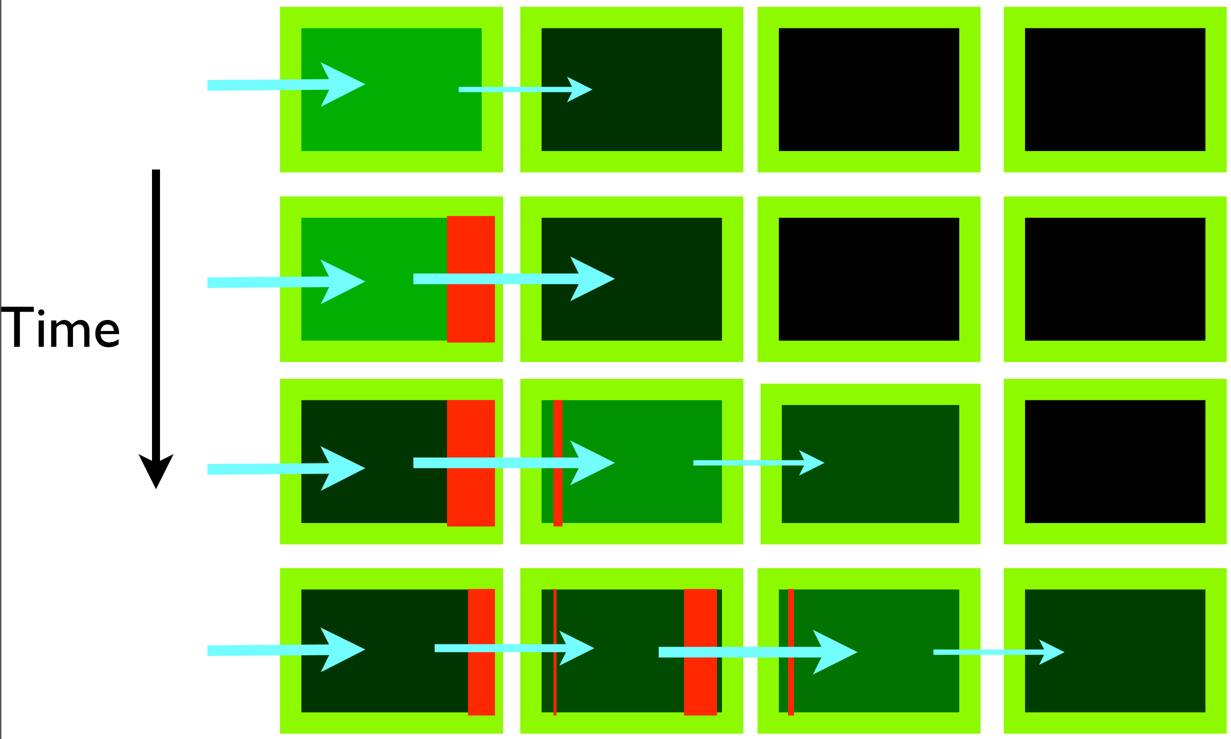
Auxin convergence points:

role in leaf vascularization

- “Biology’s way”: variation on a common theme
- If we accept that the Jönsson *et al.* and Smith *et al.* 2006 phyllotaxis mechanisms are plausible...
    - The canalization hypothesis would imply that PIN1 and auxin interact differently in shoot and leaf
- Leaves initiate during phyllotaxis, so...
    - Could auxin channels form in a mechanism similar to phyllotaxis?

Auxin induces PIN1 expression

See *e.g.* Vieten *et al.* (2005); Heisler *et al.* 2006



Auxin influx, leakage into cell 2

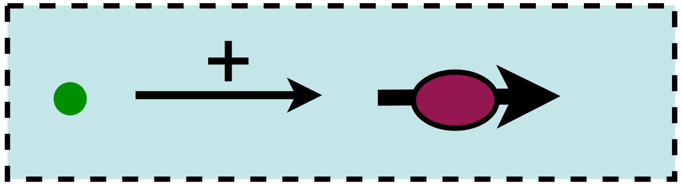
PIN1 goes up, localizes to cell 2

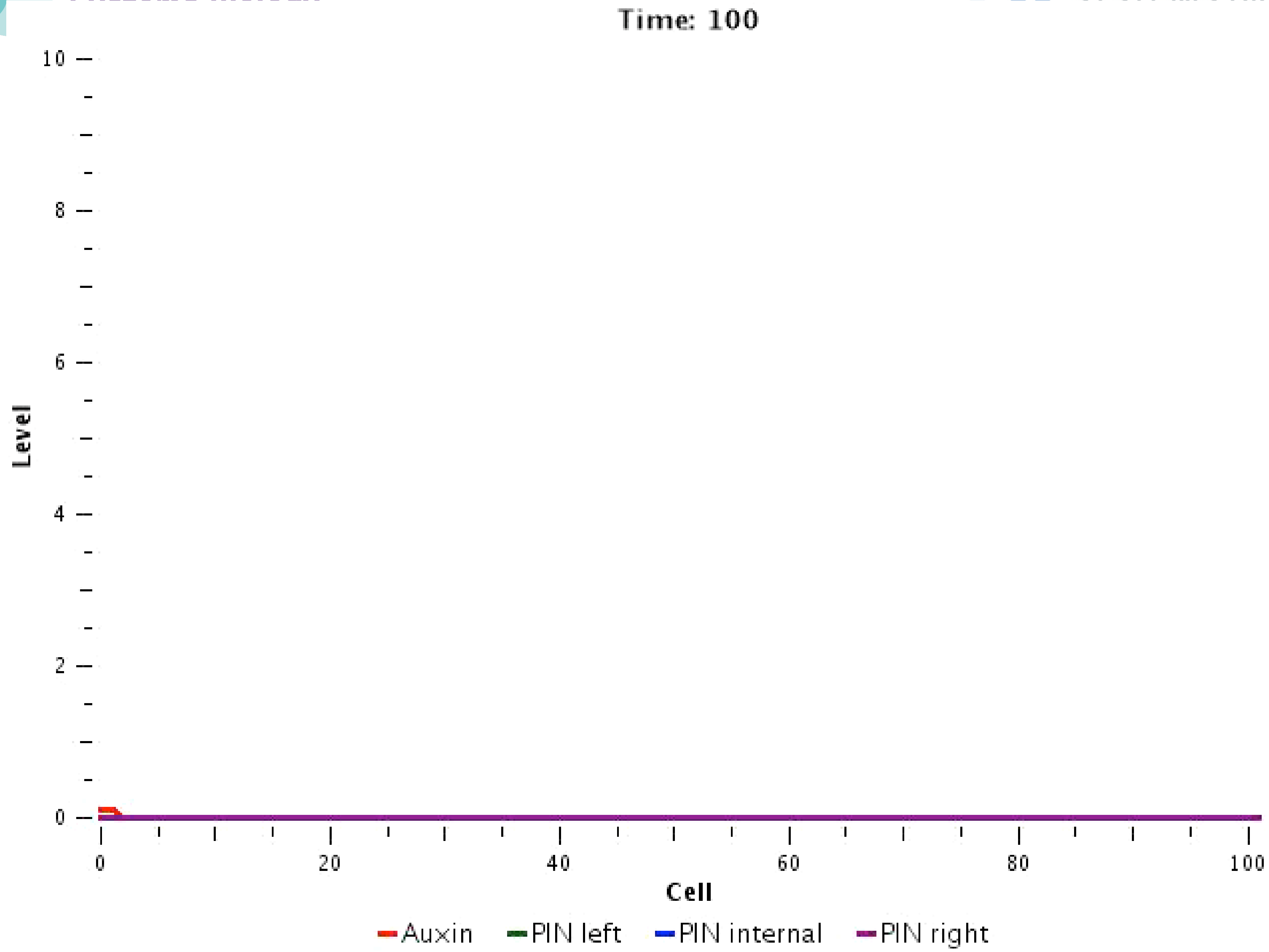
Auxin down in cell 1, PIN1 and auxin up in cell 2

reiteration

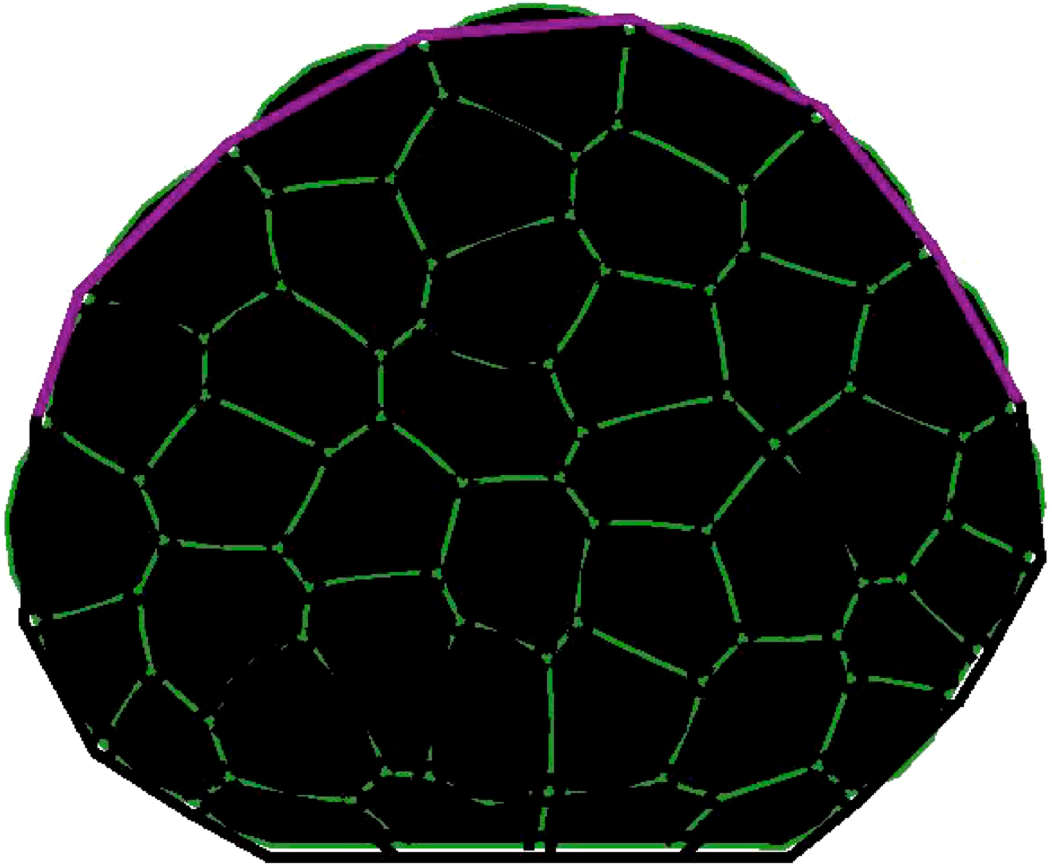
🟥 Amount of PINs at wall

🟩 Auxin concentration




Time: 100
Level
10
8
6
4
2
0
0
20
40
60
80
100
Cell
Auxin
PIN left
PIN internal
PIN right

Auxin waves in 2D

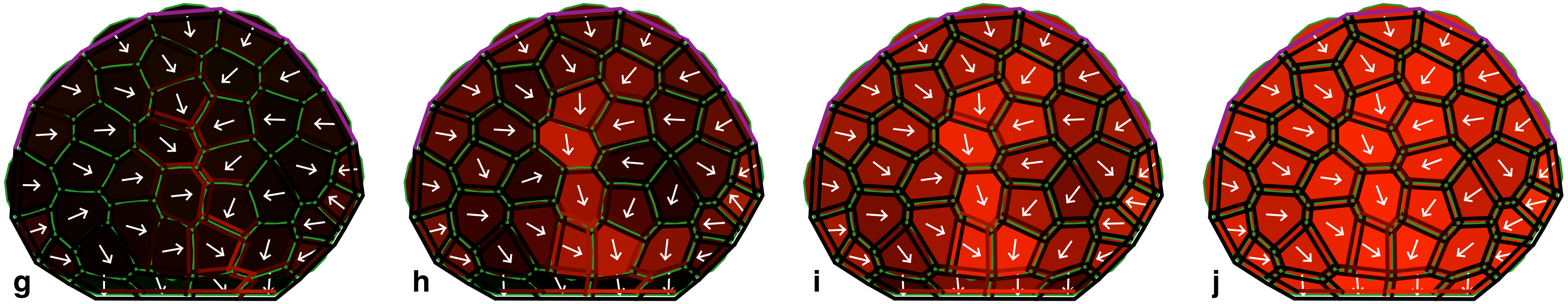


- Zero (or small) initial PIN1 concentration
- Auxin induces PIN1 transcription, and PIN1 decays independently

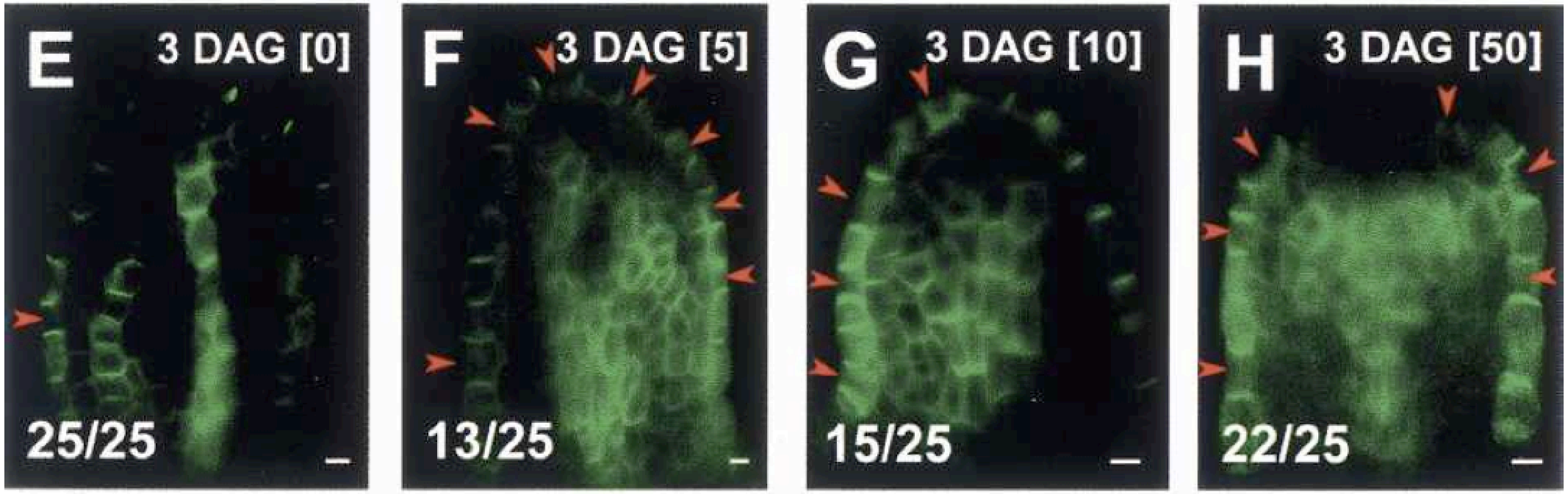
Merks *et al.* (2007). Trends in Plant Science 12(9), 384-390

Experimental validation

Effect of auxin transport inhibitor NPA



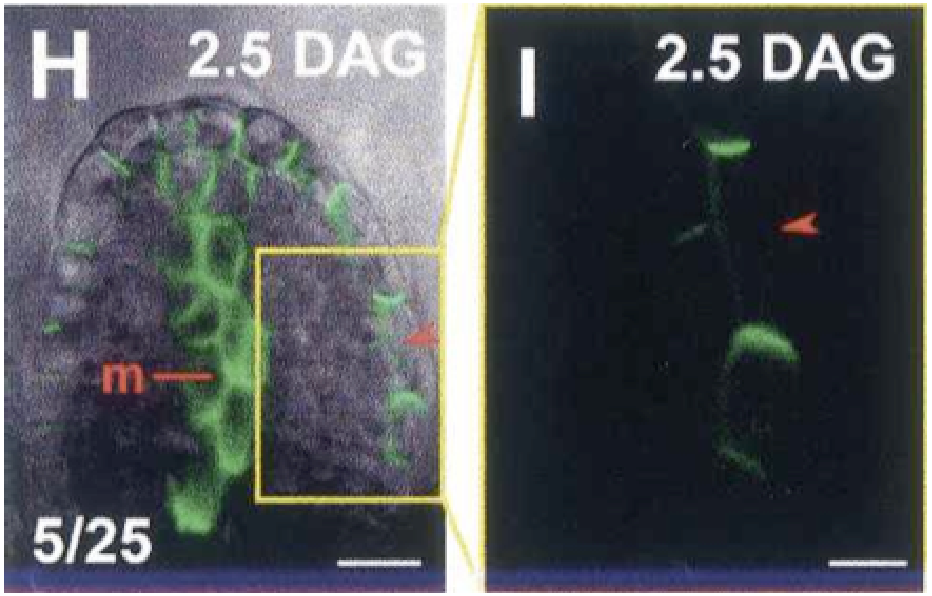
Reduce number of "PIN1 docking sites"
Increase NPA concentration

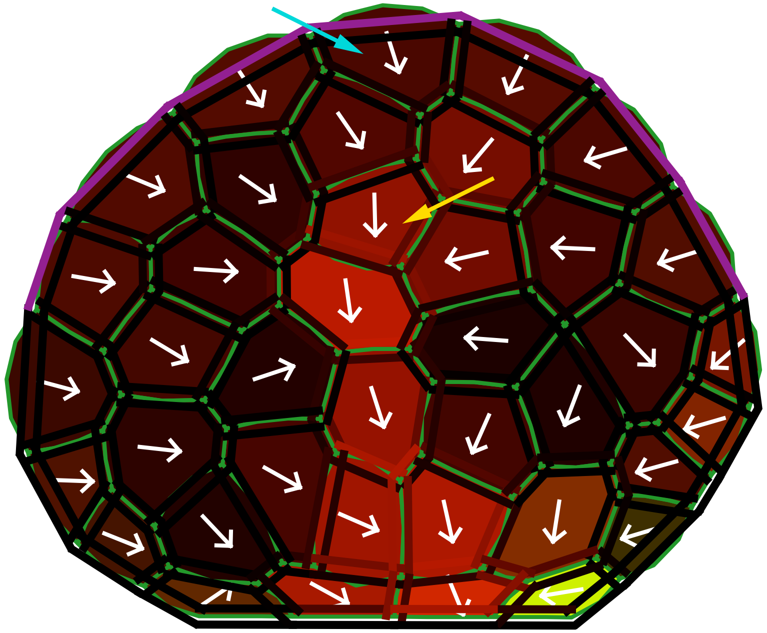


(Scarpella *et al.* 2006.)

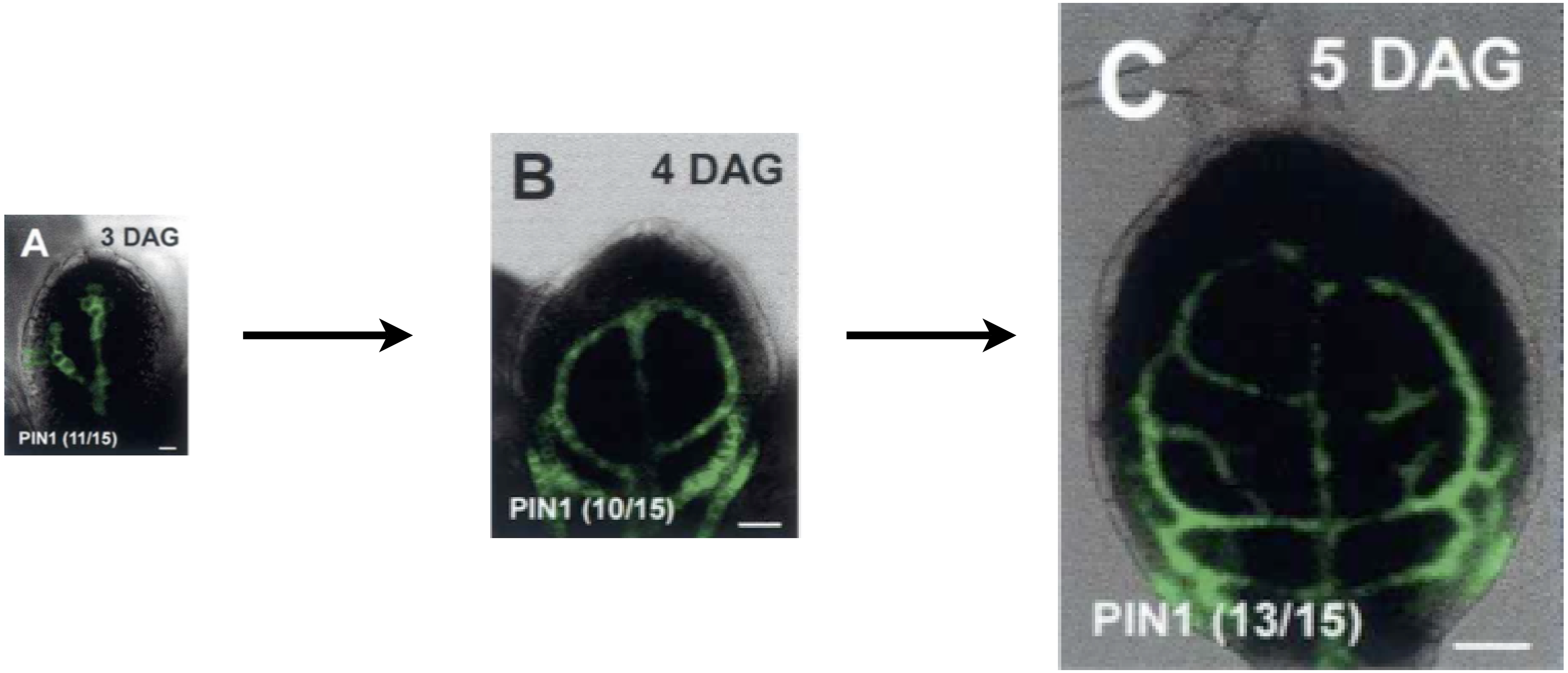
Discrepancy between model & experiment
No “PIN1” convergence at leaf margin

- Experimentally:
    - sharp PIN “convergence” points at epidermis
- In model:
    - funnel-shaped” PIN1 expression near epidermis





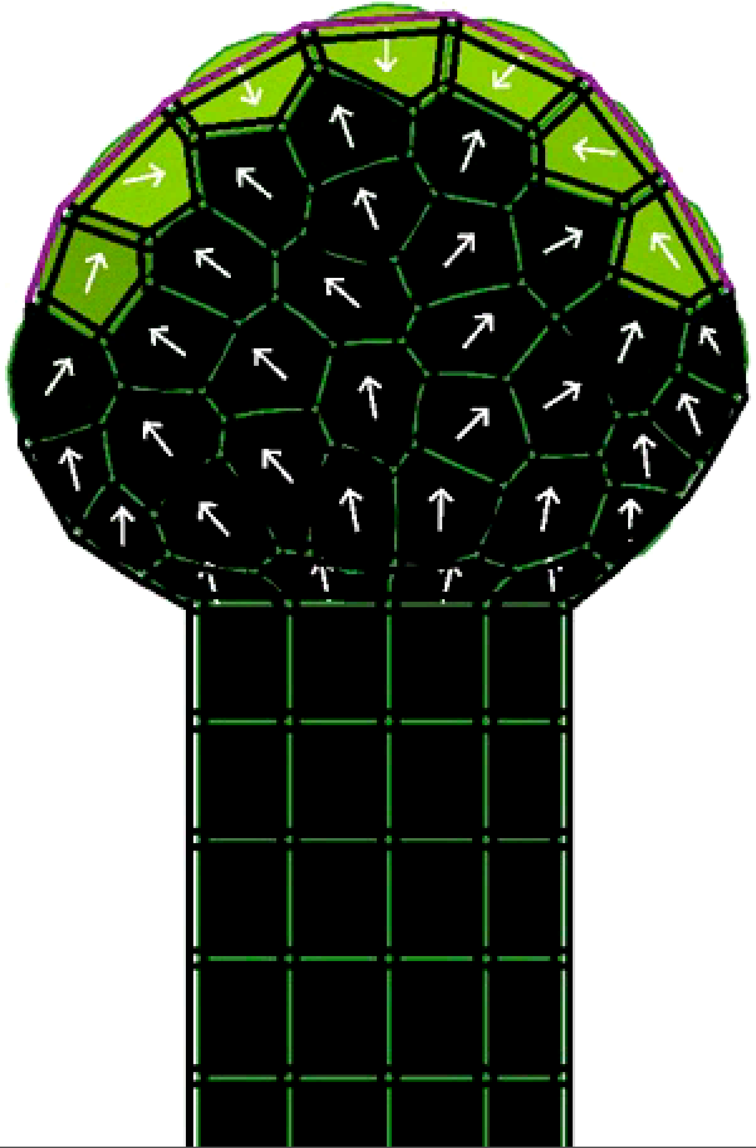
Next step: *growing* leaf



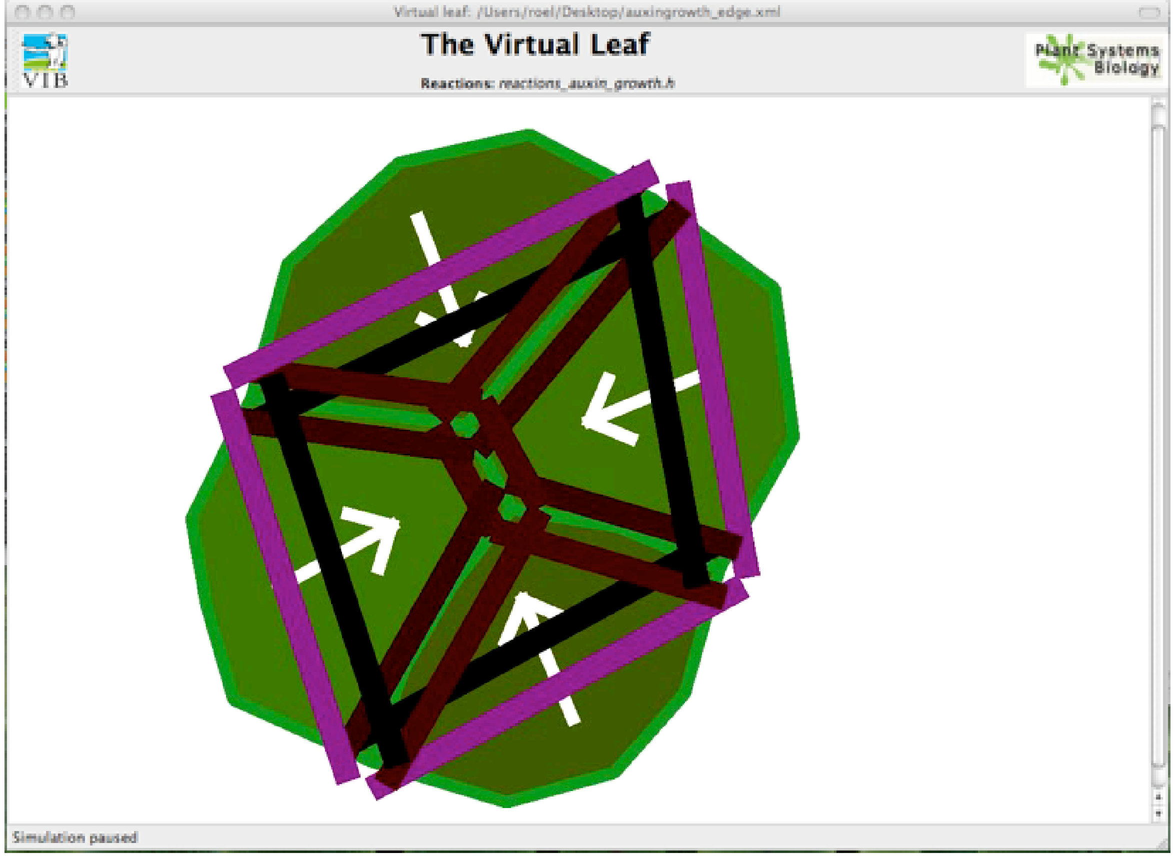
Scarpella *et al.* 2006

- Model for tissue mechanics
- Cell division and expansion rules
- Auxin enhances cell division and expansion?

Preliminary result: AUX1-model + growth

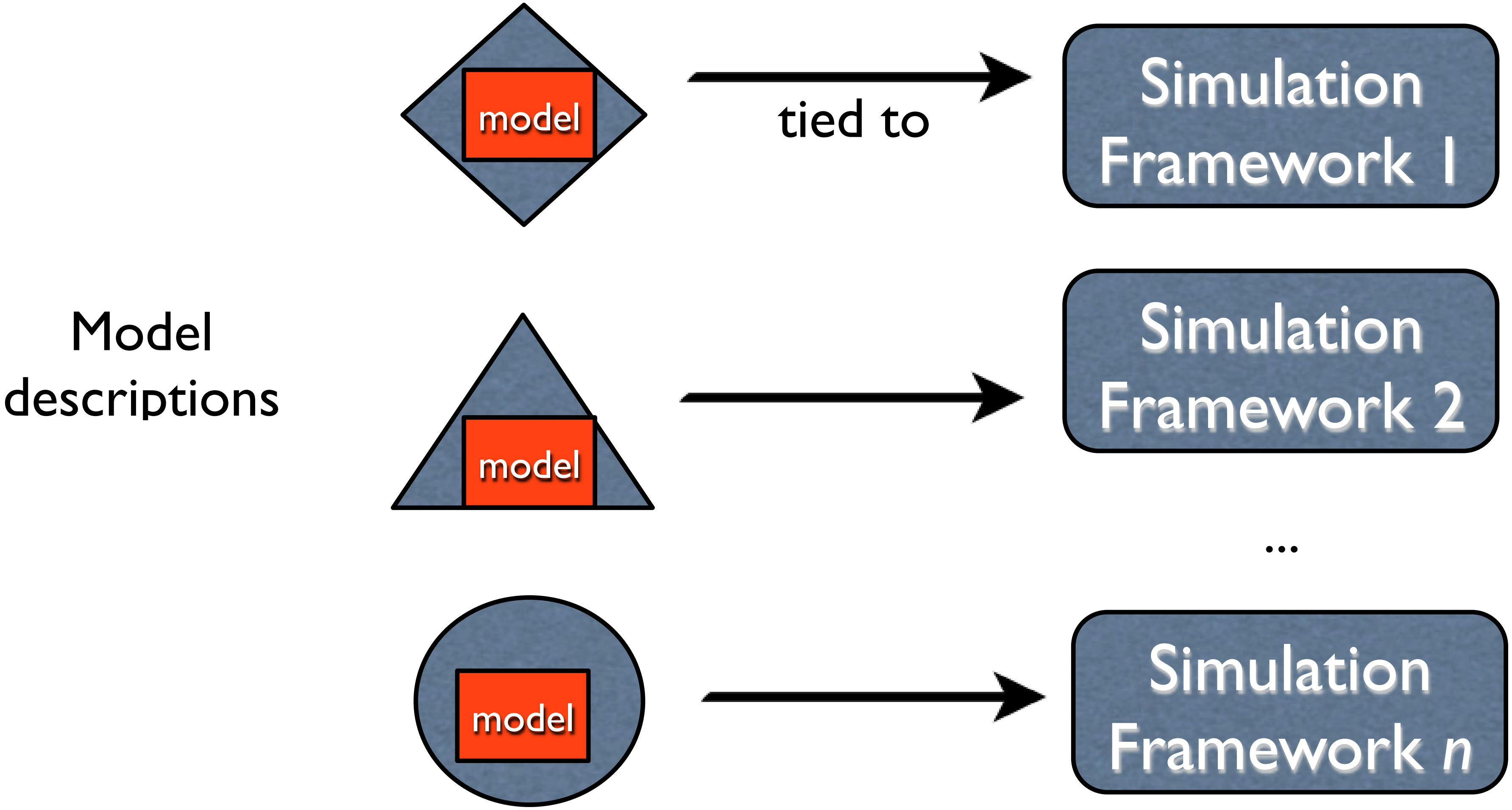


Plant tissue modeling tool



- Virtual Leaf
  - Plant development
  - XML-based file format
  - Model specification in plugin
- Domain-specific language under development

Domain-specific languages for cell-based modeling



Model descriptions

model

tied to

Simulation Framework 1

model

Simulation Framework 2

...

model

Simulation Framework *n*

Tijs van der Storm, CWI

Problem statement

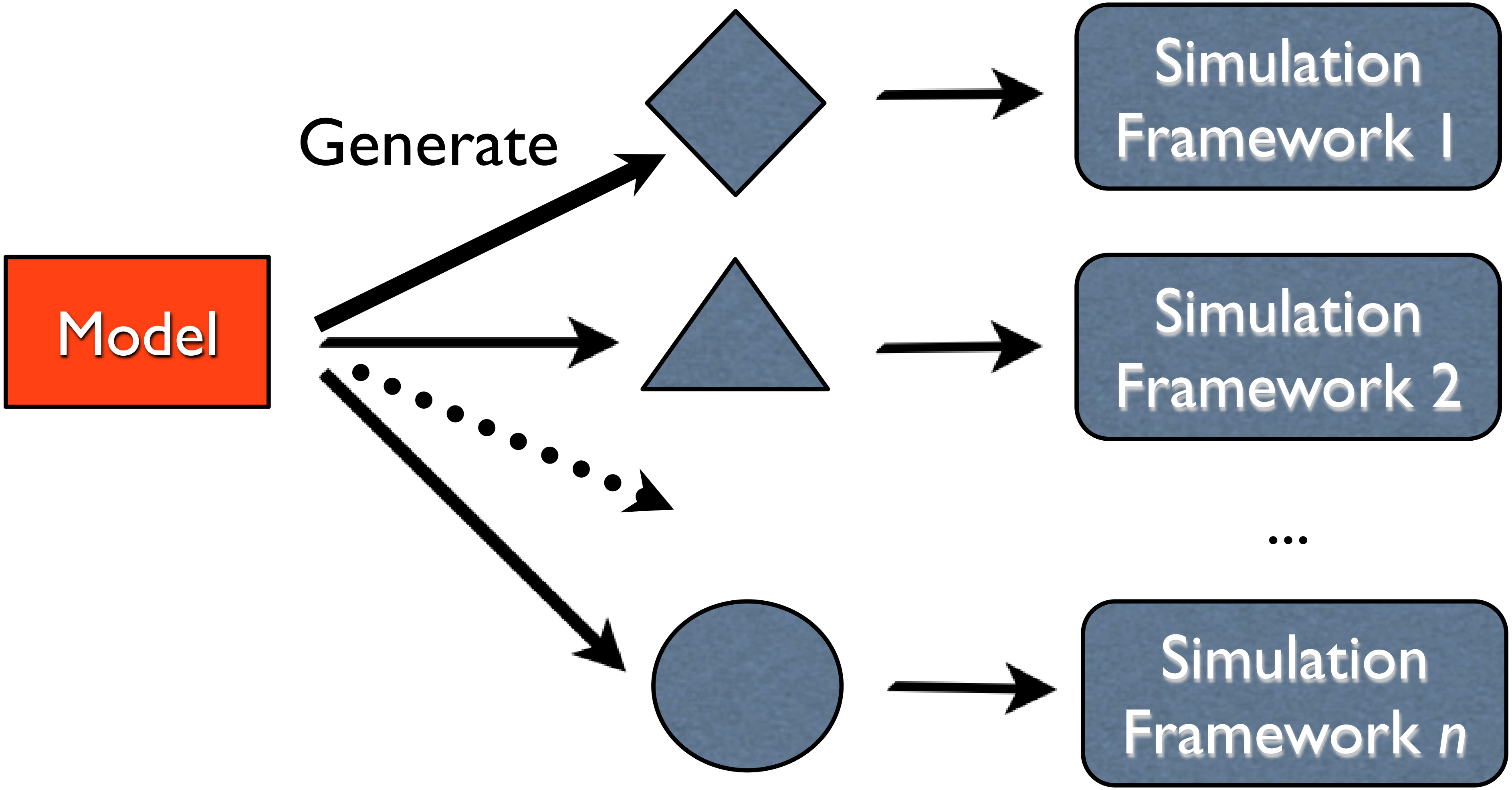
- Comparing simulations is hard
- Hard to repeat simulation experiments with alternative simulation methods
- Simulation descriptions often *entangle* concepts of the domain (cells) and simulation method

Domain-specific languages

- Capture *essence* of a domain in a modeling language
- Generate code for different back-end simulation frameworks
- Division of labor
    - Biologists focus on modeling
    - Computer scientists focus on simulation
- CWI has *the* technology to create DSLs (Paul Klint group; Meta-environment, Rascal)
- Currently starting initial experiments with *Virtual Leaf*

Tijs van der Storm, CWI

Goal



Model

Generate

Simulation Framework 1

Simulation Framework 2

...

Simulation Framework *n*

Tijs van der Storm, CWI

Model plugin code

```
// (a couple of header files)

// To be executed after cell division
void TestPlugin::OnDivide(ParentInfo &parent_info, CellBase &daughter1, CellBase &daughter2) {}

void TestPlugin::SetCellColor(CellBase &c, QColor &color) {

   color = QColor(“green”);
}


void TestPlugin::CellHouseKeeping(CellBase &c) {

   c.EnlargeTargetArea(par->cell_expansion_rate);
   if (c.Area() > par->rel_cell_div_threshold * c.BaseArea() ) {
          c.Divide();
    }
}

void TestPlugin::CelltoCellTransport(Wall *w, double *dchem_c1, double *dchem_c2) {}
void TestPlugin::WallDynamics(Wall *w, double *dw1, double *dw2) {}
void TestPlugin::CellDynamics(CellBase *c, double *dchem) { }


Q_EXPORT_PLUGIN2(testplugin, TestPlugin)
```

Summary

- Plant modeling framework for symplastic development, with only cell differentiation, division and expansion
- Traveling-wave mechanism produces auxin channels without experimentally unknown auxin flux-sensor

Netherlands Consortium for Systems Biology

CWI

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