Combining morphodynamics, hormone signaling, and cell differentiation in computational models

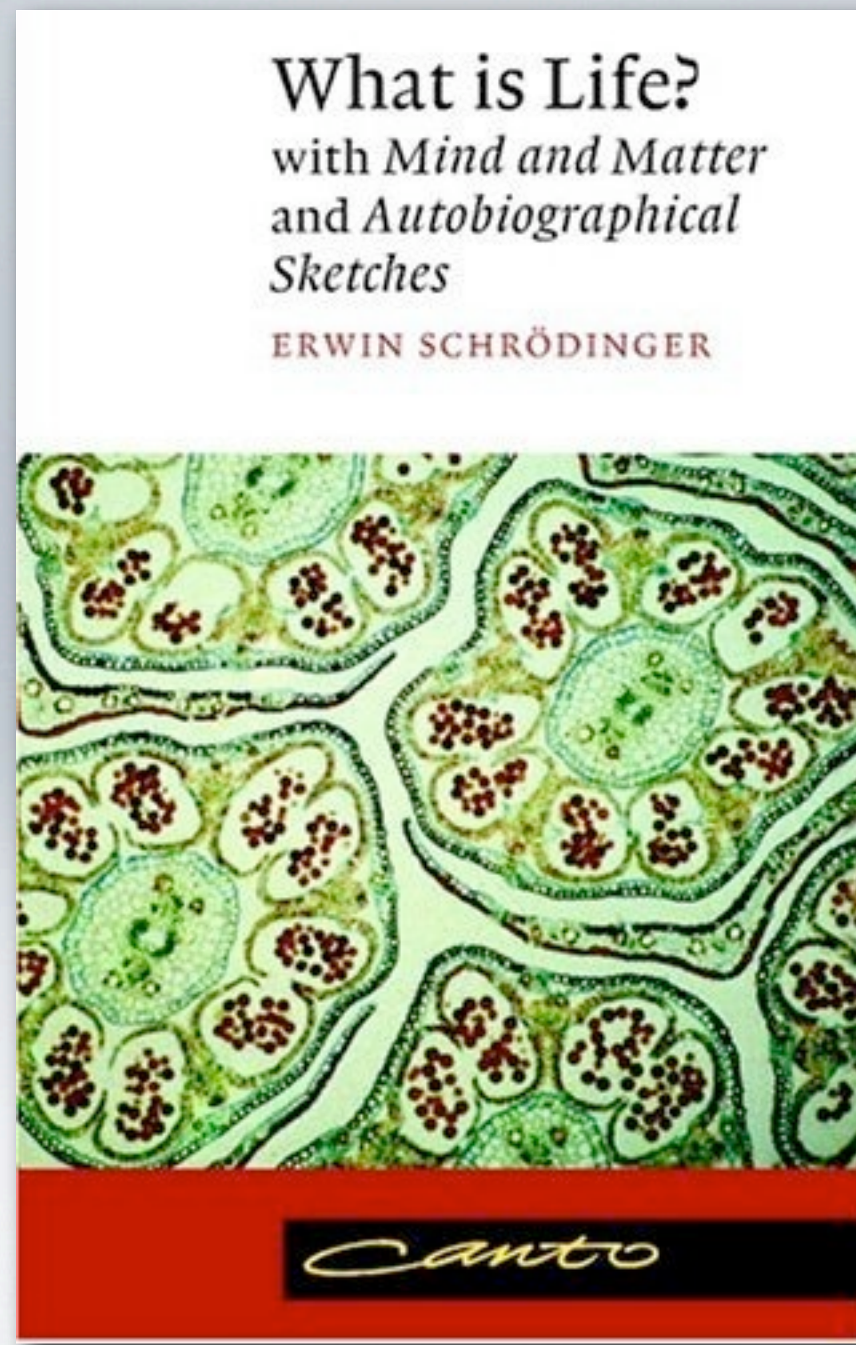
Young scientist school on *Bioinformatics and Systems Biology*
Novosibirsk, 28-29 June, 2010

Henrik Jönsson
Computational Biology & Biological Physics

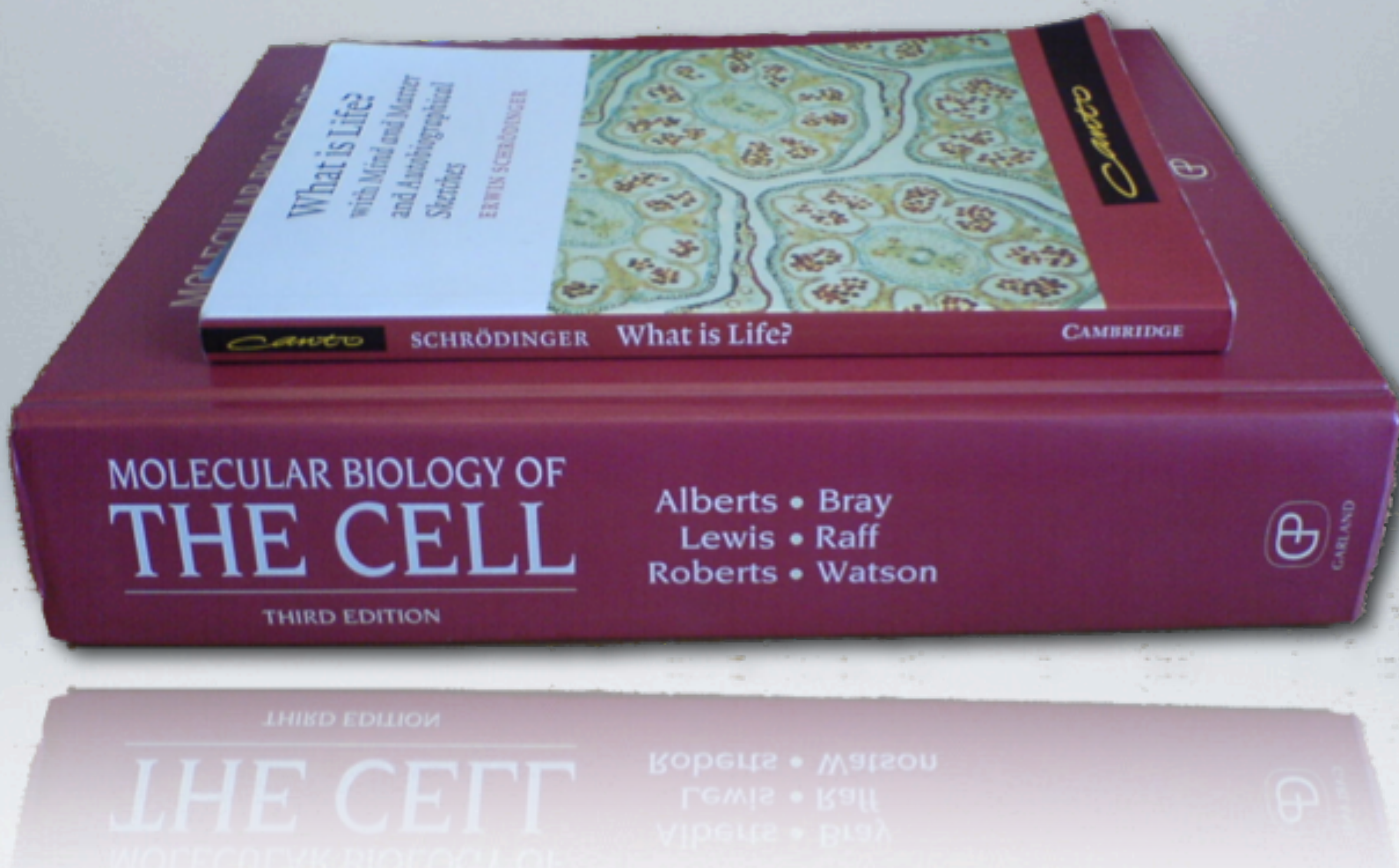
LUND UNIVERSITY

what is life?

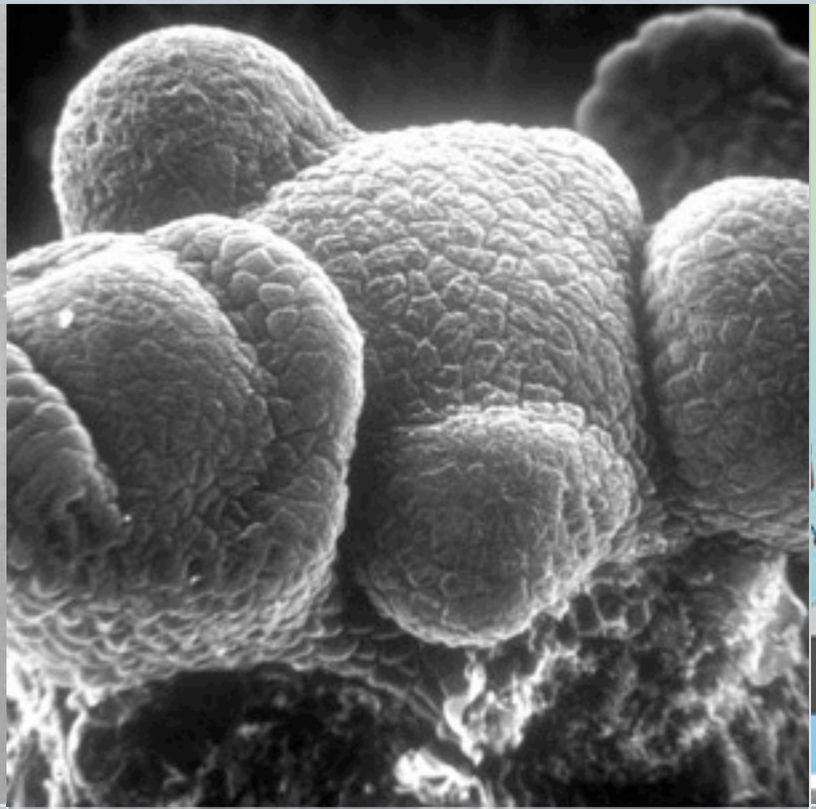
what is life?

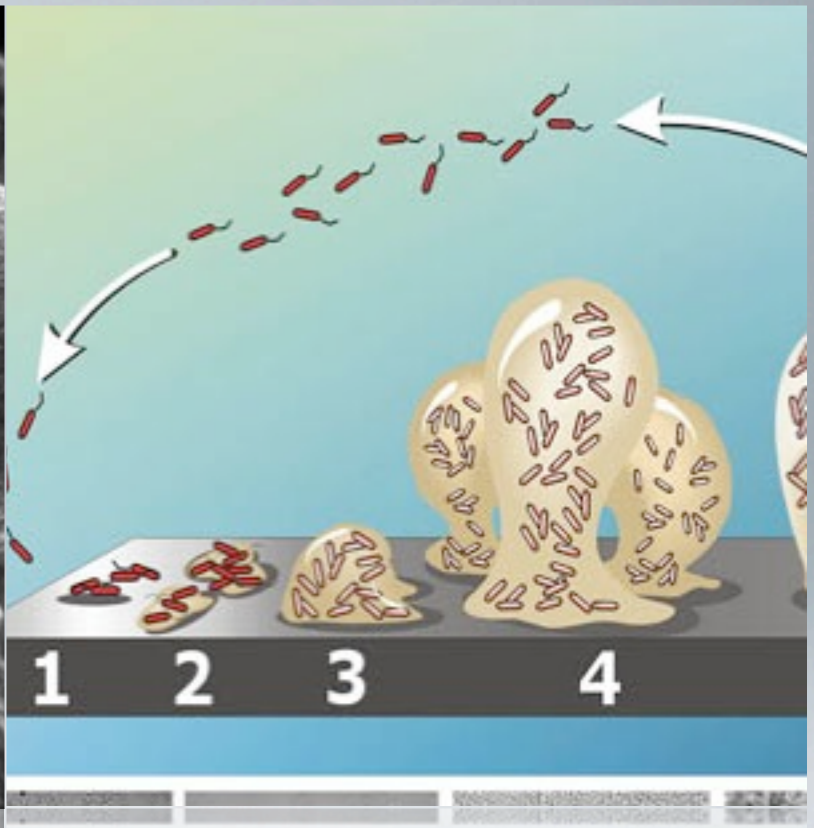

What is Life?
with Mind and Matter
and Autobiographical
Sketches
ERWIN SCHRÖDINGER
Canto

what is life?


What is Life?
with Mind and Matter
and Autobiographical
Sketches
SCHRÖDINGER What is Life?
CAMBRIDGE
MOLECULAR BIOLOGY OF
THE CELL
THIRD EDITION
Alberts • Bray
Lewis • Raff
Roberts • Watson

the problem





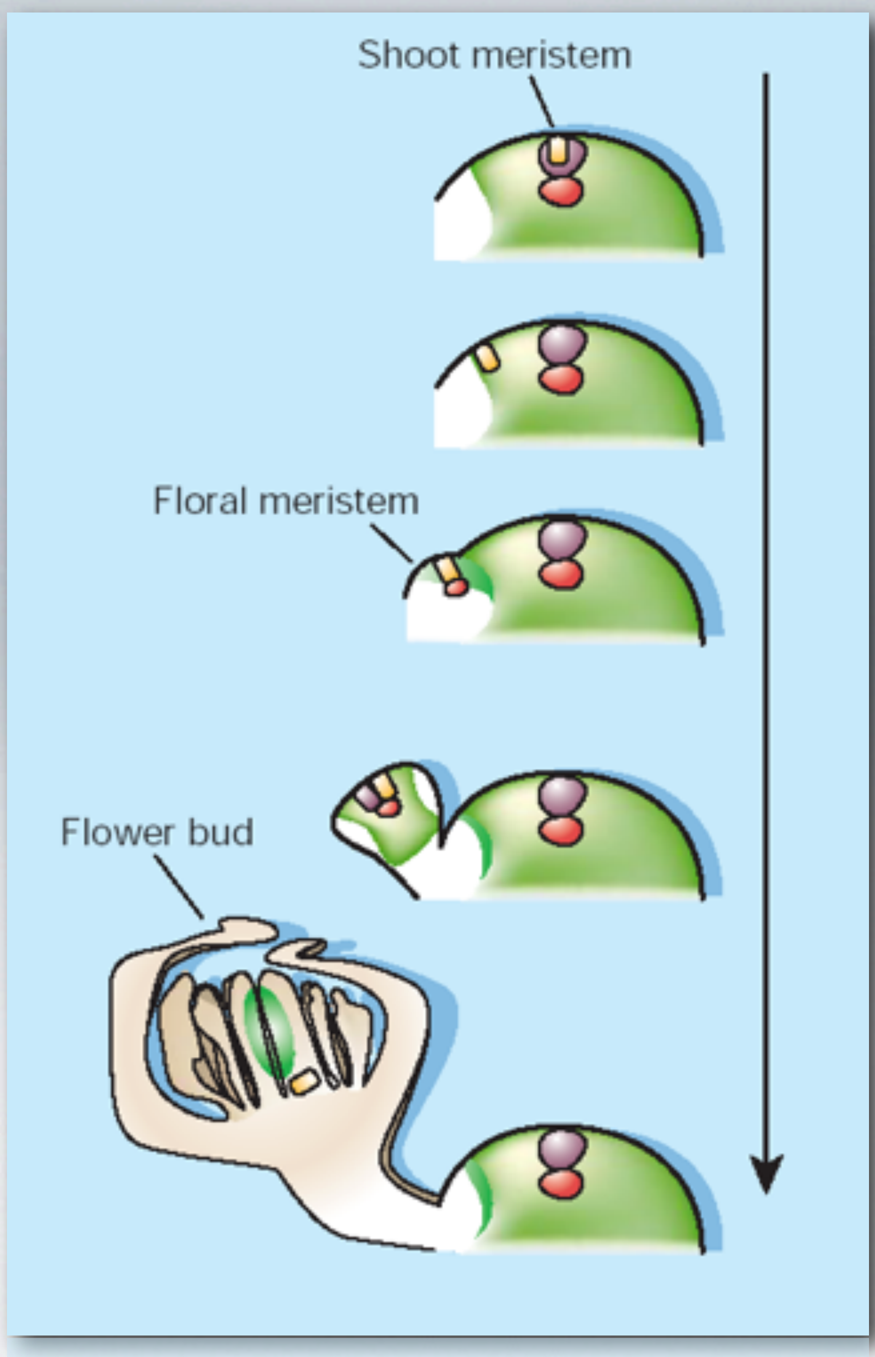
How can differentiation and morphogenesis be regulated in an correlated fashion in multicellular systems?

Plants vs animals

Plants vs animals

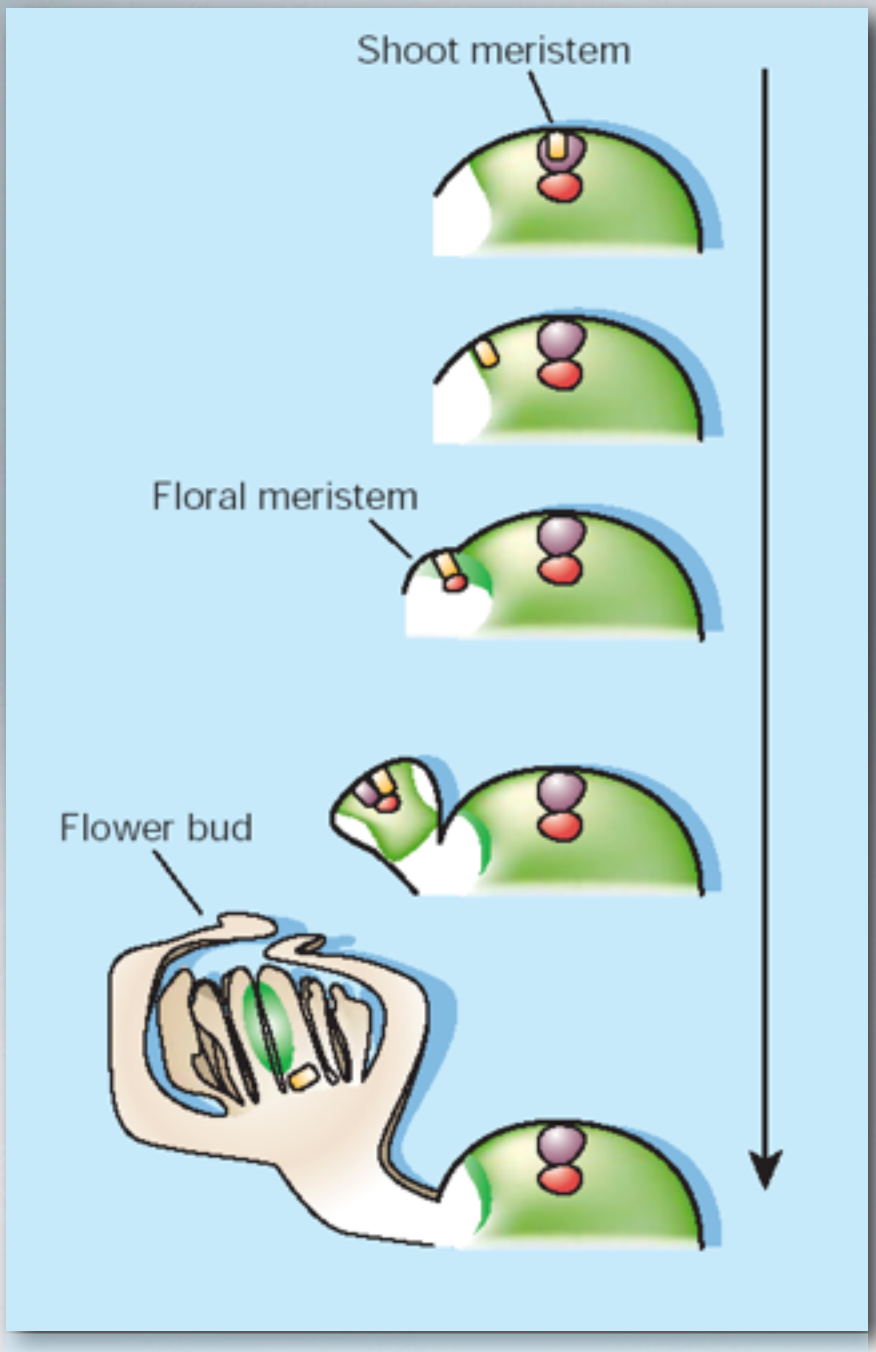
Plants vs animals

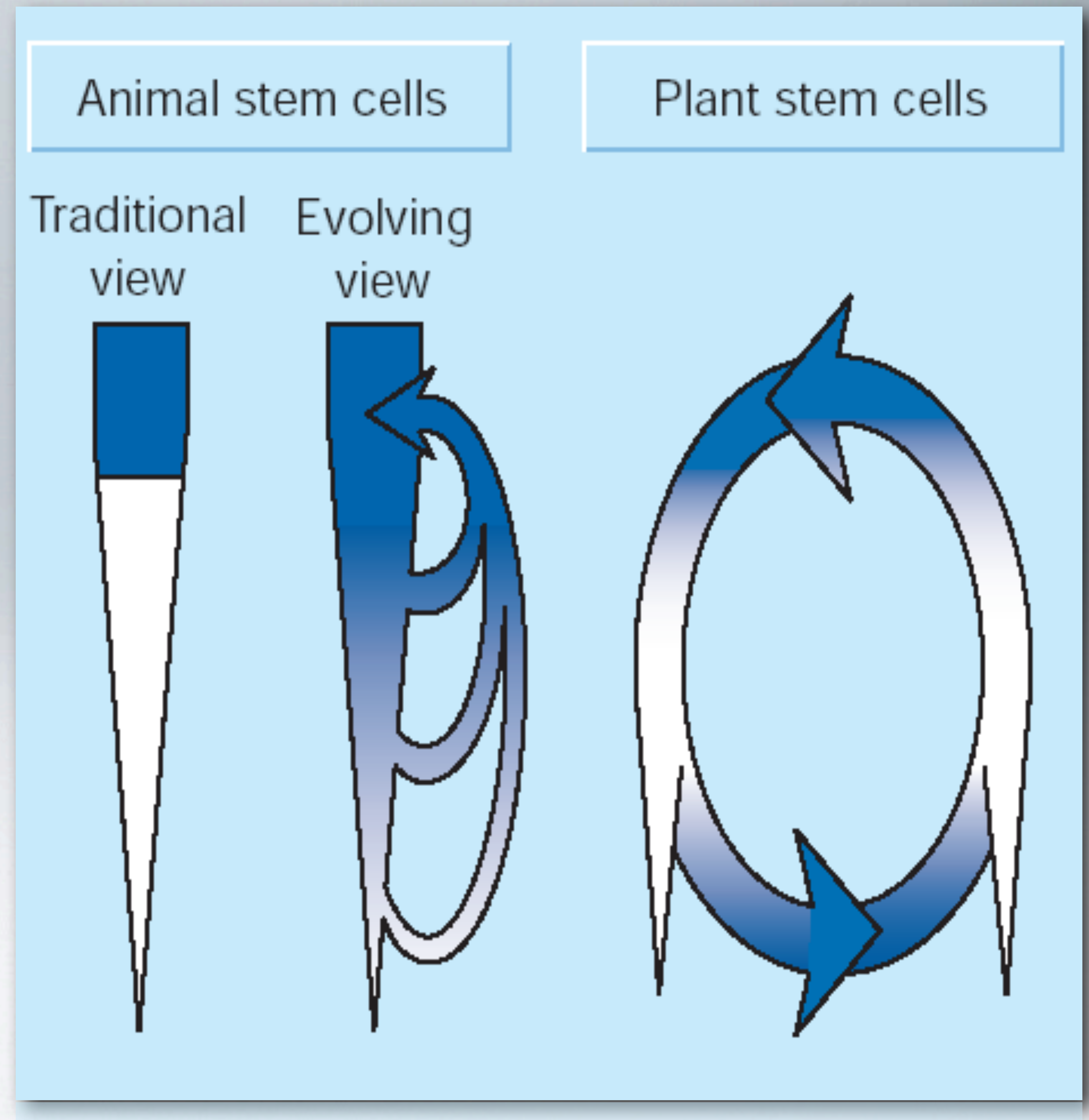
Robustness and plasticity



Nature 415, 751-754, (2002)

Robustness and plasticity





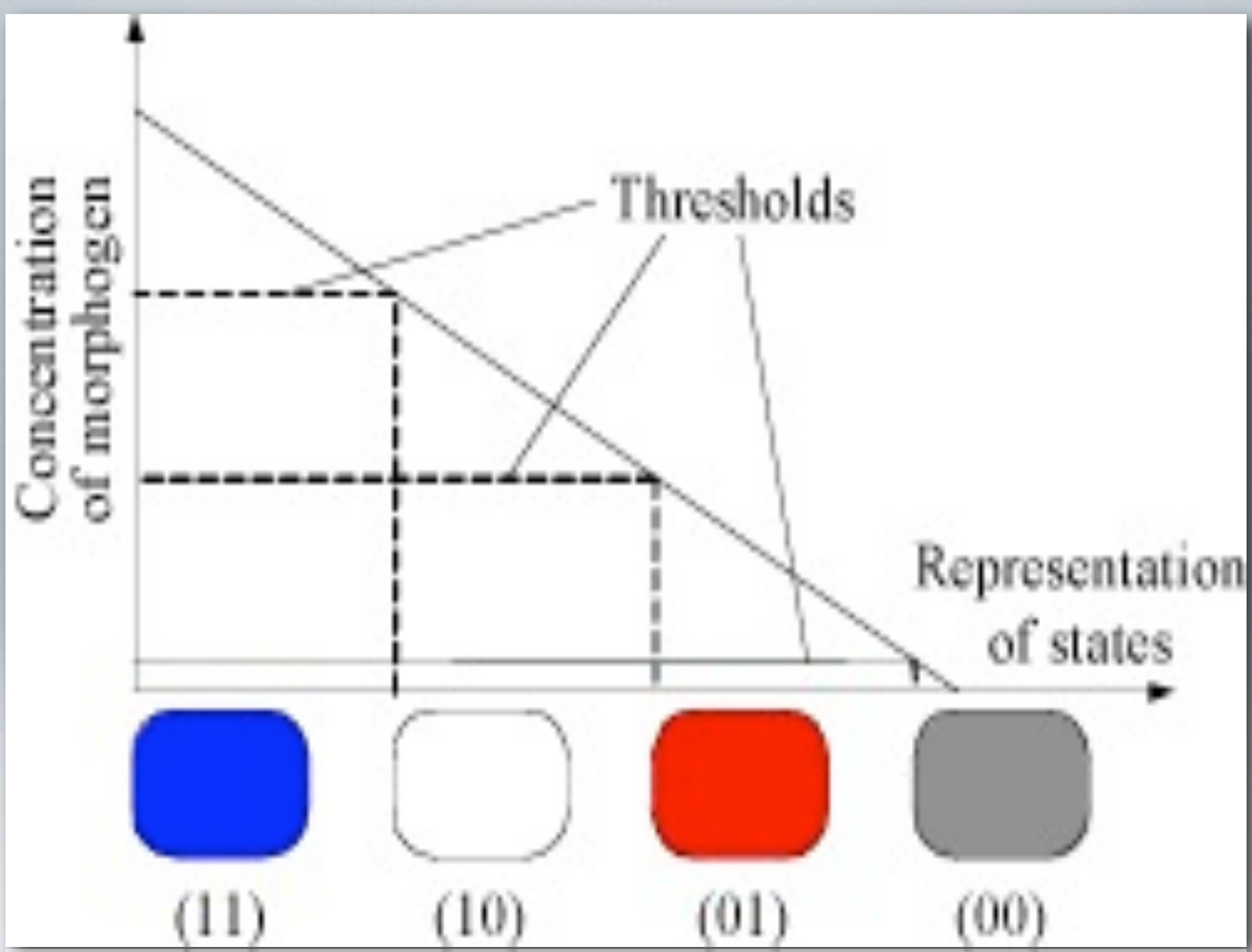
Nature 415, 751-754, (2002)

pattern generation

pattern generation

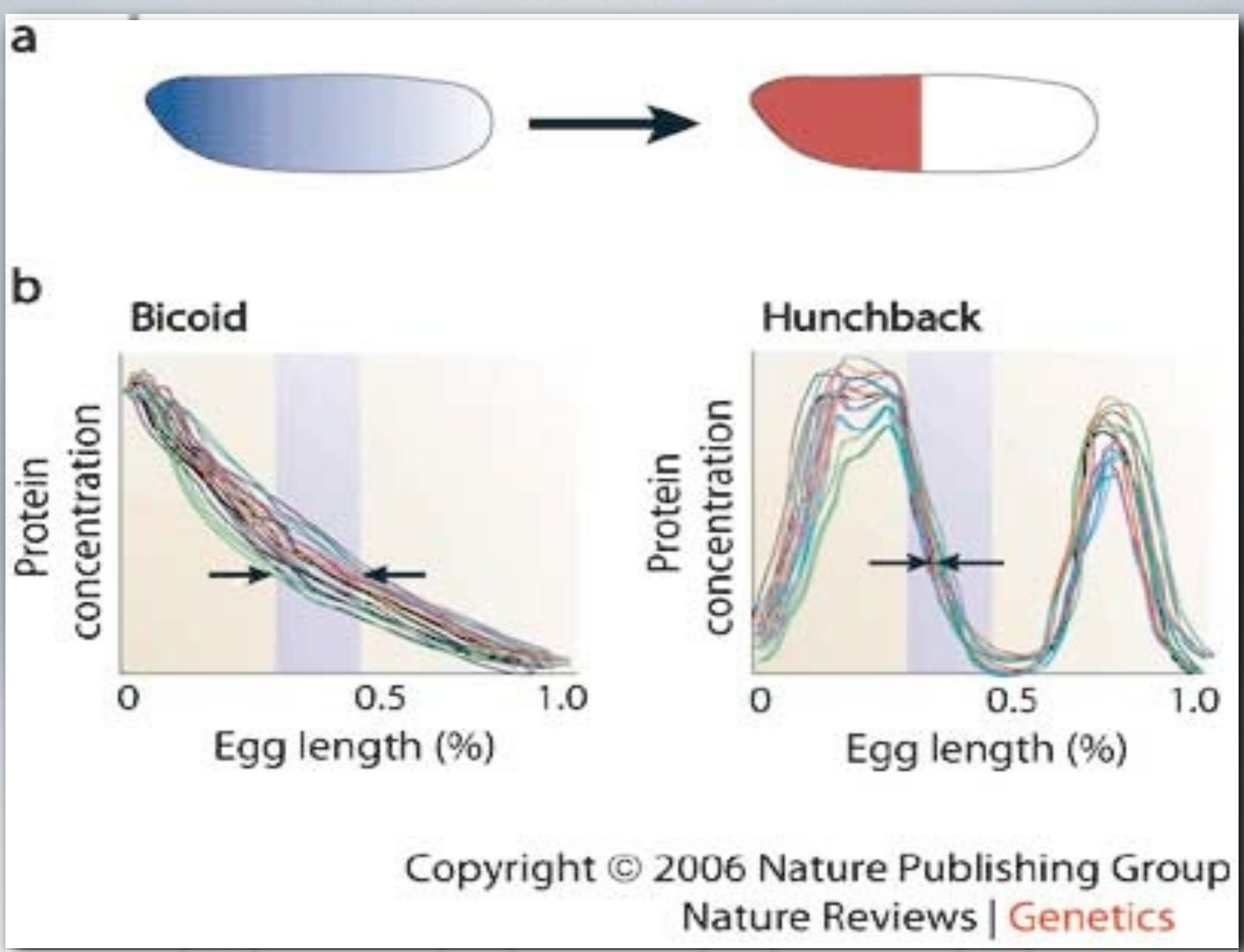
growth and mechanics in next talk...

pattern generation



morphogens

pattern generation



morphogens

spontaneous pattern generation

spontaneous pattern generation

A Turing

spontaneous pattern generation

THE CHEMICAL BASIS OF MORPHOGENESIS

By A. M. TURING, F.R.S. *University of Manchester*

(*Received* 9 *November* 1951—*Revised* 15 *March* 1952)

It is suggested that a system of chemical substances, called morphogens, reacting together and diffusing through a tissue, is adequate to account for the main phenomena of morphogenesis. Such a system, although it may originally be quite homogeneous, may later develop a pattern or structure due to an instability of the homogeneous equilibrium, which is triggered off by random disturbances. Such reaction-diffusion systems are considered in some detail in the case of an isolated ring of cells, a mathematically convenient, though biologically unusual system.

A Turing

spontaneous pattern generation

reactions + diffusion

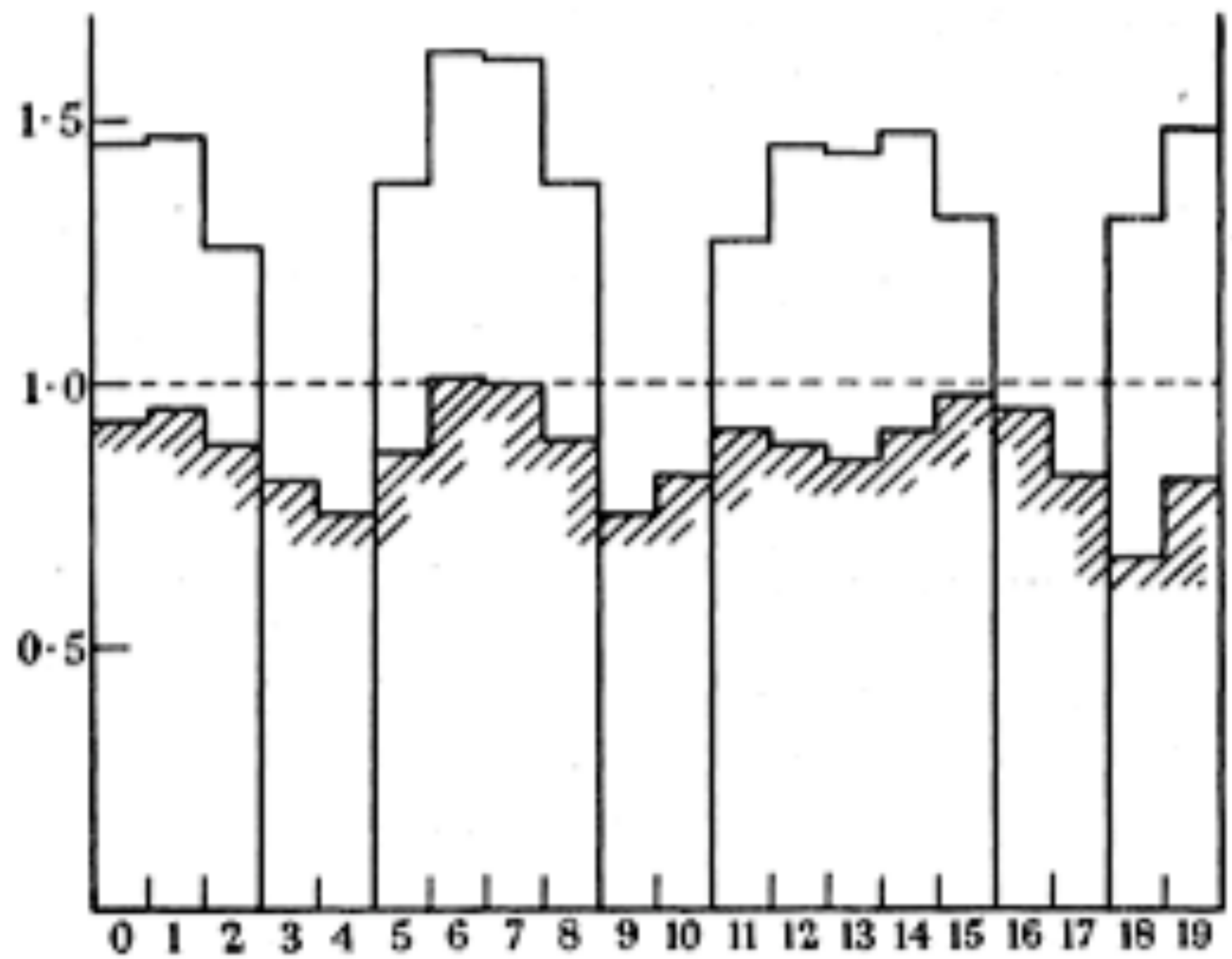
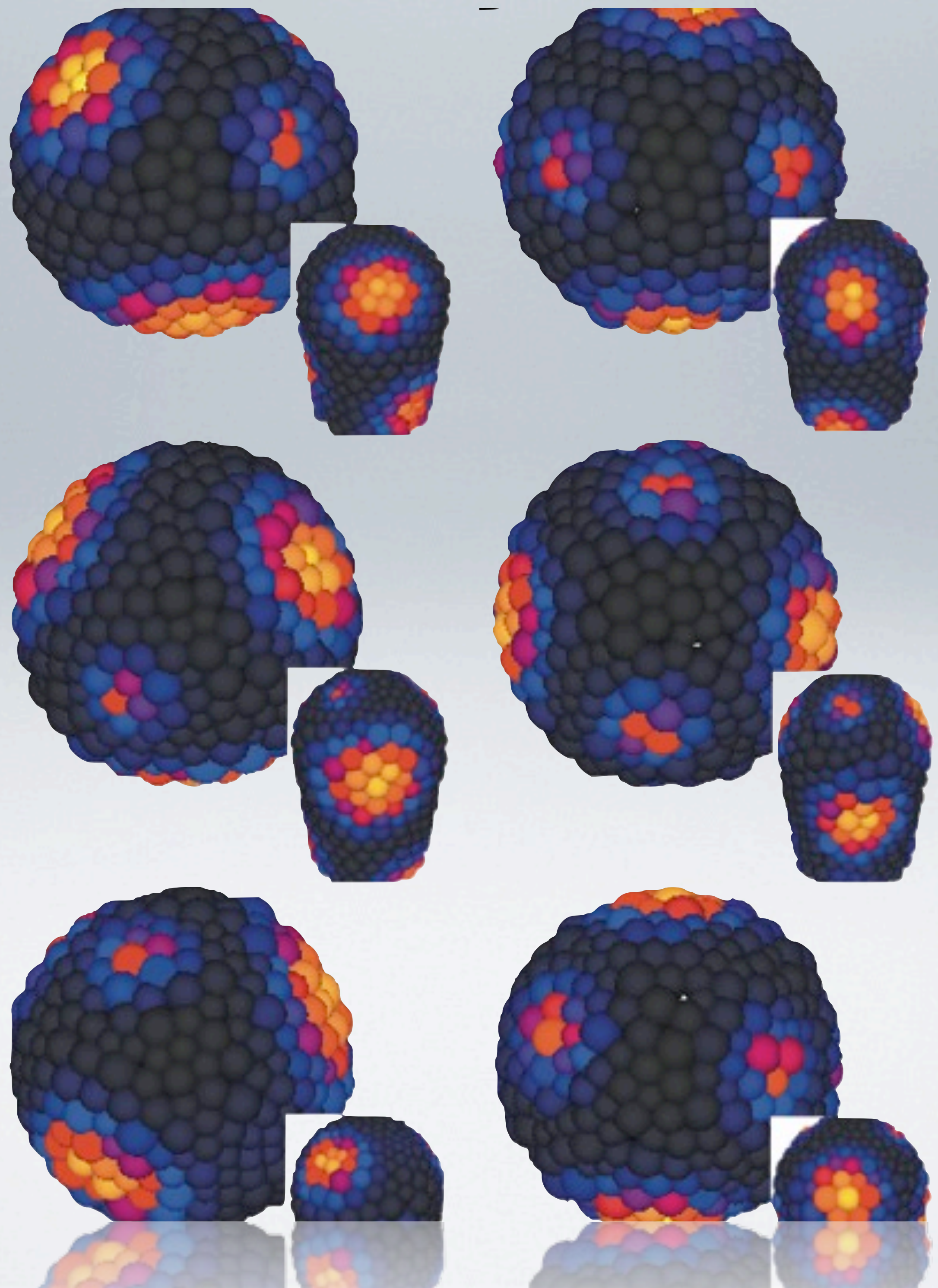


FIGURE 3. Concentrations of *Y* in the development of the first specimen (taken from table 1). ------- original homogeneous equilibrium; ////// incipient pattern; ——— final equilibrium.

A Turing

spontaneous pattern generation

regulated transport

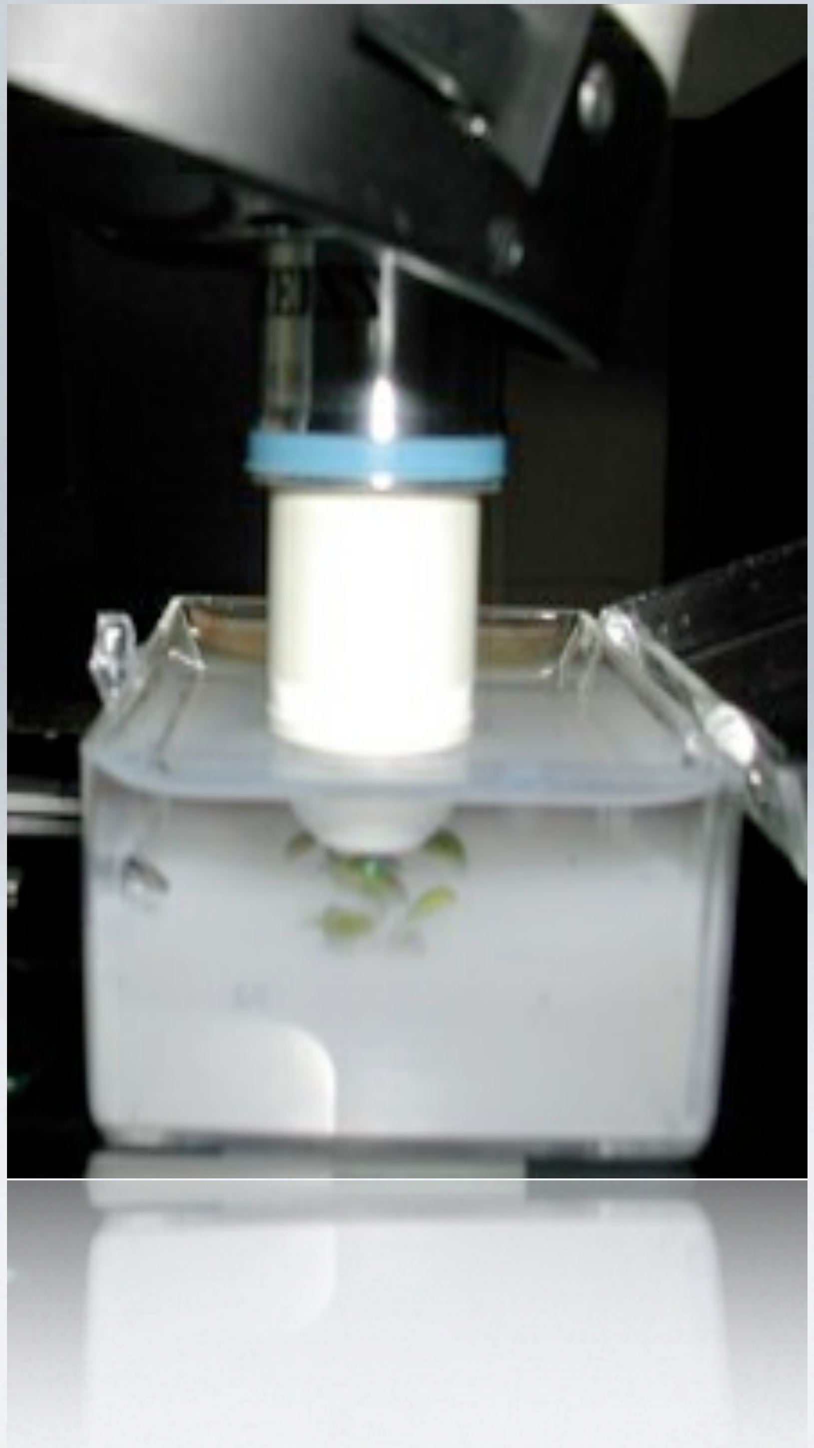


Jönsson et al (2006), ...

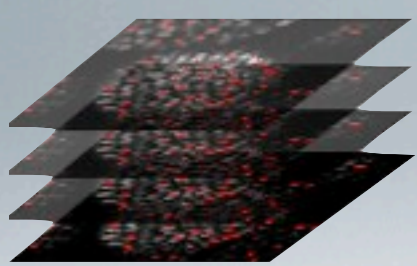
data

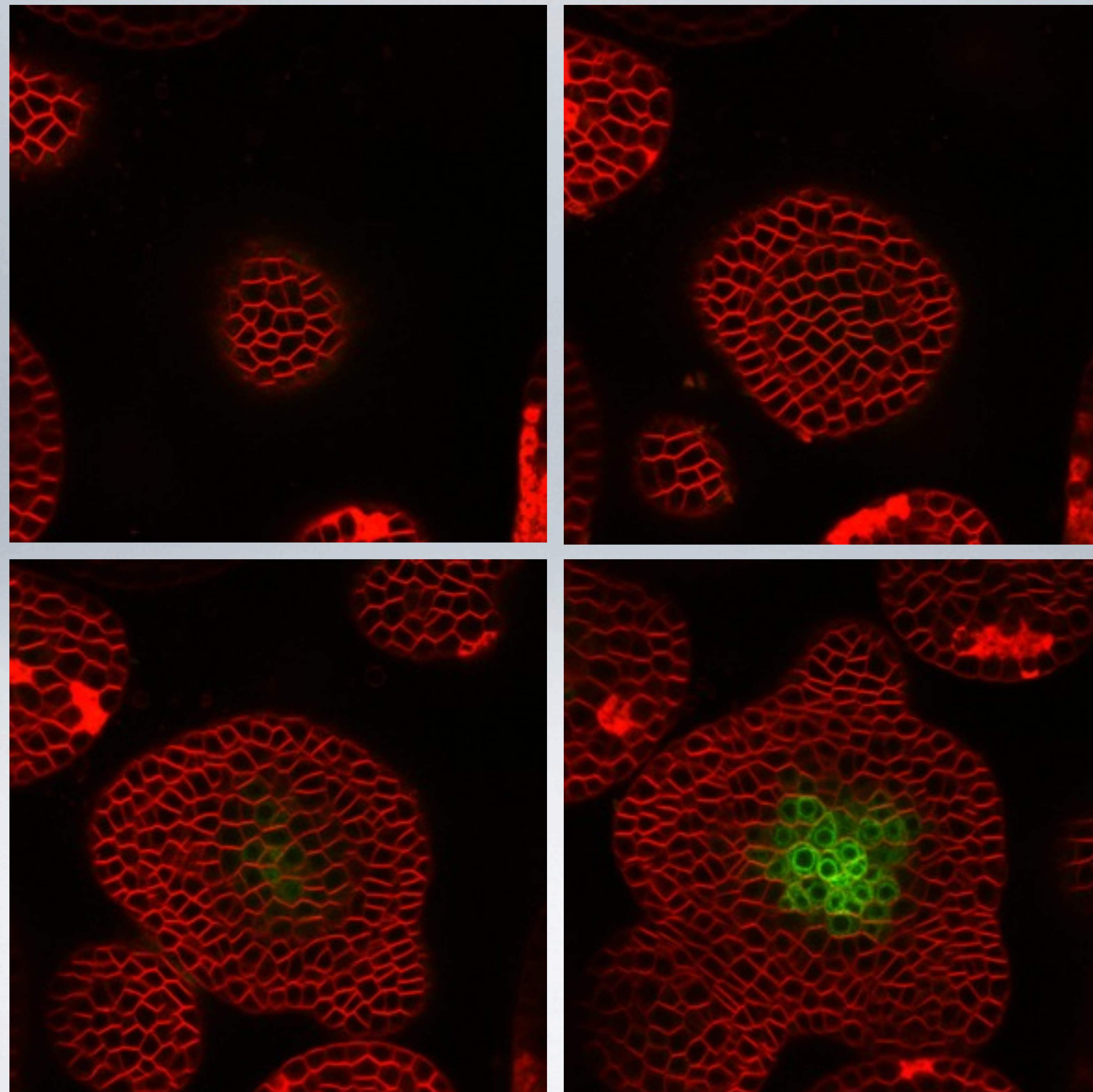
data

data



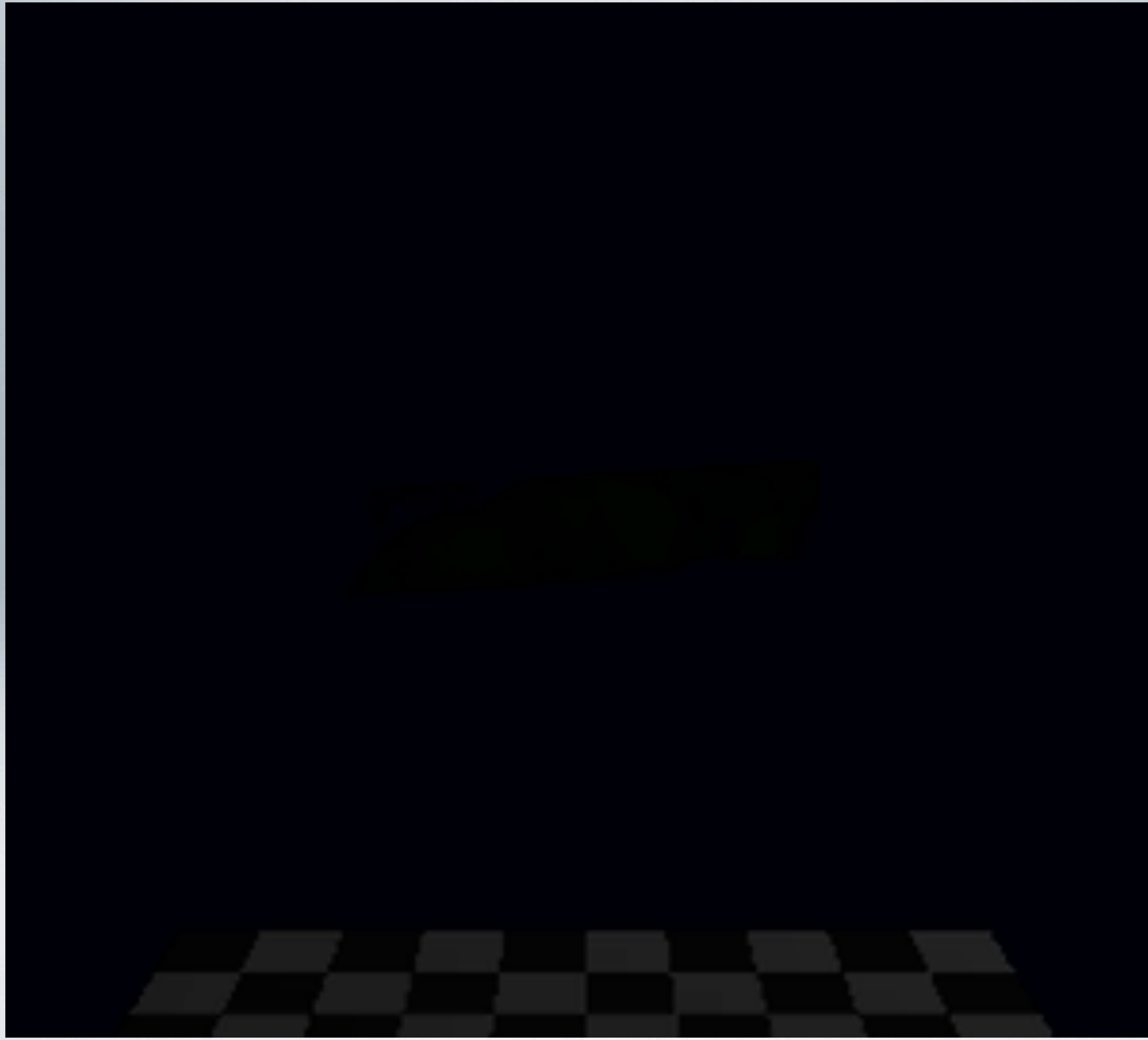
data

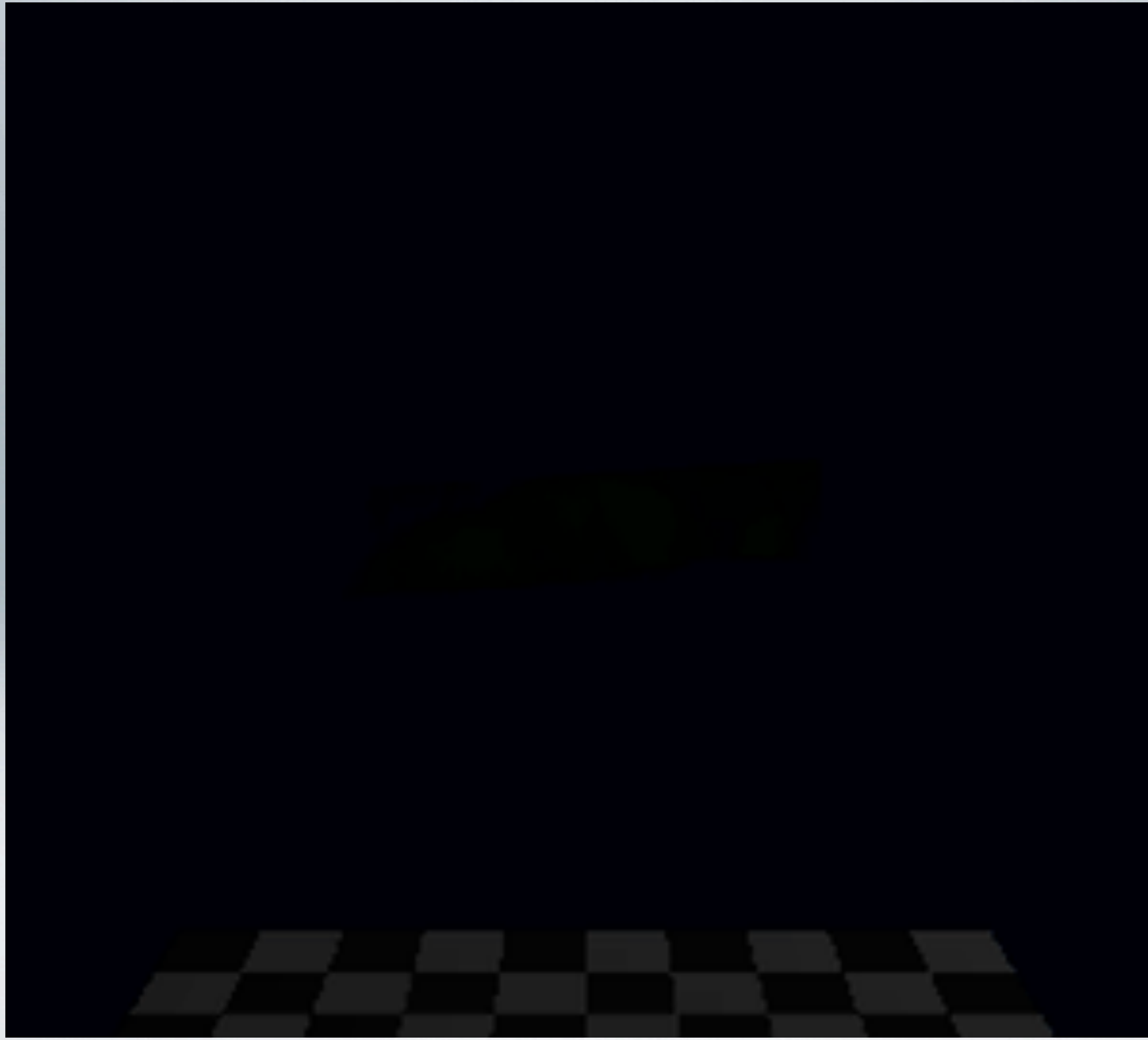




Venu Reddy

WUS::GFP





Marcus Heisler

What is science?

What is science?

“eine wissenschaft, aber nicht wissenschaft”

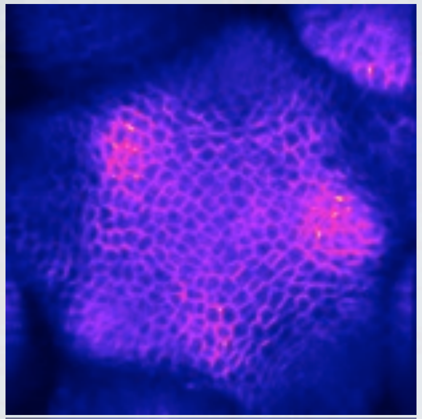
What is science?

“eine wissenschaft, aber nicht wissenschaft”

Immanuel Kant

The criterion of true science lay in its relation to mathematics…

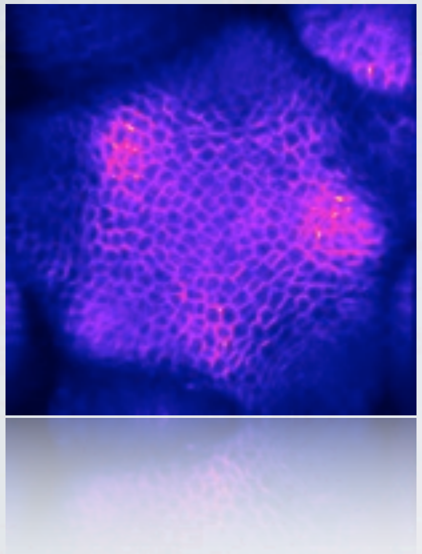
the method



experiment

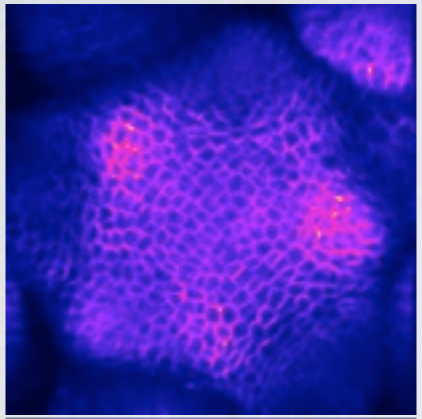
hypotheses

the method



experiment → mathematical models ← hypotheses

the method

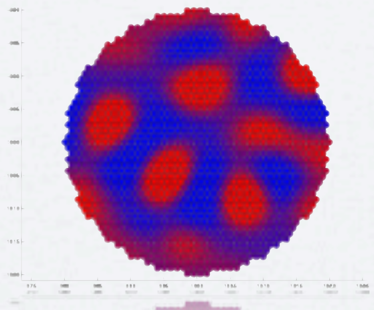


experiment

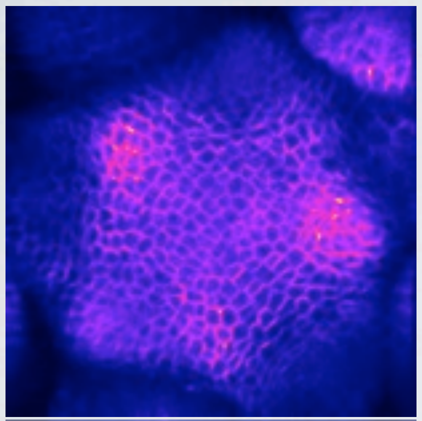
hypotheses

mathematical
models

computer simulations



the method

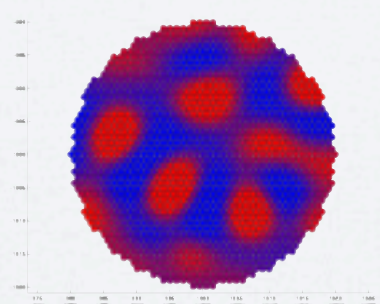


experiment

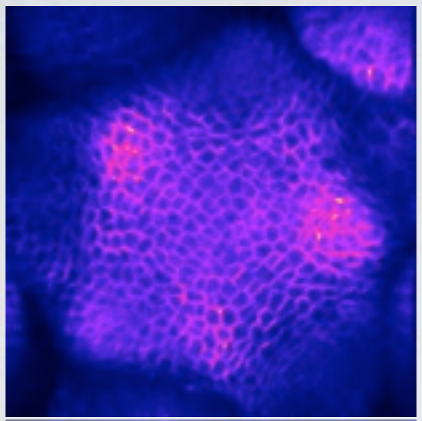
hypotheses

mathematical models

computer simulations



the method

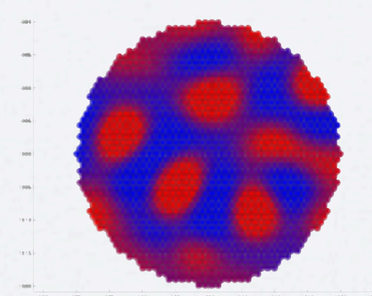


experiment

hypotheses

mathematical models

computer simulations



can this be automatized?

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- use imaging data for generating dynamic templates

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- define (differential equation) models in the computer

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- use algorithm to update models (parameters and hypotheses)

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- model predictions to propose new experiments

can this be automatized?

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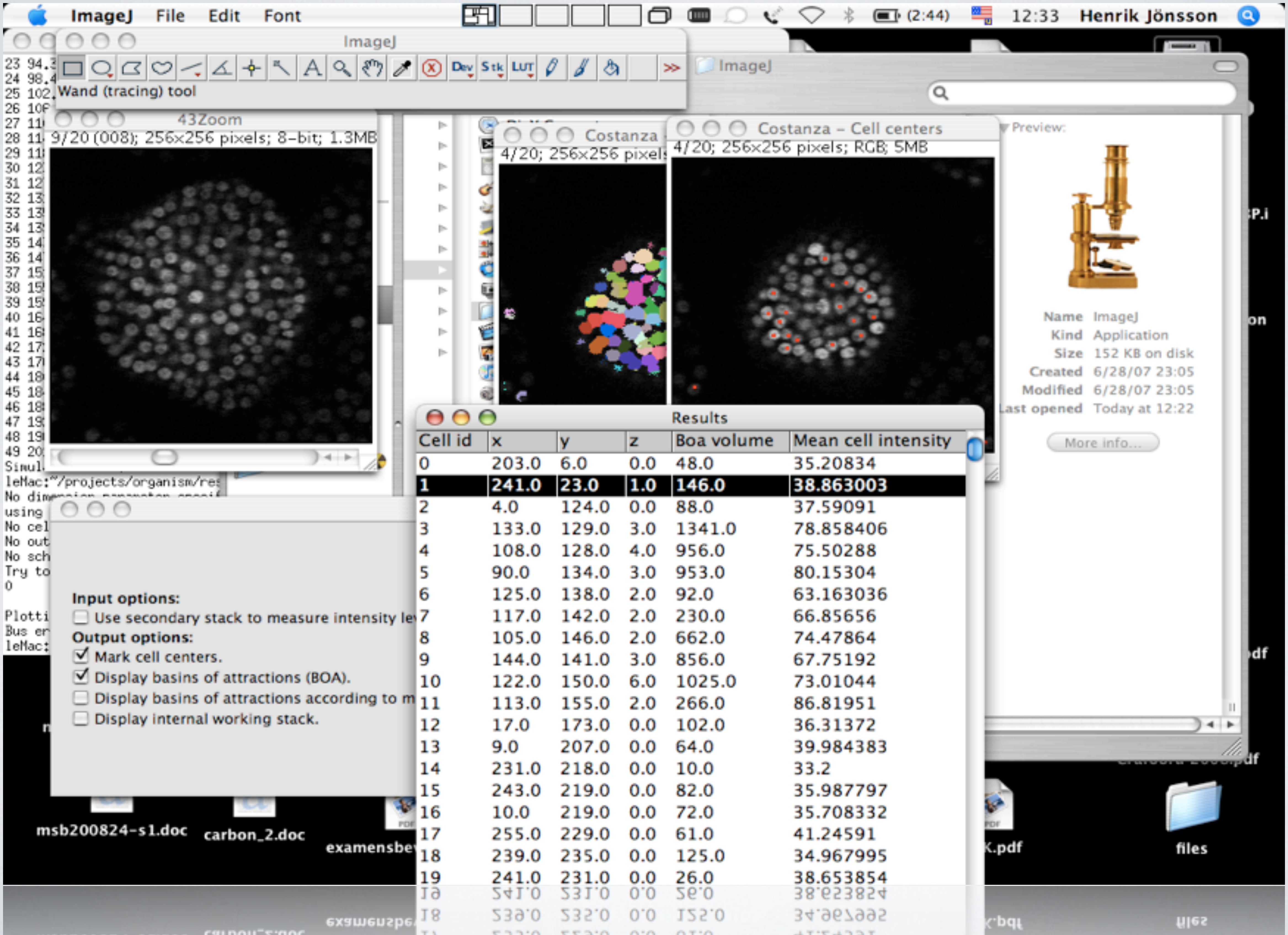
all steps in the computer

image segmentation

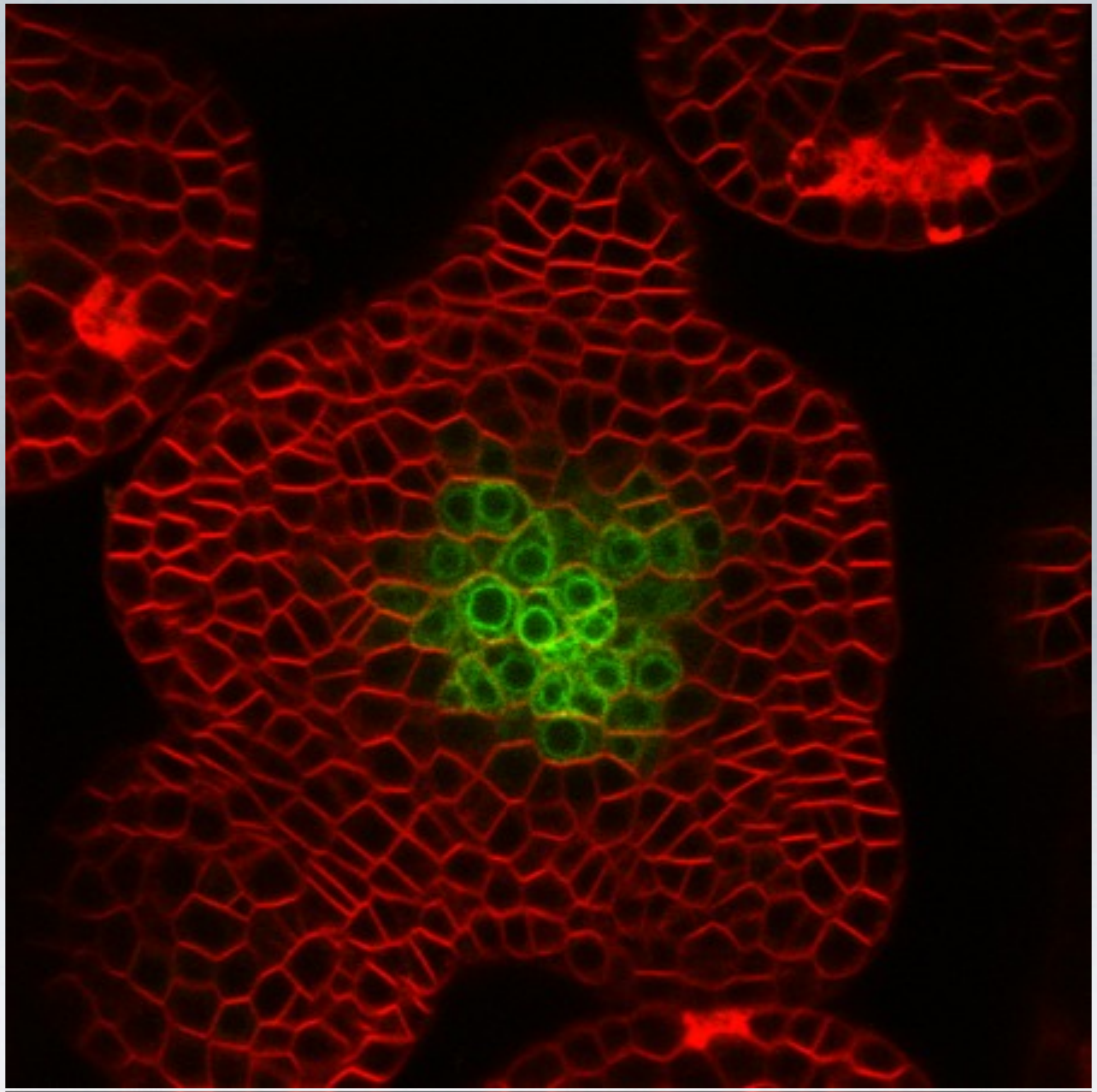
image segmentation

COnfocal STack ANalyZer Application
COSTANZA

image segmentation



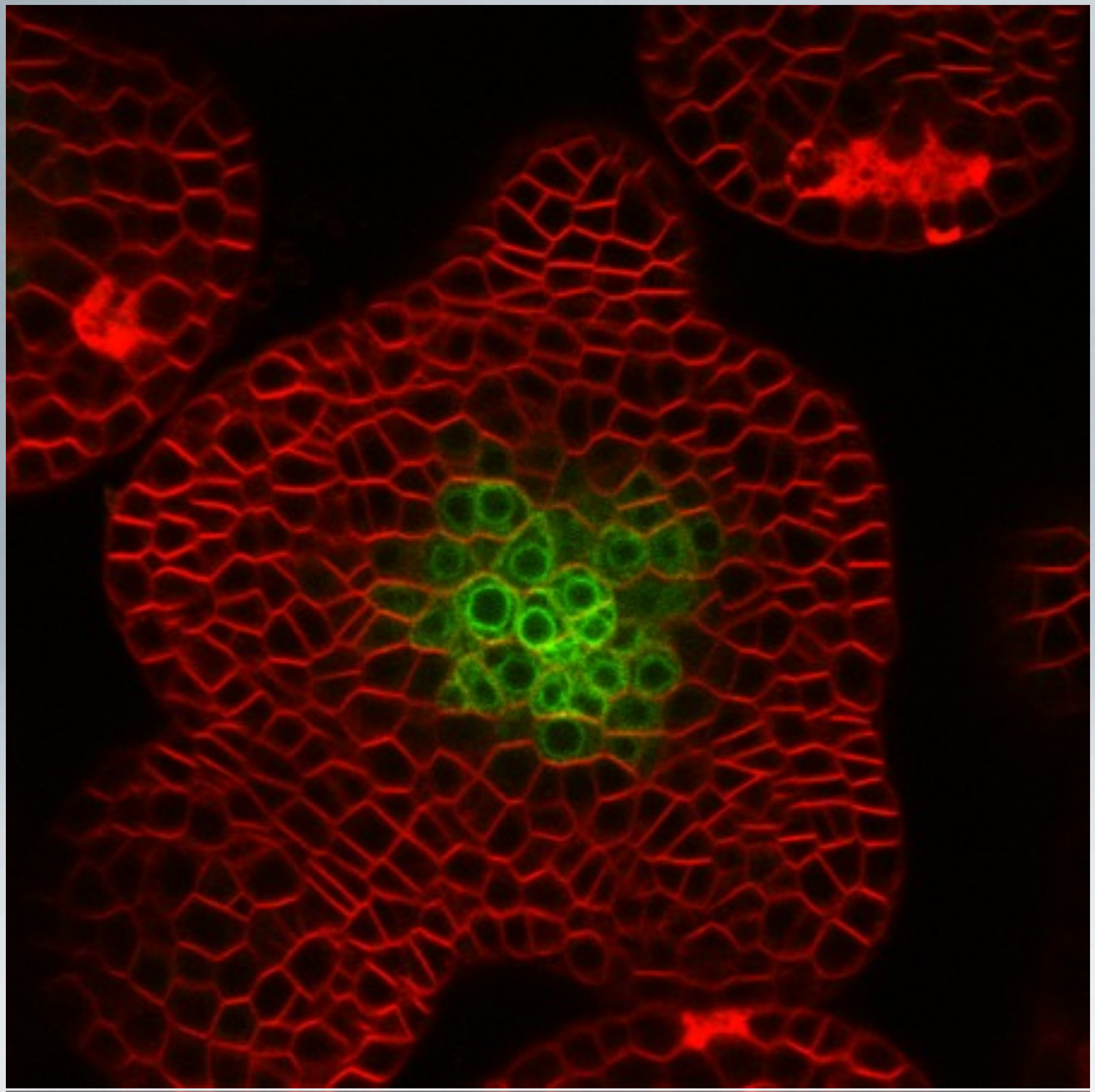
Quantitative measures from image



Green WUS::GFP
Red membrane stain

Jönsson et al (2005)

Quantitative measures from image



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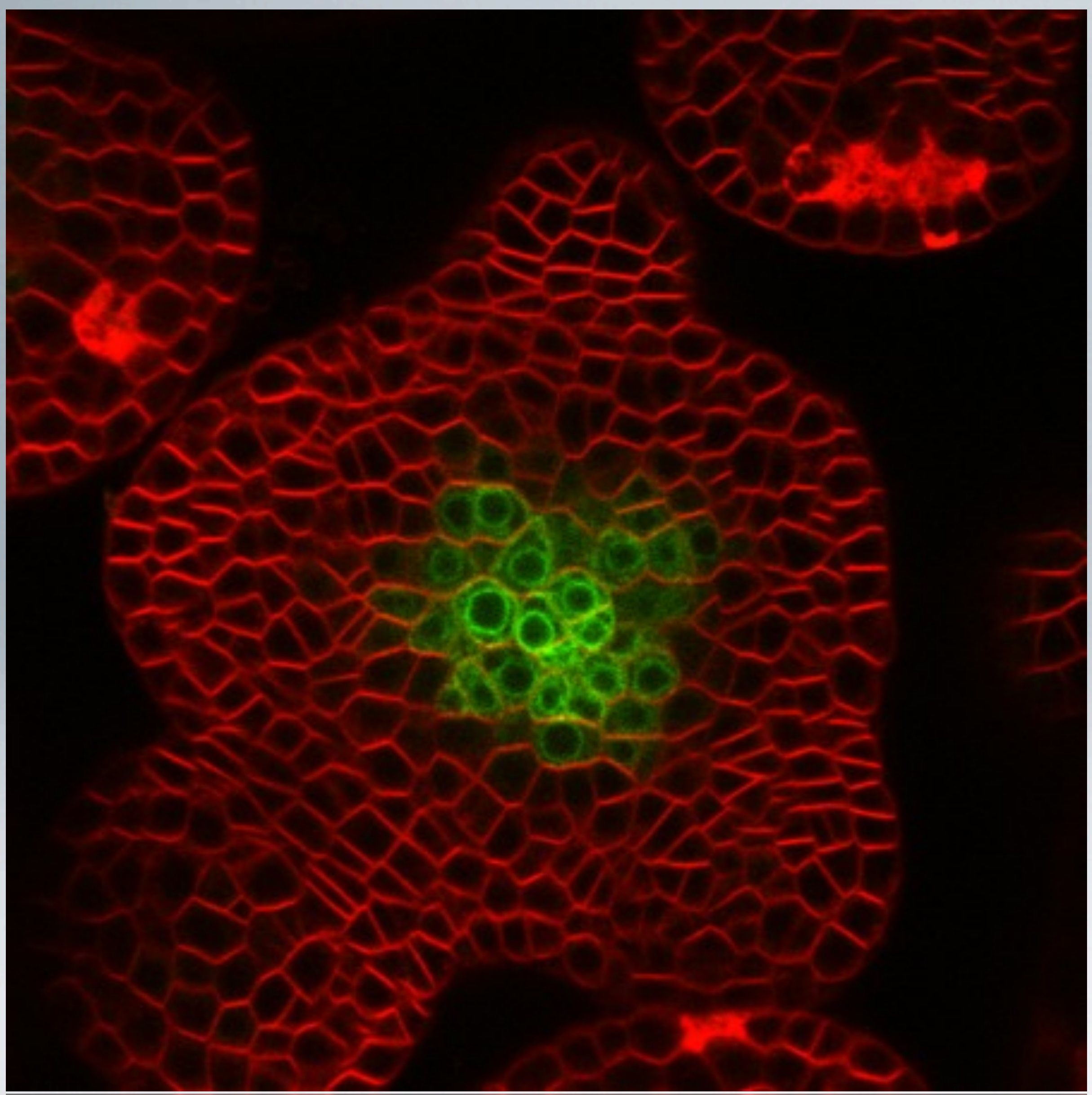
Quantitative measures from image



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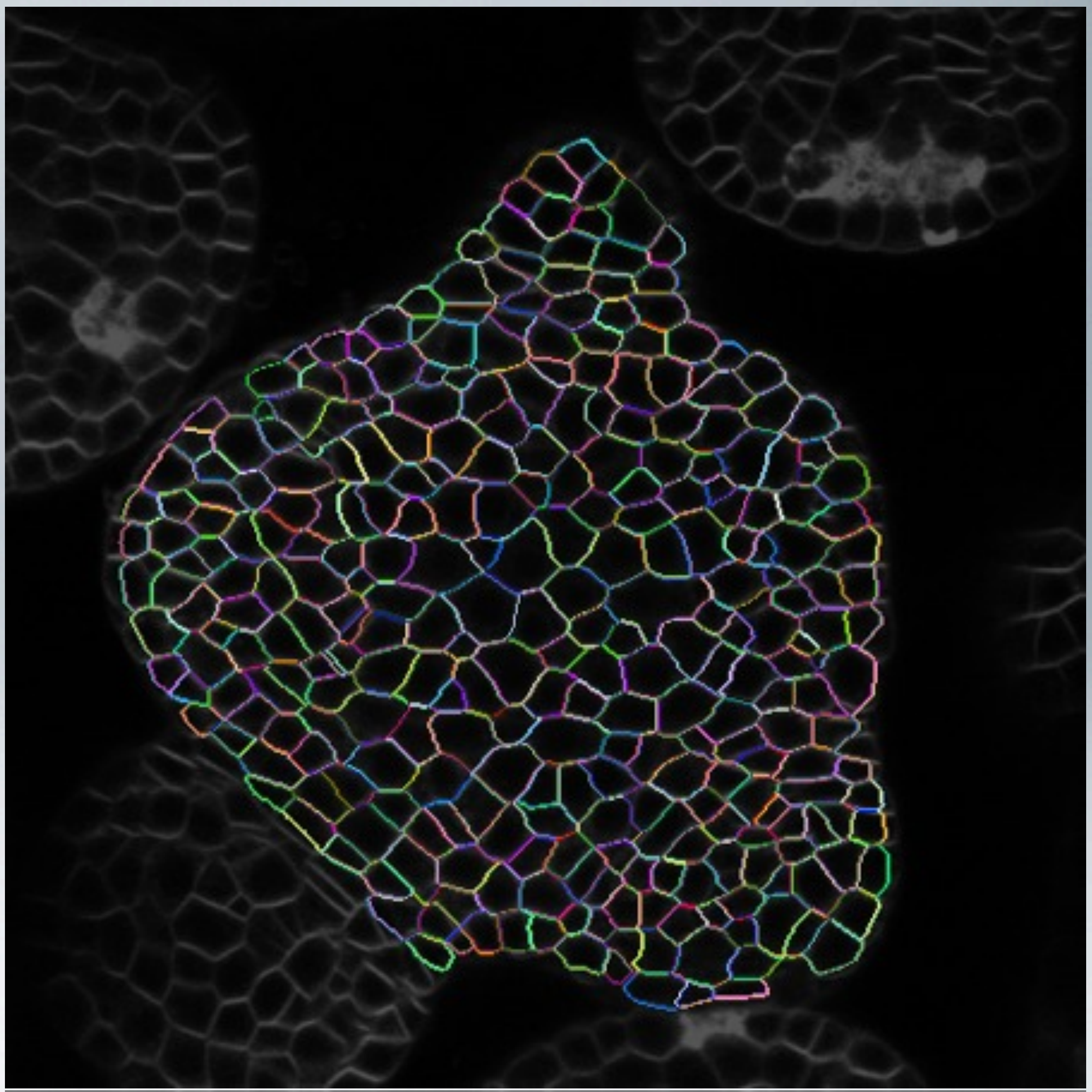
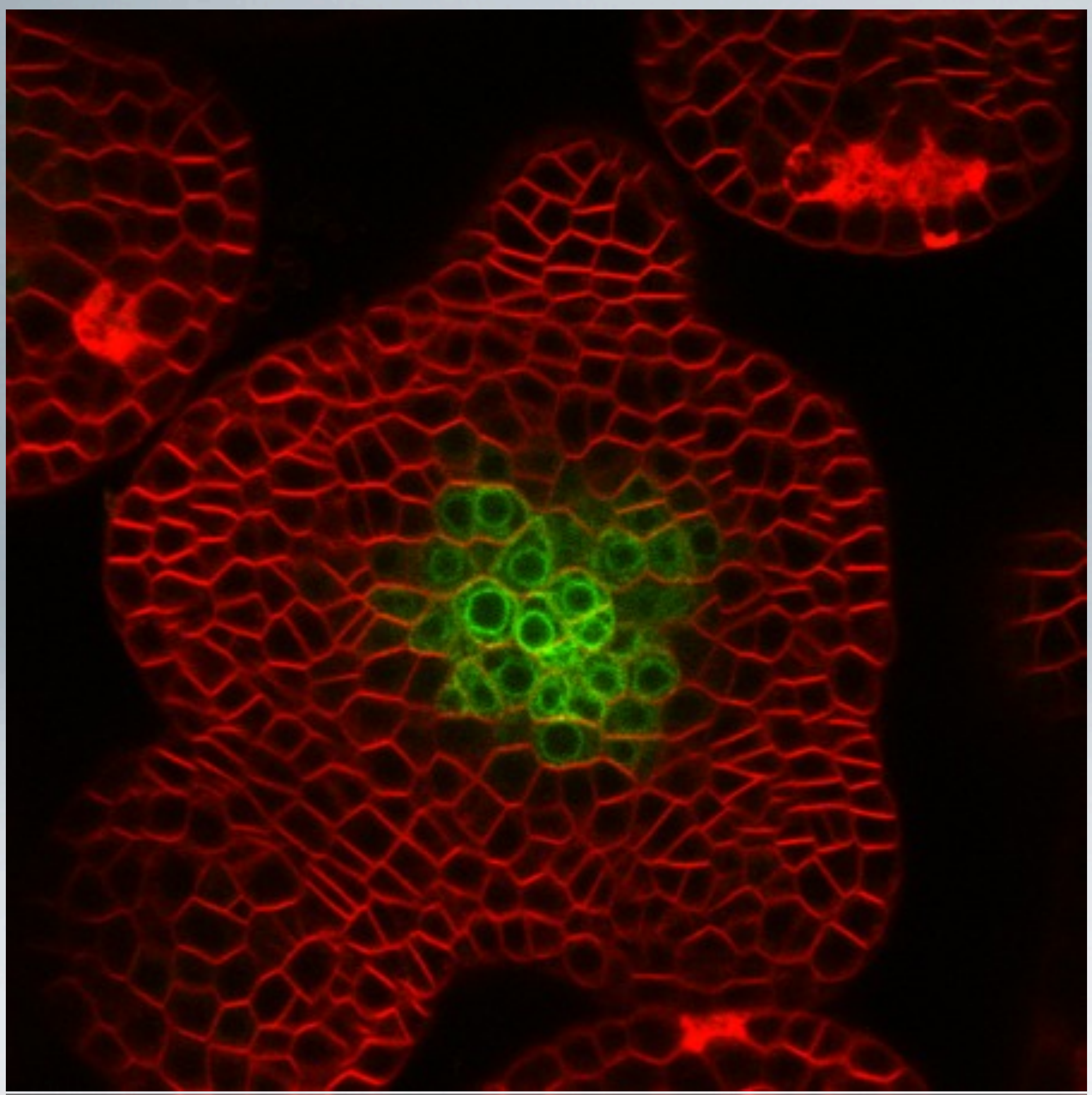
Red membrane stain



segment cells

Quantitative measures from image



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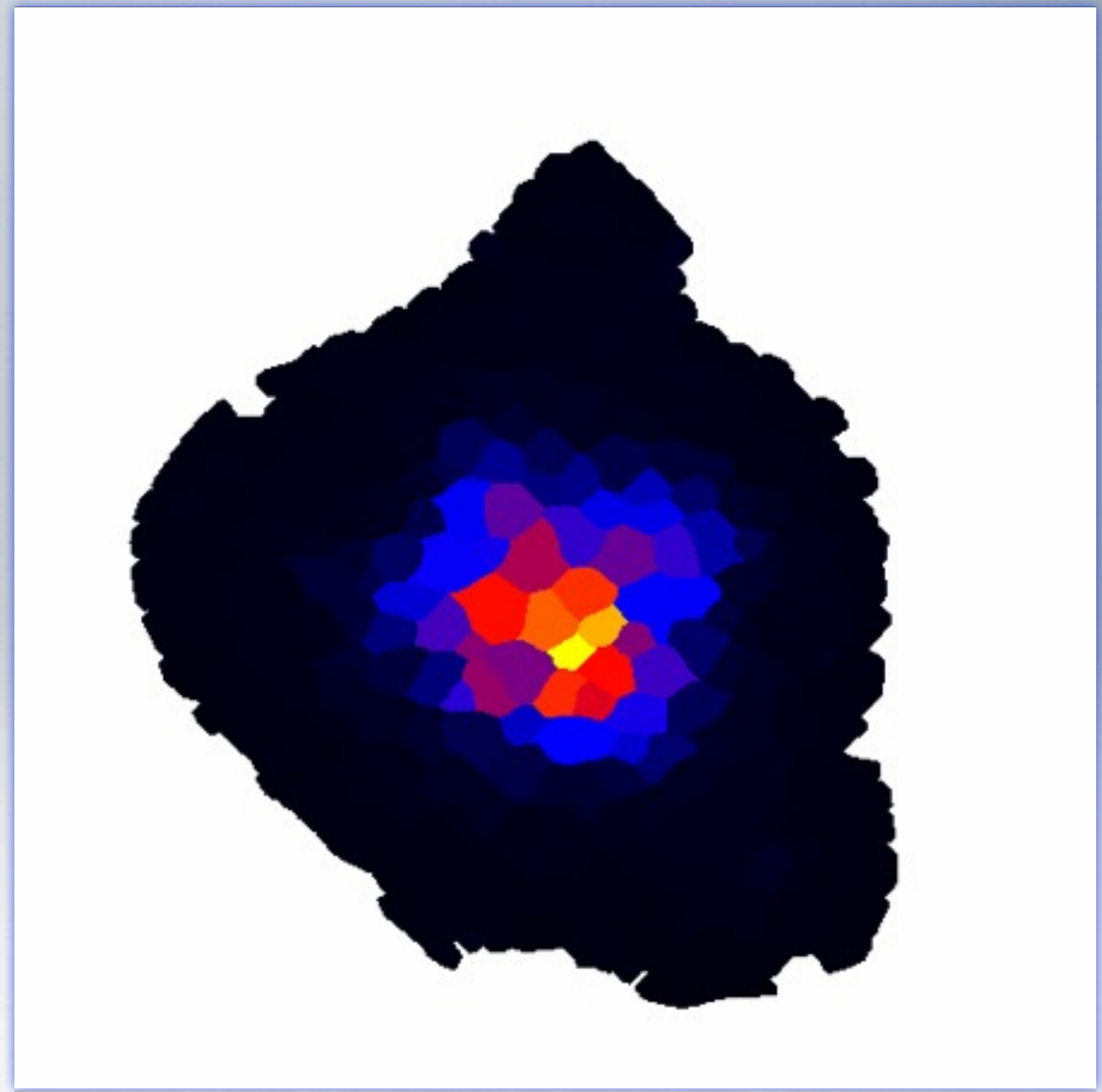
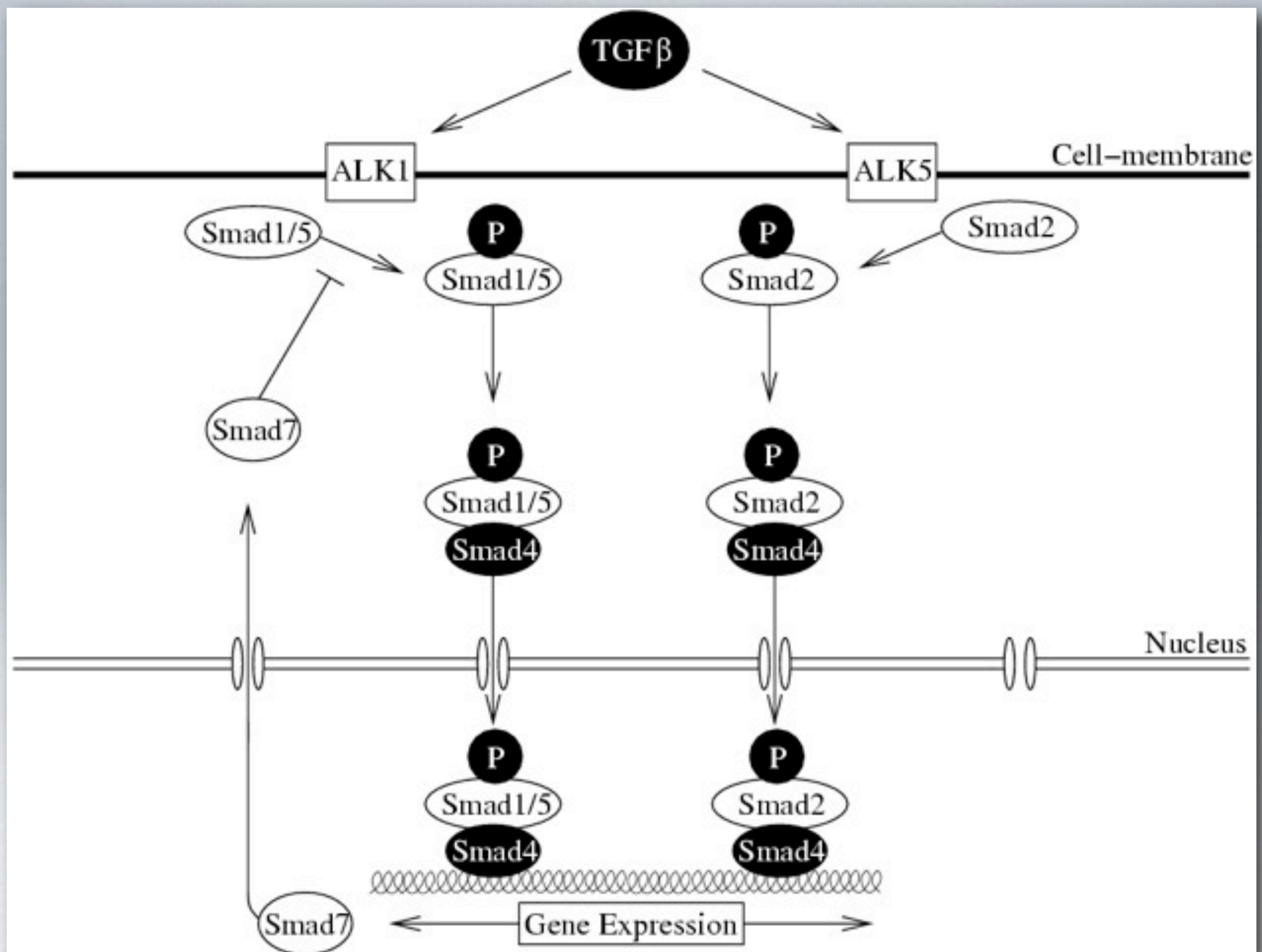


WUS "concentration"

model definitions

model definitions



model definitions

$$\emptyset \underset{p_0 p_1}{\overset{p_0}{\rightleftharpoons}} \mathrm{ALK1} \qquad (1)$$

$$\emptyset \underset{p_4 p_5}{\overset{p_4}{\rightleftharpoons}} \mathrm{Smad4} \qquad (2)$$

$$\emptyset \underset{p_8 p_9}{\overset{p_8}{\rightleftharpoons}} \mathrm{ALK5} \qquad (3)$$

$$\mathrm{TGF}\beta + \mathrm{ALK1} \underset{p_{14}}{\overset{p_{13}}{\rightleftharpoons}} \mathrm{TA1} \qquad (4)$$

$$\mathrm{PSmad1} + \mathrm{Smad4} \underset{p_{19}}{\overset{p_{18}}{\rightleftharpoons}} \mathrm{PS14} \qquad (5)$$

$$\mathrm{TGF}\beta + \mathrm{ALK5} \underset{p_{21}}{\overset{p_{20}}{\rightleftharpoons}} \mathrm{TA5} \qquad (6)$$

$$\mathrm{P_A} + \mathrm{TA1} \underset{p_{28}}{\overset{\mathrm{Smad7}\; p_{27}}{\rightleftharpoons}} \mathrm{TA1P} \qquad (7)$$

$$\mathrm{P_B} + \mathrm{TA5} \underset{p_{32}}{\overset{\mathrm{Smad7}\; p_{31}}{\rightleftharpoons}} \mathrm{TA2P} \qquad (8)$$

$$\emptyset \underset{p_2 p_3}{\overset{p_2}{\rightleftharpoons}} \mathrm{Smad1} \qquad (9)$$

$$\emptyset \underset{p_6 p_7}{\overset{p_6}{\rightleftharpoons}} \mathrm{Smad2} \qquad (10)$$

$$\emptyset \underset{p_{10}}{\overset{PS14N\;(p_{11}, p_{12})}{\rightleftharpoons}} \mathrm{Smad7} \qquad (11)$$

$$\mathrm{Smad1} \underset{p_{17}}{\overset{TA1\;(p_{15}, p_{16})}{\rightleftharpoons}} \mathrm{PSmad1} \qquad (12)$$

$$\mathrm{Smad2} \underset{p_{24}}{\overset{TA5\;(p_{22}, p_{23})}{\rightleftharpoons}} \mathrm{PSmad2} \qquad (13)$$

$$\mathrm{PSmad2} + \mathrm{Smad4} \underset{p_{26}}{\overset{p_{25}}{\rightleftharpoons}} \mathrm{PS24} \qquad (14)$$

$$\mathrm{PS14} \underset{k_{30}}{\overset{p_{29}}{\rightleftharpoons}} \mathrm{PS14N} \qquad (15)$$

model definitions

mass action dynamics

$$\frac{dA_1}{dt} = p_0(1 - p_1 A_1) - p_{13} T_\beta A_1 + p_{14} T_1$$

$$\frac{dS_1}{dt} = p_2(1 - p_3 S_1) - \frac{p_{15} T_1 S_1}{p_{16} + S_1} + p_{17} P_1$$

$$\frac{dS_4}{dt} = p_4(1 - p_5 S_4) - p_{18} P_1 S_4 + p_{19} P_{14} - p_{25} P_2 S_4 + p_{26} P_{24}$$

$$\frac{dS_2}{dt} = p_6(1 - p_7 S_2) - \frac{p_{22} T_1 S_2}{p_{23} + S_2} + p_{24} P_2$$

$$\frac{dA_5}{dt} = p_8(1 - p_9 A_5) - p_{20} T_\beta A_5 + p_{21} T_5$$

$$\frac{dS_7}{dt} = \frac{p_{11} P_{14}}{p_{12} + P_{14}} - p_{10} S_7$$

$$\frac{dP_1}{dt} = \frac{p_{15} T_1 S_1}{p_{16} + S_1} - p_{17} P_1 - p_{18} P_1 S_4 + p_{19} P_{14}$$

$$\frac{dP_{14}}{dt} = p_{18} P_1 S_4 - p_{19} P_{14} - p_{29} P_{14} + p_{30} P_{14N}$$

$$\frac{dP_{14N}}{dt} = p_{29} P_{14} - p_{30} P_{14N}$$

$$\frac{dP_2}{dt} = \frac{p_{22} T_1 S_2}{p_{23} + S_2} - p_{24} P_2 - p_{25} P_2 S_4 + k_{17} P_{26}$$

$$\frac{dP_{24}}{dt} = p_{25} P_2 S_4 - p_{26} P_{24}$$

$$\frac{dT_1}{dt} = p_{13} T_\beta A_1 - p_{14} T_1 - p_{27} S_7 P_{P1} T_1 + p_{28} T_{1P}$$

$$\frac{dT_5}{dt} = p_{20} T_\beta A_5 - p_{21} T_5 - p_{31} S_7 P_{P2} T_5 + p_{32} T_{5P}$$

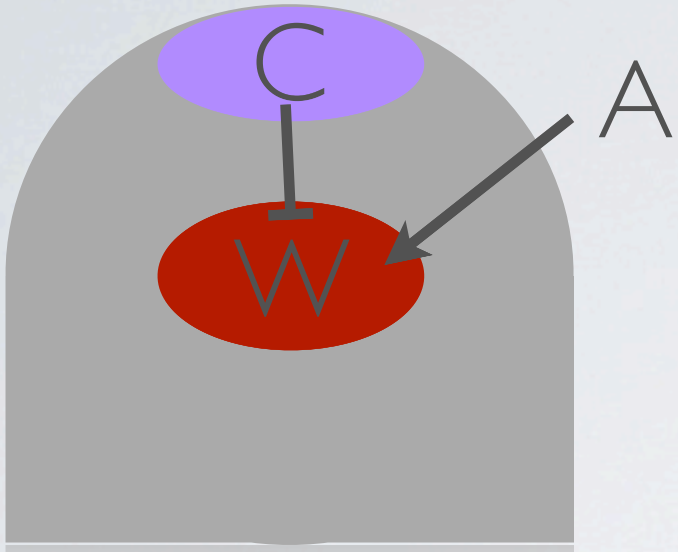
$$\frac{dP_A}{dt} = -p_{27} S_7 P_A T_1 + p_{28} T_{1P}$$

$$\frac{dP_B}{dt} = -p_{31} S_7 P_B T_1 + p_{32} T_{1P}$$

$$\frac{dT_{1P}}{dt} = p_{27} S_7 P_A T_1 - p_{28} T_{1P}$$

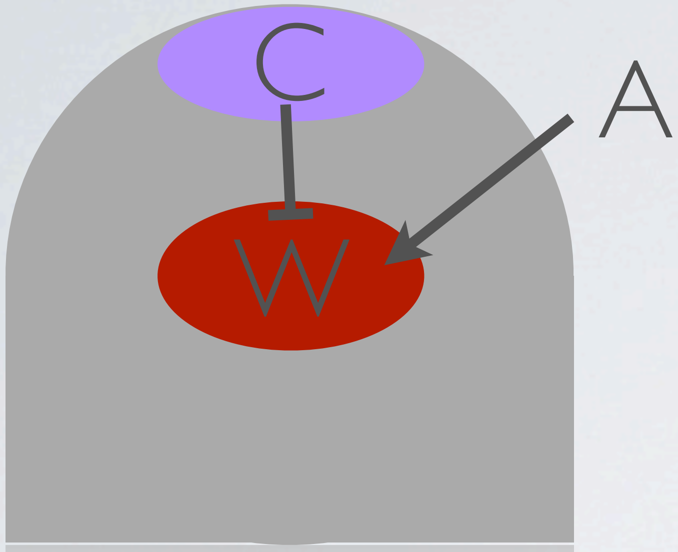
$$\frac{dT_{5P}}{dt} = p_{31} S_7 P_B T_5 - p_{32} T_{5P}$$

model definitions



$$\frac{d[W]}{dt} = \frac{V_{max} K_C^n [A]^n}{(K_C^n + [C]^n)(K_A^n + [A]^n)} - k[W]$$

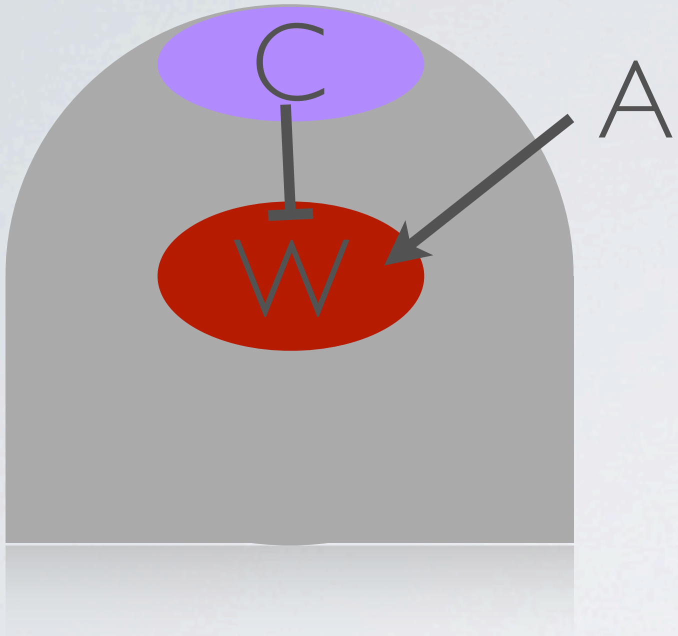
model definitions



transcription　　　　　　degradation

$$\frac{d[W]}{dt} = \frac{V_{max} K_C^n [A]^n}{(K_C^n + [C]^n)(K_A^n + [A]^n)} - k[W]$$

model definitions

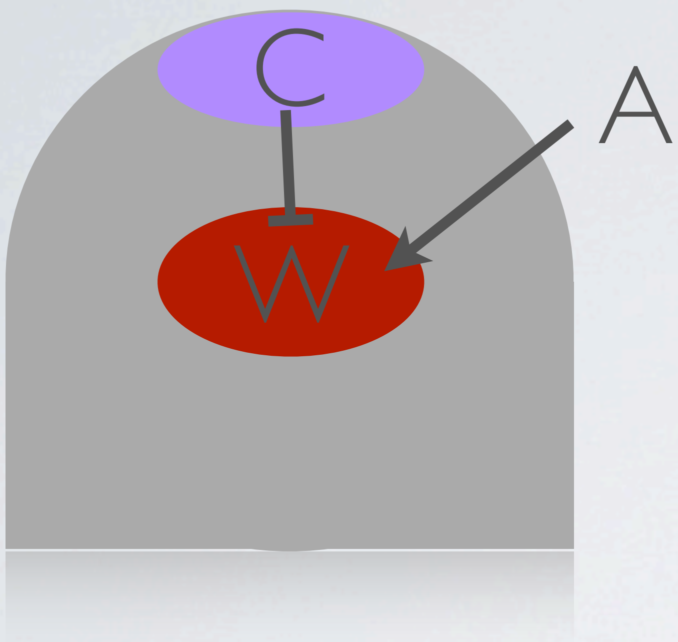


transcription degradation

$$\frac{d[W]}{dt} = \frac{V_{max} K_C^n [A]^n}{(K_C^n + [C]^n)(K_A^n + [A]^n)} - k[W]$$

$$\frac{d[Ws]}{dt} = k_1[W] - k_2[Ws] + D\nabla^2[Ws]$$

model definitions



transcription

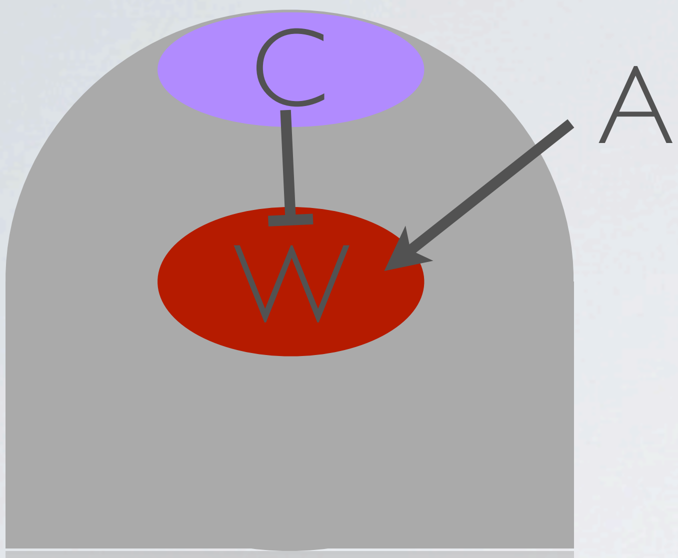
degradation

$$\frac{d[W]}{dt} = \frac{V_{max} K_C^n [A]^n}{(K_C^n + [C]^n)(K_A^n + [A]^n)} - k[W]$$

$$\frac{d[Ws]}{dt} = k_1[W] - k_2[Ws] + D\nabla^2[Ws]$$

diffusion

model definitions



transcription

degradation

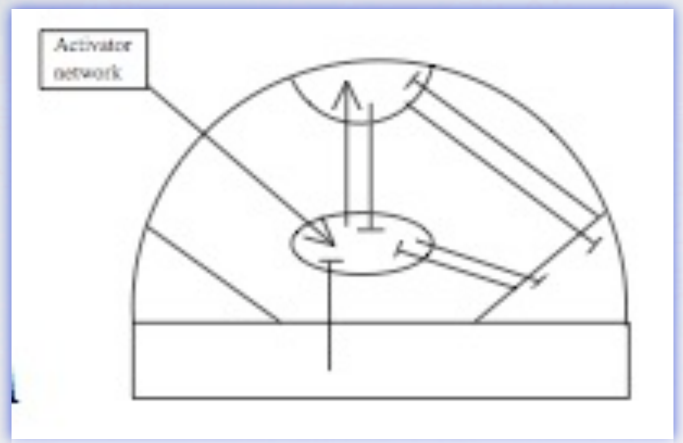
$$\frac{d[W]}{dt} = \frac{V_{max} K_C^n [A]^n}{(K_C^n + [C]^n)(K_A^n + [A]^n)} - k[W]$$

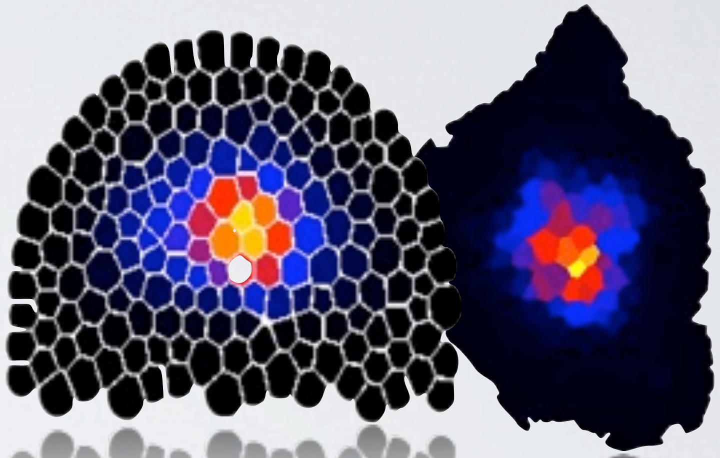
$$\frac{d[Ws]}{dt} = k_1[W] - k_2[Ws] + D\nabla^2[Ws]$$

protein?

diffusion

computational approach

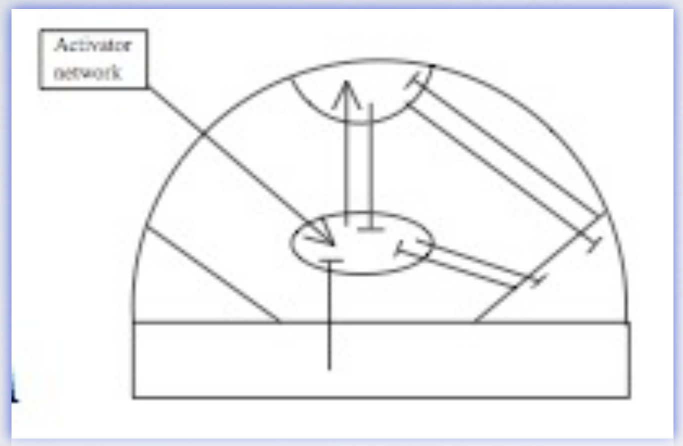


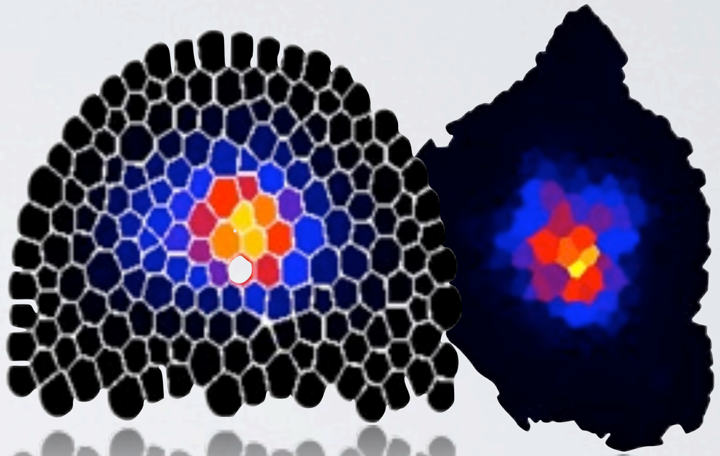


Model(s)

Data

computational approach



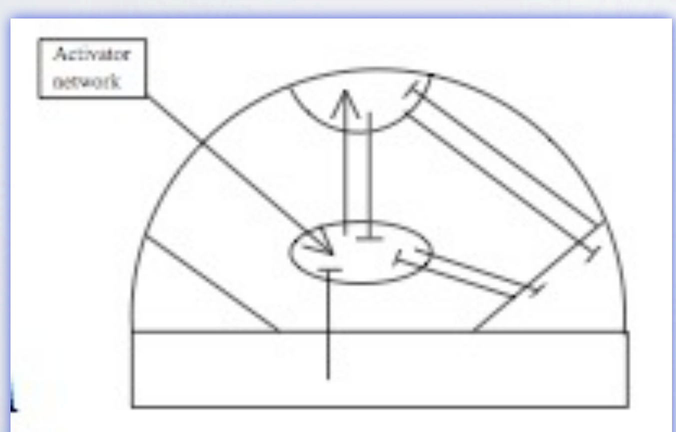


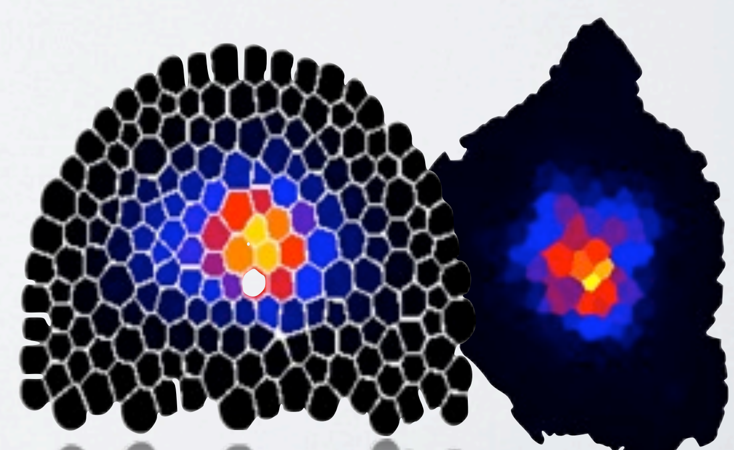
Model(s) ⟷ Data

predictive models VS parameter fitting

computational approach

Model(s) ⟷ Data

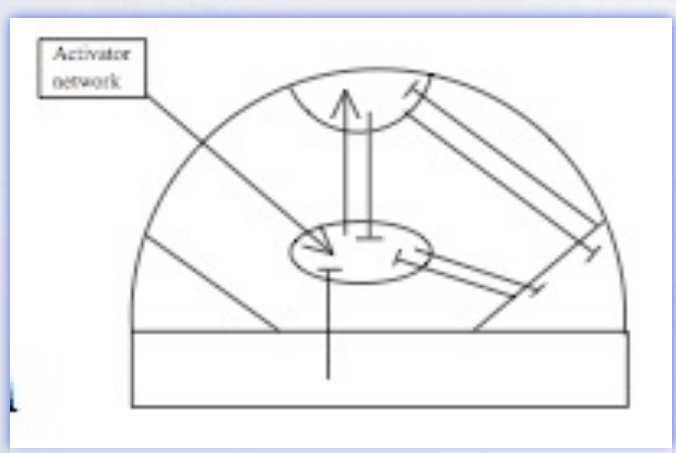


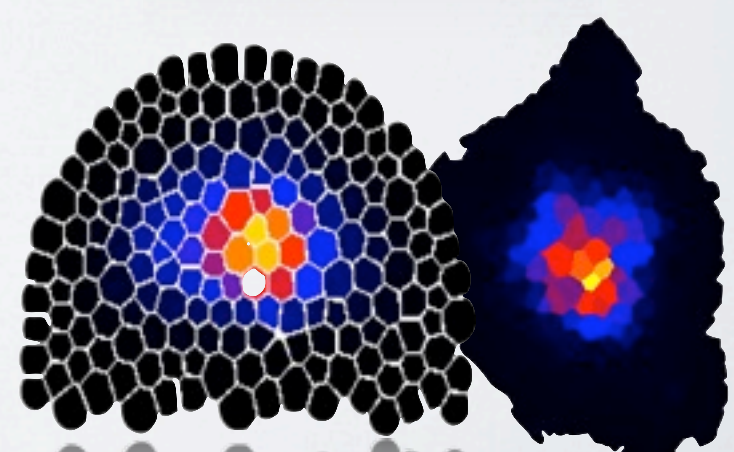


computational approach

Model(s)

Data



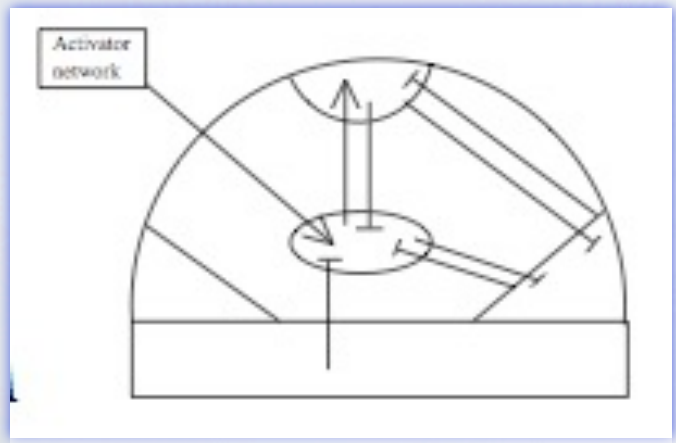


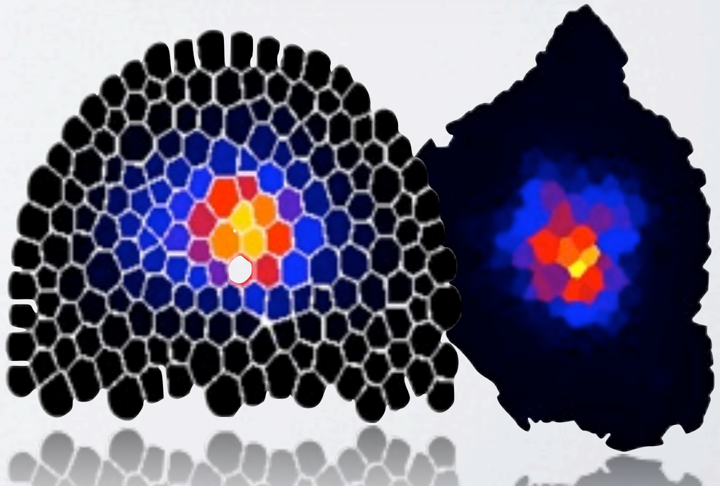
computational approach

optimize / train

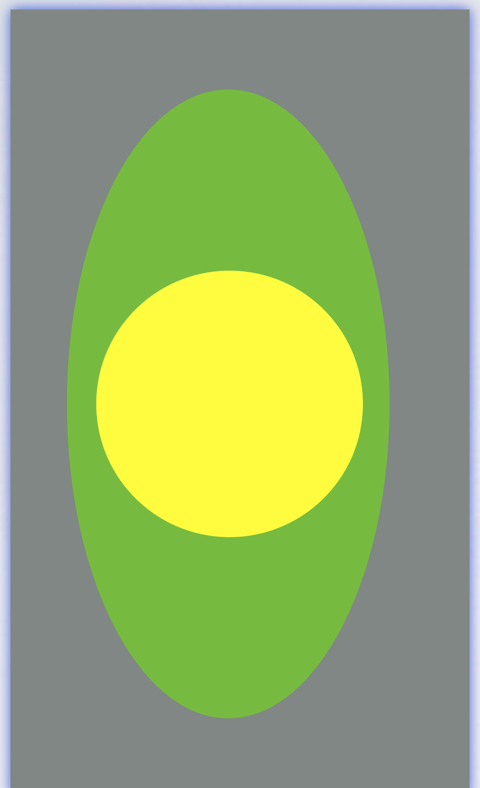
Model(s)

Data



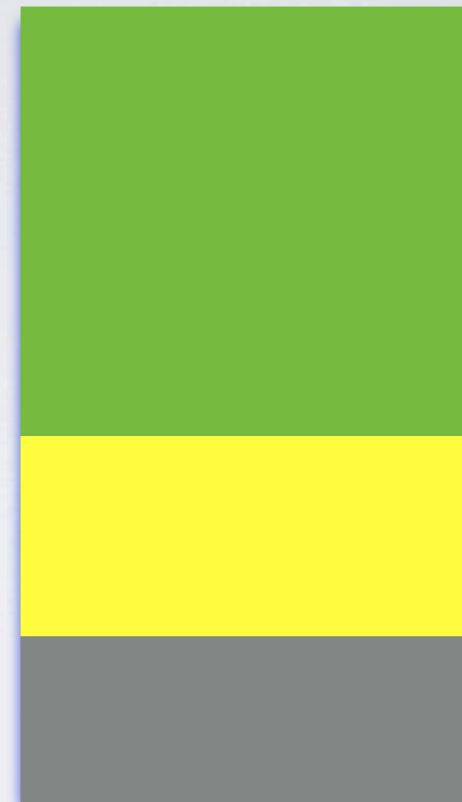


computational approach



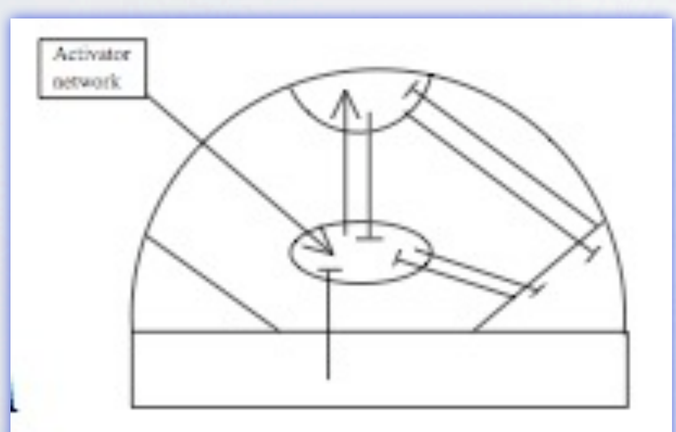
optimize / train

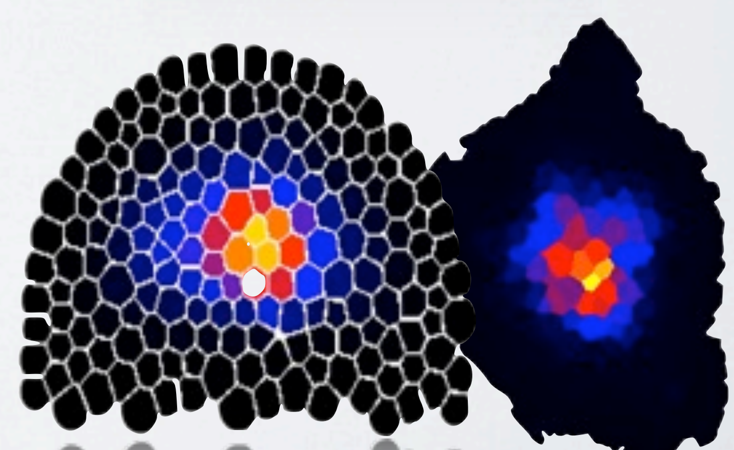
filter / test



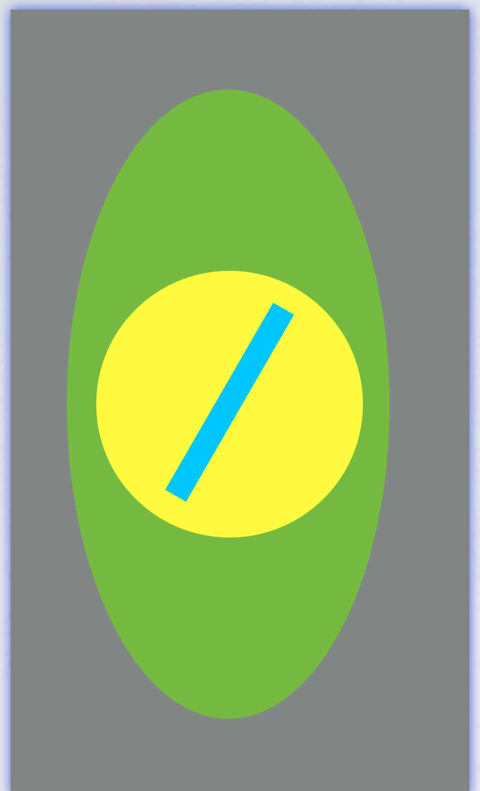
Model(s)

Data





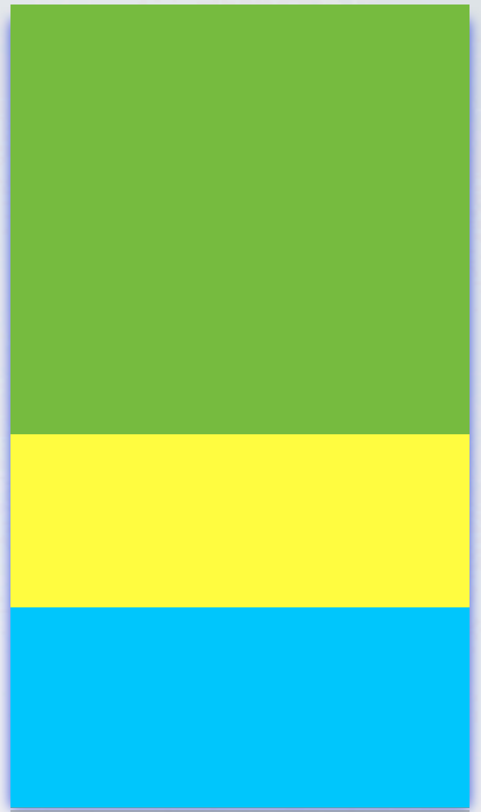
computational approach



optimize / train

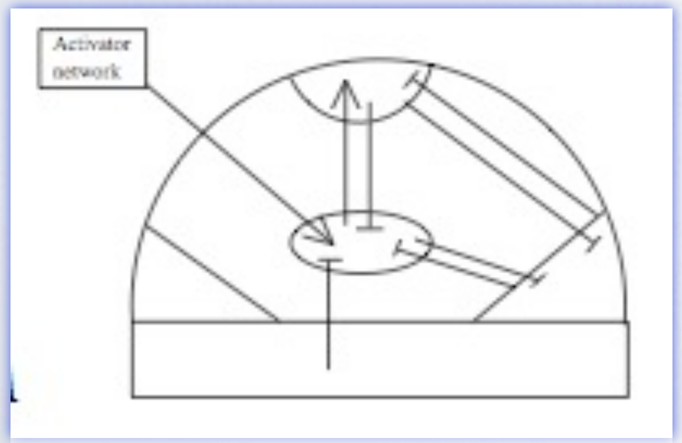
filter / test

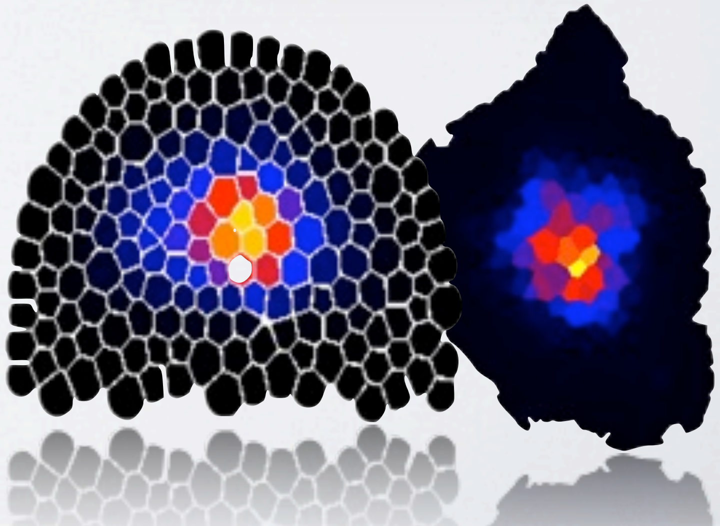
analyze / validate



Model(s)

Data





computer modeling

computer modeling

...computer manipulation of a mathematical model...

(Leopold and Hall 1966)

computer modeling

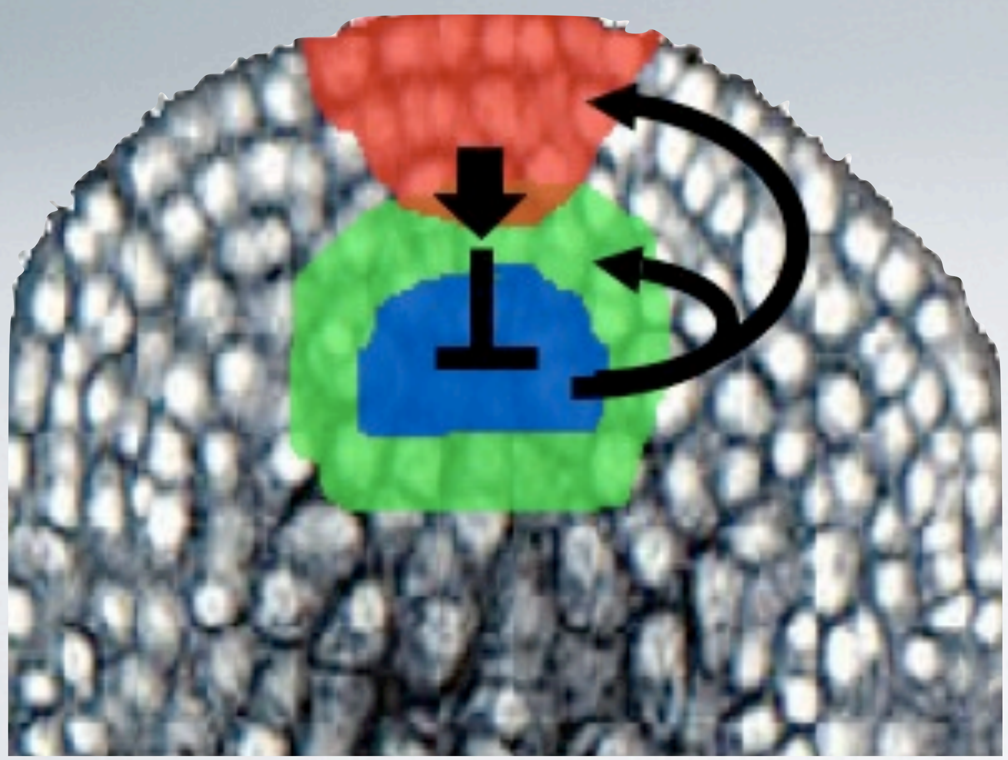
...com

odel...

stem cell regulation

stem cell regulation

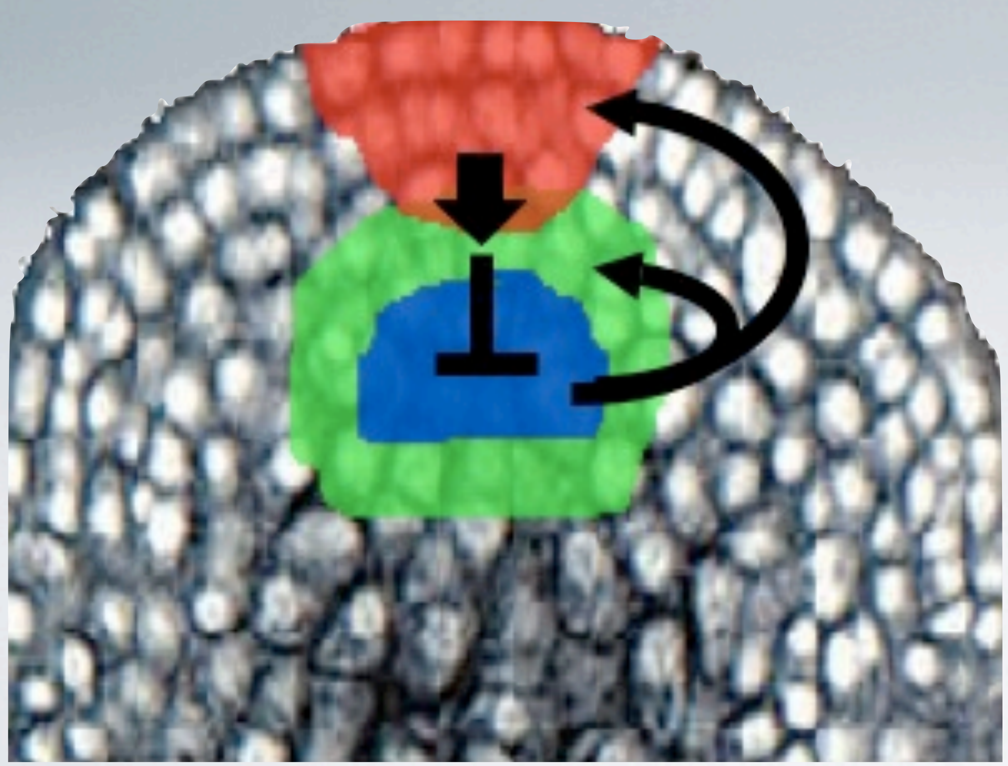
- CLV3 marks stem cells and WUS ‘defines’ an organizing center



- CLV3 extracellular peptide
- CLV1 receptor
- WUS transcription factor

stem cell regulation

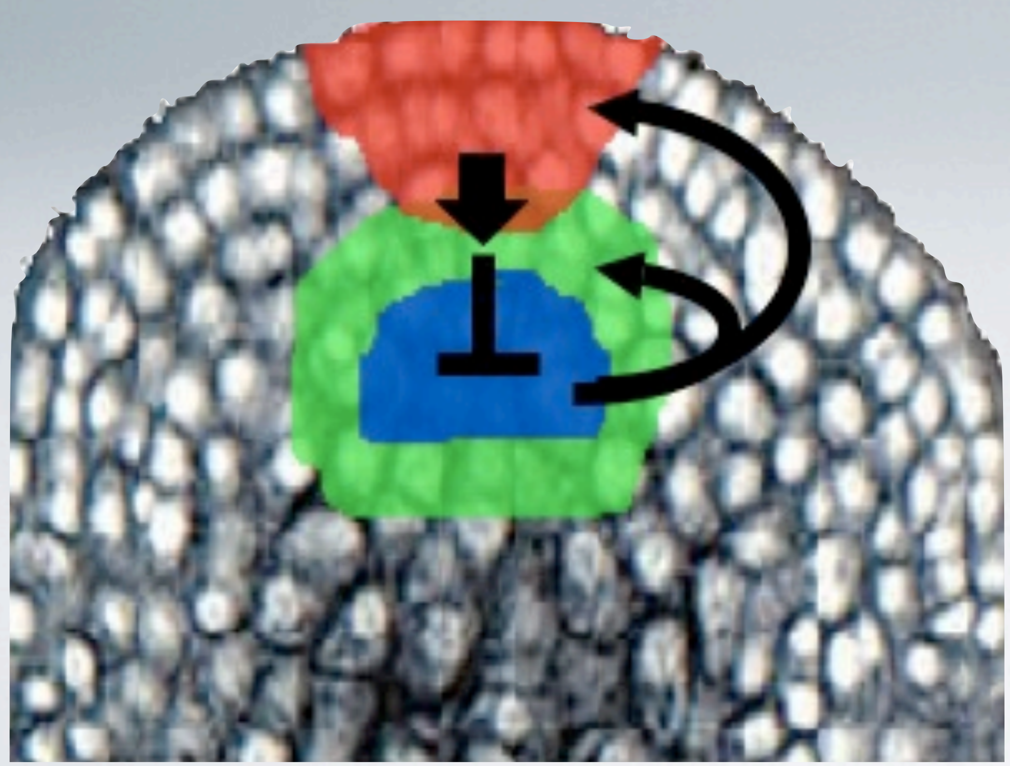
- CLV3 marks stem cells and WUS ‘defines’ an organizing center
- WUS activates CLV3 (stem cells)



- CLV3 extracellular peptide
- CLV1 receptor
- WUS transcription factor

stem cell regulation

- CLV3 marks stem cells and WUS ‘defines’ an organizing center
- WUS activates CLV3 (stem cells)
- CLV3/CLV1 network repress WUS



- CLV3 extracellular peptide
- CLV1 receptor
- WUS transcription factor

What activates WUS?

What activates WUS?

How is the CLV3 to WUS signal mediated?

What activates WUS?

How is the WUS to CLV3 signal mediated?

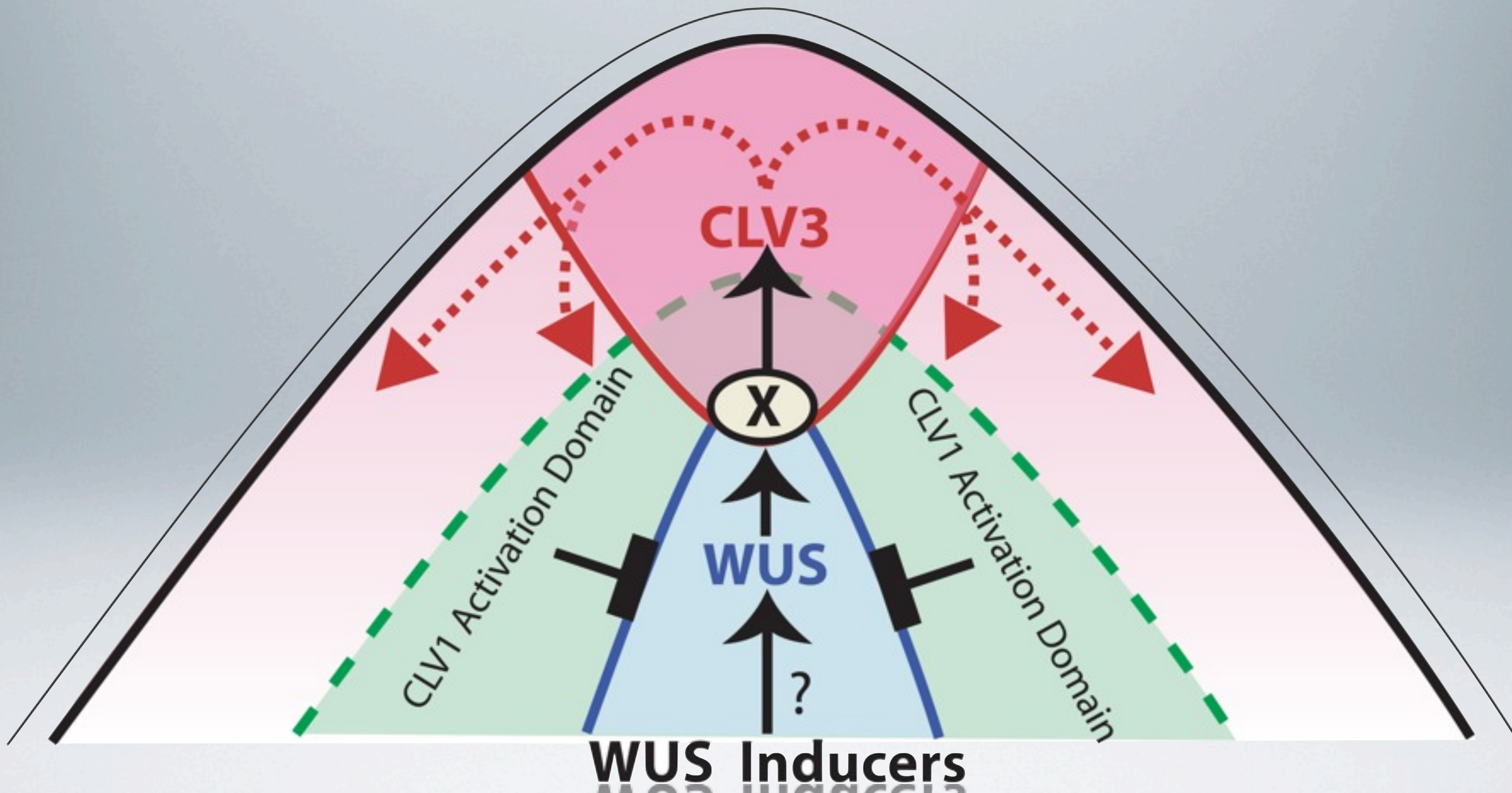
How is the CLV3 to WUS signal mediated?

What activates WUS?

How is the WUS to CLV3 signal mediated?

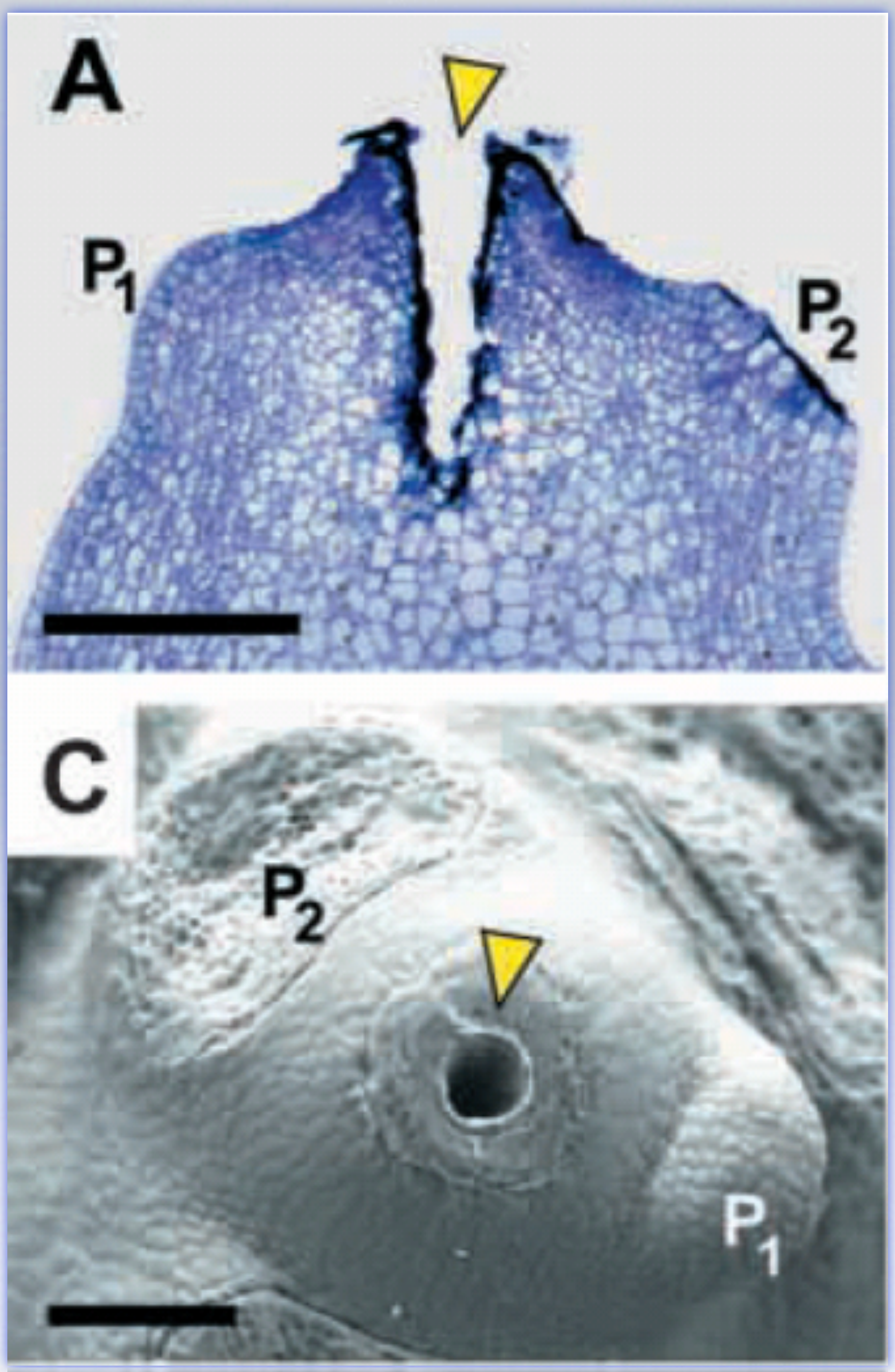
How is the CLV3 to WUS signal mediated?

What activates WUS?



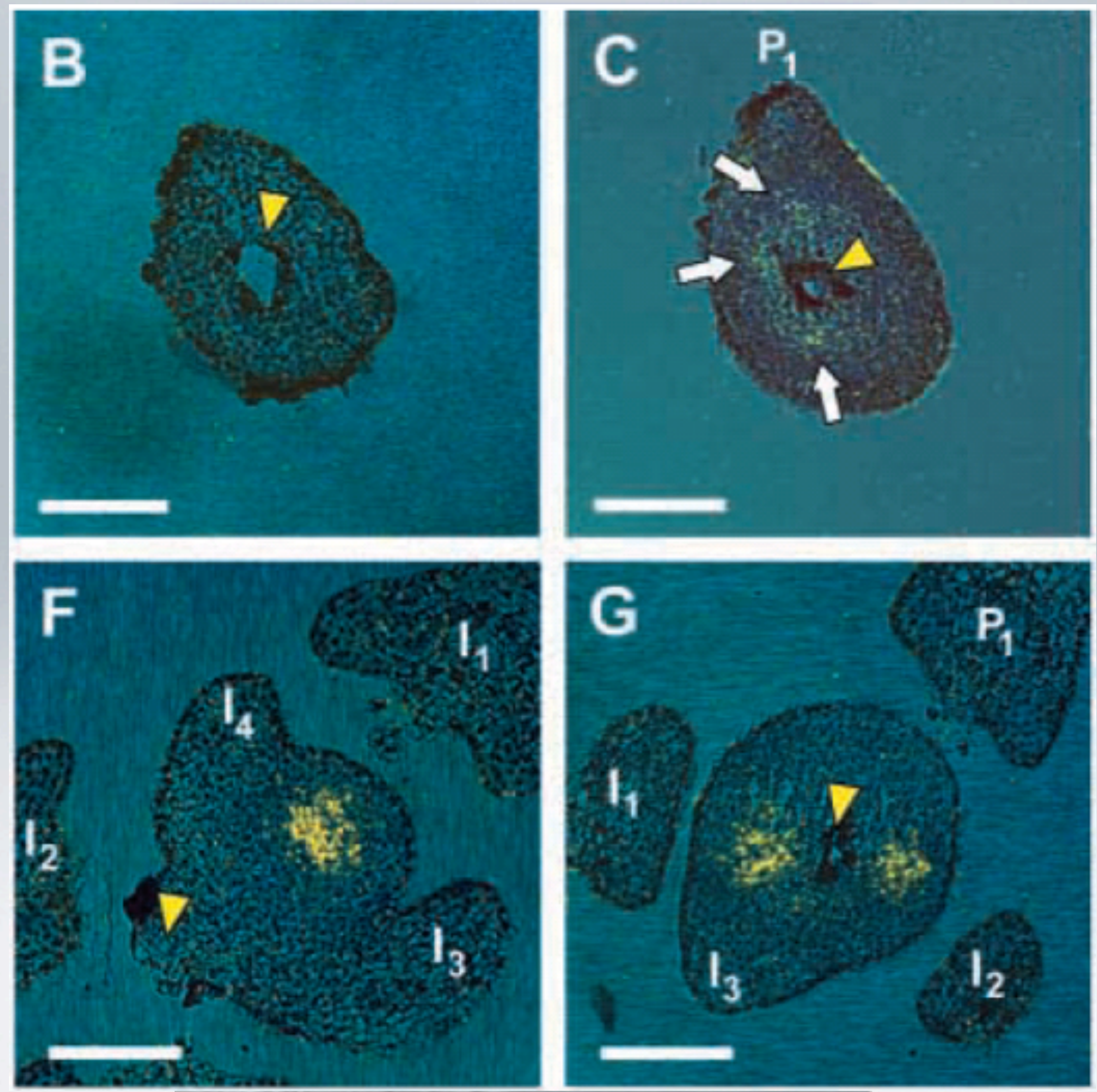
Jönsson et al (2005)

Laser ablation experiment



Reinhardt et al 2003

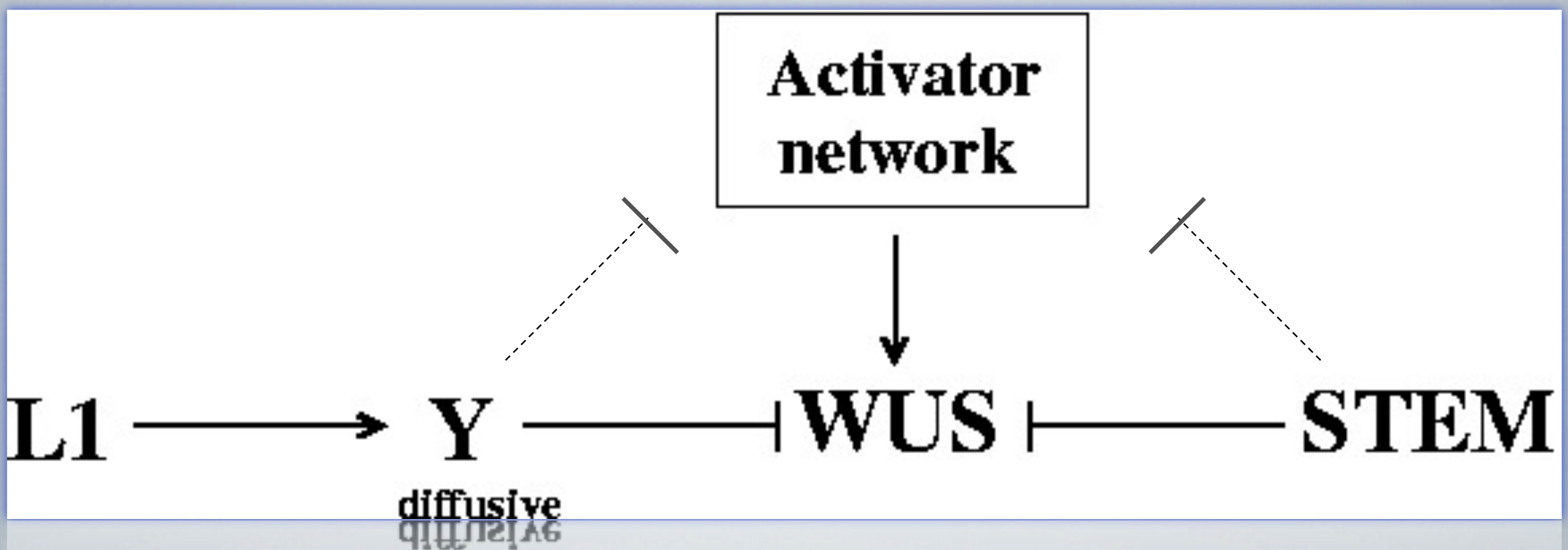
Laser ablation experiment



WUS expression

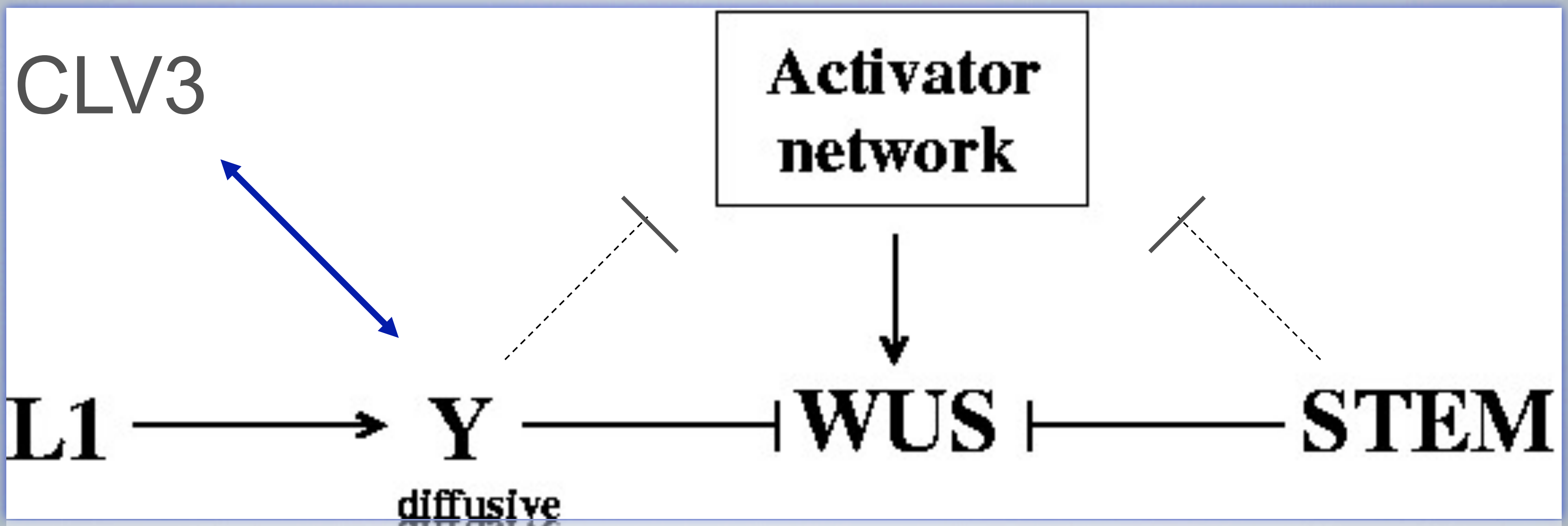
Reinhardt et al 2003

WUS network



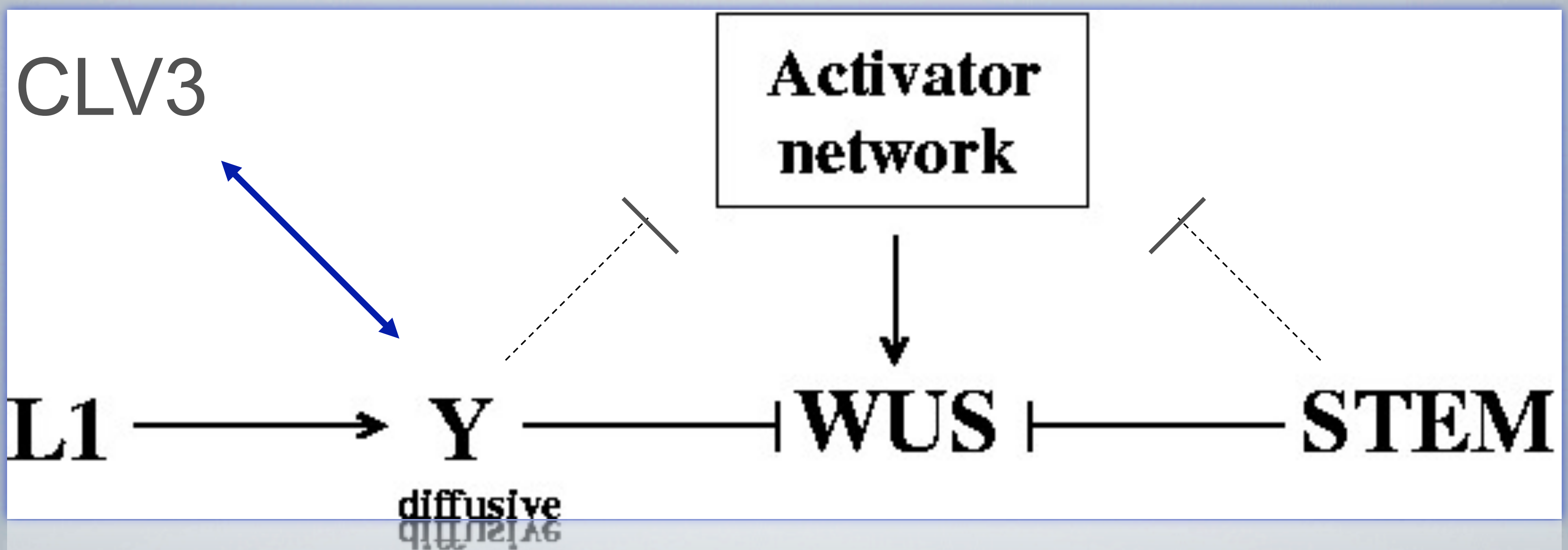
Jönsson et al (2005)

WUS network

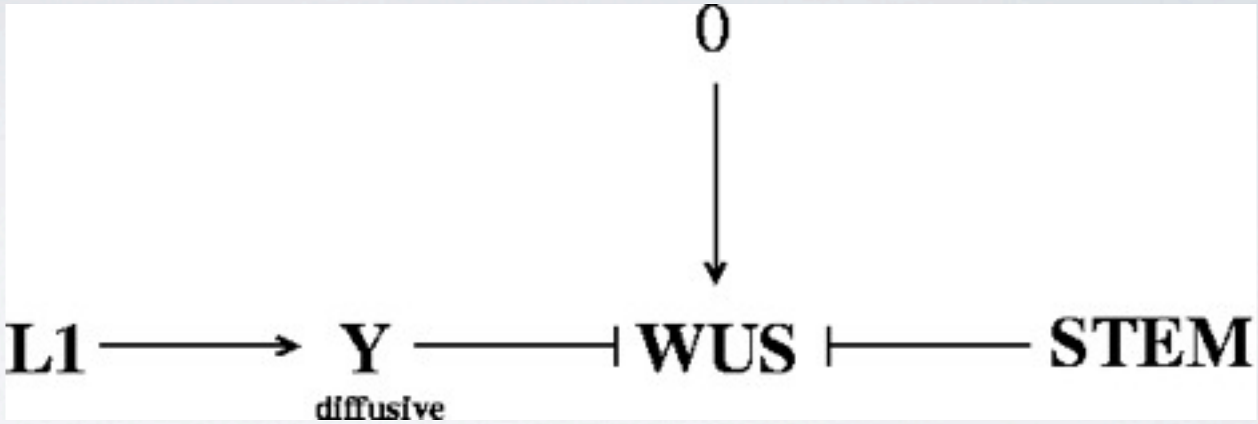


Jönsson et al (2005)

WUS network

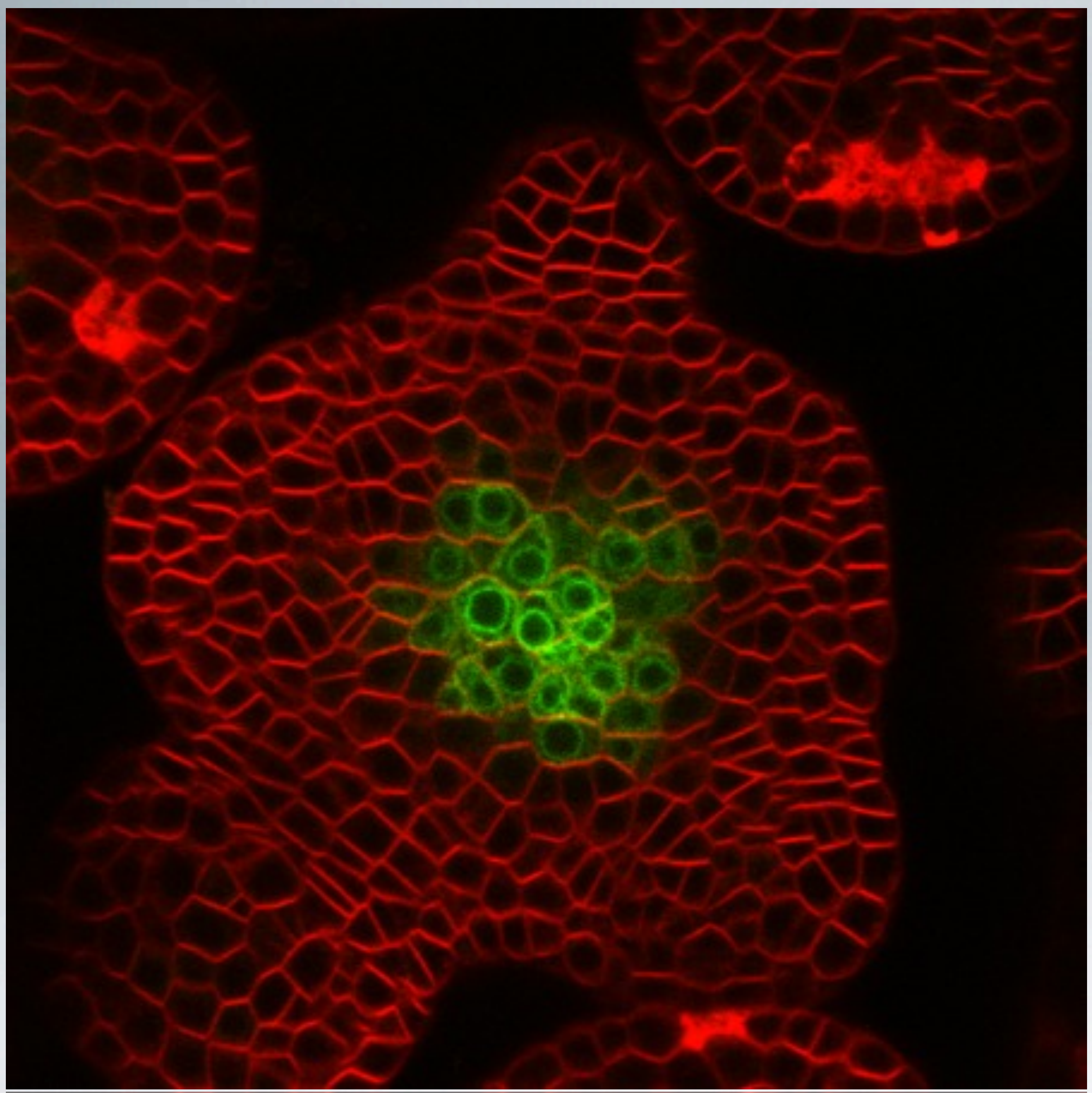


Comparison network



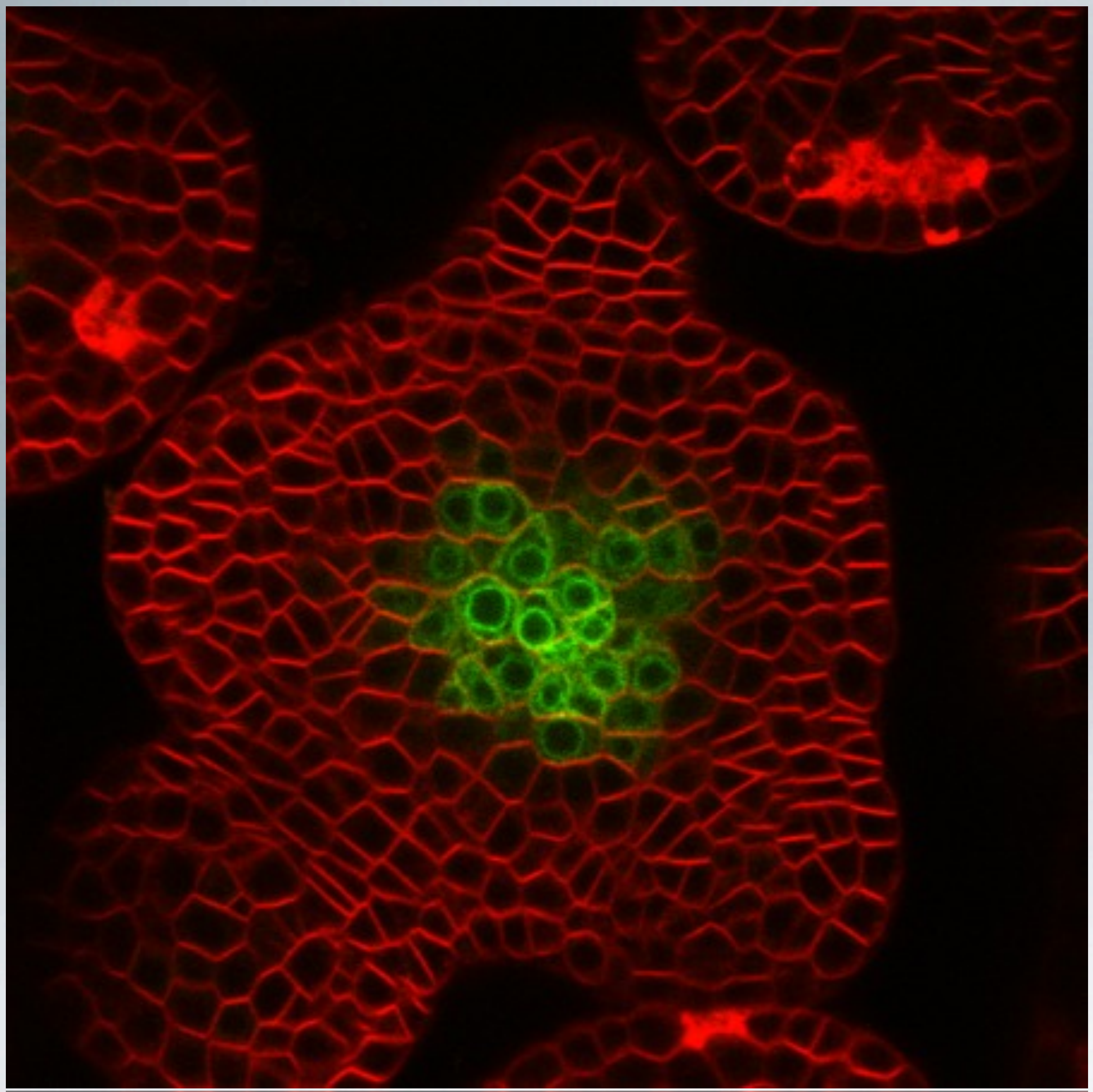
Jönsson et al (2005)

Quantitative measures from image



Green WUS::GFP
Red membrane stain

Quantitative measures from image



Green WUS::GFP
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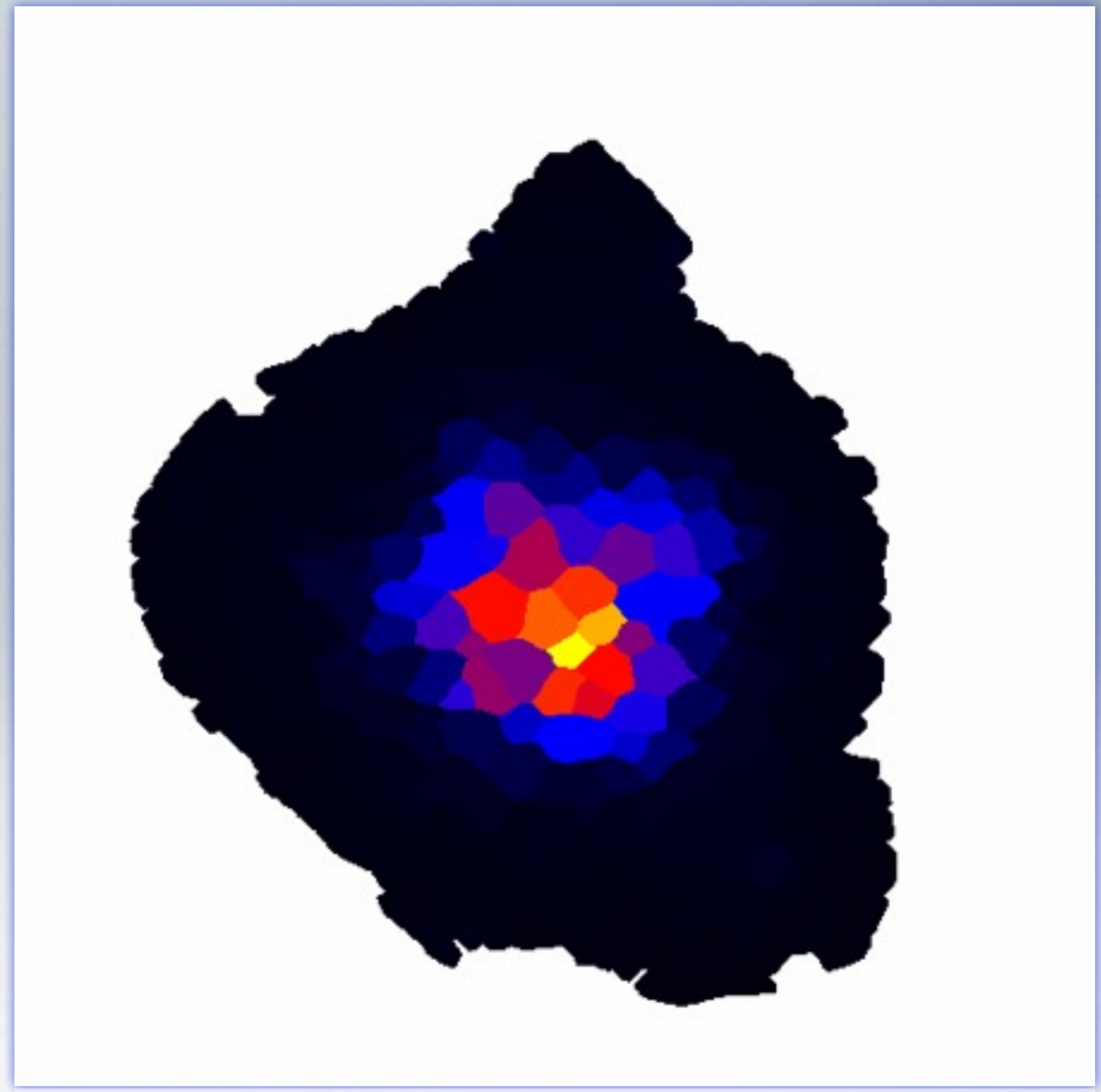
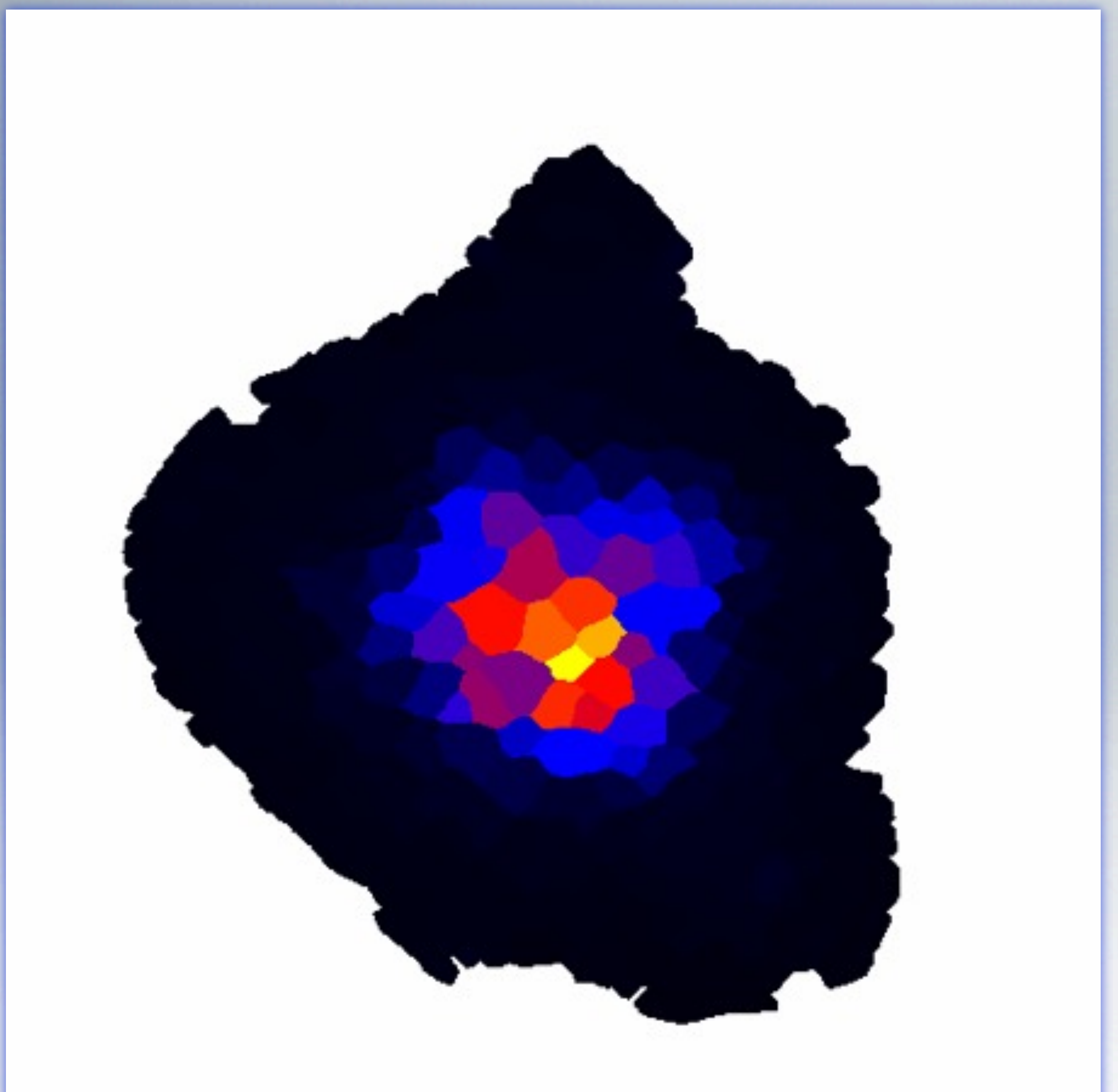


WUS “concentration”

WUS network simulation

Cell volumes, wall areas, and neighbors from template

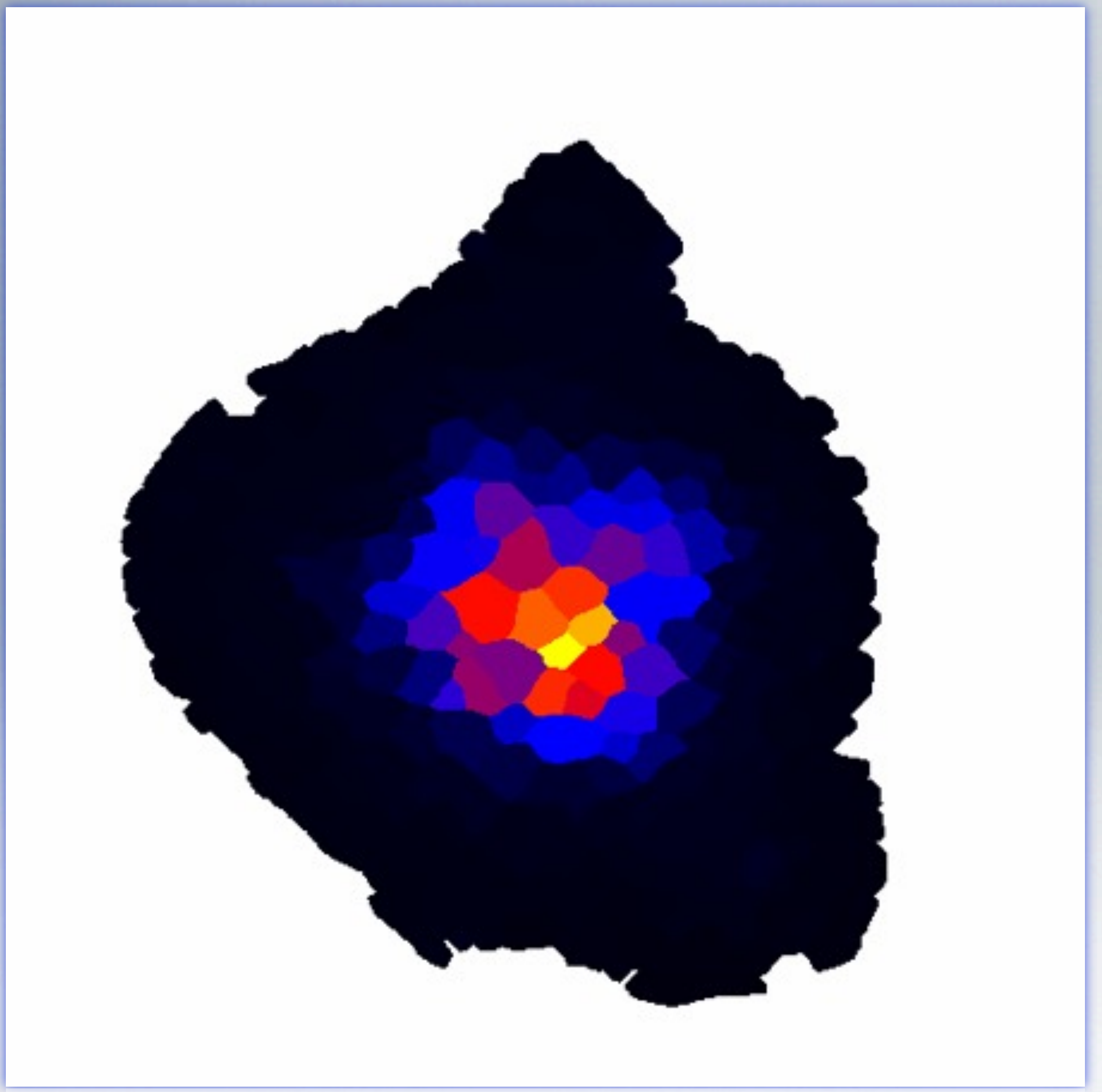


Template

Simulation

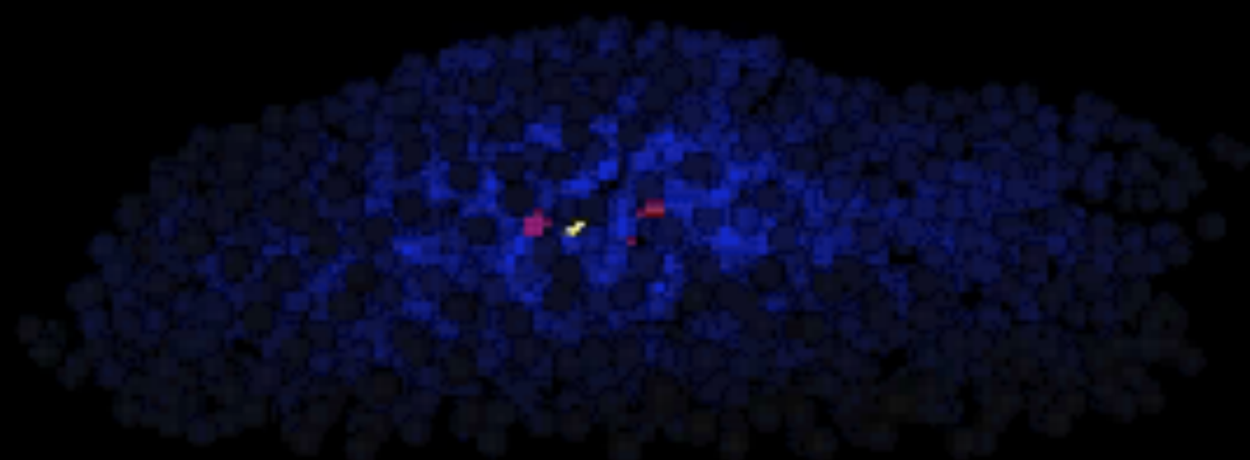
WUS network simulation

Cell volumes, wall areas, and neighbors from template

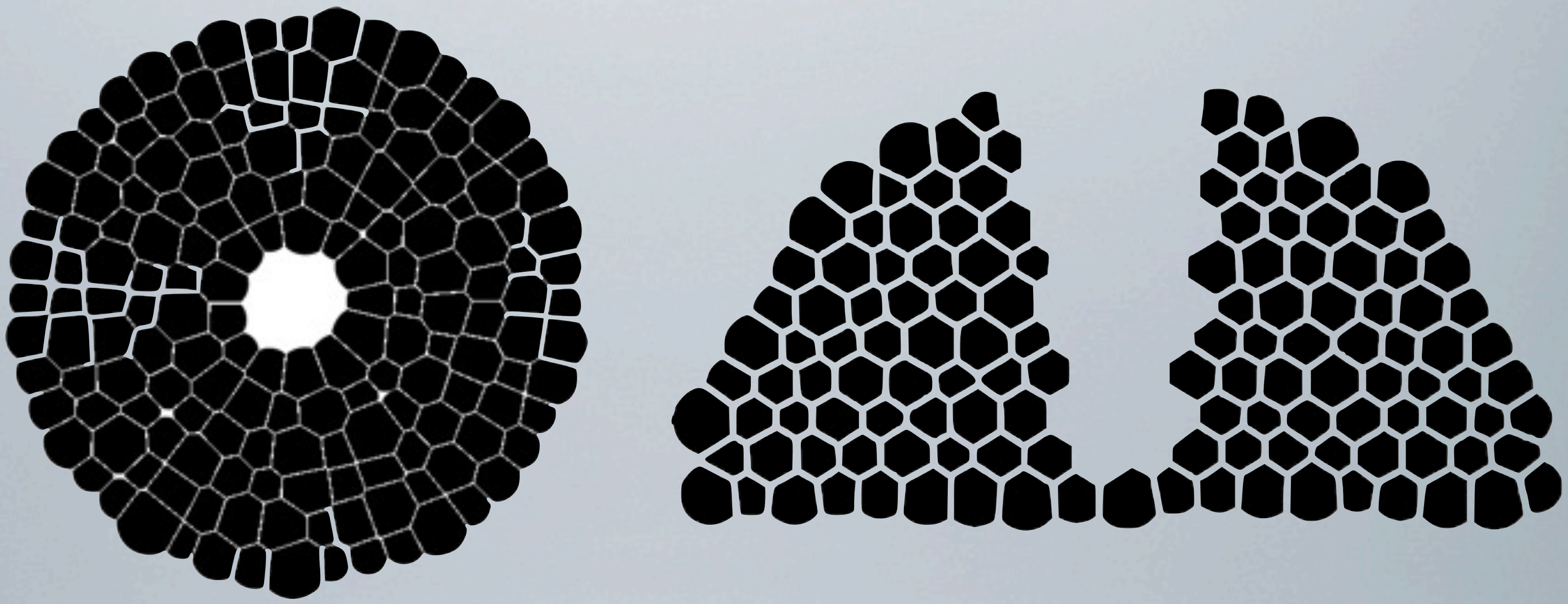


Template

Simulation

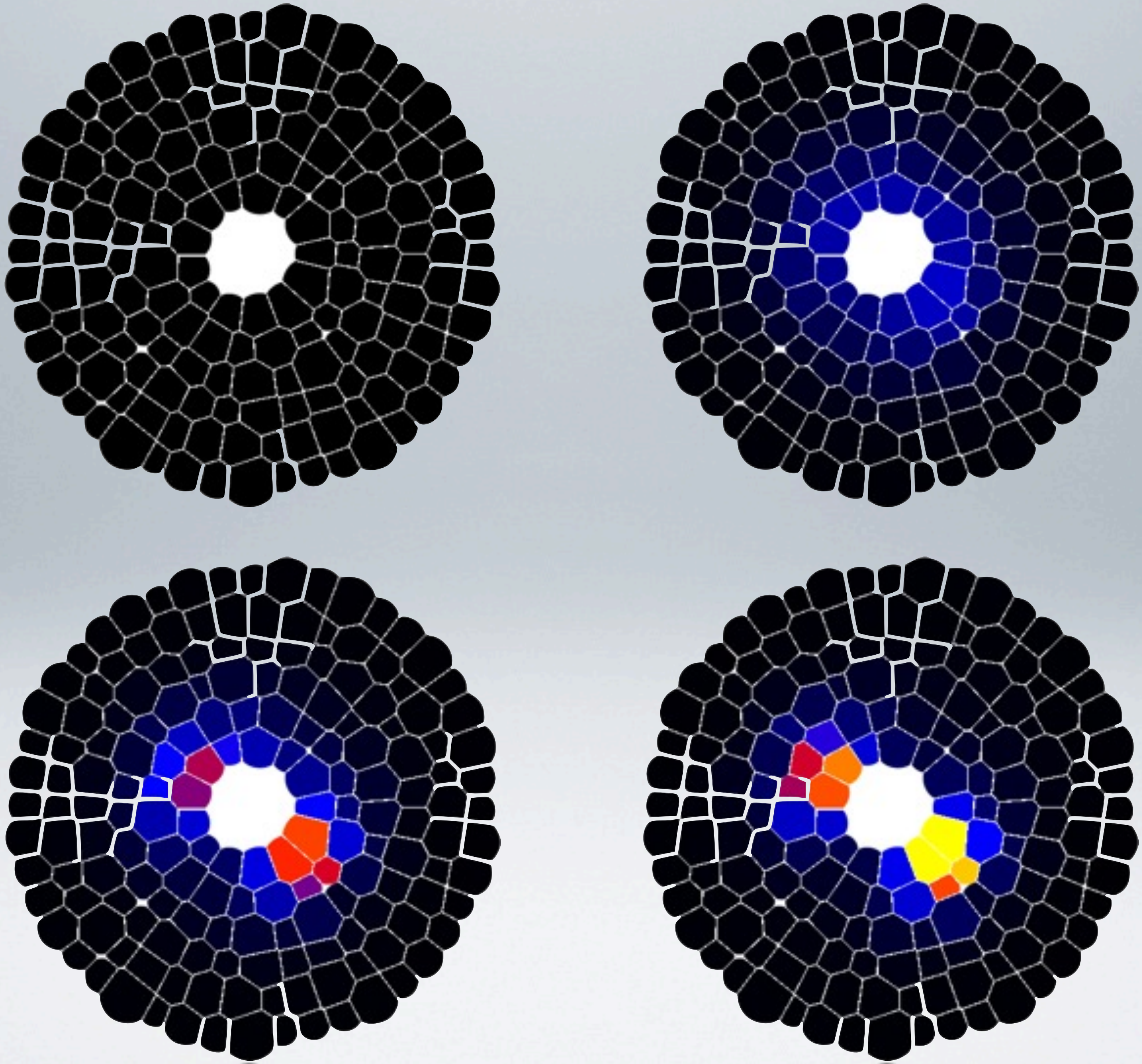


Laser ablation simulation



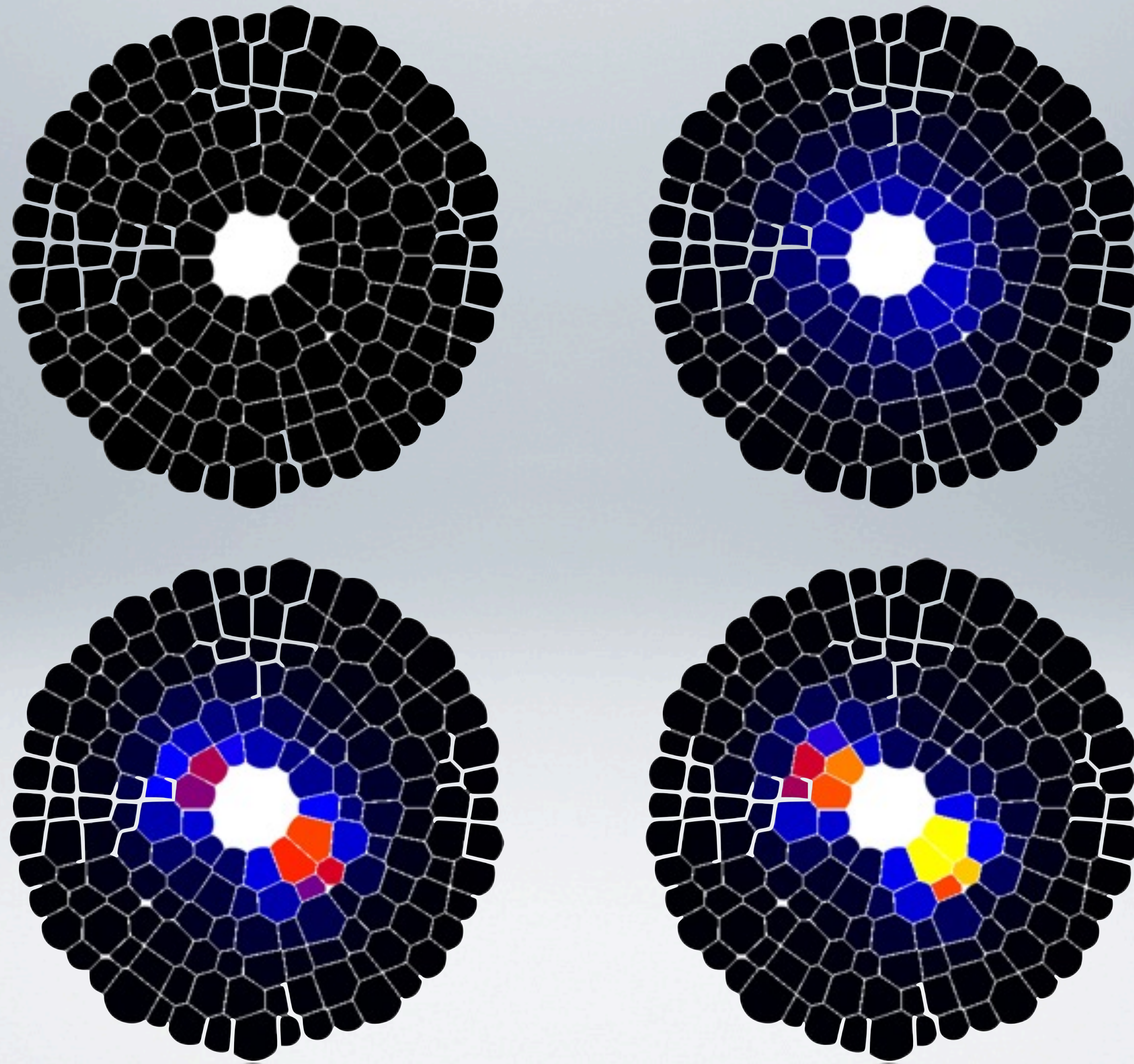
Jönsson et al (2005)

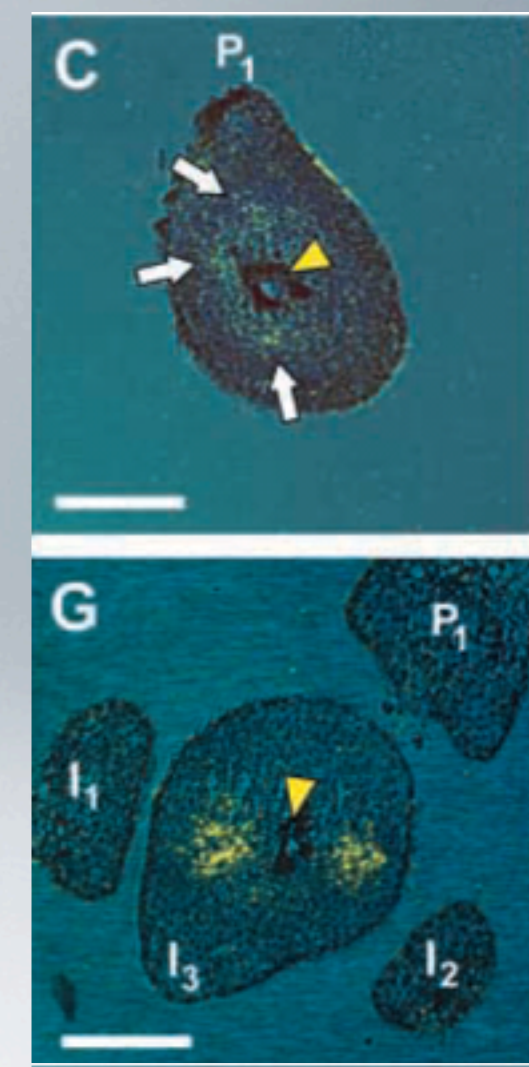
Laser ablation simulation



Jönsson et al (2005)

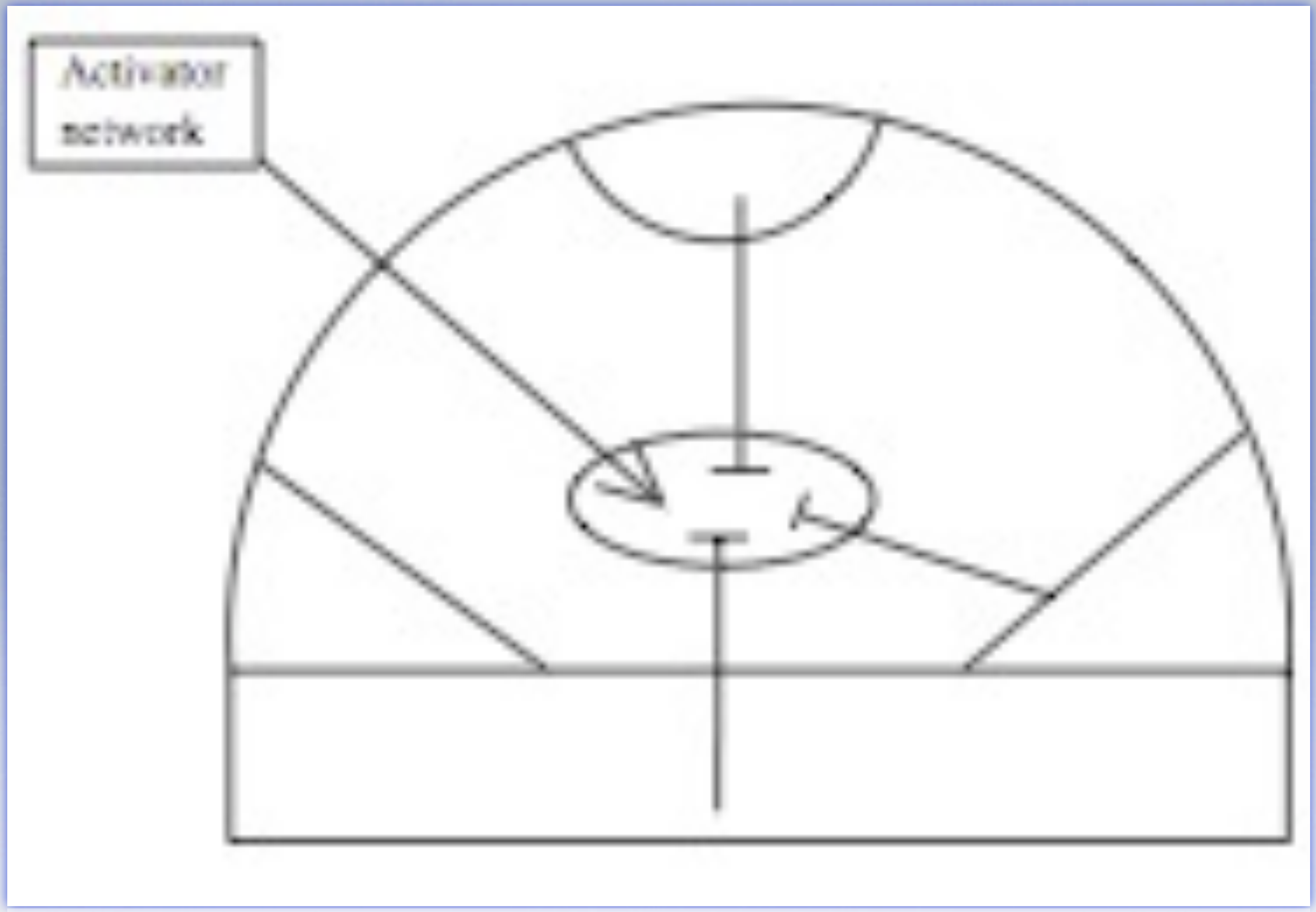
Laser ablation simulation





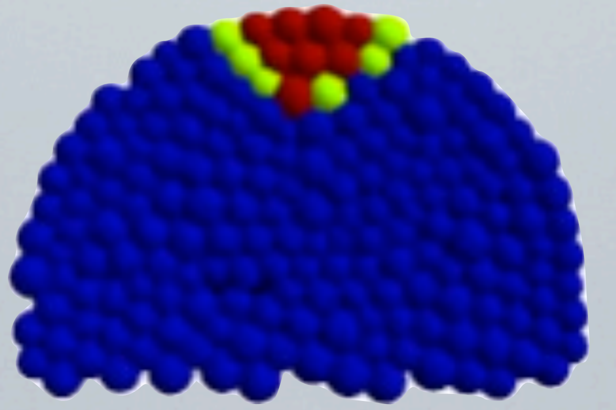
Jönsson et al (2005)

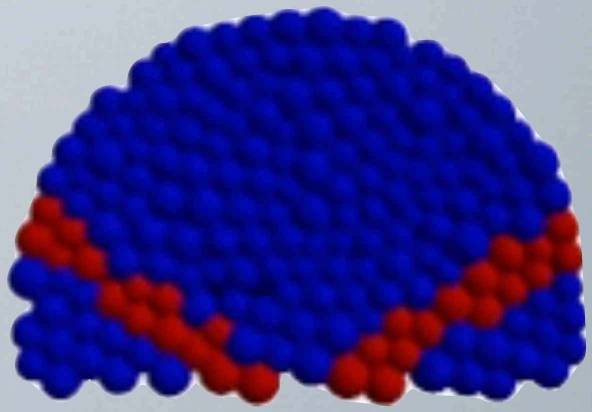
CLV3 based WUS repression



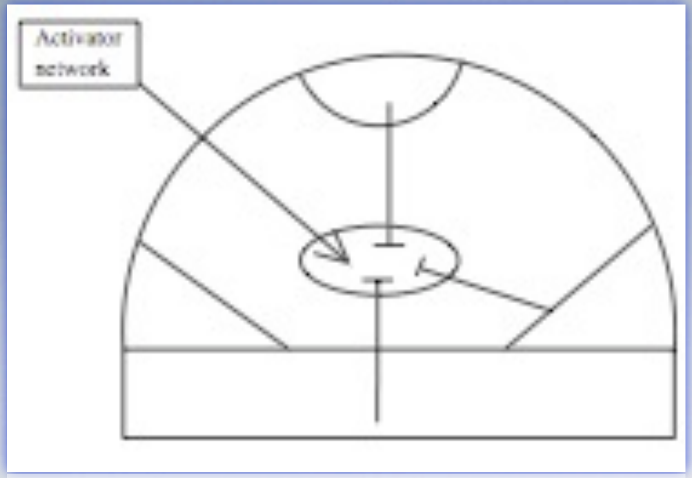
S Engman

CLV3 based WUS repression



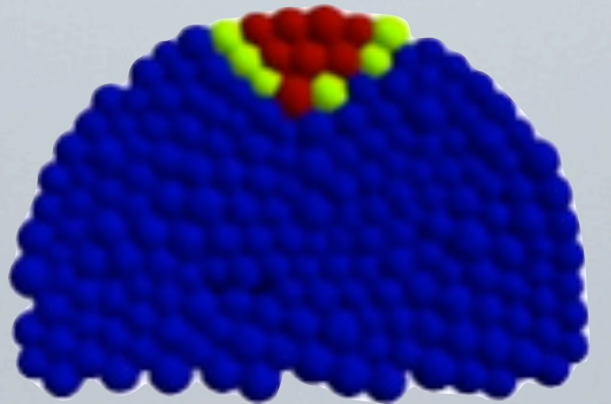


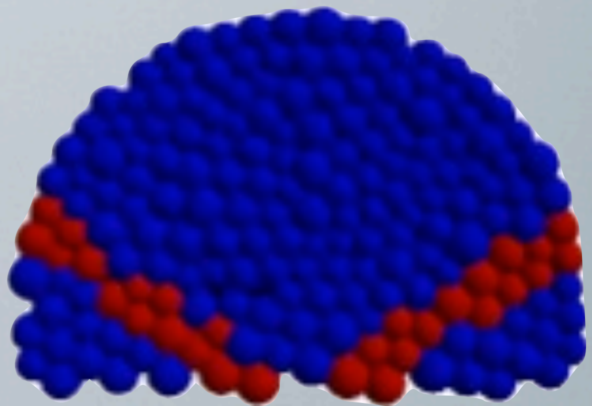
CLV3 + PZ repressors static



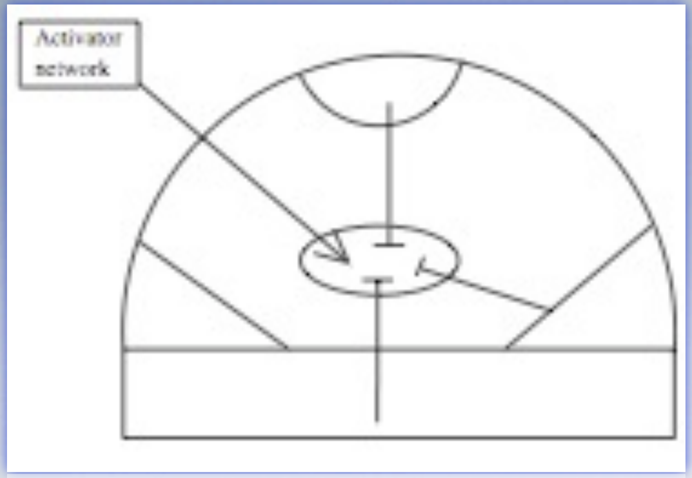
S Engman

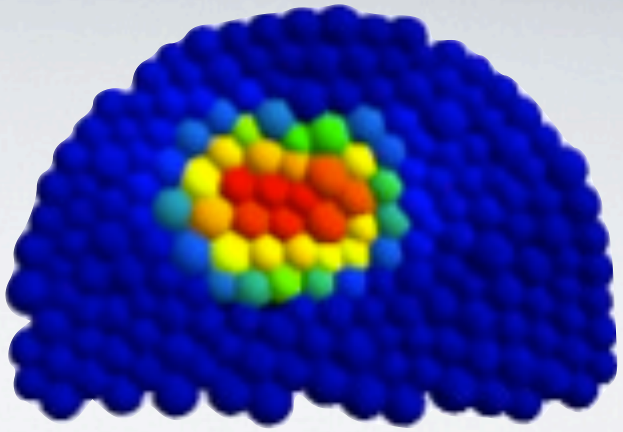
CLV3 based WUS repression





CLV3 + PZ repressors static

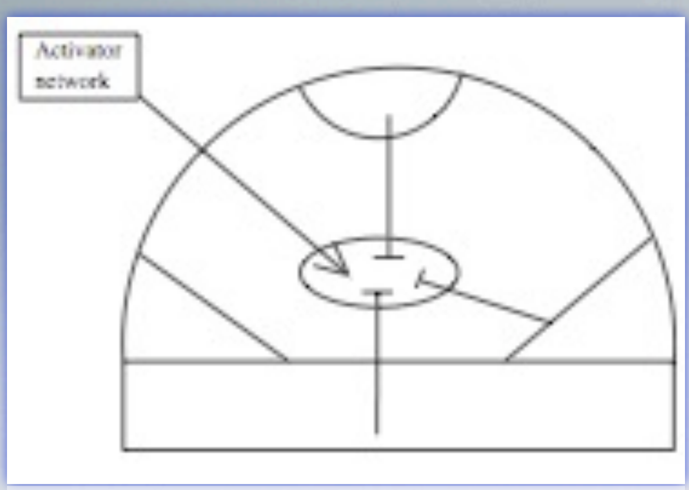


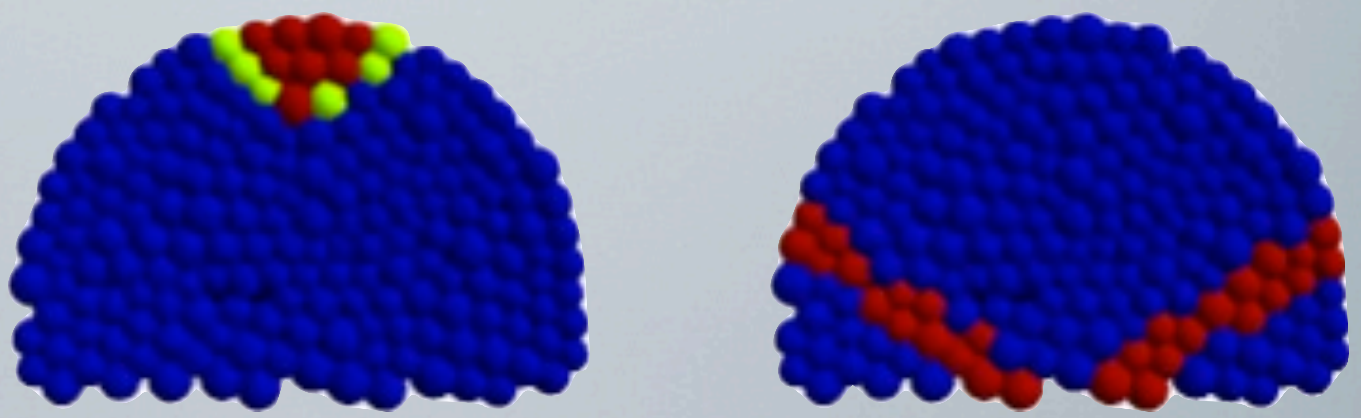


WUS

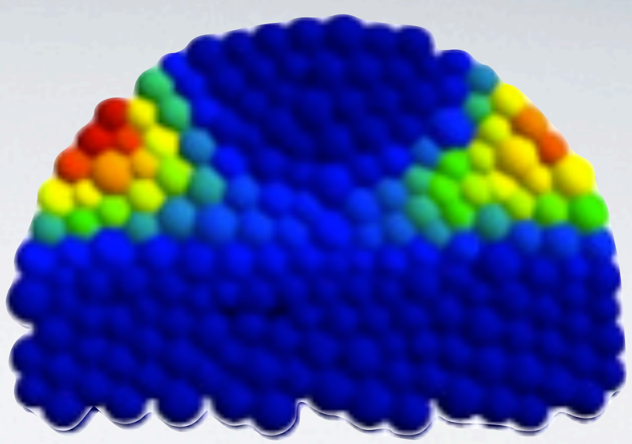
S Engman

CLV3 based WUS repression





CLV3 + PZ repressors static

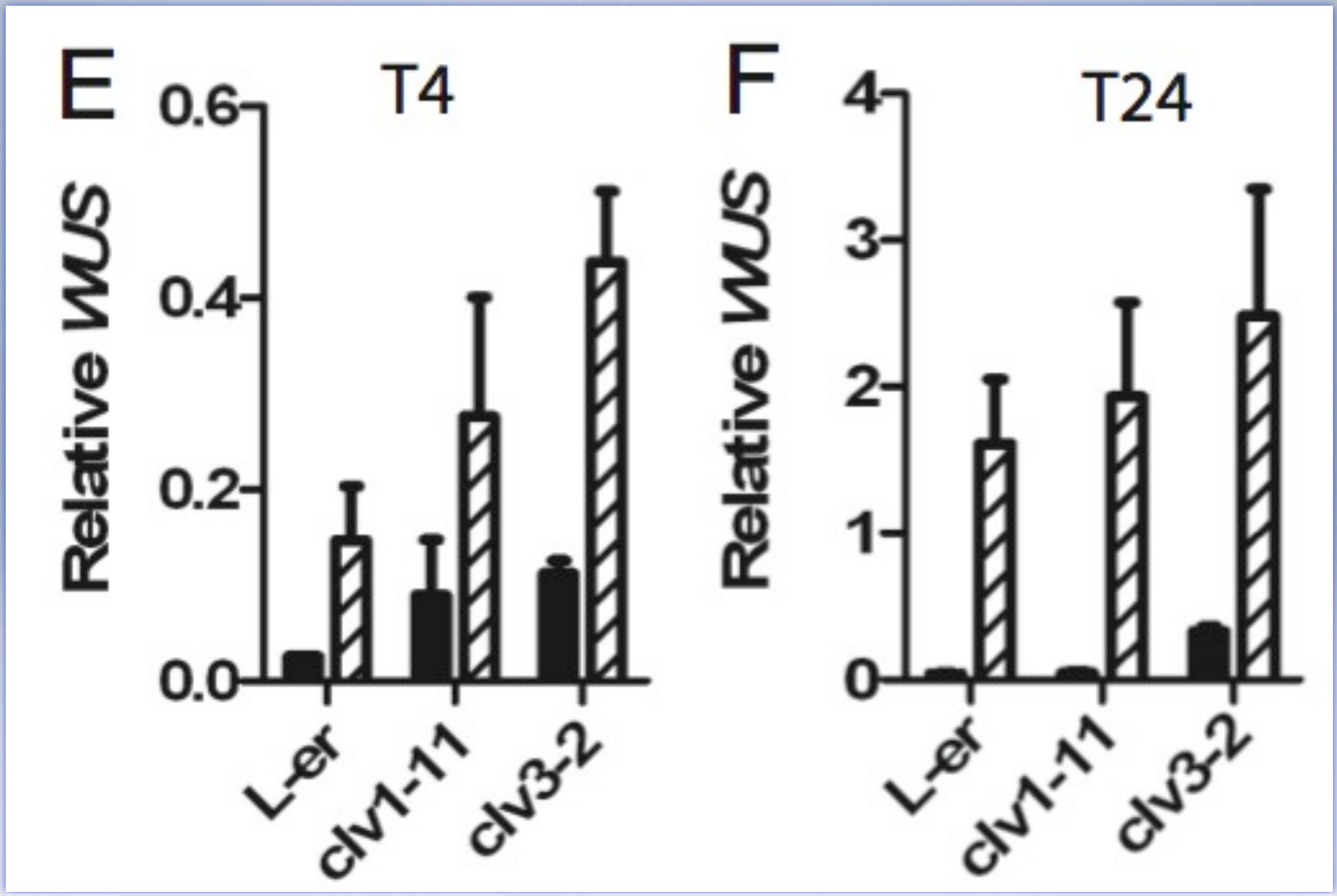


WUS

Activator needed!

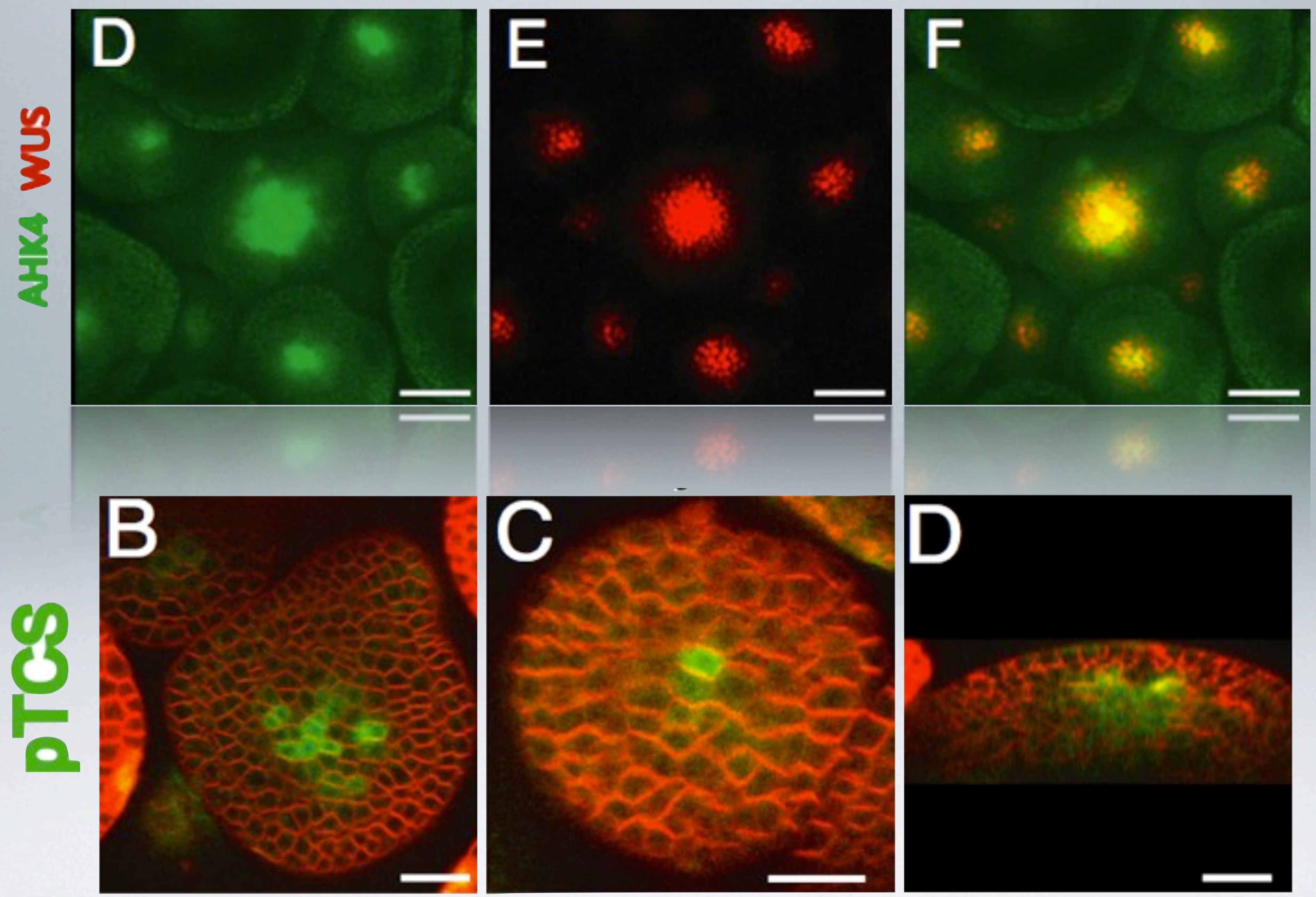
S Engman

Cytokinin activator?



Gordon et al (2009)

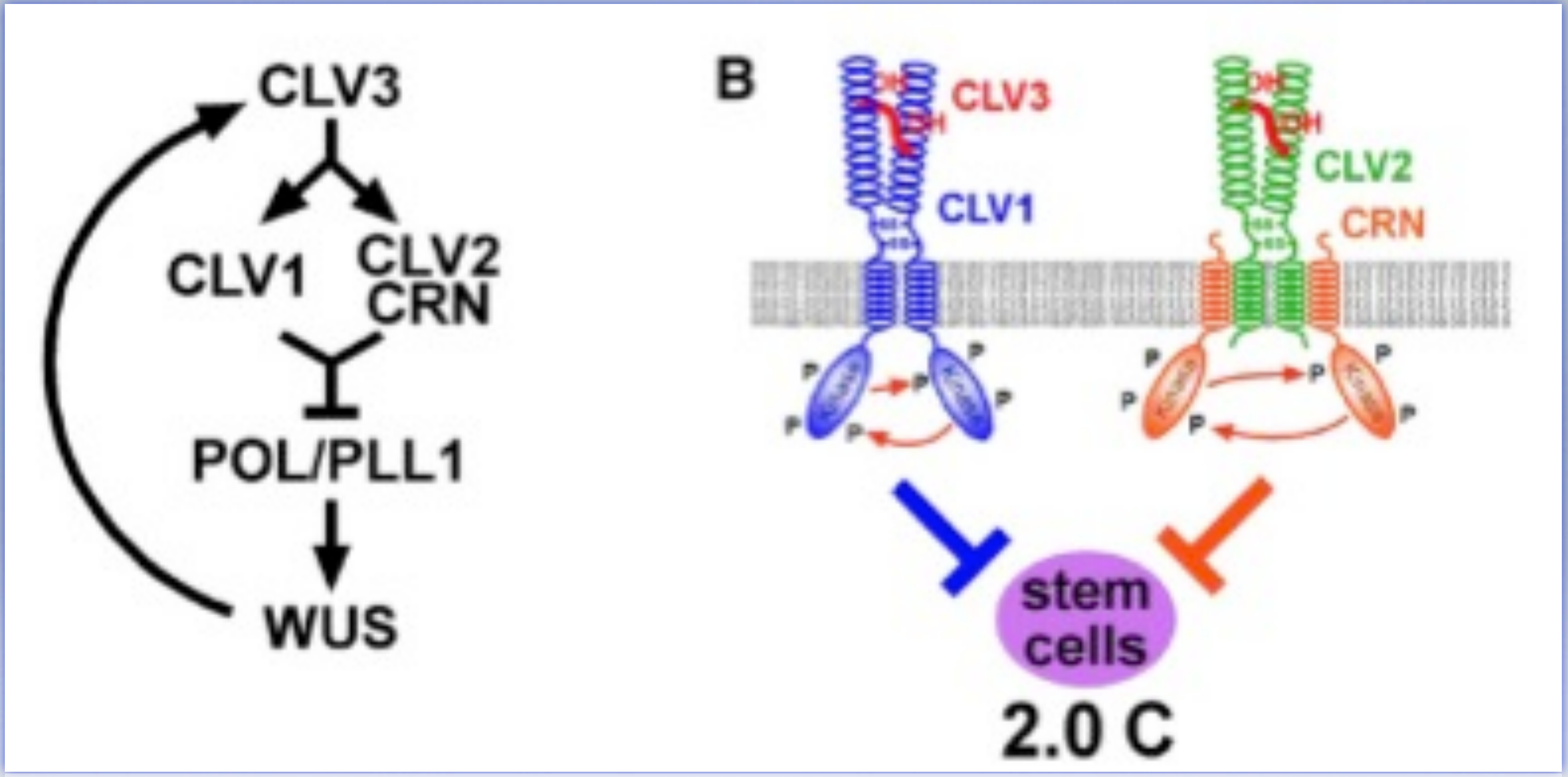
Cytokinin activator?



Gordon et al (2009)

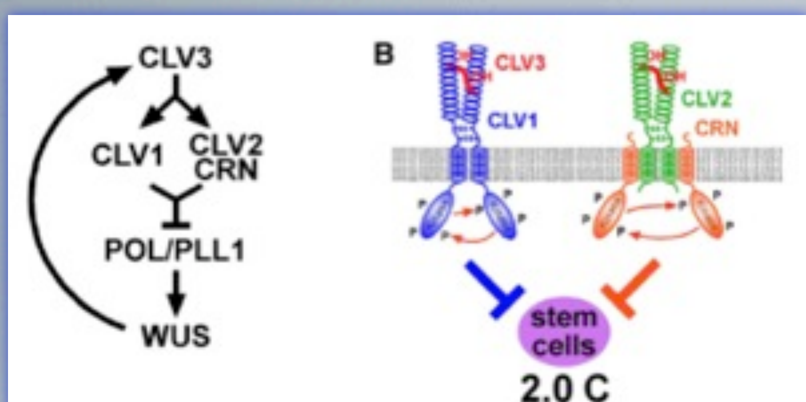
How is the CLV3 to WUS signal mediated?

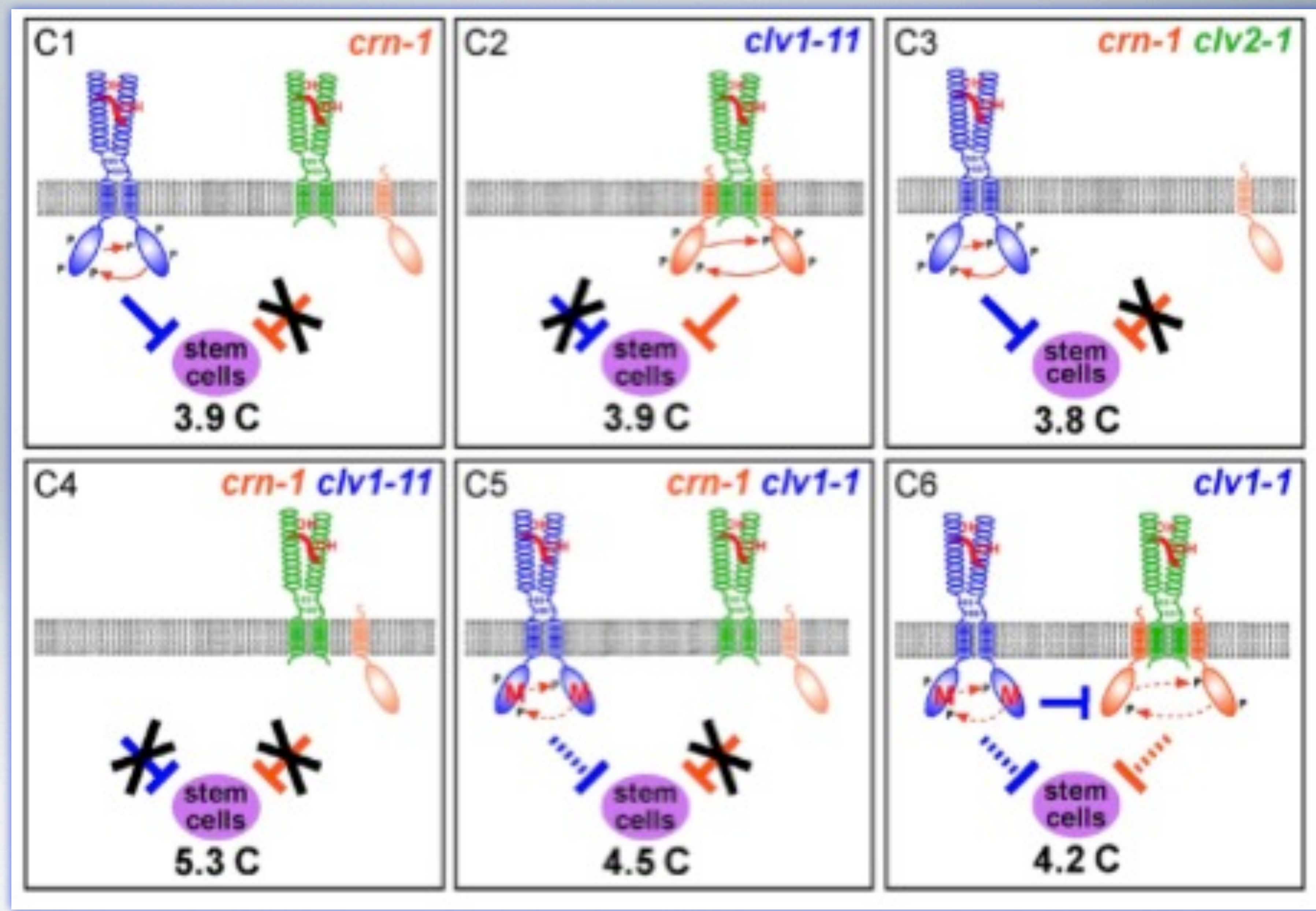
How is the CLV3 to WUS signal mediated?



Muller et al (2008)

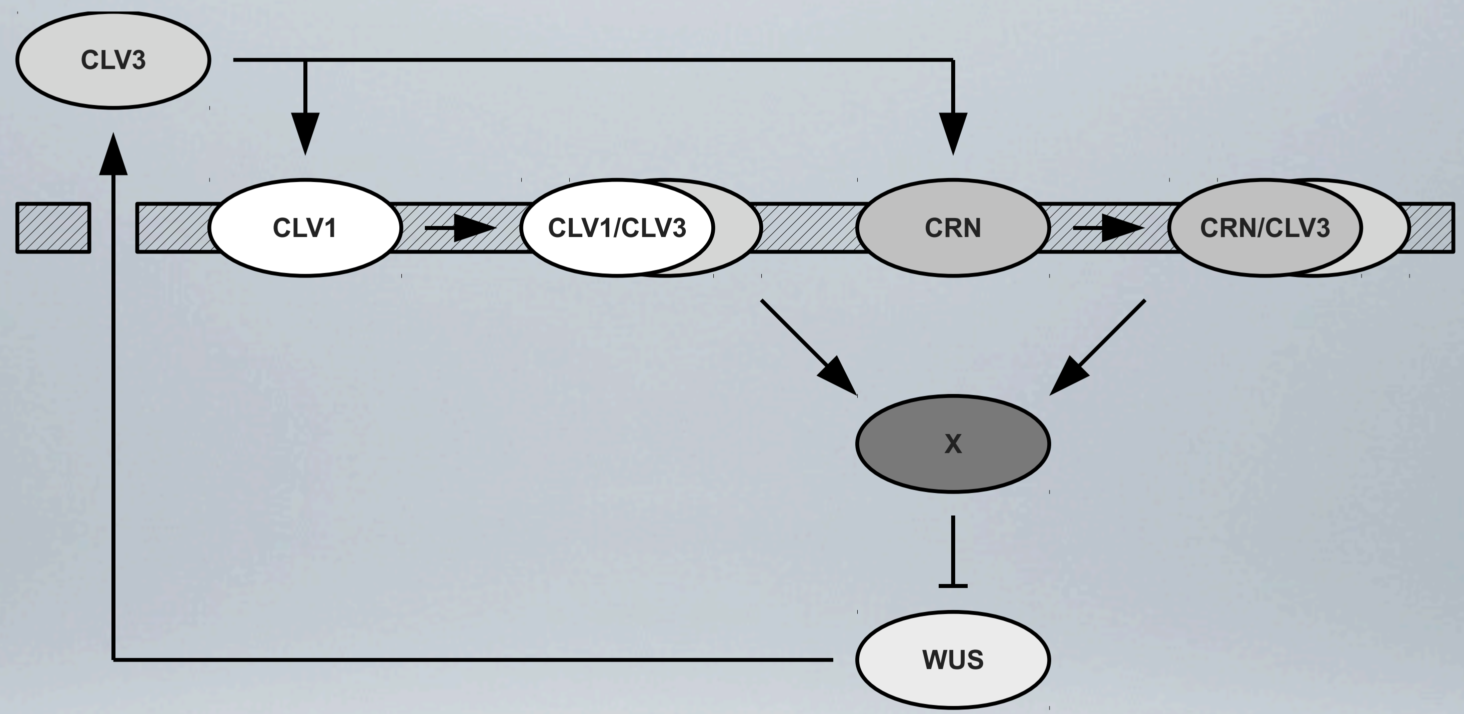
How can clv1 non-null mutants have stronger phenotypes than a clv1 null mutant?





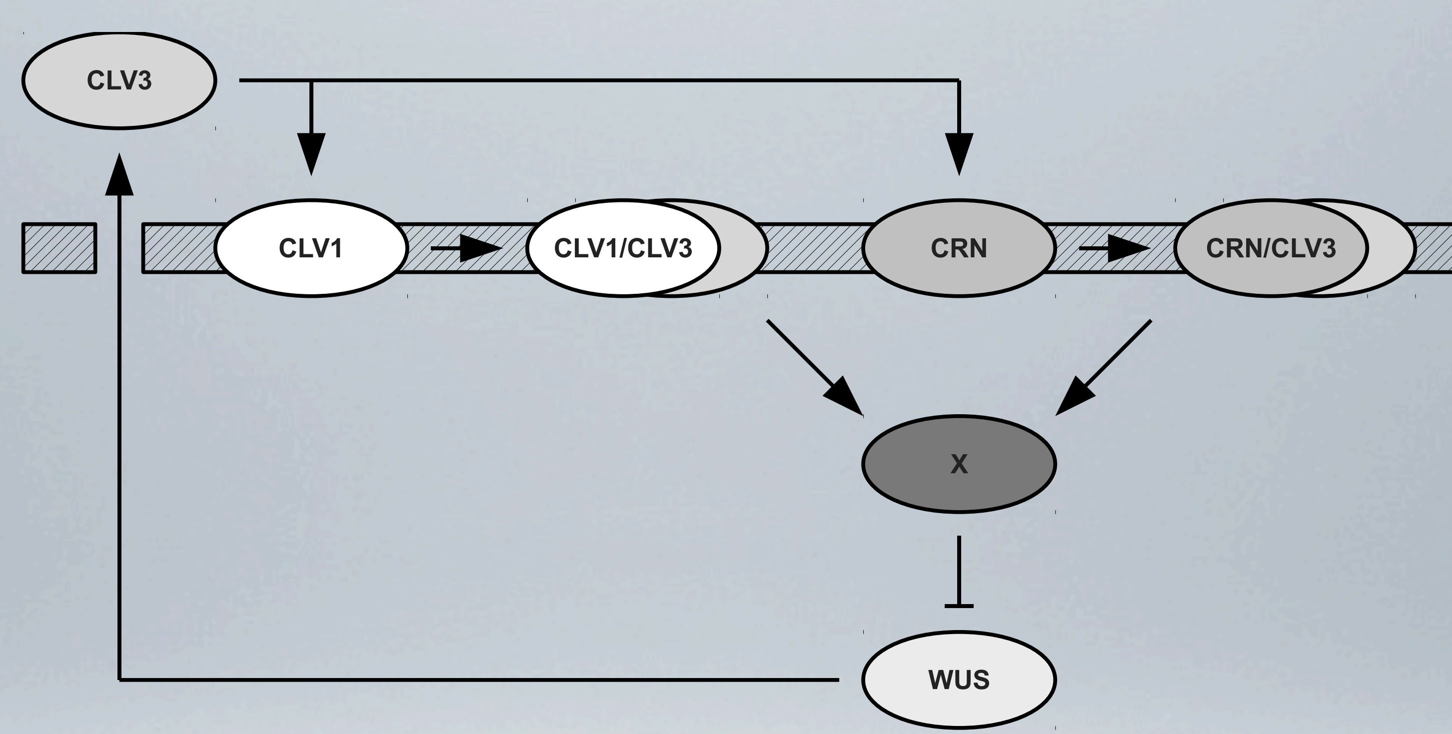
Muller et al (2008)

Can differences in mutant implementation alter wild type predictions?

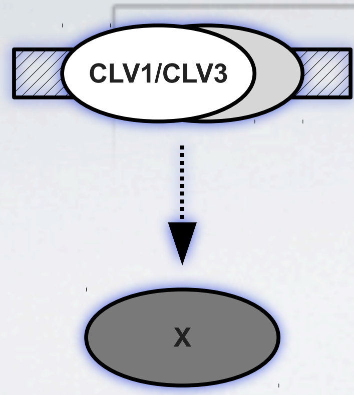


Sahlin et al (submitted)

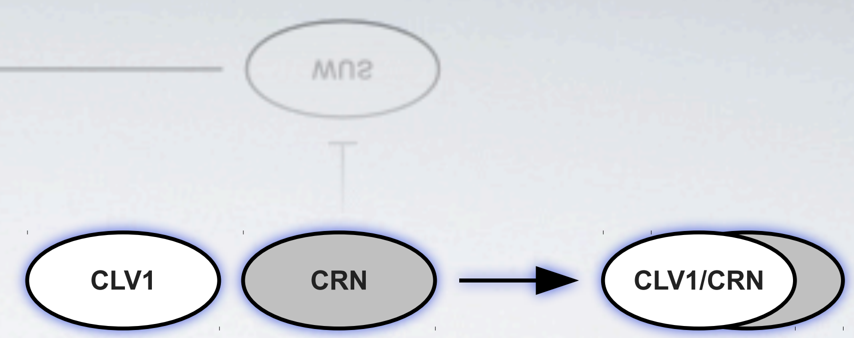
Can differences in mutant implementation alter wild type predictions?



clv1-1
(non-null)



loss-of-signal



interference

Sahlin et al (submitted)

Finding predictive models

Sahlin et al (submitted)

Finding predictive models

- Optimize towards wt and 4 single mutants

Sahlin et al (submitted)

Finding predictive models

- Optimize towards wt and 4 single mutants
- Test with two double mutants

Sahlin et al (submitted)

WT comparison

hypotheses for mutant compared with mutant free models

Sahlin et al (submitted)

biological predictions

Sahlin et al (submitted)

biological predictions

- Loss-of-signal mutant uses CLV3 sequestration and requires CLV1-CLV3 internalization

Sahlin et al (submitted)

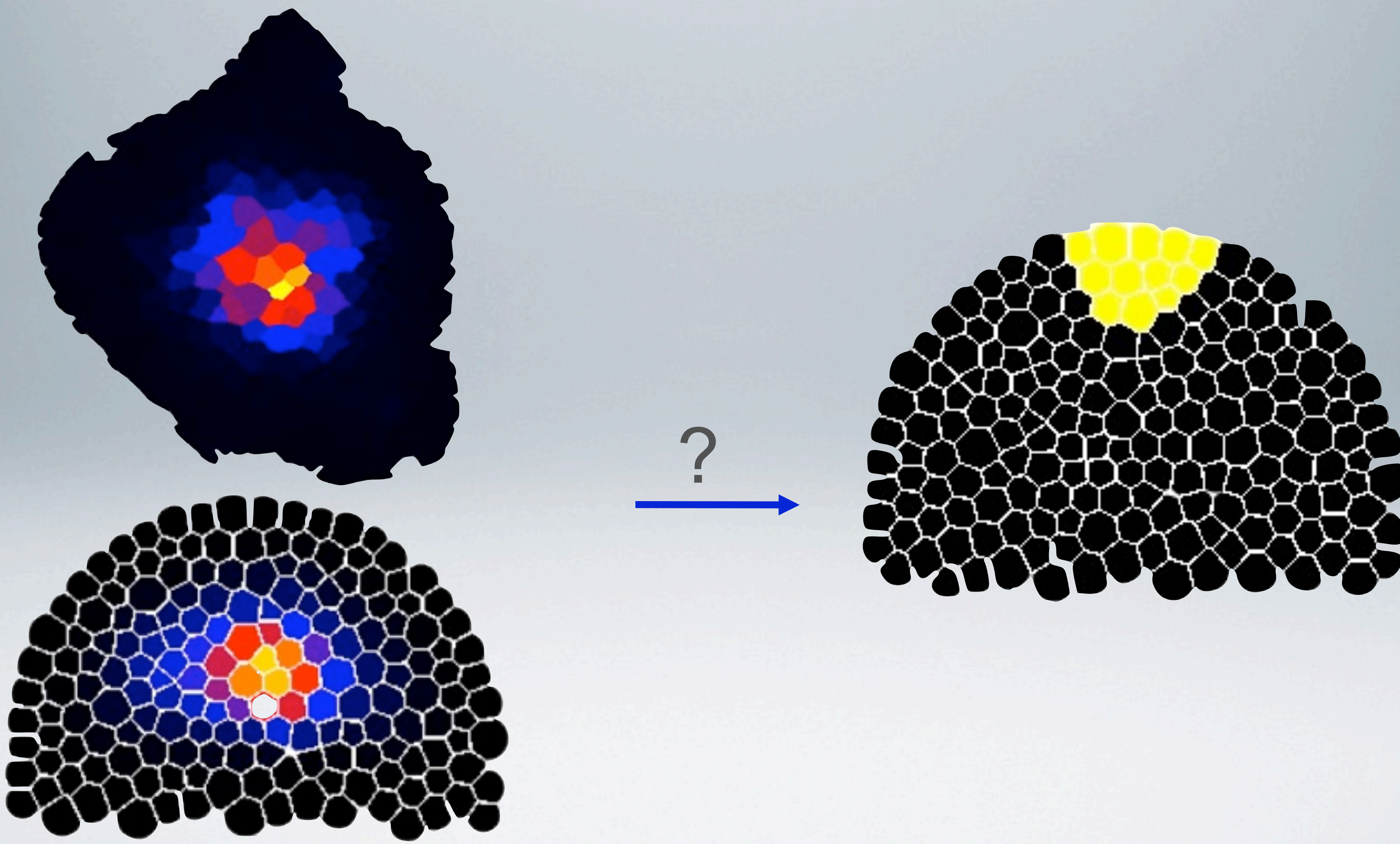
biological predictions

- Loss-of-signal mutant uses CLV3 sequestration and requires CLV1-CLV3 internalization
- Interference model leads to abundance of receptors

Sahlin et al (submitted)

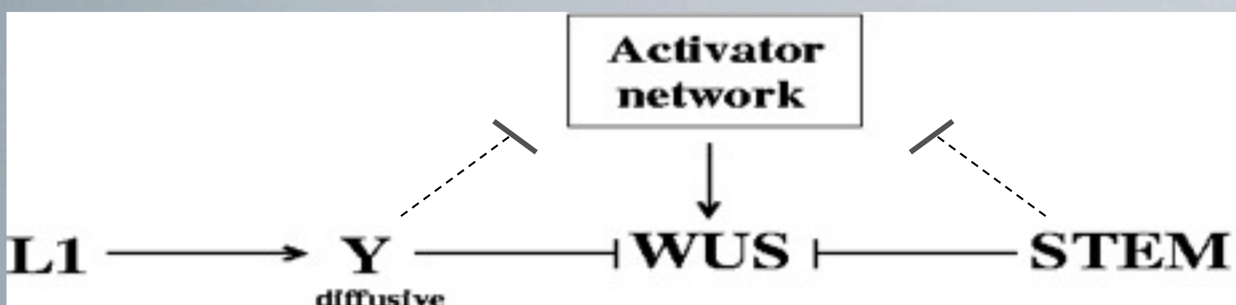
How is the WUS to CLV3 signal mediated?

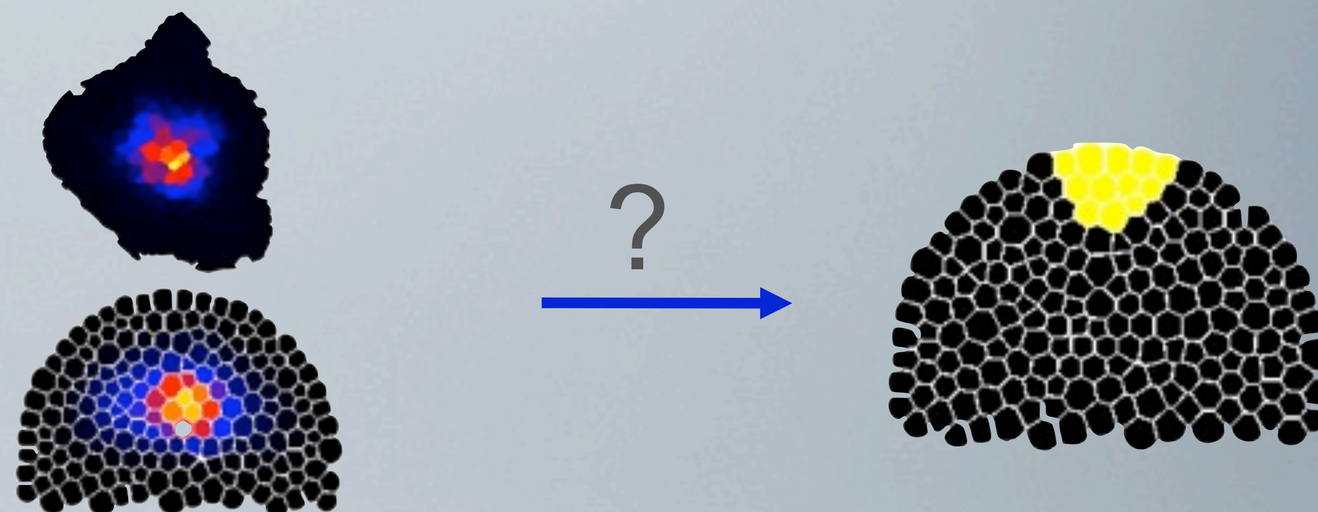
How is the WUS to CLV3 signal mediated?



Parameter optimization: from WUS

WUS model from Jönsson et al (2005)





Parameter optimization: from WUS

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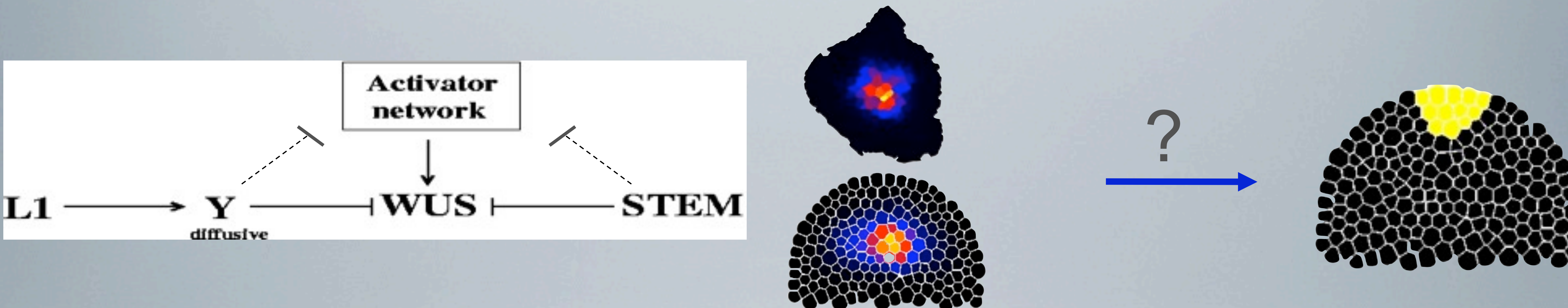
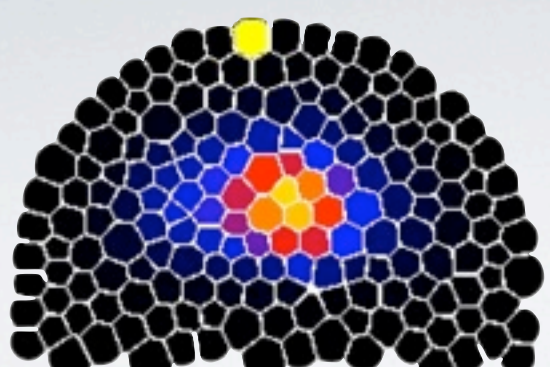


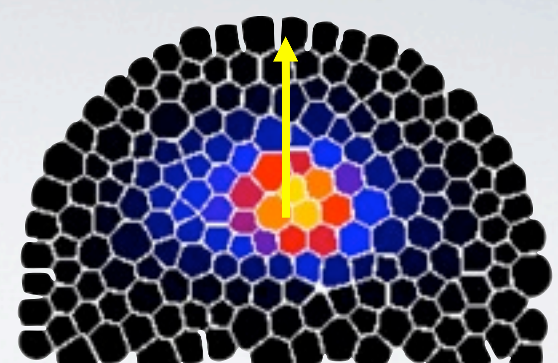
'Optimize' hypotheses for WUS -> CLV3

WUS + L1

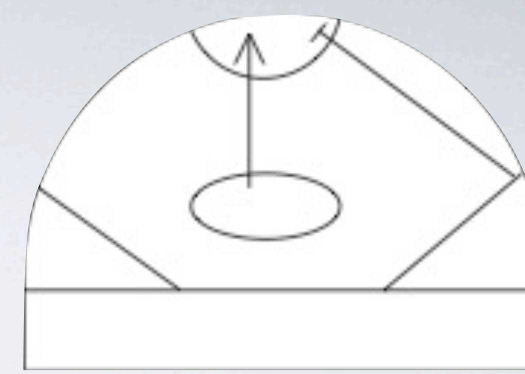
Jönsson et al (2003)



WUS+apical



WUS directional



WUS + PZ

CLV3 expression domain optimization

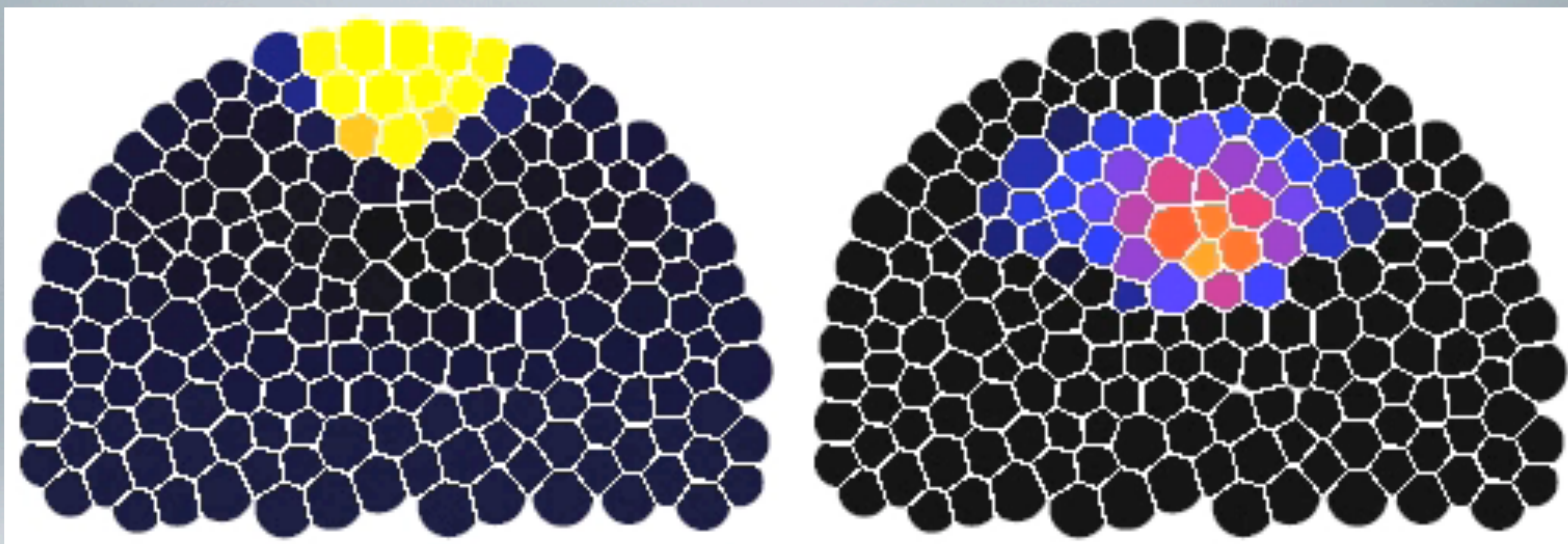
clv3

wus

P Melke

Jönsson et al (2003, 2005)

CLV3 expression domain optimization



clv3 wus

P Melke

Jönsson et al (2003, 2005)

Thank you!

http://www.thep.lu.se/~henrik/

The computable plant
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Marcus Heisler
Venu Reddy

Bruce Shapiro
Eric Mjolsness

Sarah Engman
Jeremy Gruel
Pawel Krupinski
Pontus Melke
Patrik Sahlin
Christopher Sturk
(Computational Biology
& Biological Physics
Lund University)

Vetenskapsrådet

HFSP

Thank you!

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