Theoretical approaches to epithelial dynamics

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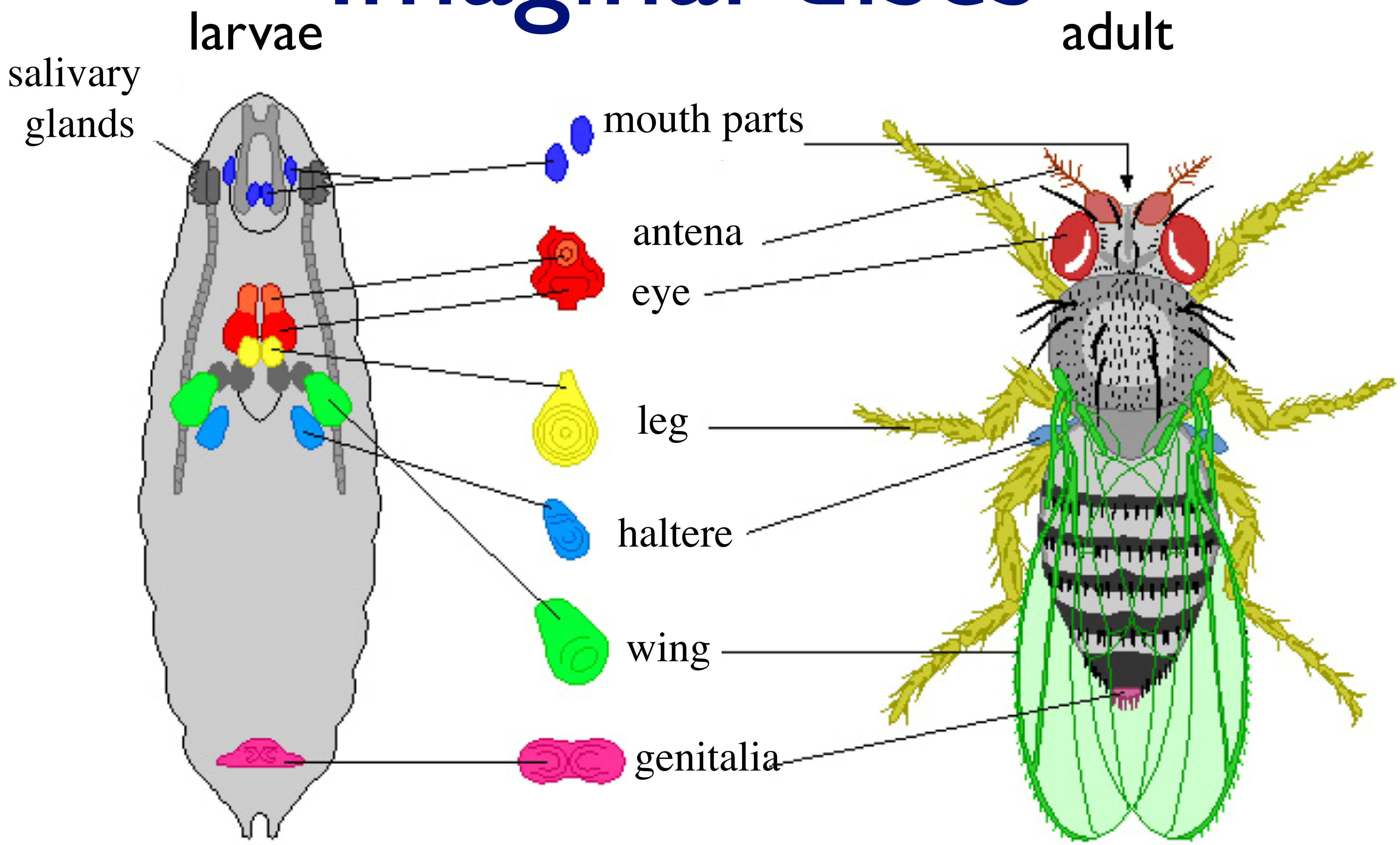
Morphogenesis in animals and plants,
search for principles
KITP, August 1, 2019

MAX-PLANCK-GESELLSCHAFT

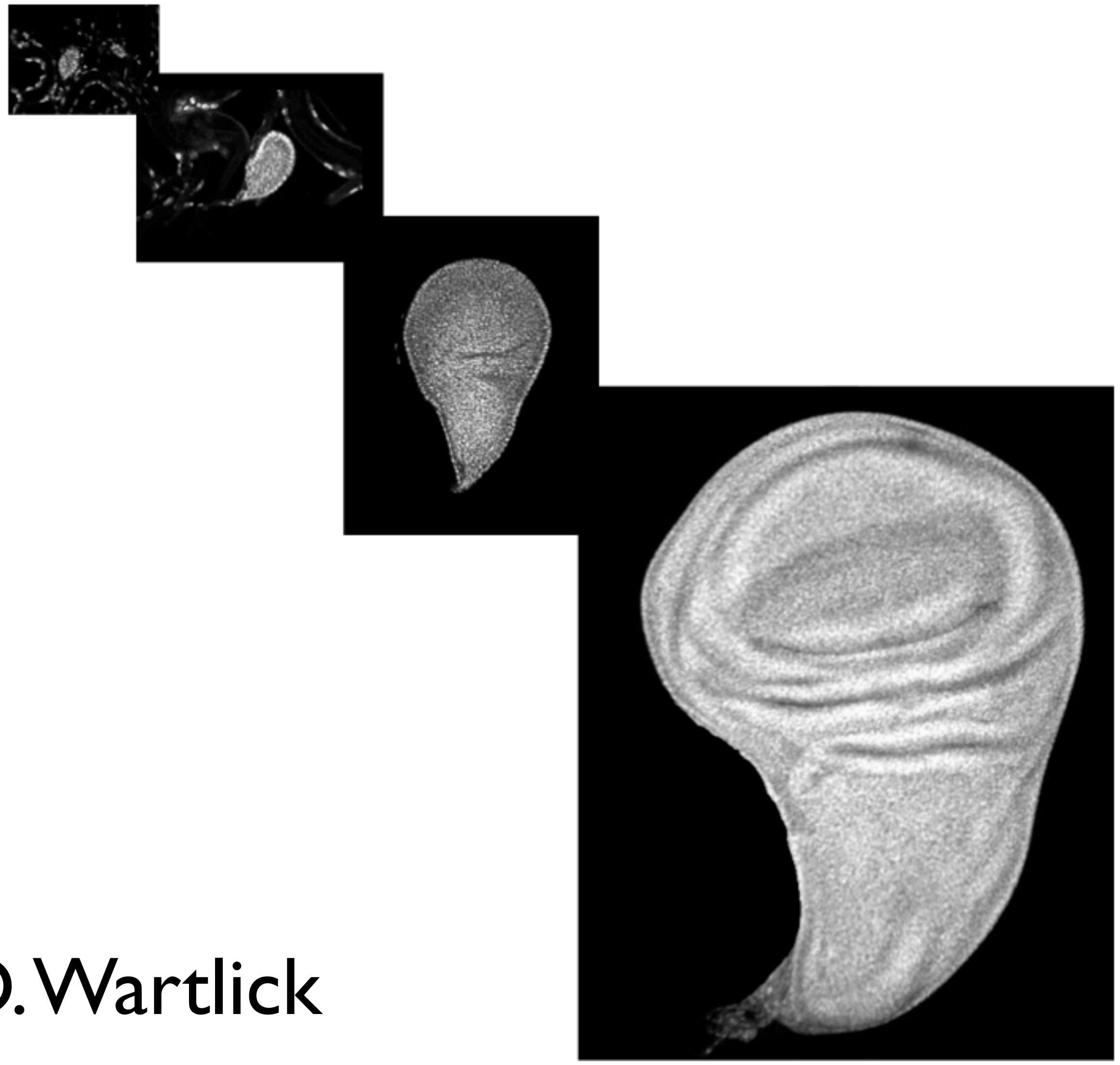
mpipks

Fly development: Imaginal discs

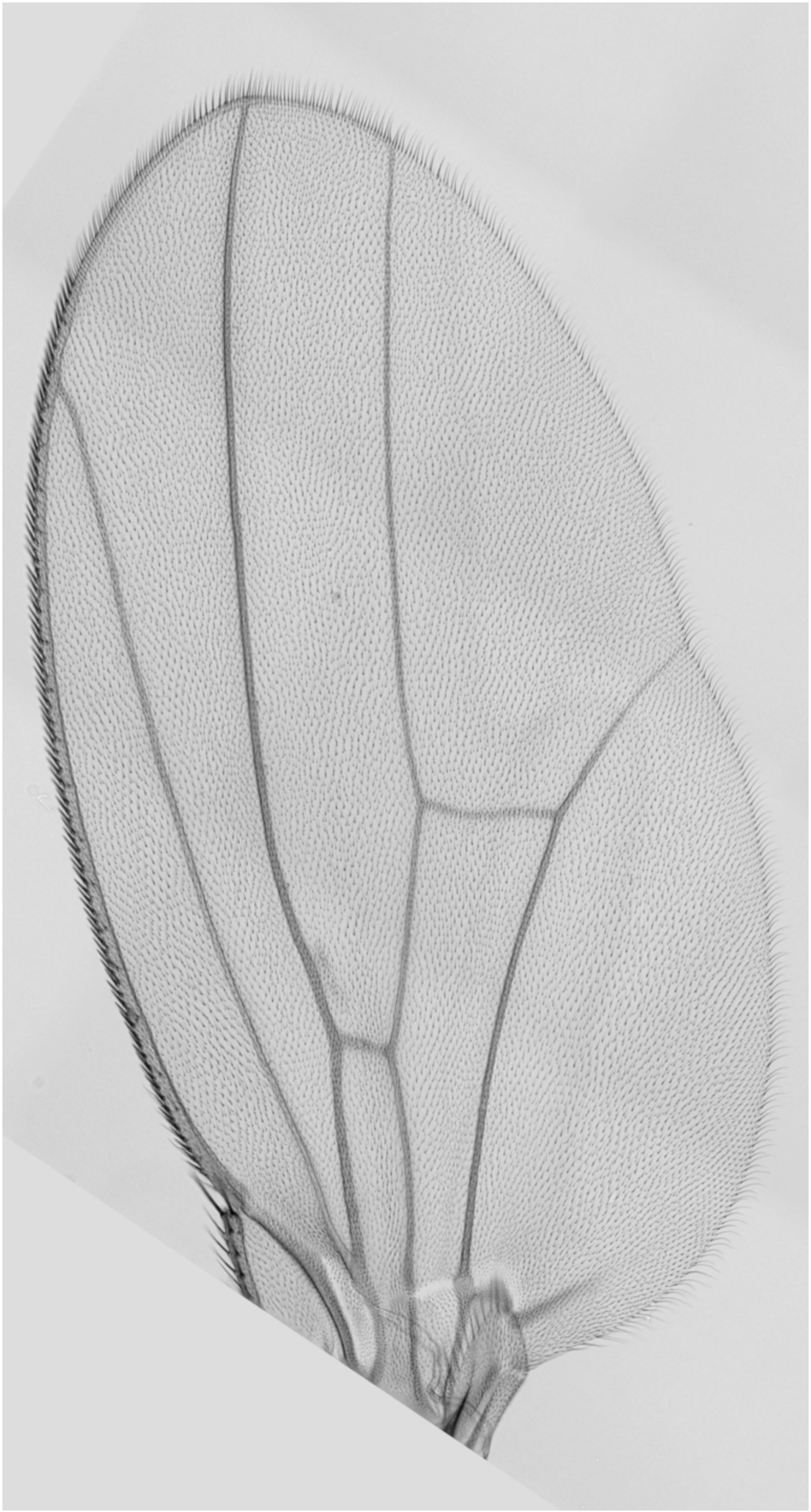


Wolpert, L. Principles of development. *Oxford Univ. Press* (2002)

Fly wing imaginal disc



O. Wartlick

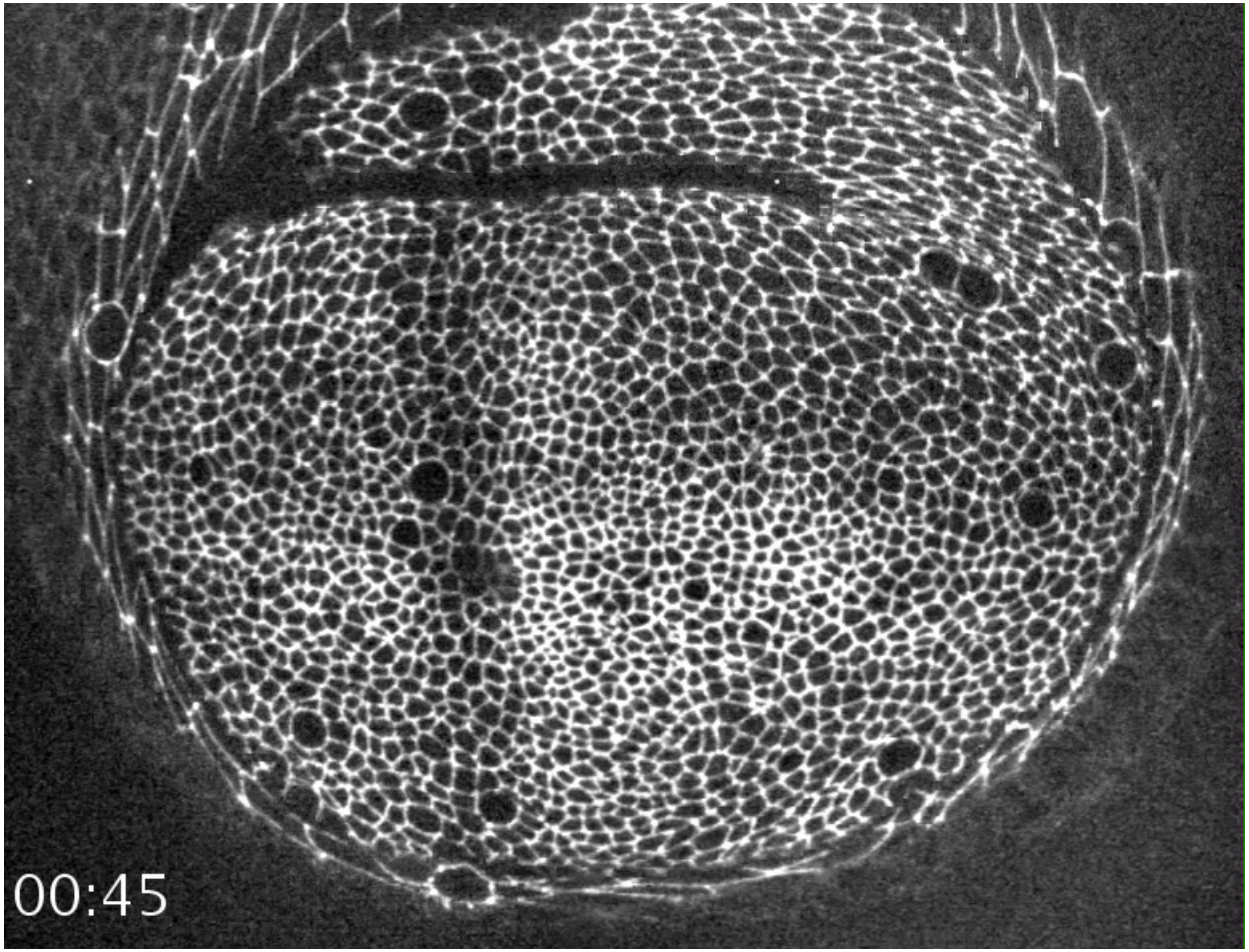


From 50 to 50,000 cells within 5 days
(10 rounds of cell division).

Wing imaginal disk

wing disk in culture medium + ecdysone

E-cadherin GFP



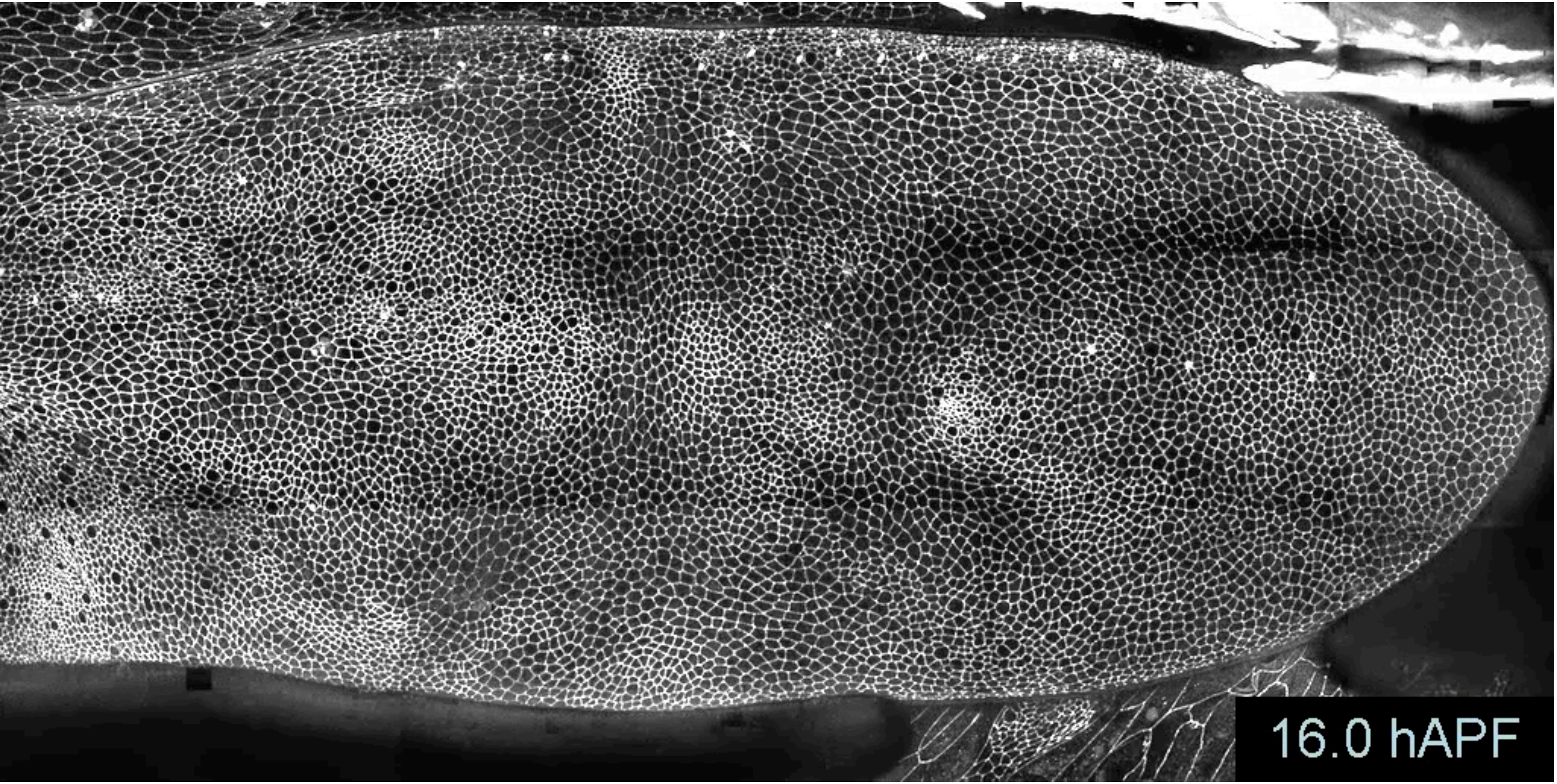
wing disk

wing pouch

Nathalie Dye, Suzanne Eaton

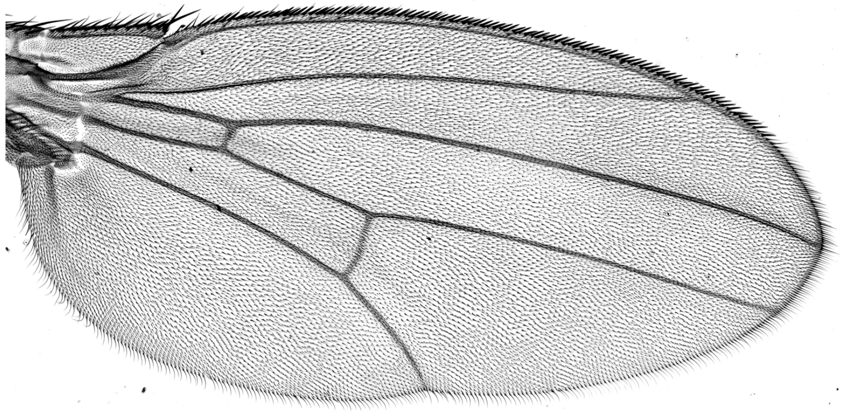
13 hours time lapse

Dynamics in the pupal wing



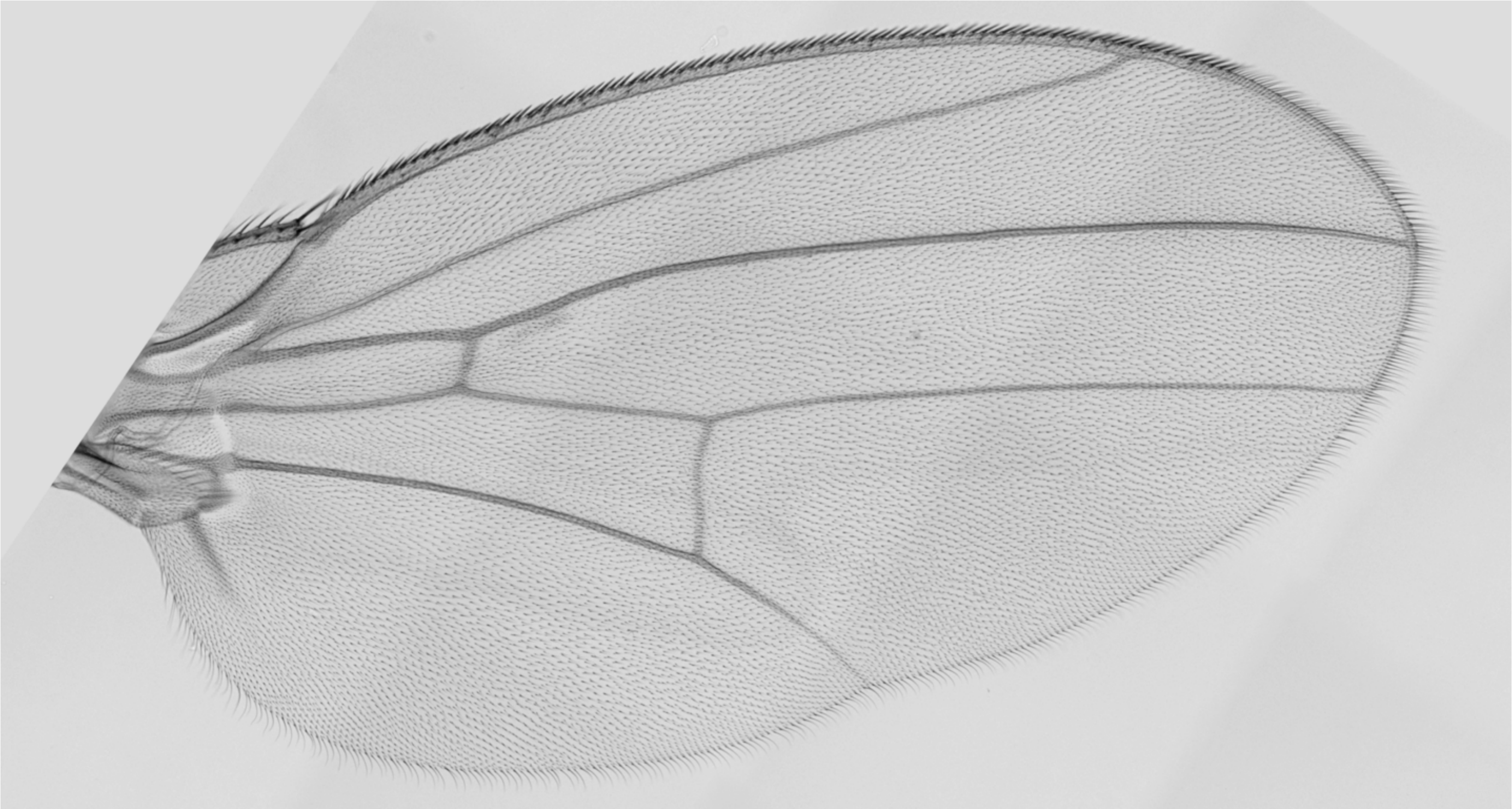
17 hours time lapse

E-cadherin GFP

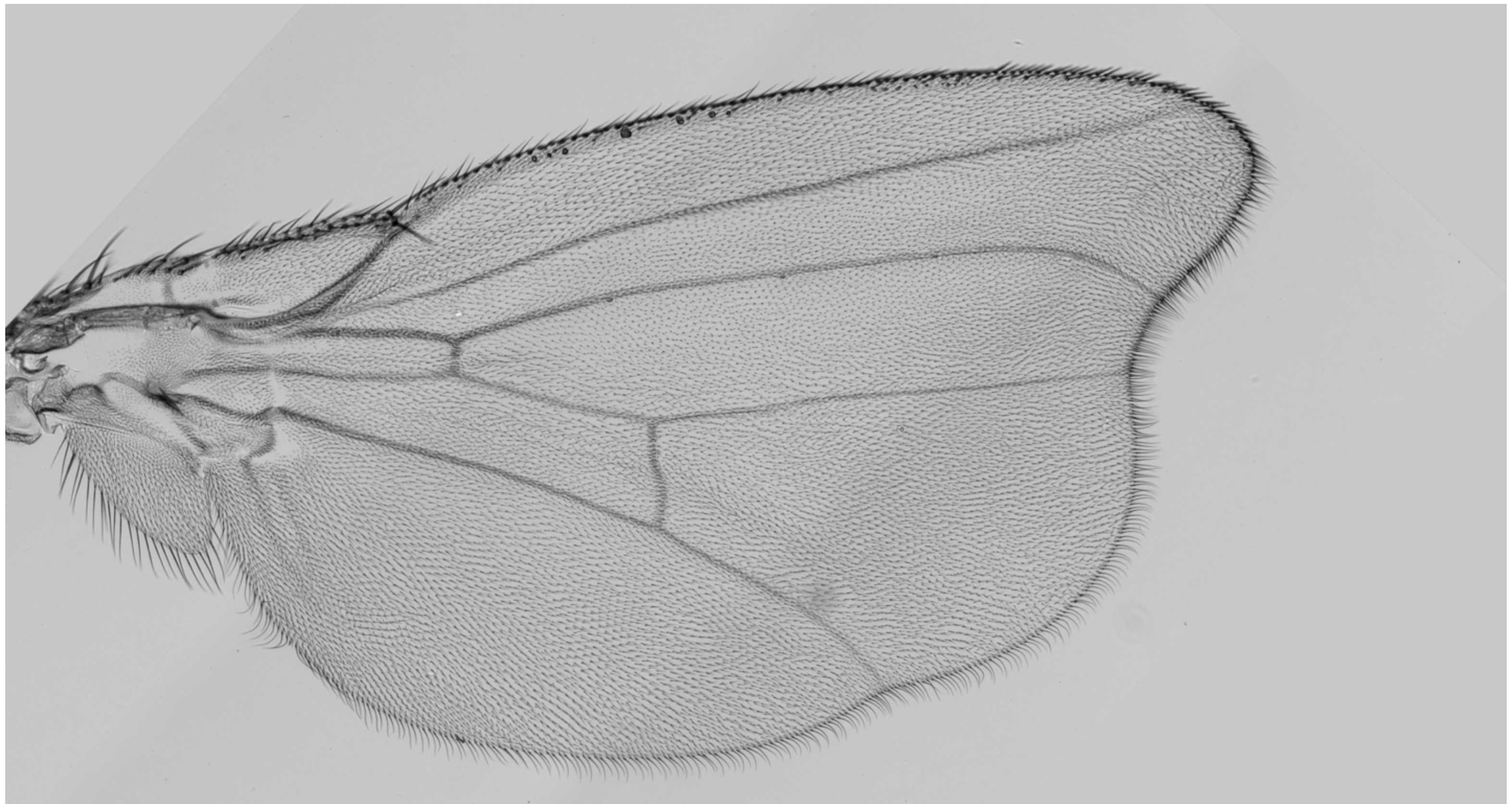


Raphael Etournay, Suzanne Eaton

Tissue size and shape



Wild type wing



Mutant of the dumpy gene

abnormal wing shape

Etournay et al. eLife.07090 (2015)

Outline

Physics of tissue remodeling

Self organization of growth

Outline

Physics of tissue remodeling

Self organization of growth

Max
Physi

Mark
Matt
Laur

Max
Cell

Nath
K.Ver
Raph
Suzan

Crick

IIT Bo

Tissue remodeling

Max Planck Institute for the Physics of Complex Systems, Dresden

mpipks

Marko Popovic
Matthias Merkel
Laura Geisler
Aboutaleb Amiri
Joris Paijmans
Charlie Duclut

center for
systems biology
dresden

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden

Nathalie Dye
K.Venkatesan Iyer
Raphael Etournay
Suzanne Eaton
Carl Modes
Romina Piscitello
Jana Fuhrmann
Corinna Blasse

Crick Institute, London

Guillaume Salbreux

IIT Bombay

Mandar Inamdar

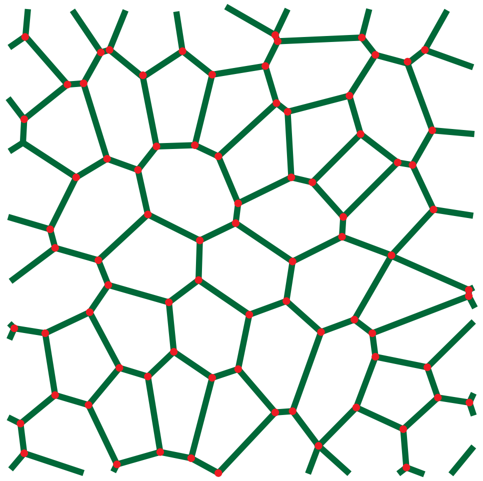
Tissue dynamics and patterning

Active mechanical properties

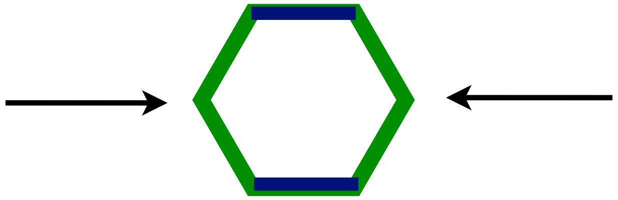
cell division

cell extrusion

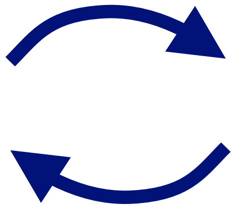
cellular force generation



Force dipoles



cell rearrangements, flows



force generation

chemical signals

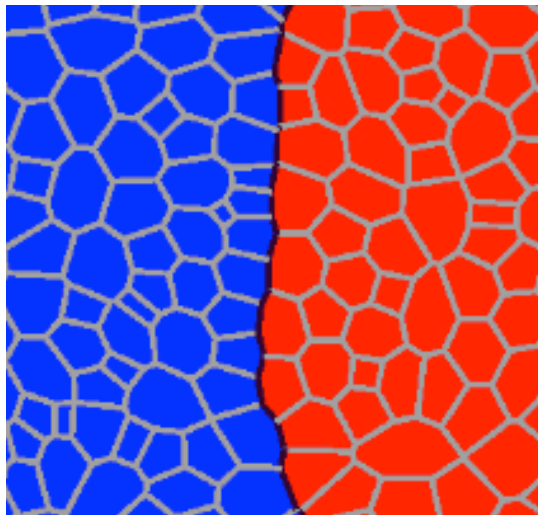
activation

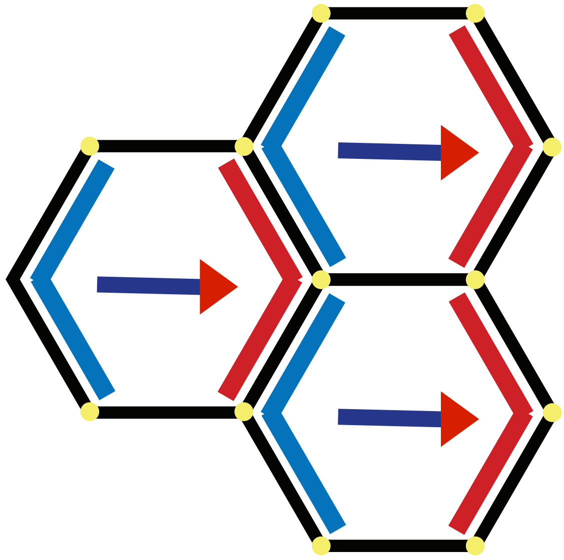
Chemical signals

morphogen gradients

cell-cell signaling

cell polarity





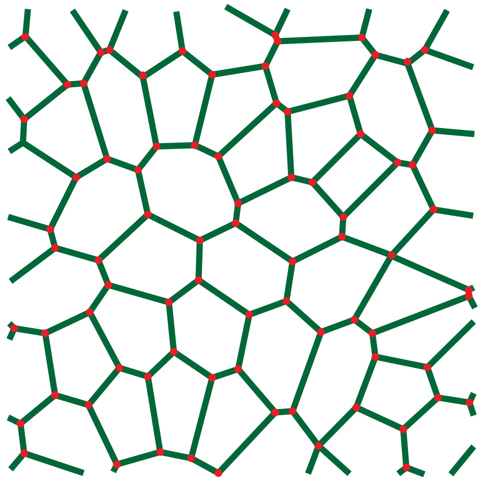
Tissues as active materials

Active mechanical properties

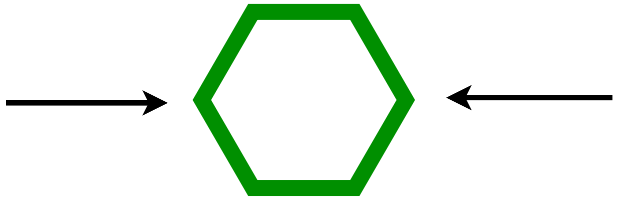
cell division

cell extrusion

cellular force generation



Force dipoles



cell rearrangements, flows

- Tissue deformations generated by cellular processes

- Active visco-elastic material properties: elastic stresses and cells flows

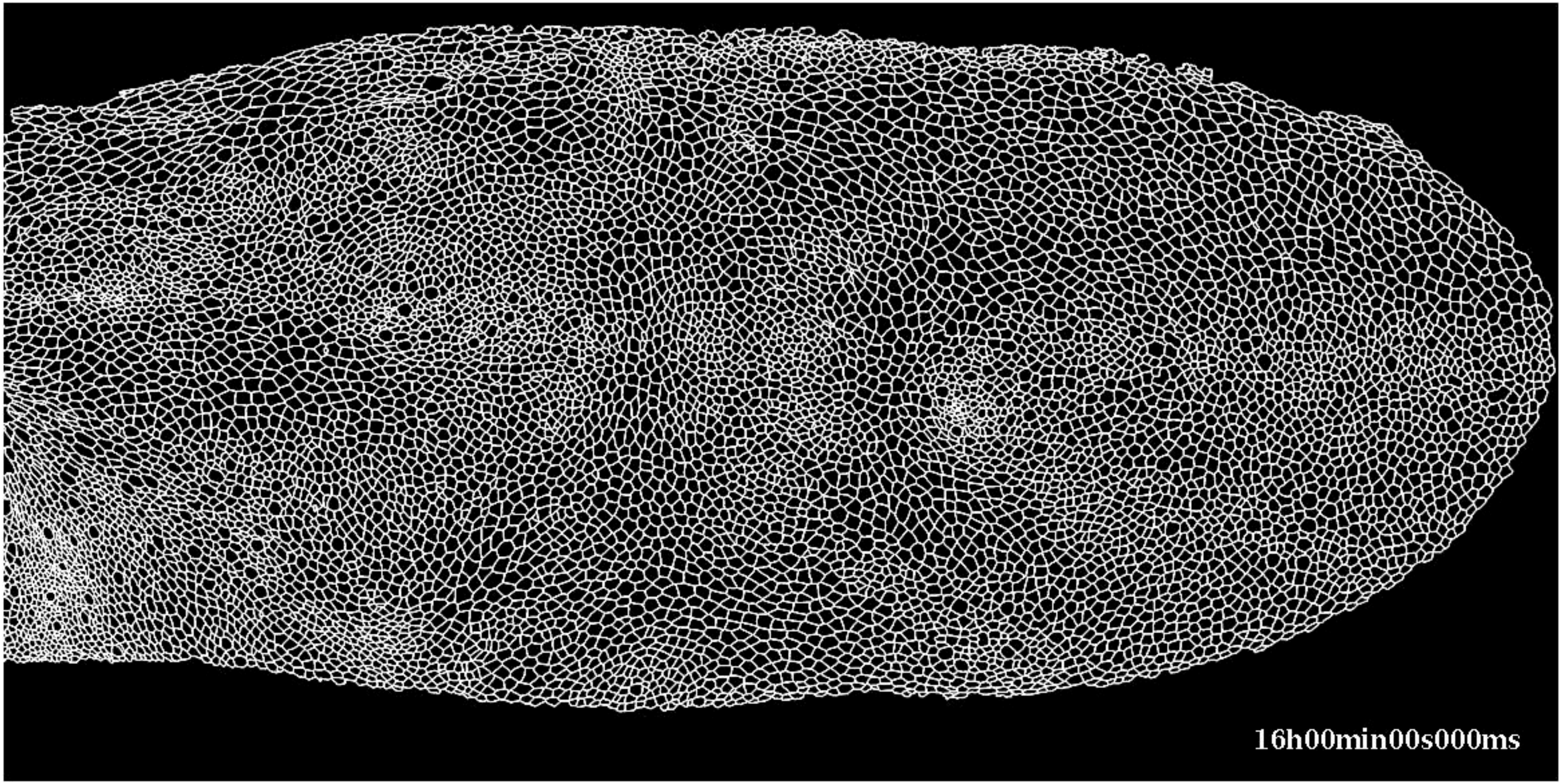
- Active and passive cell rearrangements

Etournay et al. eLife.07090 (2015)
Etournay et al. eLife.14334 (2016)

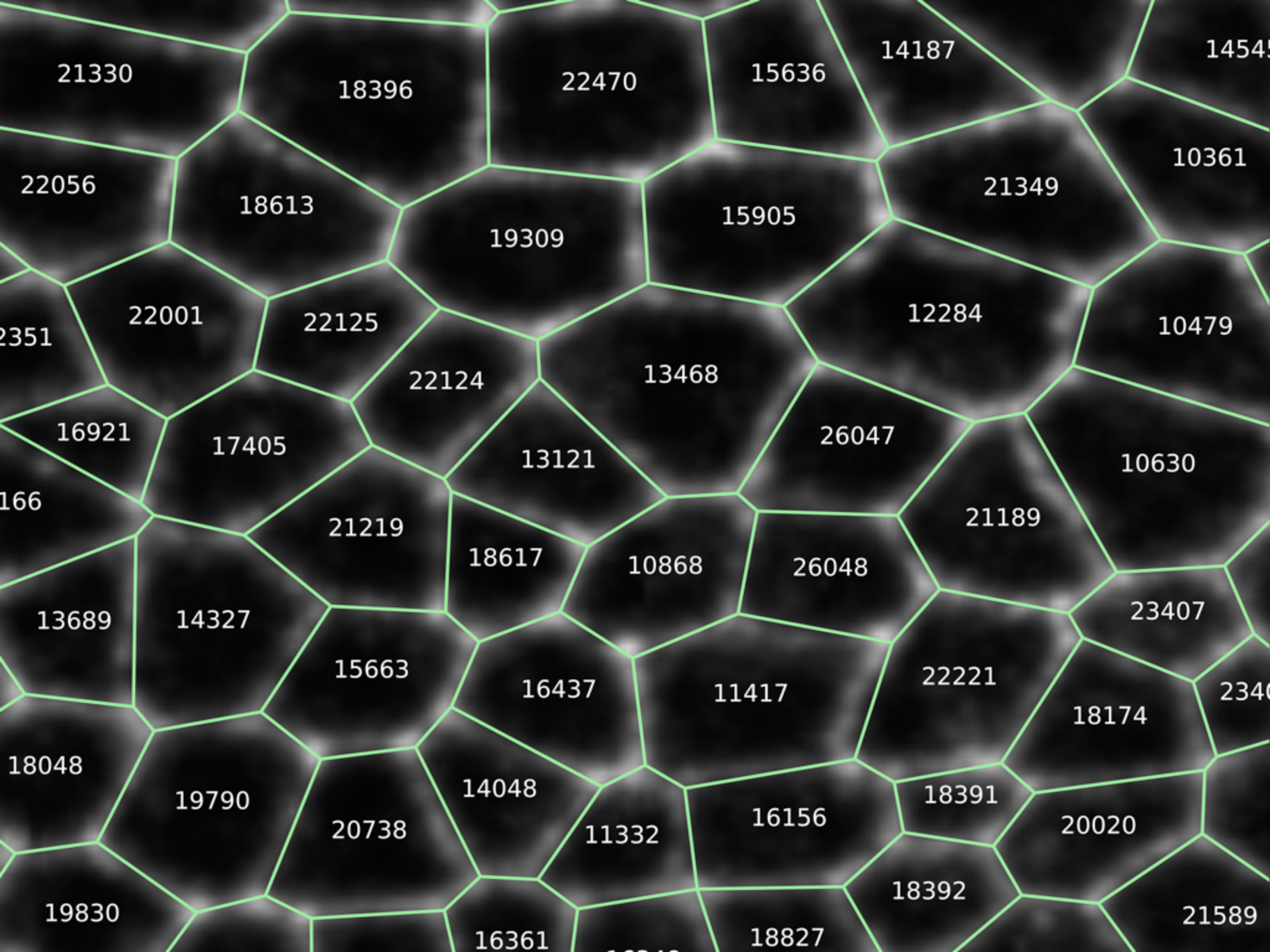
Merkel et al. Phys. Rev. E 95 (2017)
Dye et al. Development 144, 4406 (2017)
Popovic et al. New J. Physics 19 (2017)

Quantification of tissue dynamics

Image analysis: segmentation of cellular network



track the positions and shapes of all cells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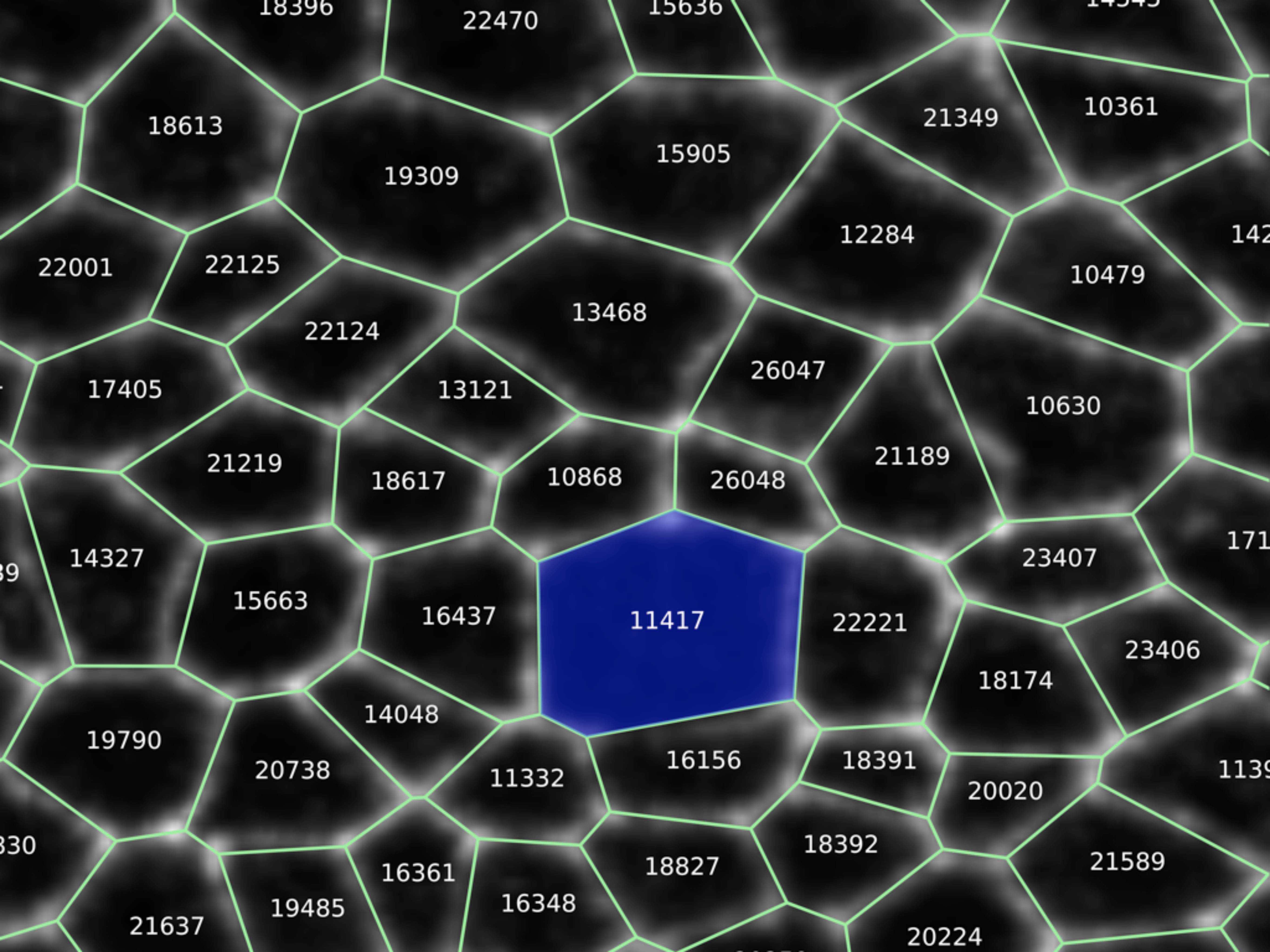
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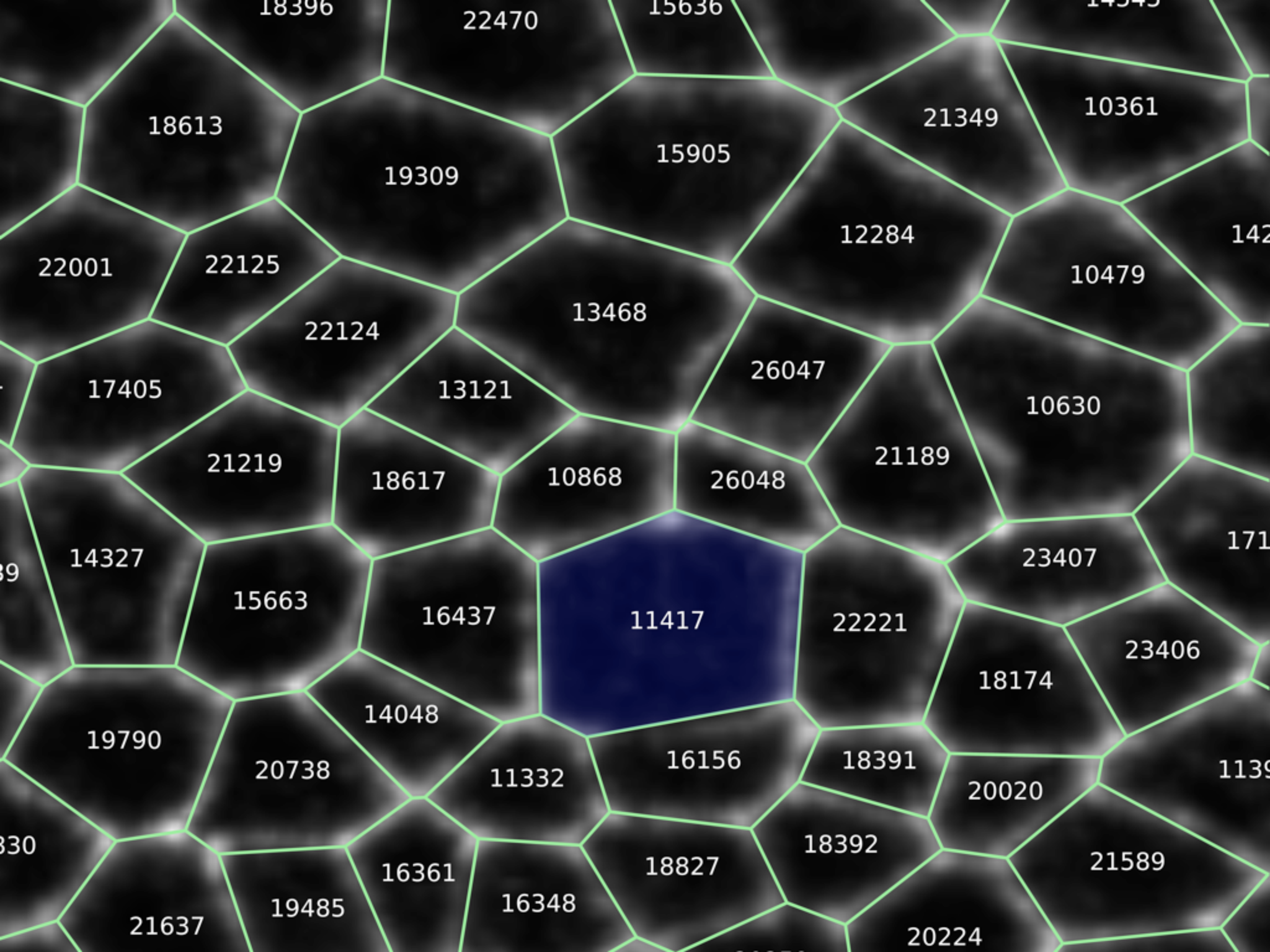
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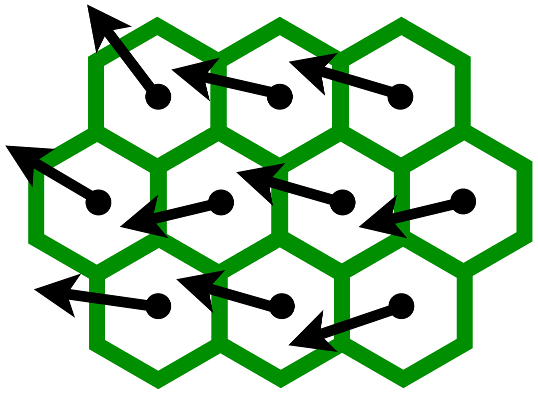
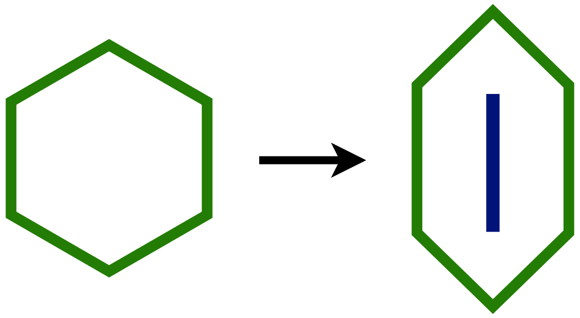
Cell and tissue deformations



Polygon displacement field $\mathbf{d}$

displacement gradient

deformation tensor



$$\begin{pmatrix} u_{xx} & u_{xy} \\ u_{yx} & u_{yy} \end{pmatrix} \qquad \mathbf{u} = \nabla\, \mathbf{d}$$

Deformation tensor

isotropic

anisotropic

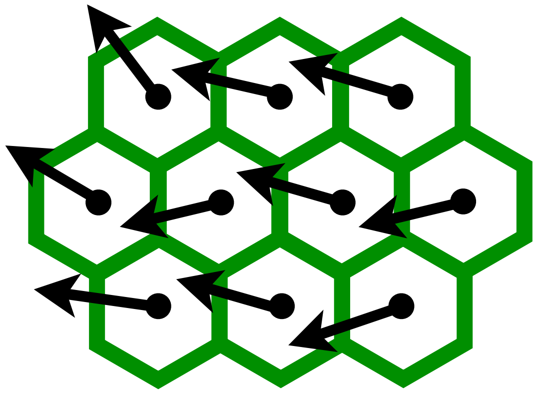
$$\mathbf{u} = \tilde{\mathbf{u}} + \frac{\nabla \cdot \mathbf{d}}{2}\, \mathbb{I} + \theta\, \epsilon$$

shear

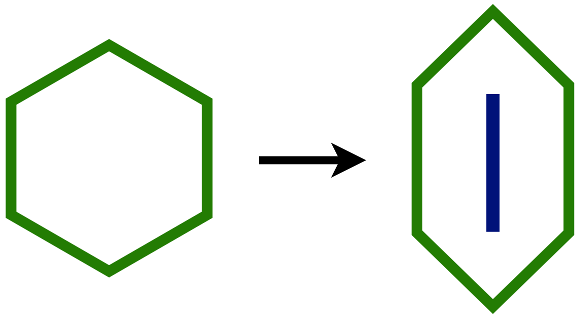
compression/growth

rotation

Cell and tissue deformations



Polygon displacement field $\mathbf{d}$



deformation tensor

displacement gradient

$$\begin{pmatrix} u_{xx} & u_{xy} \\ u_{yx} & u_{yy} \end{pmatrix} \qquad \mathbf{u} = \nabla\, \mathbf{d}$$

Deformation rate tensor

$$\mathbf{v} = \frac{d}{dt}\mathbf{u}$$

anisotropic

isotropic

$$\mathbf{v} = \tilde{\mathbf{v}} + \frac{\nabla \cdot \mathbf{v}}{2}\mathbb{I} + \omega\epsilon$$

shear

compression/growth

rotation

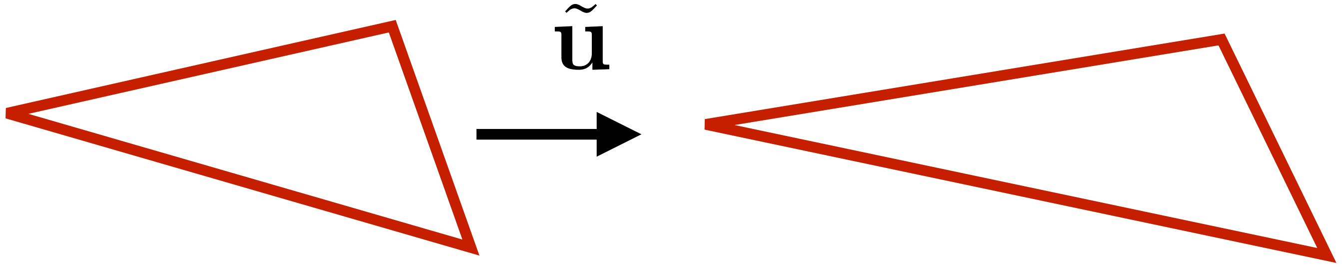
Shape tensor

Triangle shape tensor $\mathbf{Q}$ $\begin{pmatrix} Q_{xx} & Q_{xy} \\ Q_{xy} & -Q_{xx} \end{pmatrix}$ triangle shear deformation

$$\tilde{\mathbf{u}} = \Delta\mathbf{Q}$$

(corotational) change in shape

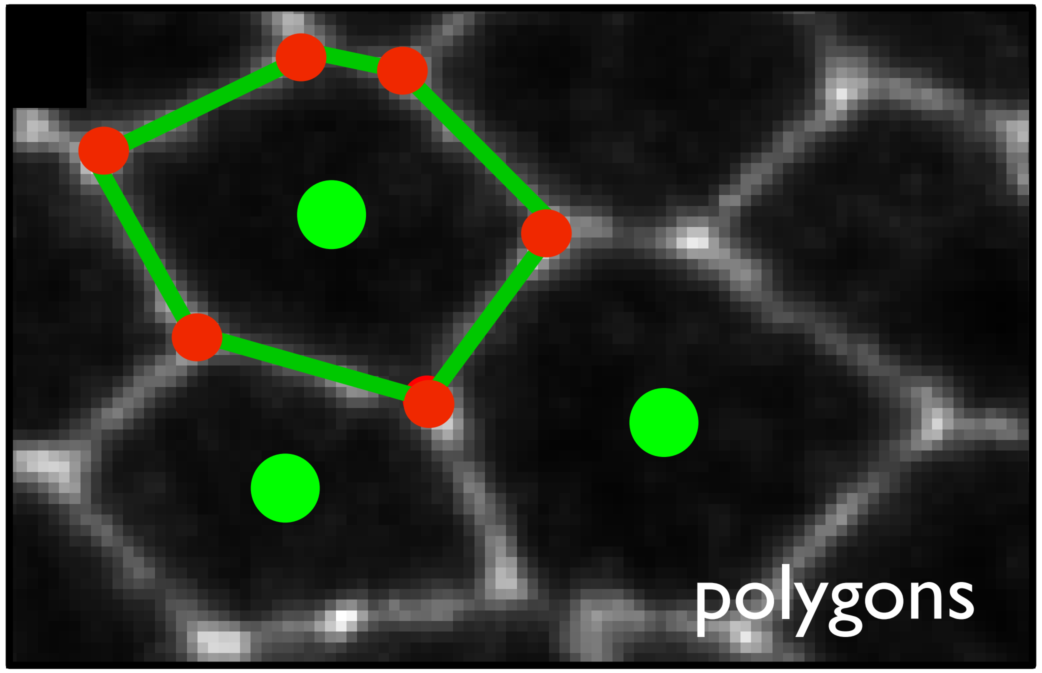
triangle deformation

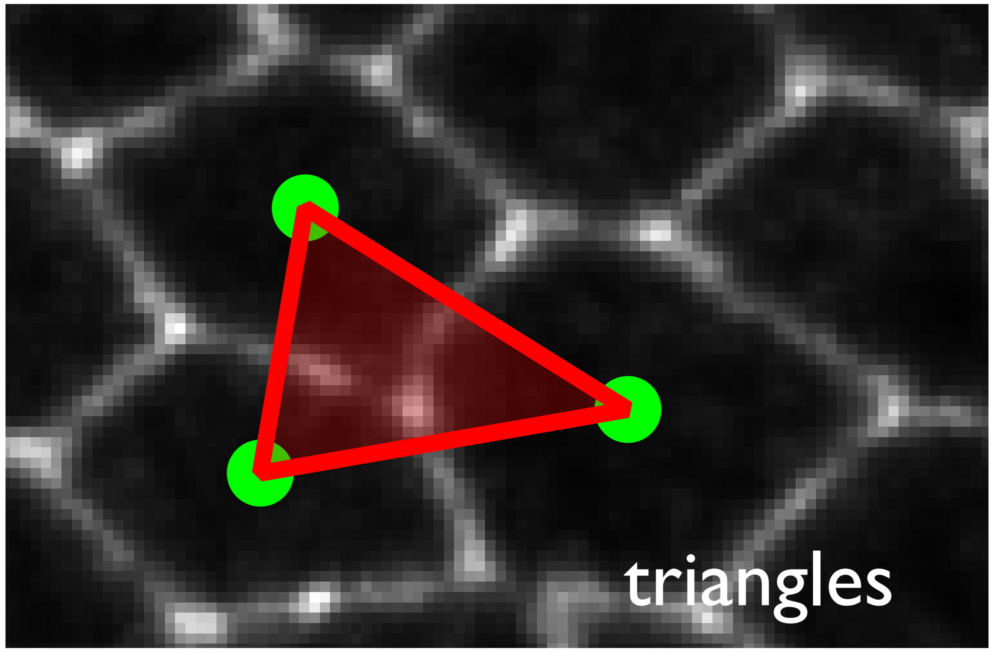


initial shape $\mathbf{Q}$

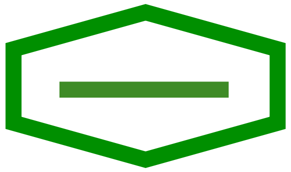
final shape $\mathbf{Q}'$

$$\Delta\mathbf{Q} = \mathbf{Q}' - \mathbf{Q}$$





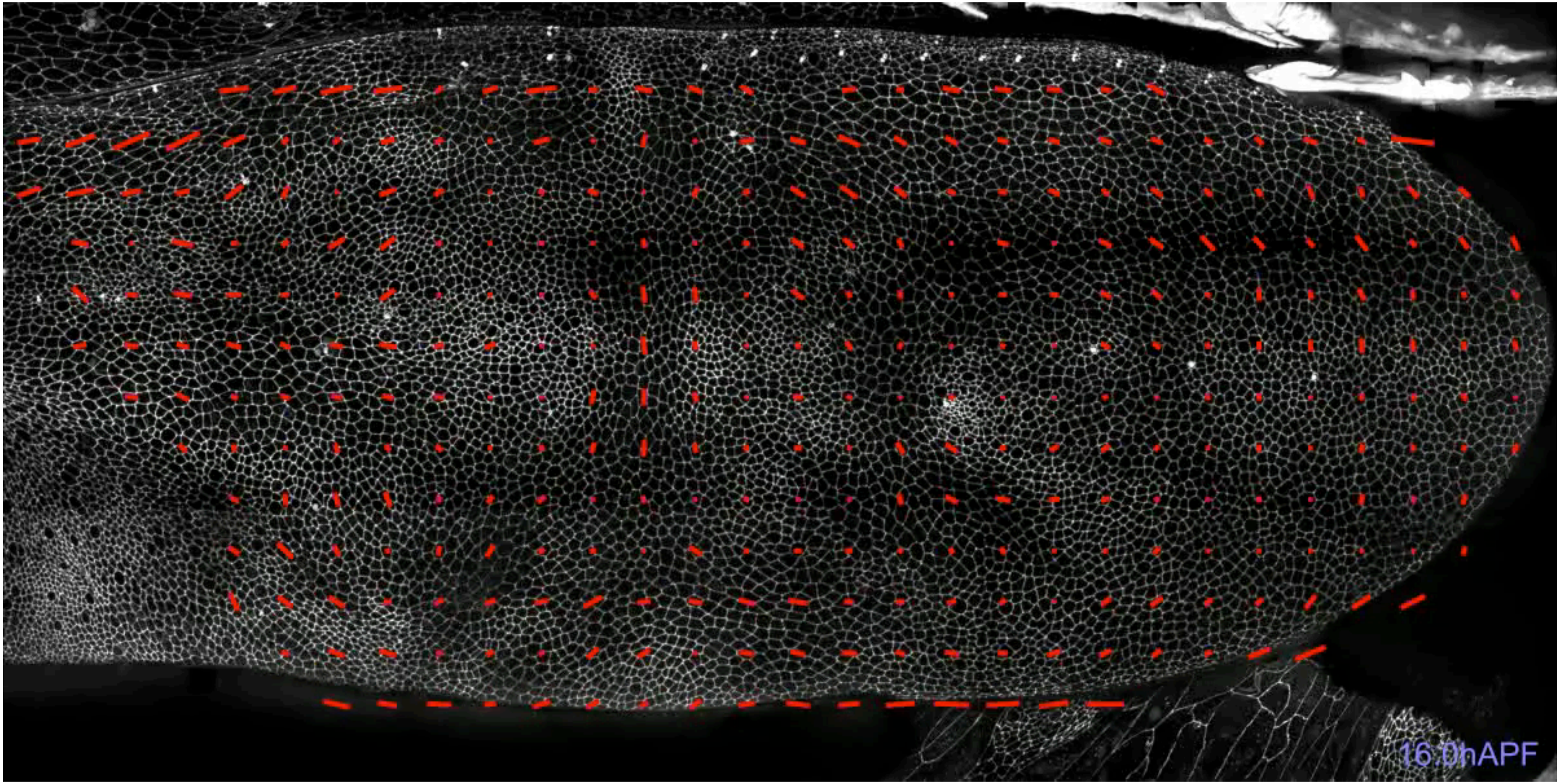
Cell elongation



$\mathbf{Q}$

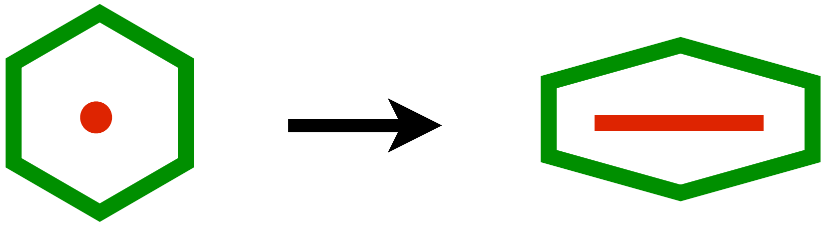
average elongation of cell-triangles

Cell shape dynamics



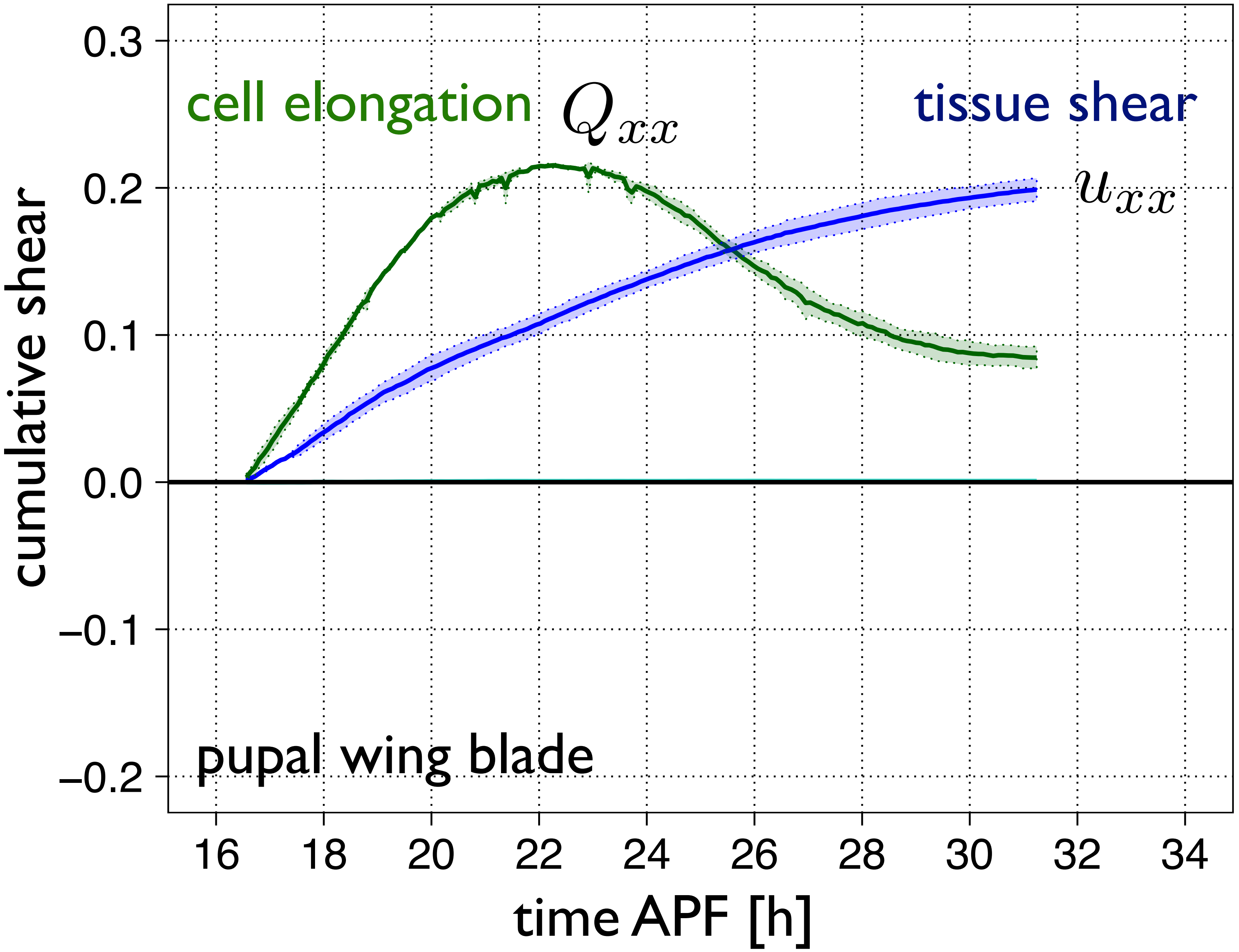
cell elongation patterns

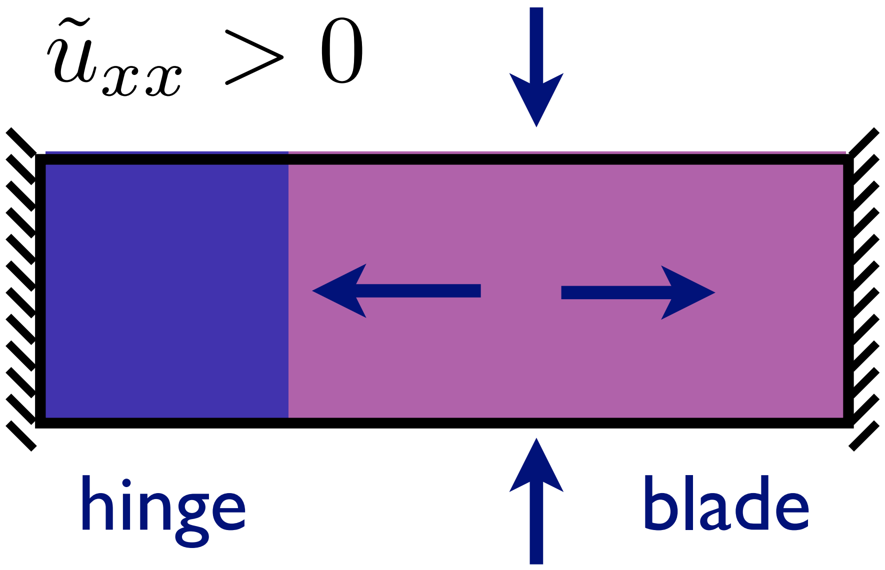
$\mathbf{Q}$

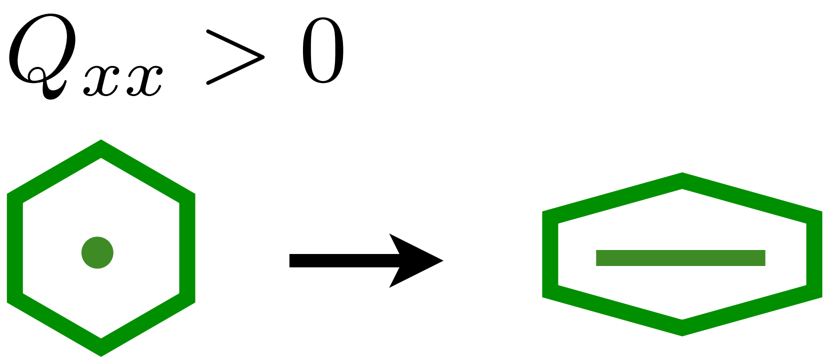


$Q_{xx} > 0$

Cell and tissue shear







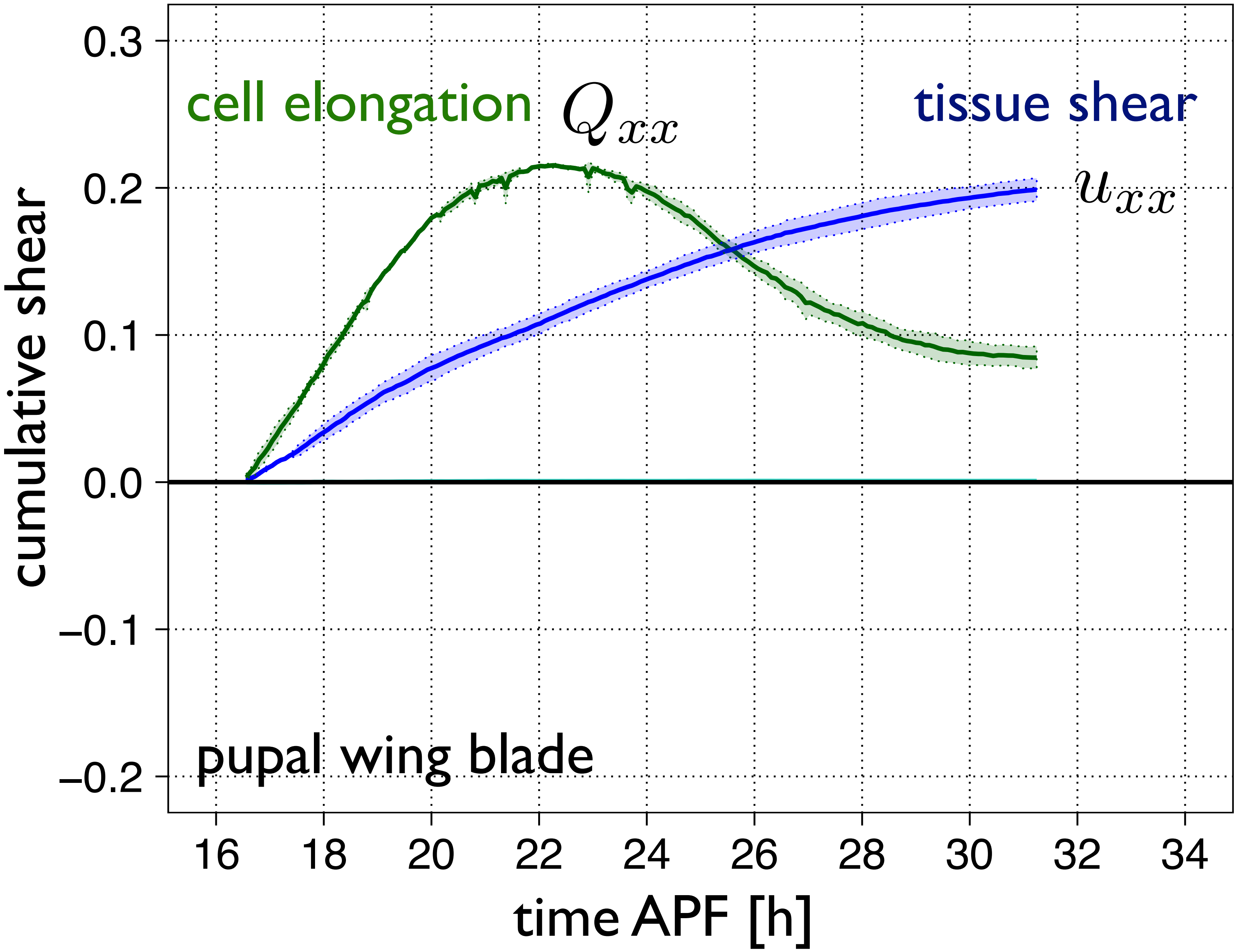
tissue shear rate

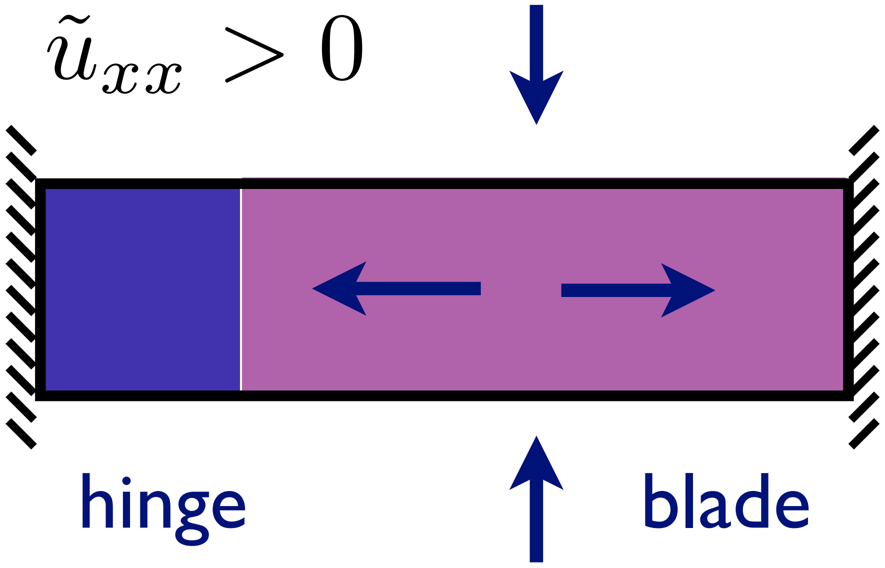
$$\tilde{\mathbf{v}} = \frac{d}{dt}\tilde{\mathbf{u}}$$

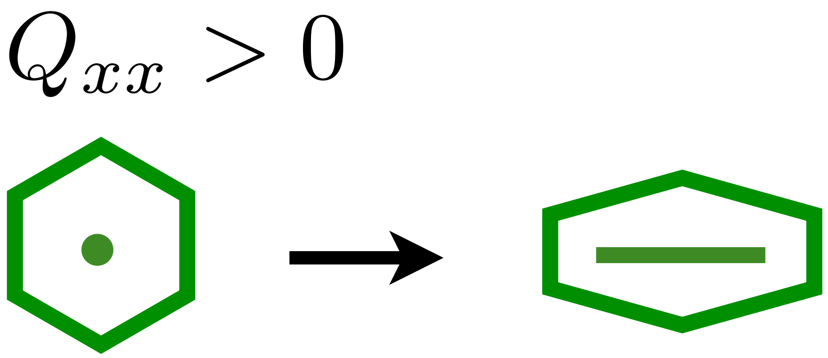
tissue shear cell shape change

$$\tilde{\mathbf{u}} \neq \Delta\mathbf{Q}$$

Cell and tissue shear







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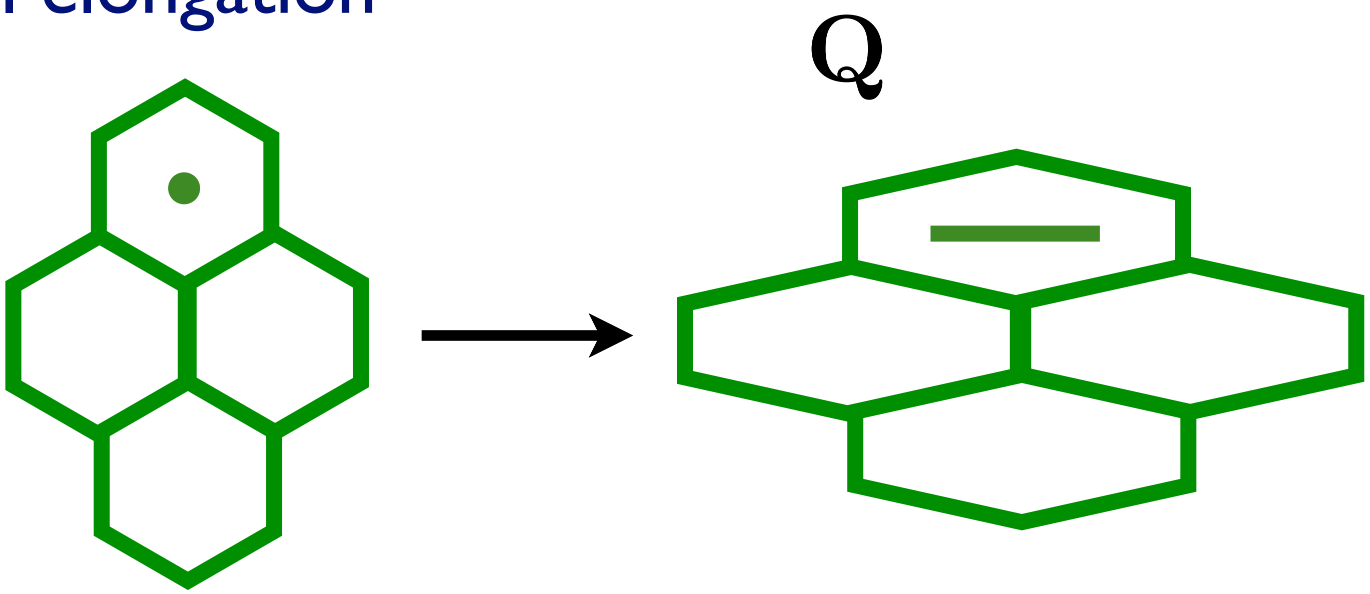
Cell and tissue shear

Cell elongation



Shear deformation

$$\tilde{\mathbf{u}} = \Delta\mathbf{Q}$$

co-rotational change
of elongation

shear rate

$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt}$$

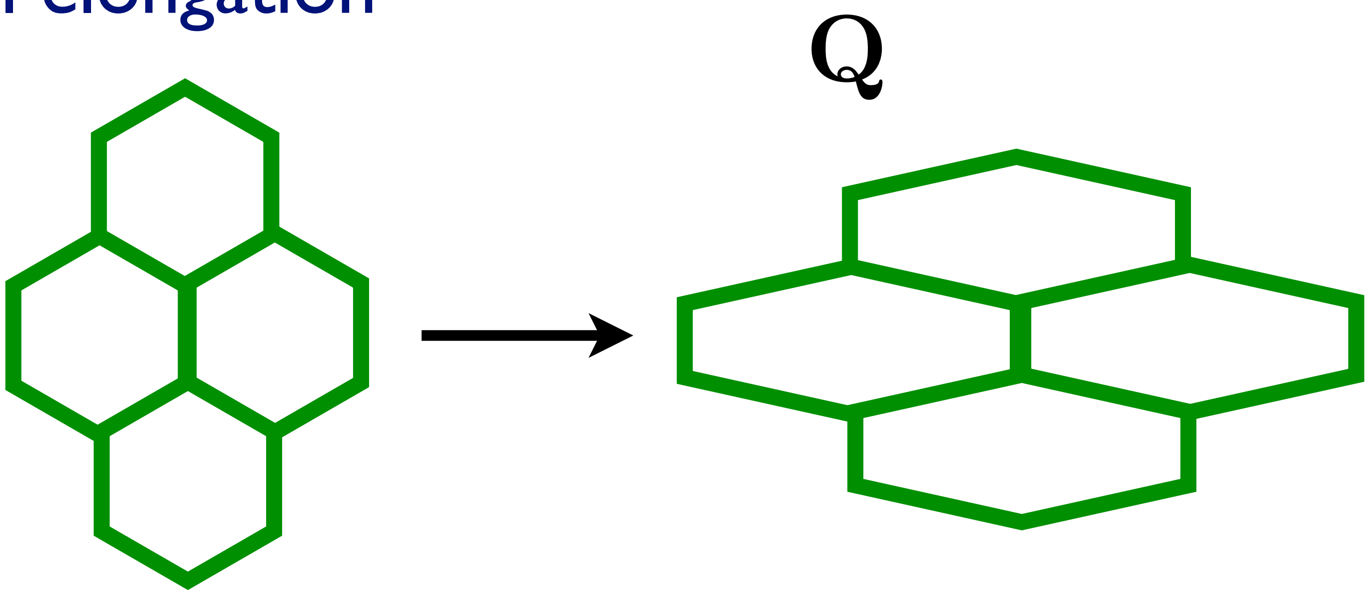
corotational time derivative
of elongation

Etournay et al. eLife.07090 (2015)

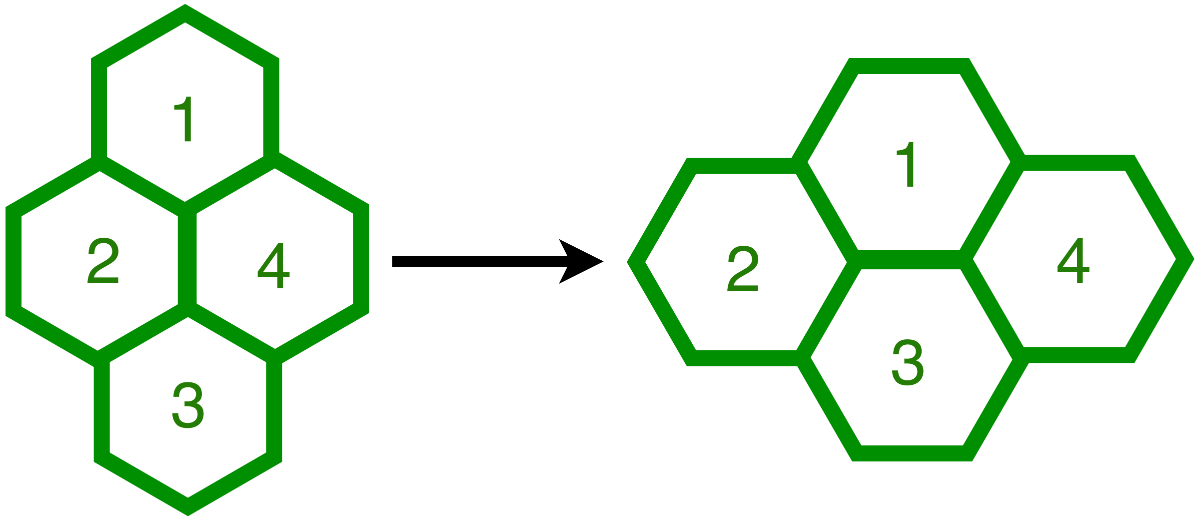
Merkel et al. Phys. Rev. E 95 (2017)

Cell and tissue shear

Cell elongation



Neighbor exchange (T1 process)



tissue shear rate

$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

cell shear rate

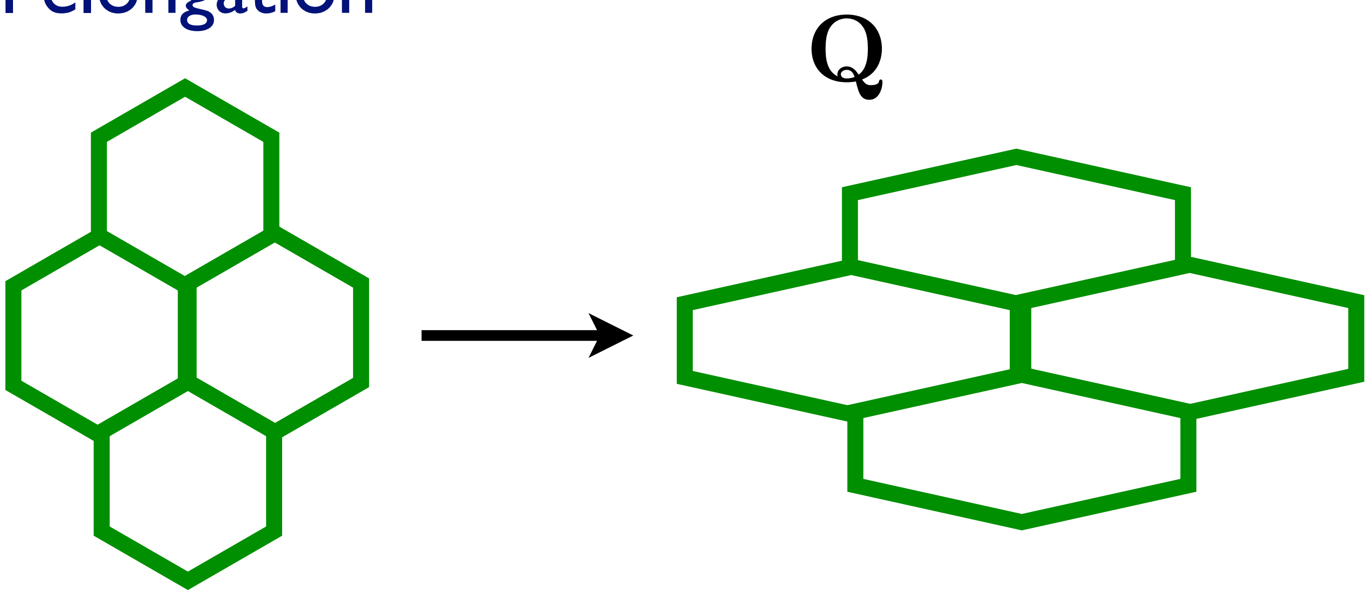
shear by cell rearrangements

Etournay et al. eLife.07090 (2015)

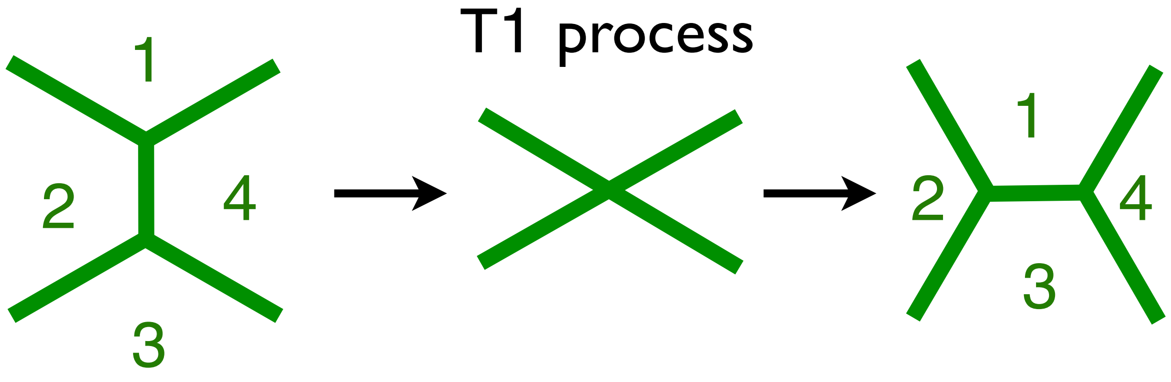
Merkel et al. Phys. Rev. E 95 (2017)

Cell and tissue shear

Cell elongation



Neighbor exchange (T1 process)



tissue
shear rate

$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

cell shear rate

shear by cell rearrangements

Etournay et al. eLife.07090 (2015)

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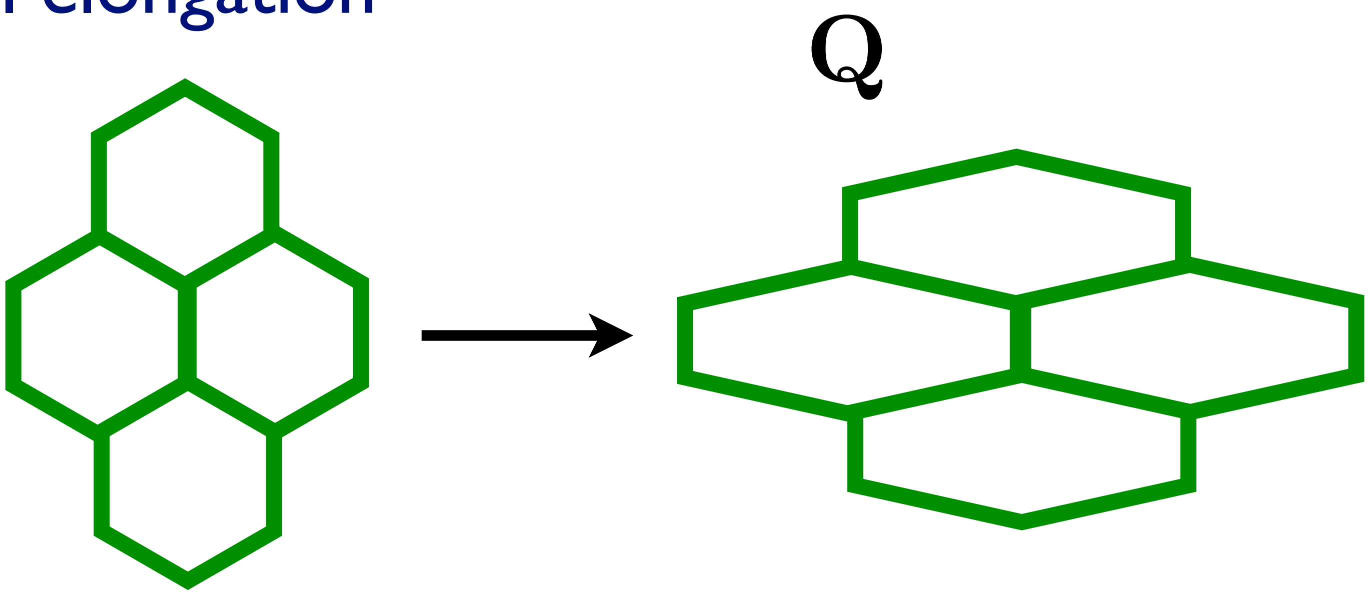
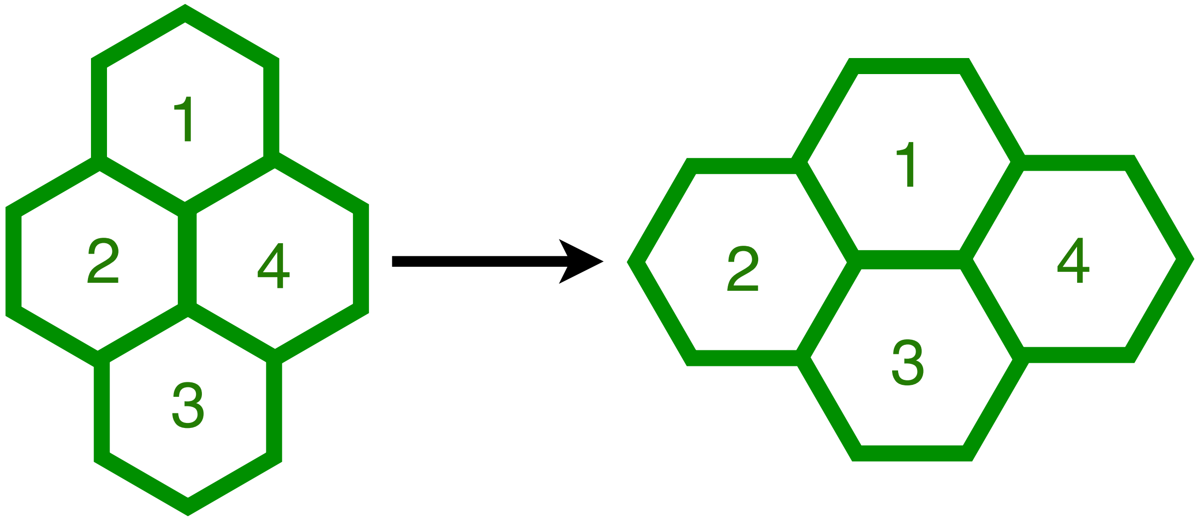
Cell and tissue shear

Cell elongation



Neighbor exchange (T1 process)



tissue shear rate

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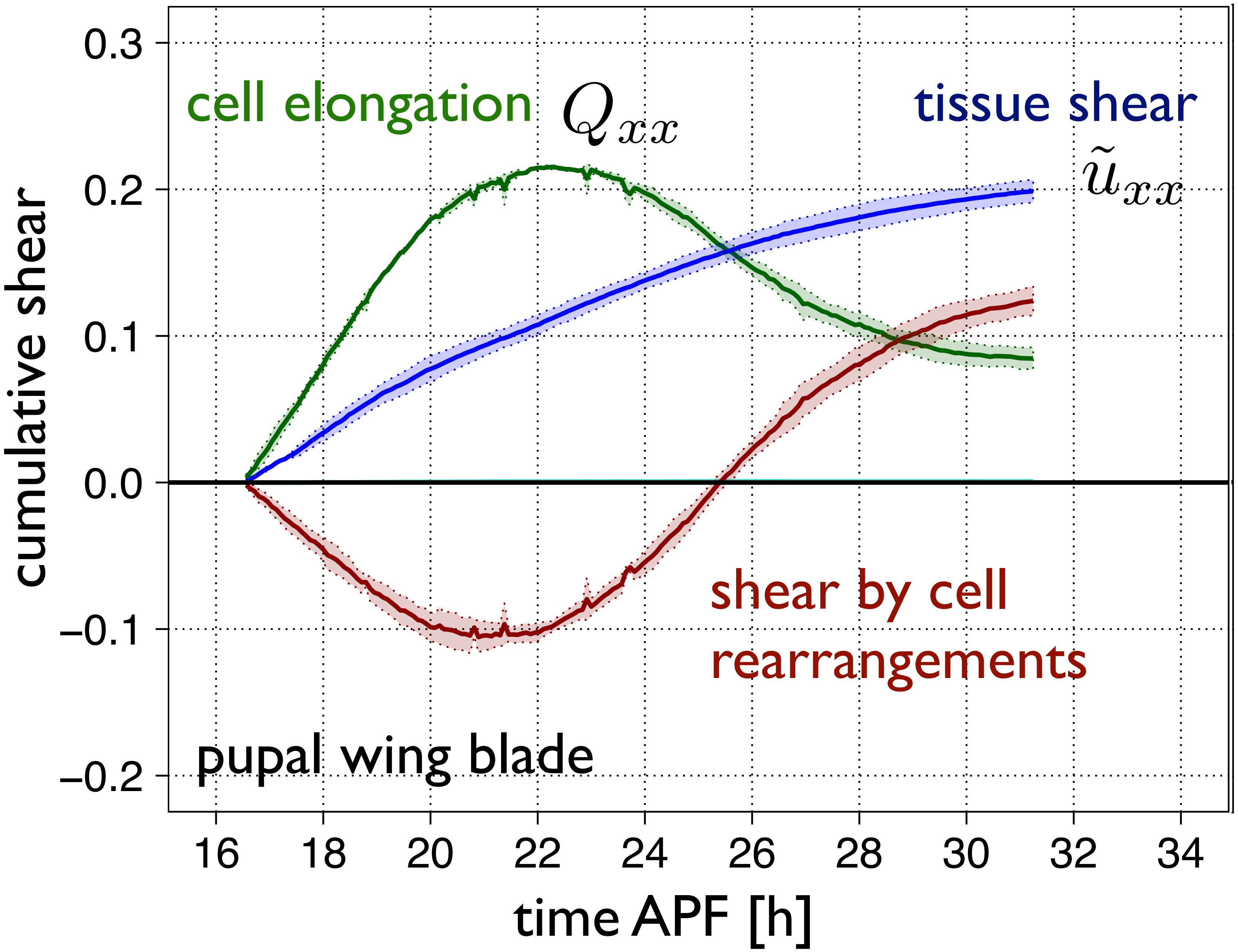
cell shear rate

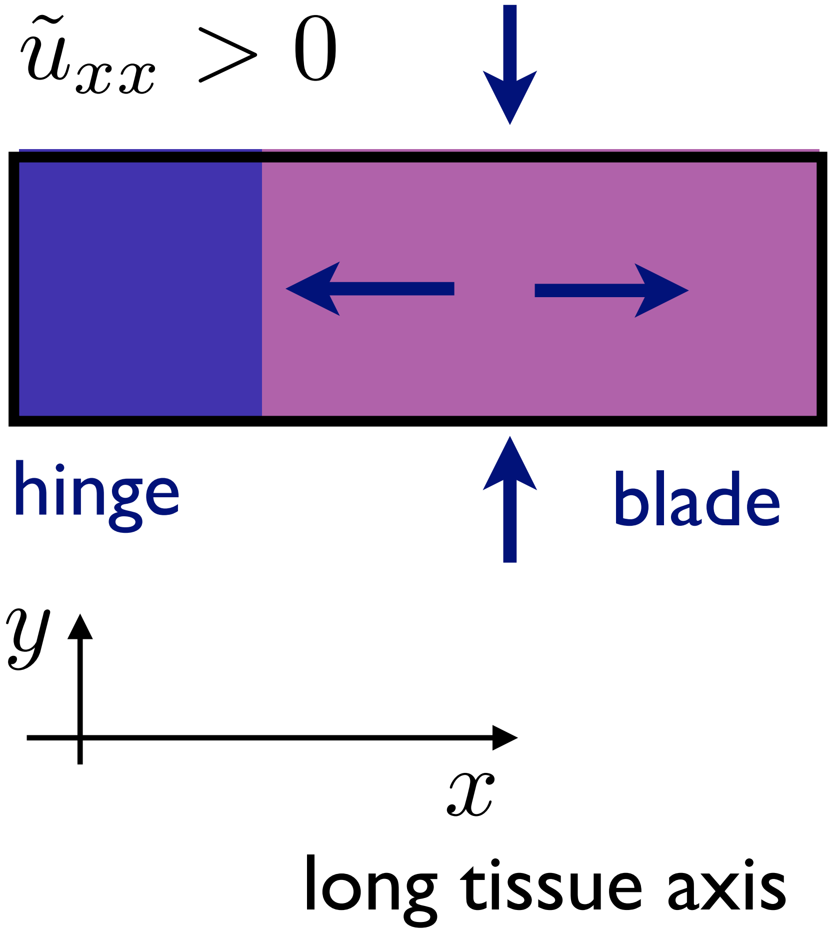
shear by cell rearrangements

Etournay et al. eLife.07090 (2015)

Merkel et al. Phys. Rev. E 95 (2017)

Shear deformations





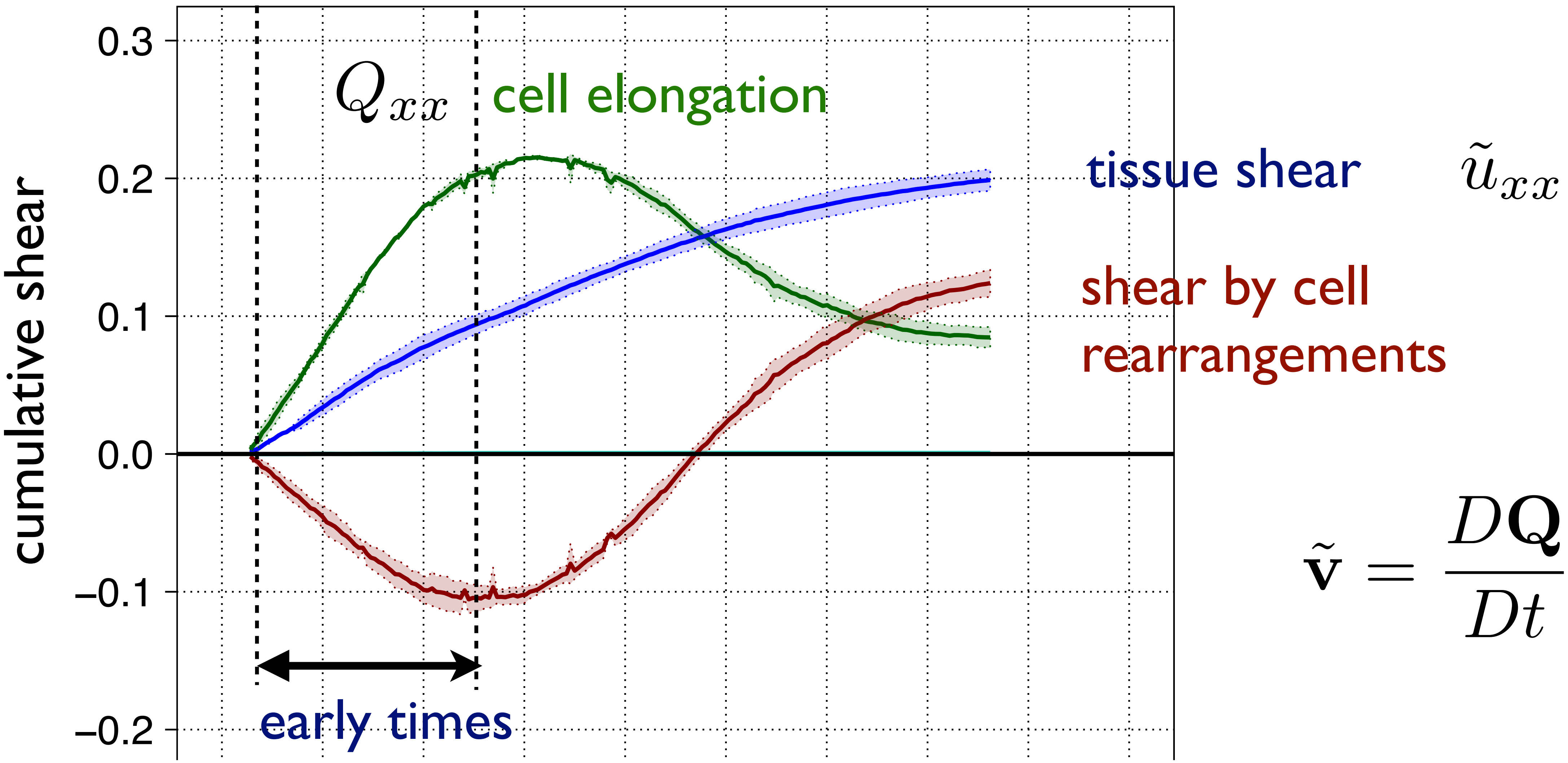
tissue shear rate

cell shear rate

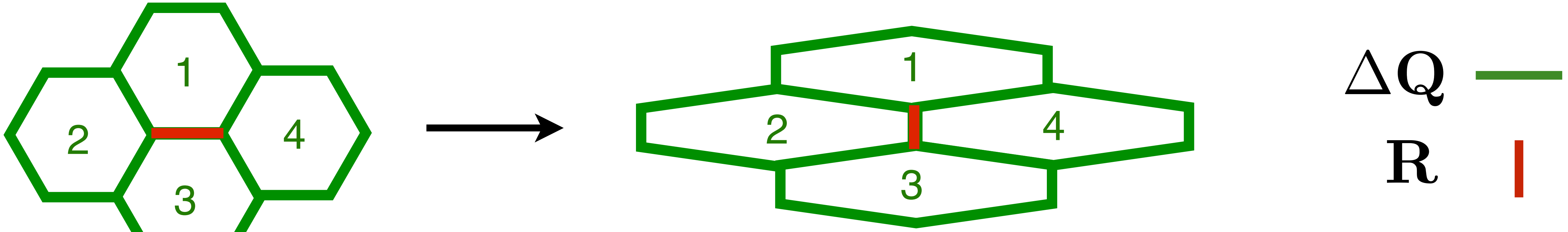
$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

shear rate by cell rearrangements

Early times

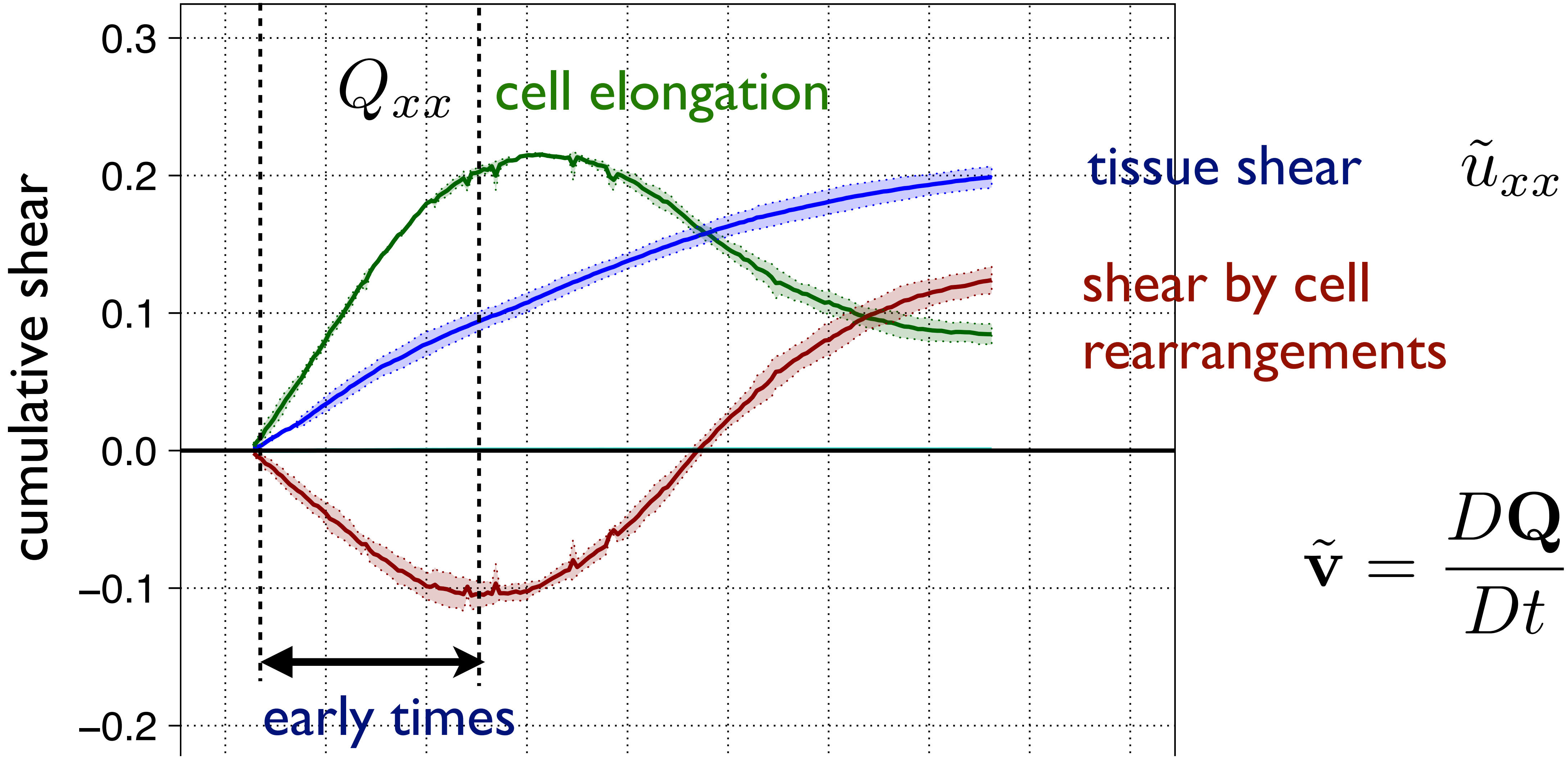


$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

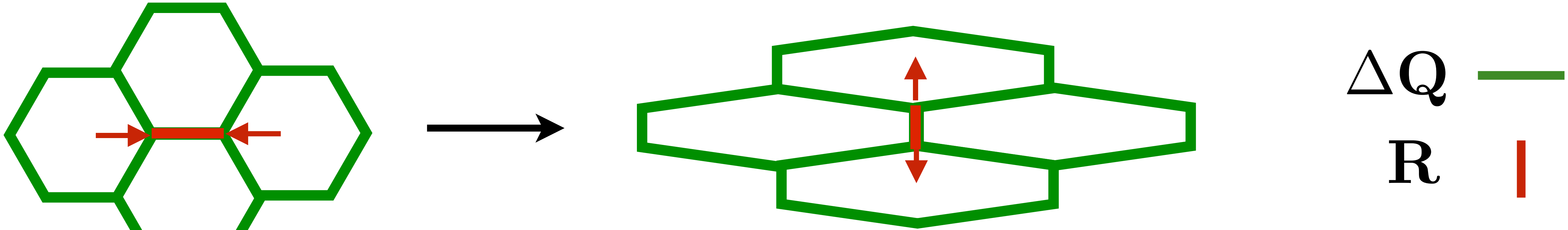


T1 transitions stretch cells

Early times

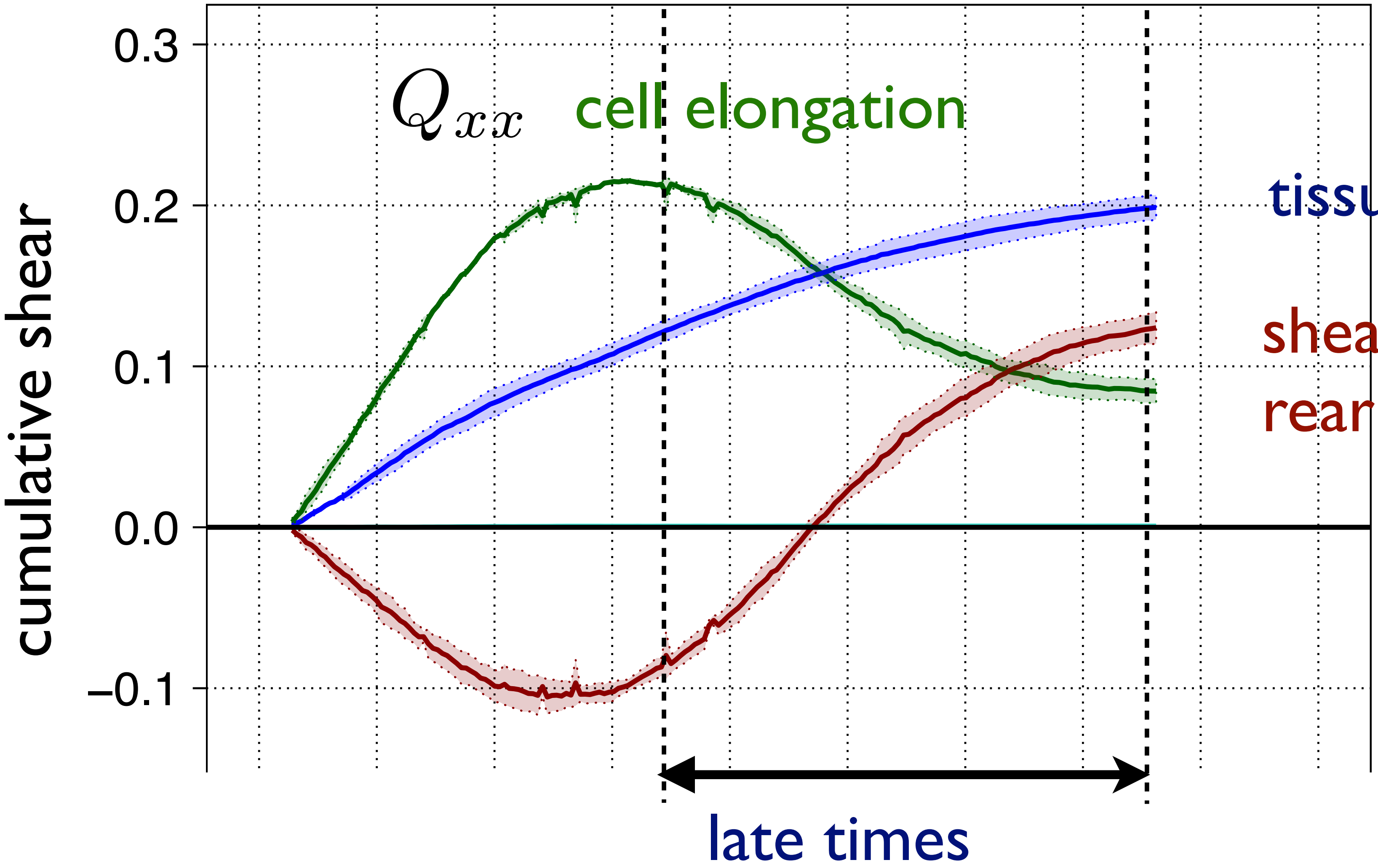


$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

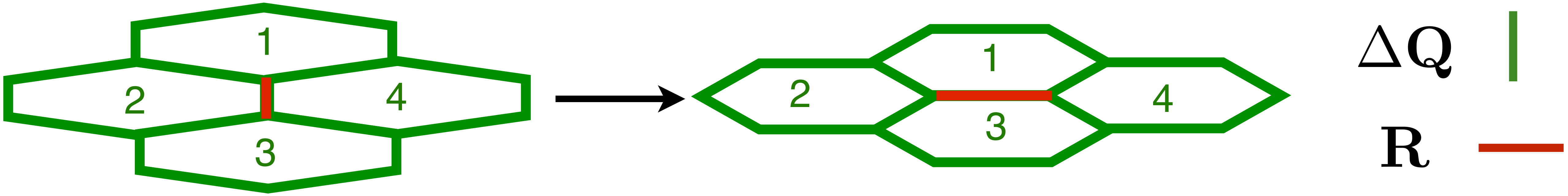


T1 transitions stretch cells

Later times

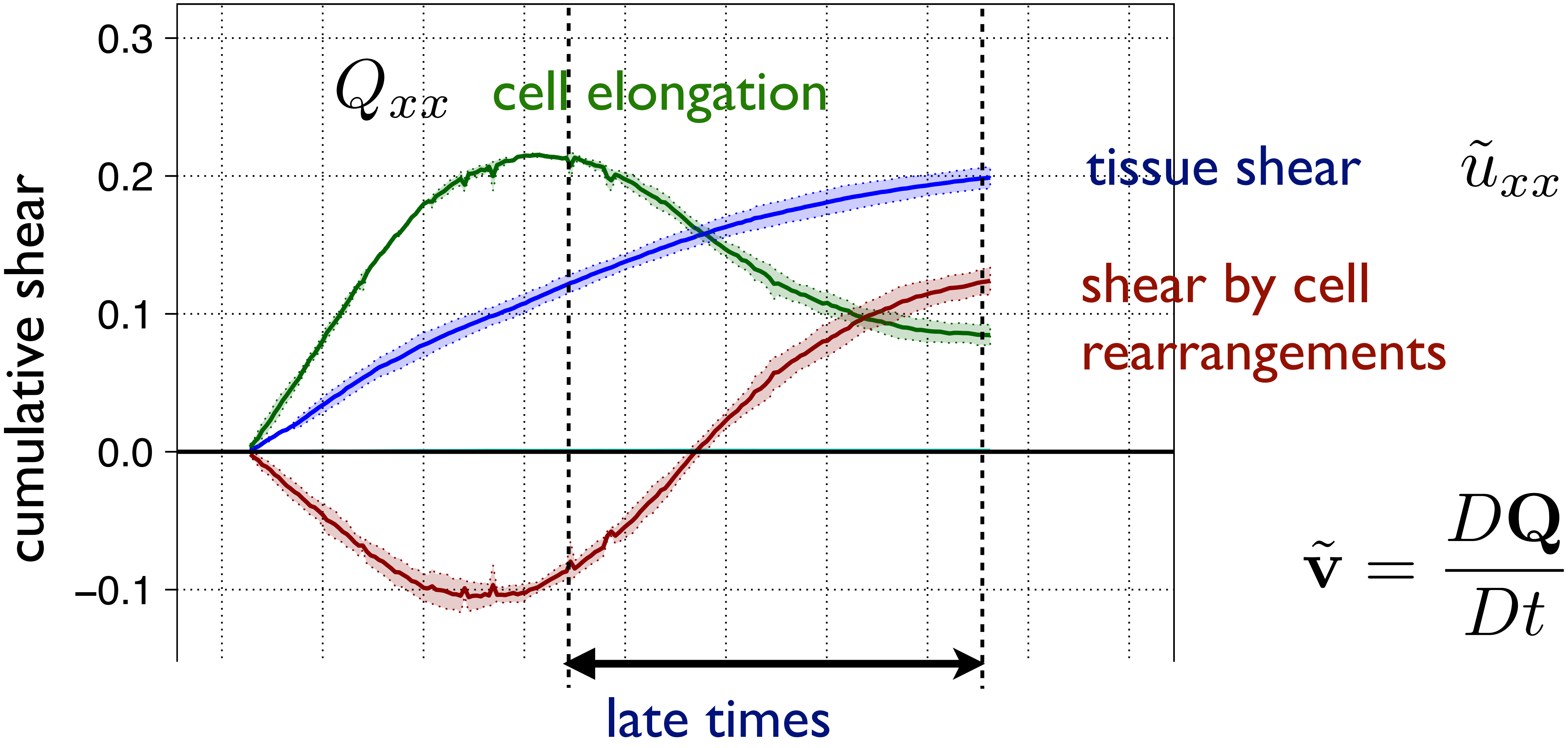


$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

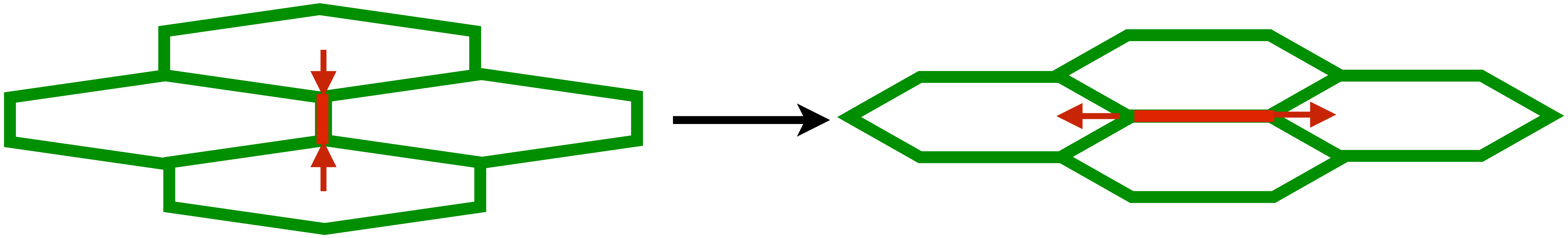


T1 relax cell elongation

Later times



$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

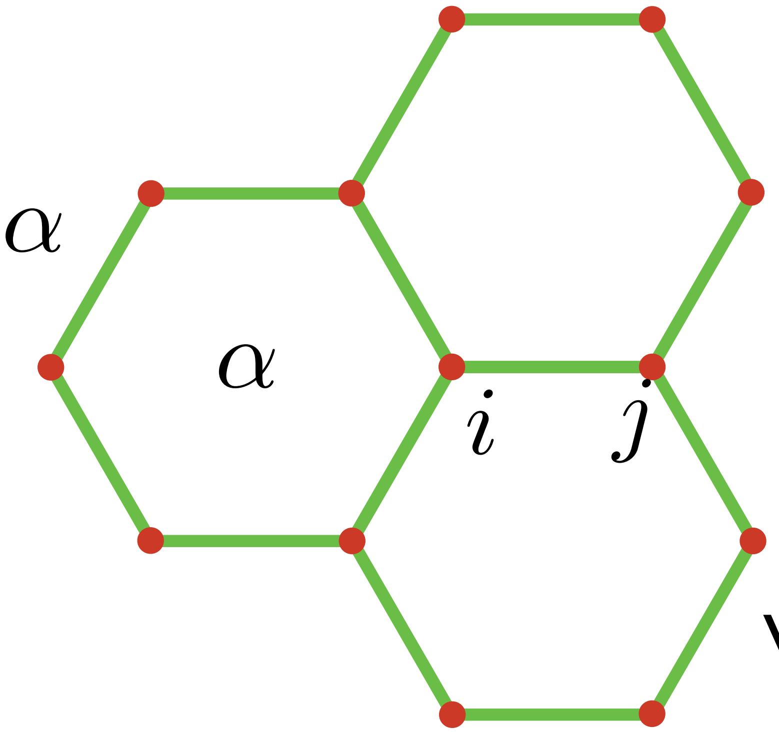


T1 relax cell elongation

$\Delta \mathbf{Q}$ |

$\mathbf{R}$ —

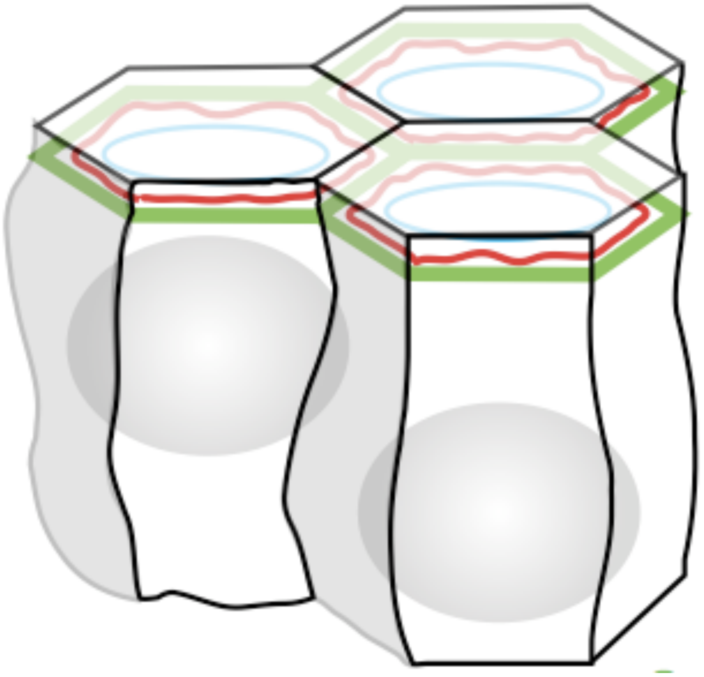
Network mechanics



cell α

cell boundary $< i,j >$

vertex i j



Work function

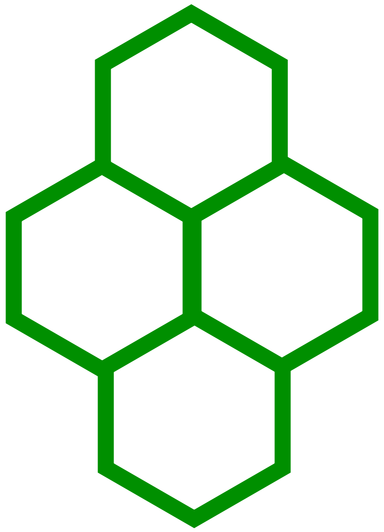
$$W(\mathbf{R}_i) = \sum_{\alpha} \frac{K}{2}(A_\alpha - A^{(0)})^2 + \sum_{\langle i,j \rangle} \Lambda_{ij} L_{ij}$$

vertex force

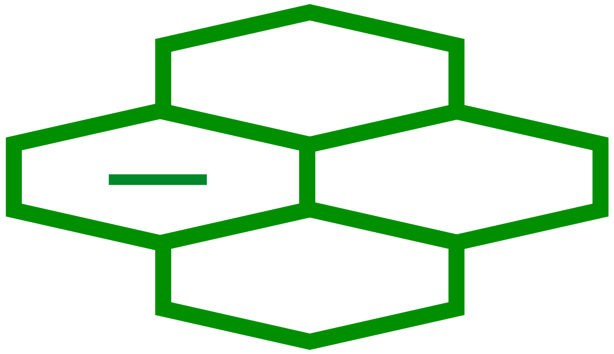
$$f_i = -\frac{\partial E}{\partial \mathbf{R}_i}$$

area elasticity	K	A_α	cell area
cell bond tension	Λ_{ij}	L_{ij}	cell boundary length

Network shear stress



$\mathbf{Q} = 0$



$\mathbf{Q}$ —

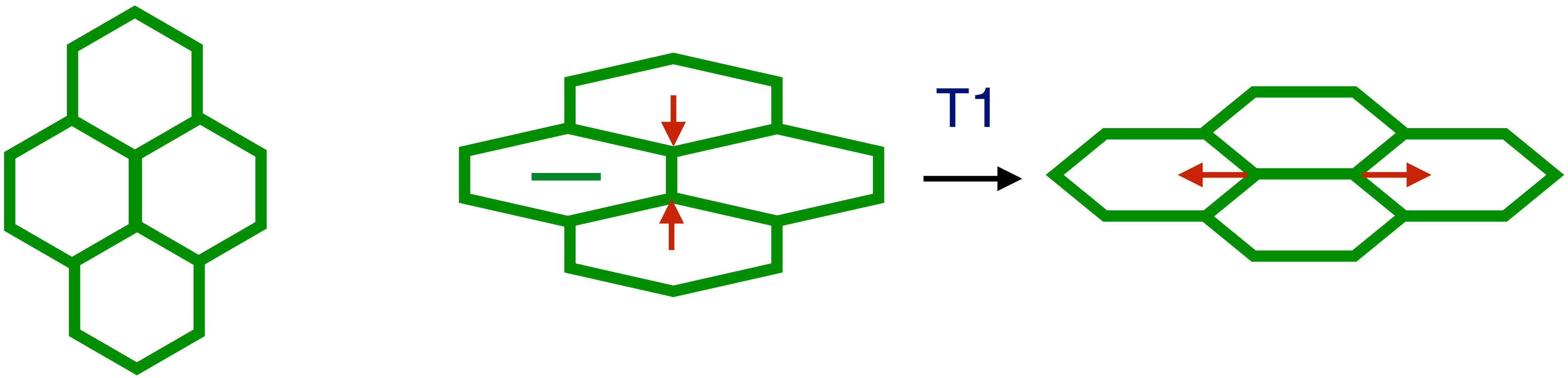
Elastic shear stress associated with cell shape change

tissue shear stress

elastic stress

$$\tilde{\sigma} = K\mathbf{Q}$$

T1 transitions biased by cell shape



$\mathbf{Q} = 0$

$\mathbf{Q}$ —

$\mathbf{R}$ —

Cell elongation drives cell rearrangement

$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q}$$

→ Relaxation of shear stress

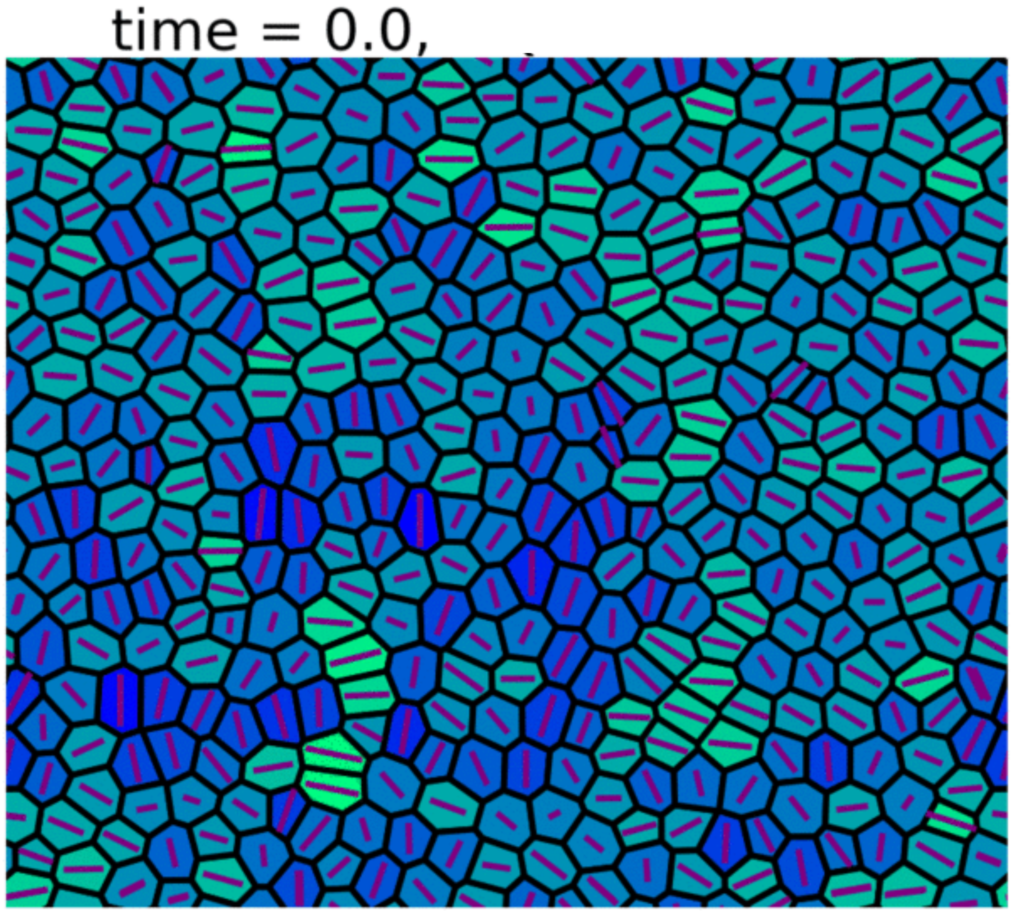
tissue shear stress

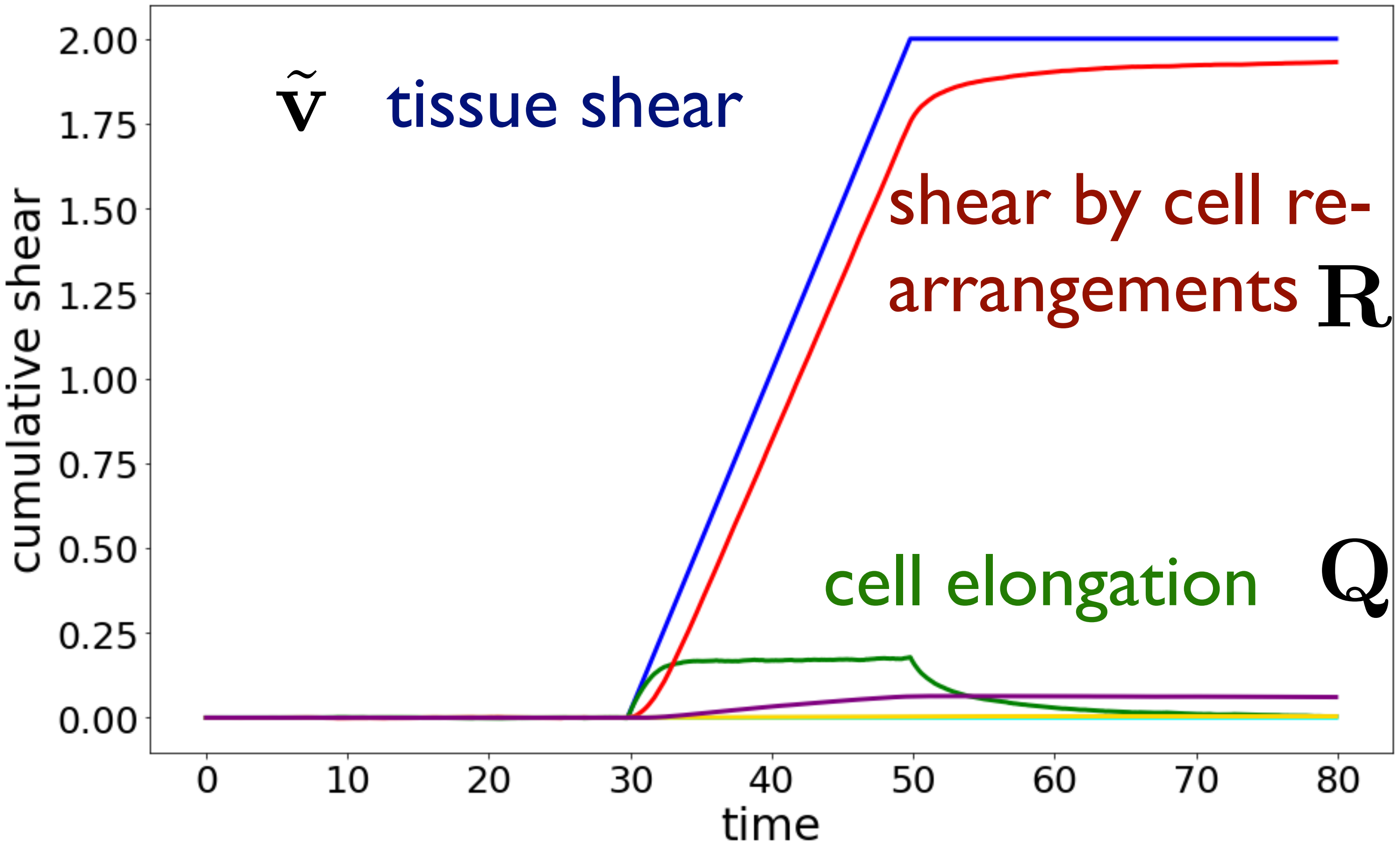
elastic stress

$$\tilde{\sigma} = K\mathbf{Q}$$

T1 transitions biased by cell shape

T1 transition relax tissue stress





$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q}$$

$$\tilde{\sigma} = K\mathbf{Q}$$

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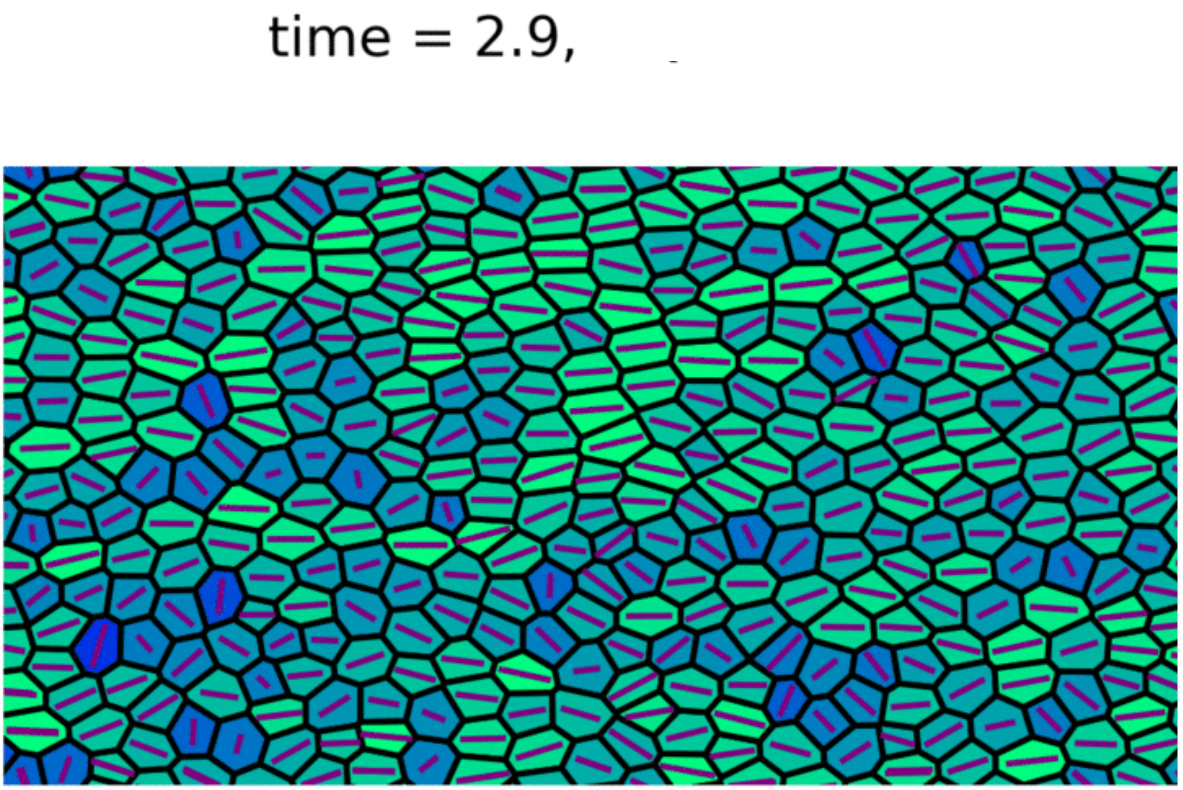
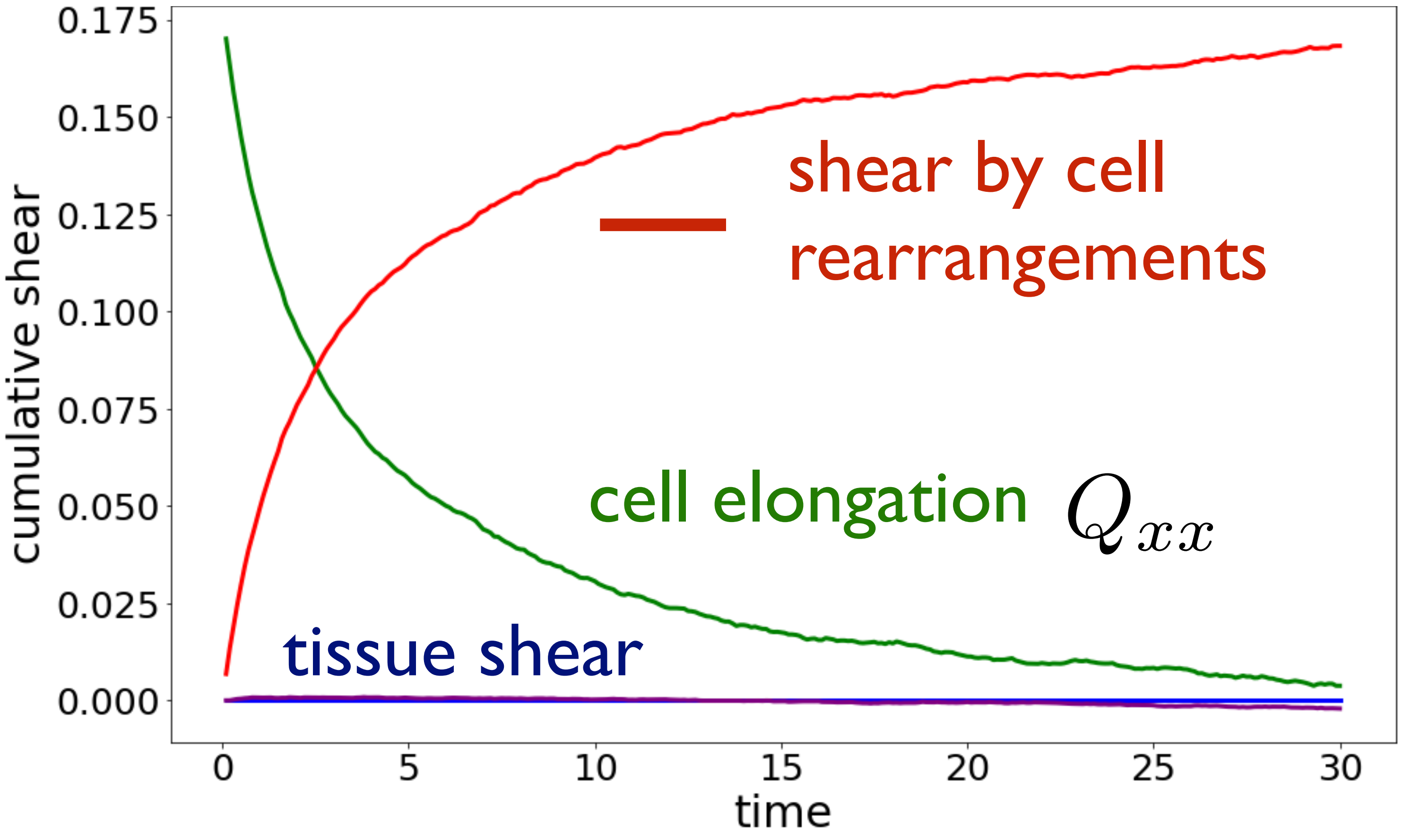
T1 transitions biased by cell shape

T1 transition relax tissue stress



cell elongation —



$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

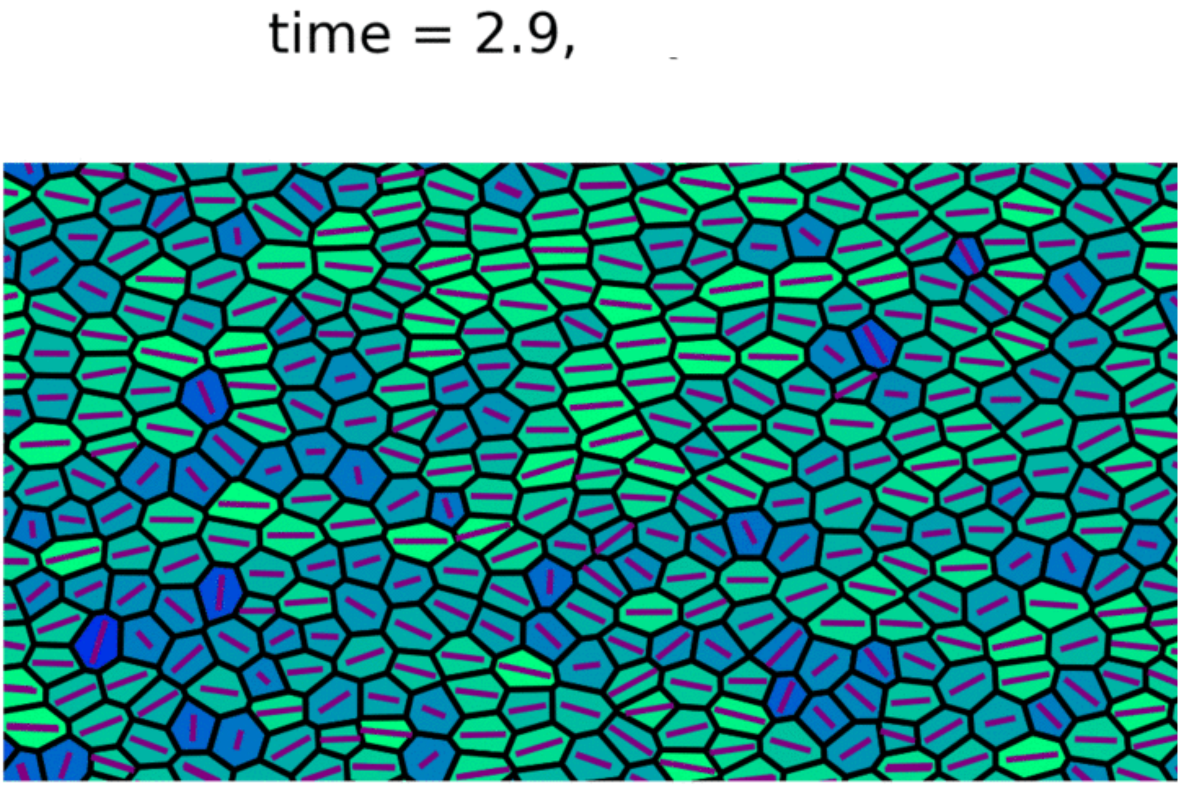
$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q}$$

no shear $\tilde{\mathbf{v}} = 0$

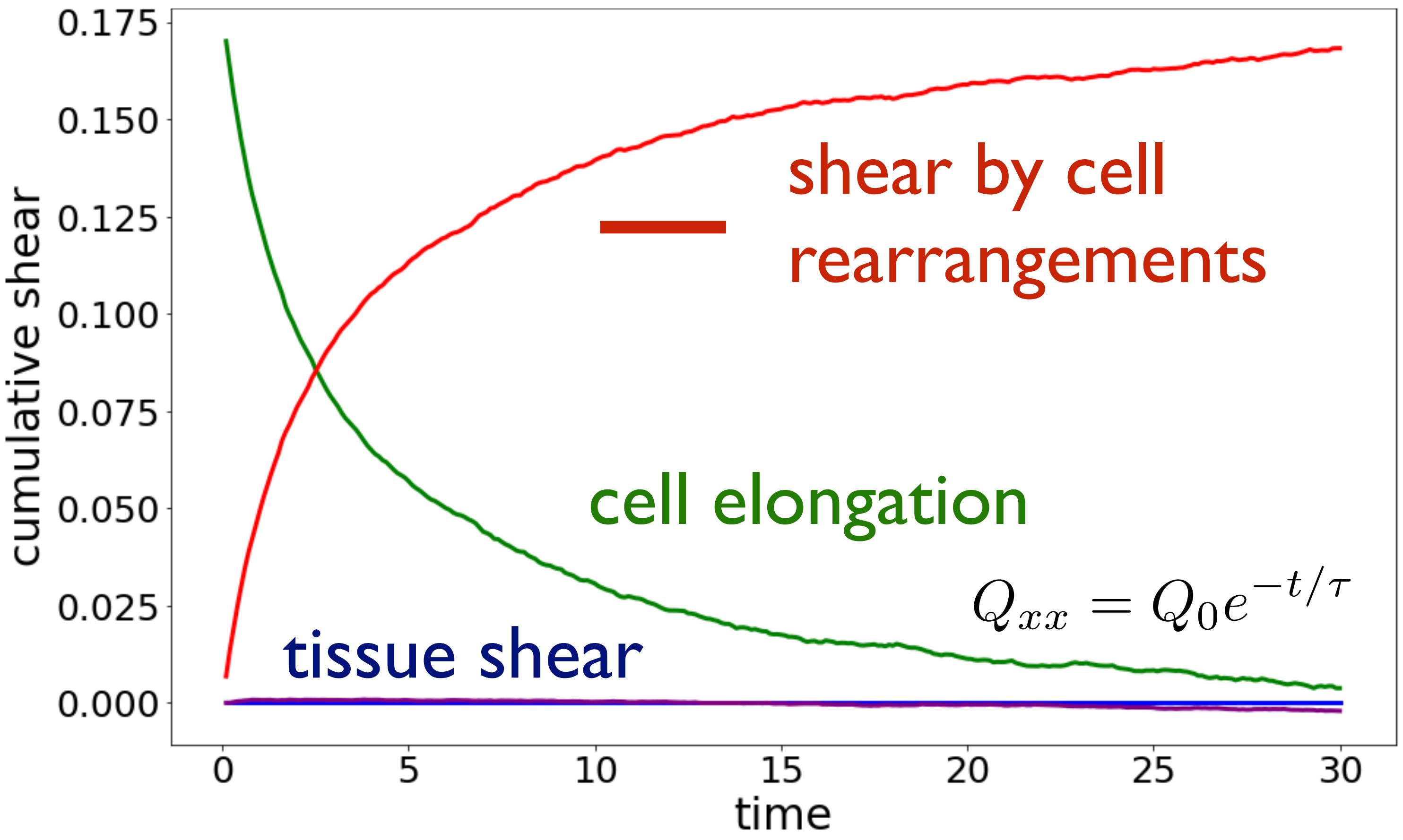
$$\tilde{\sigma} = K\mathbf{Q}$$

T1 transitions biased by cell shape

T1 transition relax tissue stress



cell elongation —



$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

no shear $\tilde{\mathbf{v}} = 0$

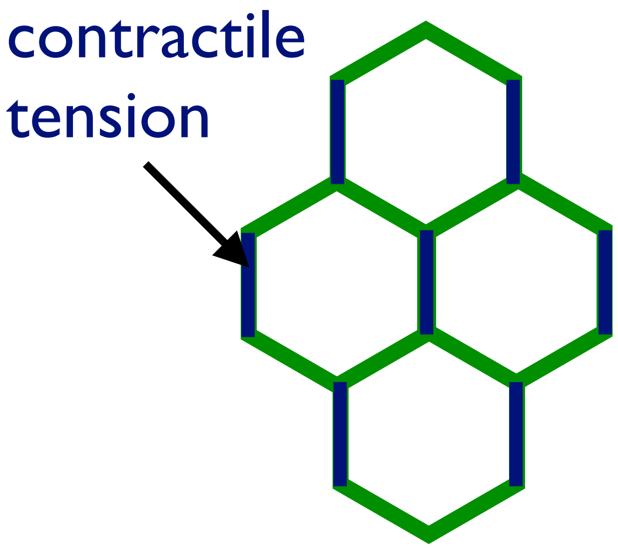
$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q}$$

$$\frac{d\mathbf{Q}}{dt} = -\frac{1}{\tau}\mathbf{Q}$$

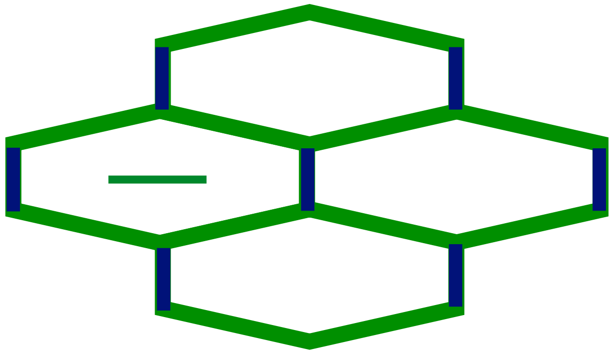
Anisotropic cell bond tension

high tension of vertical bonds

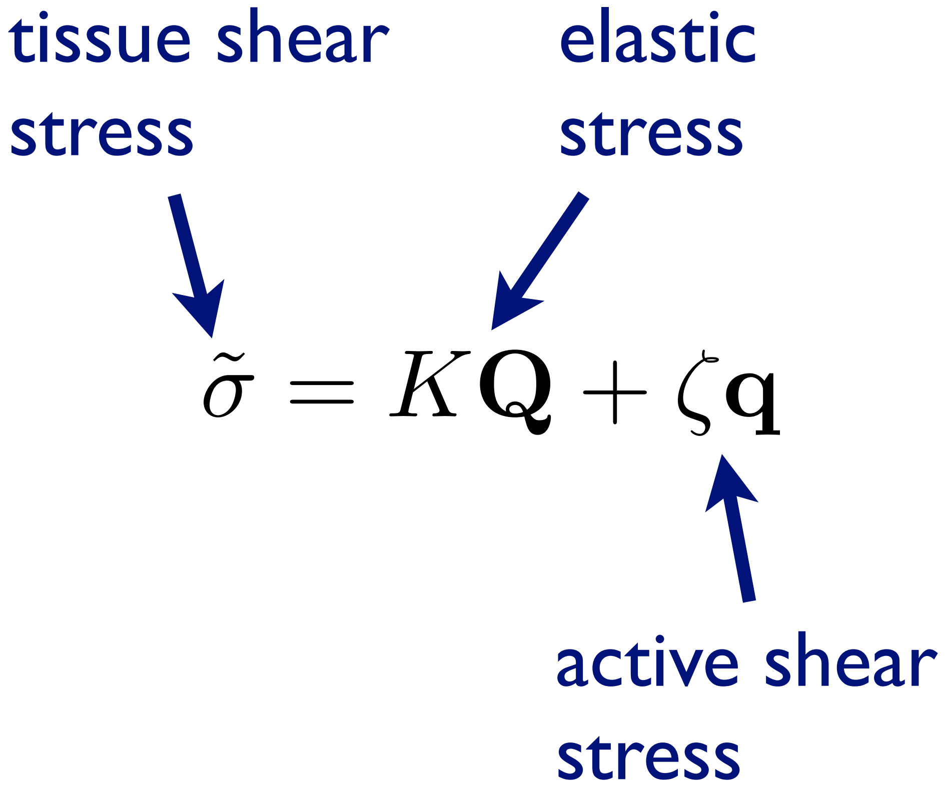
low tension of horizontal bonds



$\mathbf{Q} = 0$



$\mathbf{Q}$ —



$$\tilde{\sigma} = K\mathbf{Q} + \zeta\mathbf{q}$$

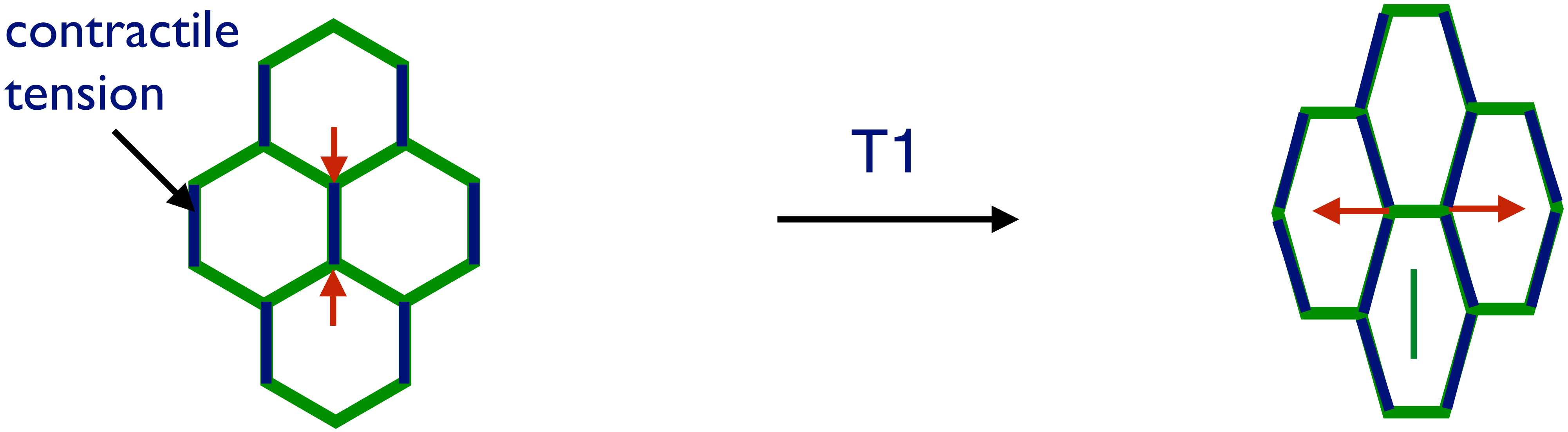
$\mathbf{q}$ | local cell anisotropy

$\zeta > 0$

T1 driven by cell bond tension

high tension of vertical bonds

low tension of horizontal bonds



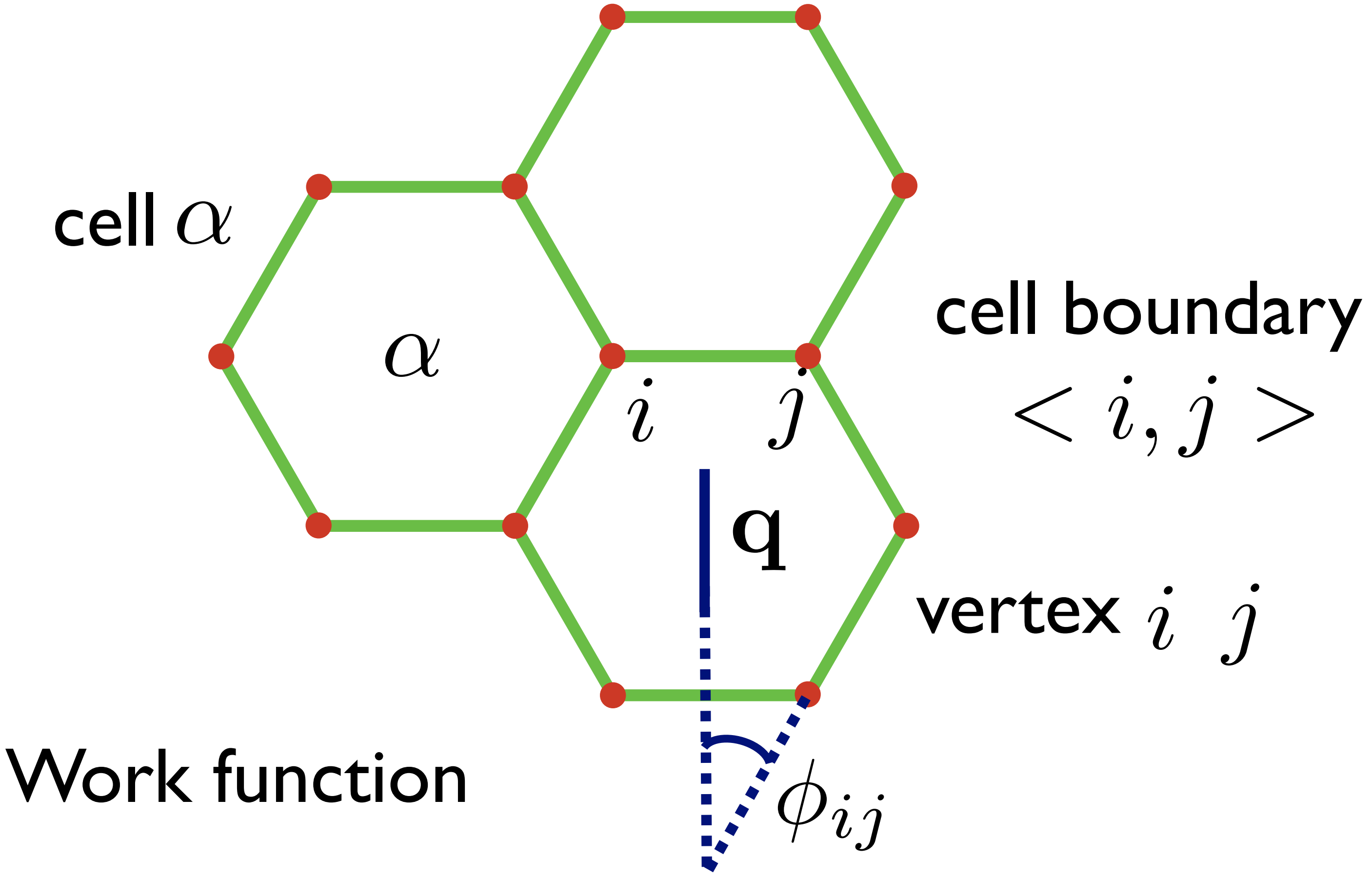
$\mathbf{q}$ | local cell anisotropy

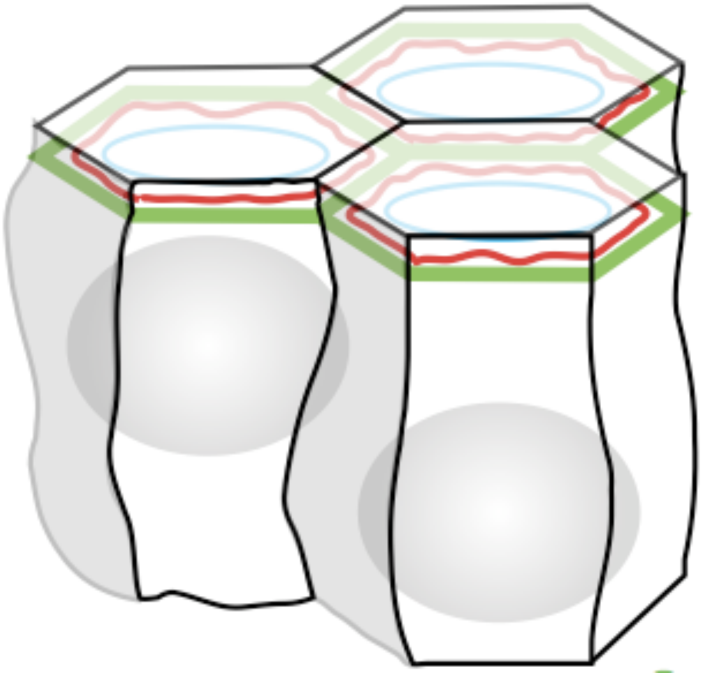
$\mathbf{R}$ —

$\mathbf{Q}$ |

$$\mathbf{R} = \lambda \mathbf{q} \qquad \lambda < 0$$

Network mechanics





Work function

$$W(\mathbf{R}_i) = \sum_{\alpha} \frac{K}{2}(A_\alpha - A^{(0)})^2 + \sum_{\langle i,j \rangle} \Lambda_{ij} L_{ij}$$

vertex force

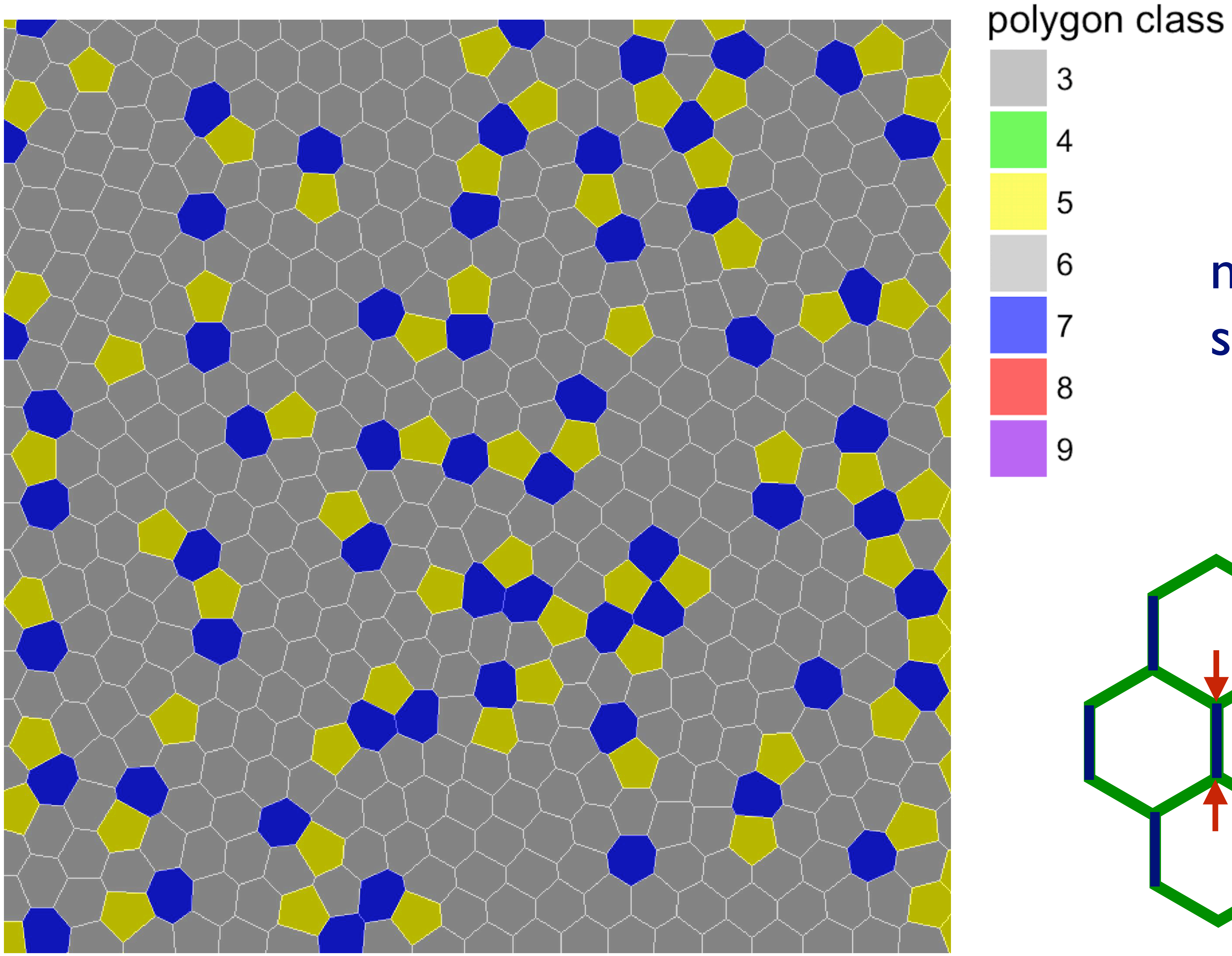
$$f_i = -\frac{\partial E}{\partial \mathbf{R}_i}$$

anisotropic bond tension

$$\Lambda_{ij} = \Lambda_0 + \Lambda_1 \cos(2\phi_{ij})$$

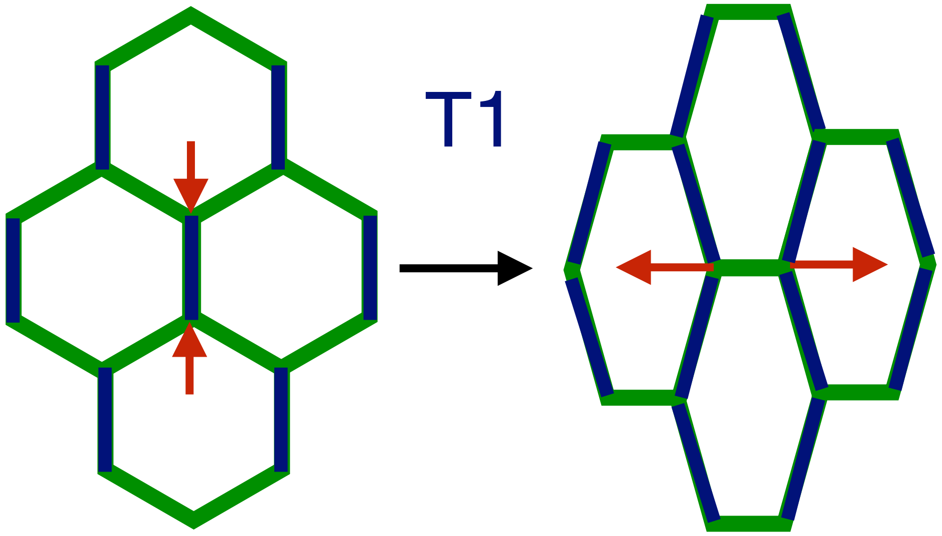
$\mathbf{q}$ | local cell anisotropy

T1 driven by cell bond tension



$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

no tissue shear $$\tilde{\mathbf{v}} = 0$$



$\mathbf{q}$ | local cell anisotropy

$\mathbf{R}$ — cell rearrangements

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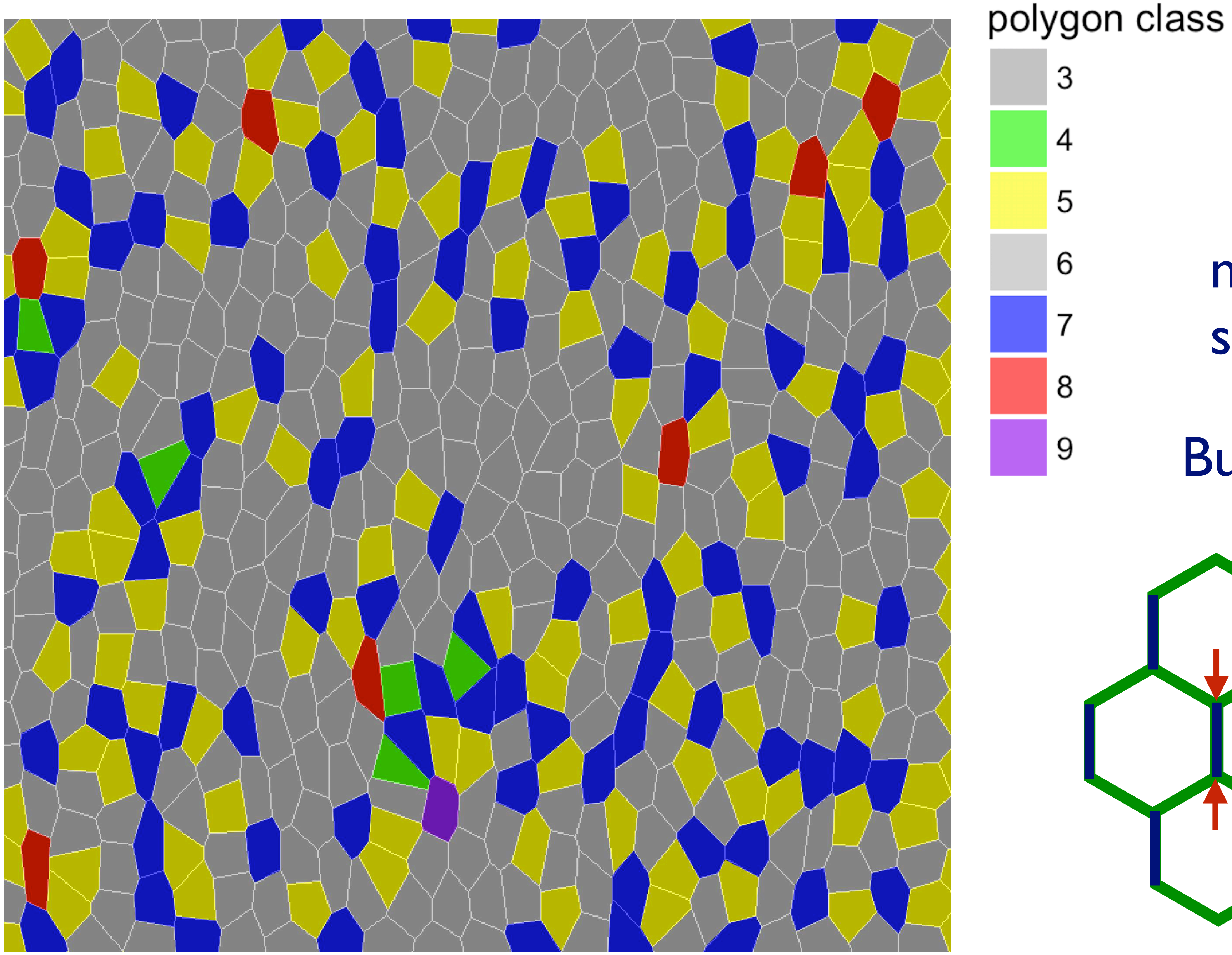
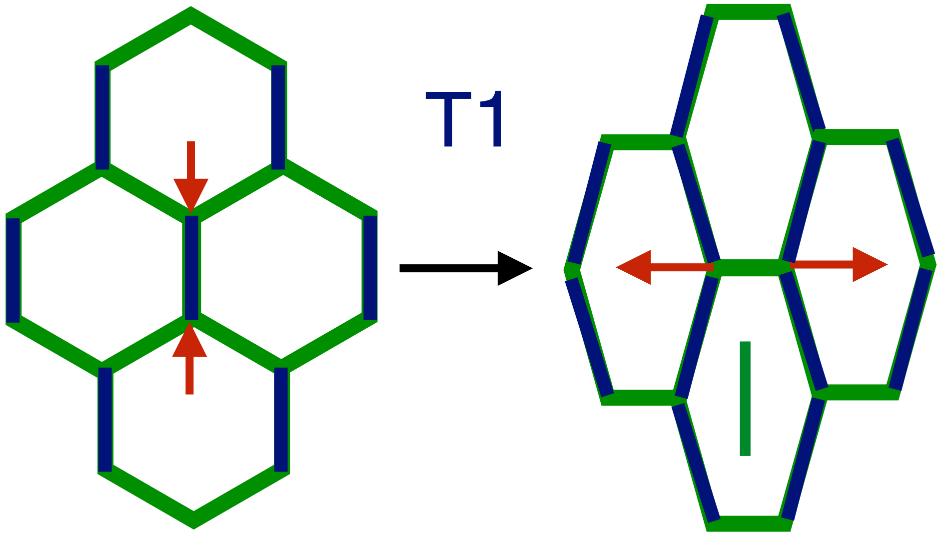
T1 driven by cell bond tension



$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

no tissue shear $\tilde{\mathbf{v}} = 0$

Buildup of shear stress



$\mathbf{q}$ | local cell anisotropy

$\mathbf{R}$ — cell rearrangements

$\Delta\mathbf{Q}$ | average cell elongation

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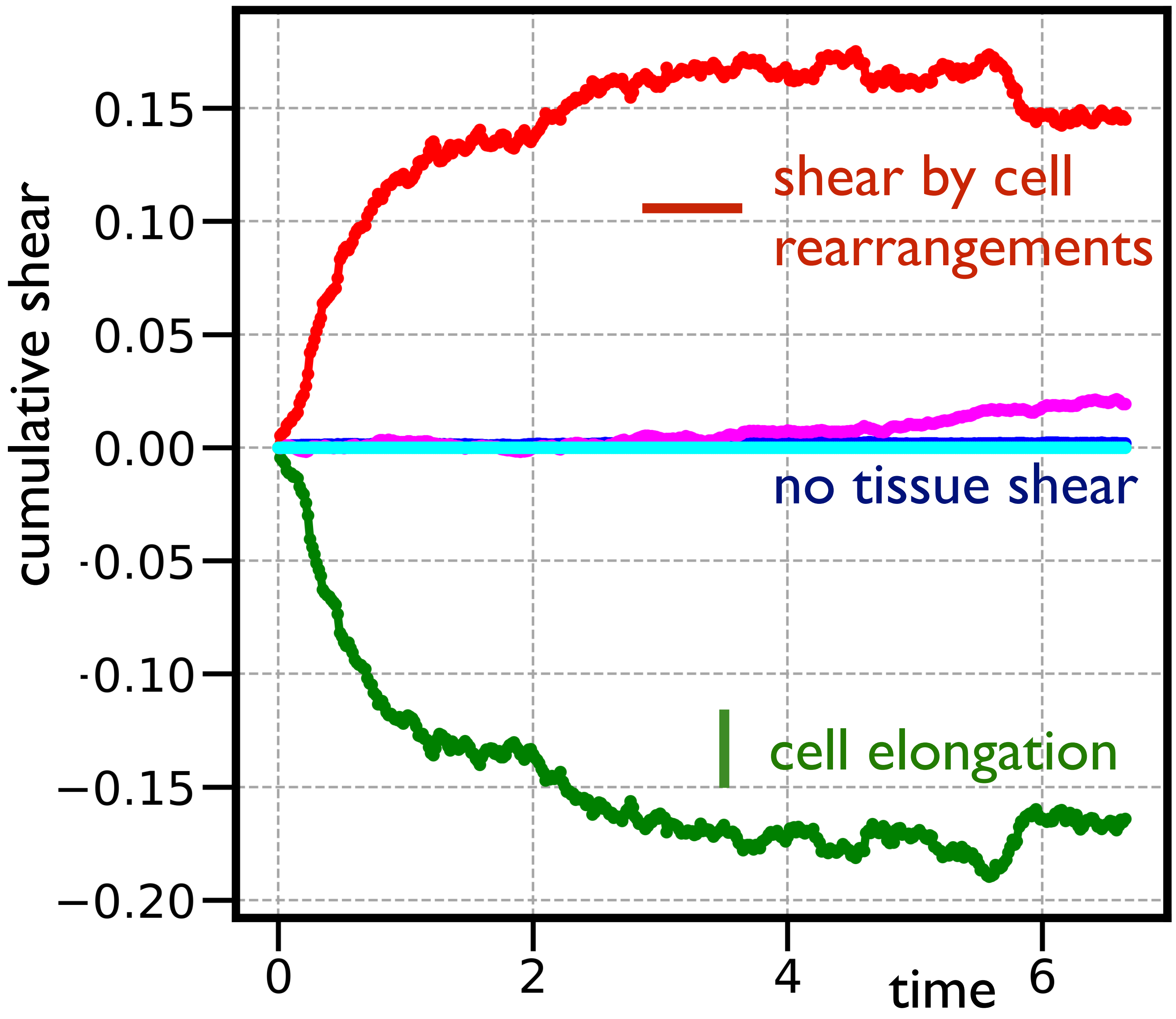
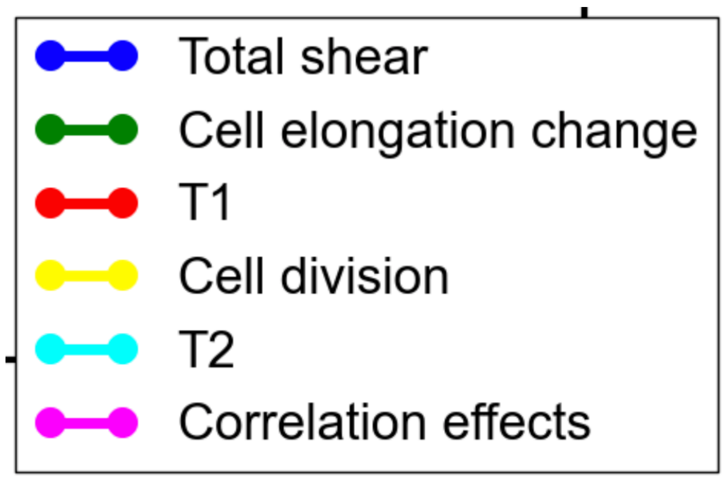
T1 driven by cell bond tension

shear decomposition





$\mathbf{q}$ | local cell anisotropy

$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q} + \lambda \mathbf{q}$$

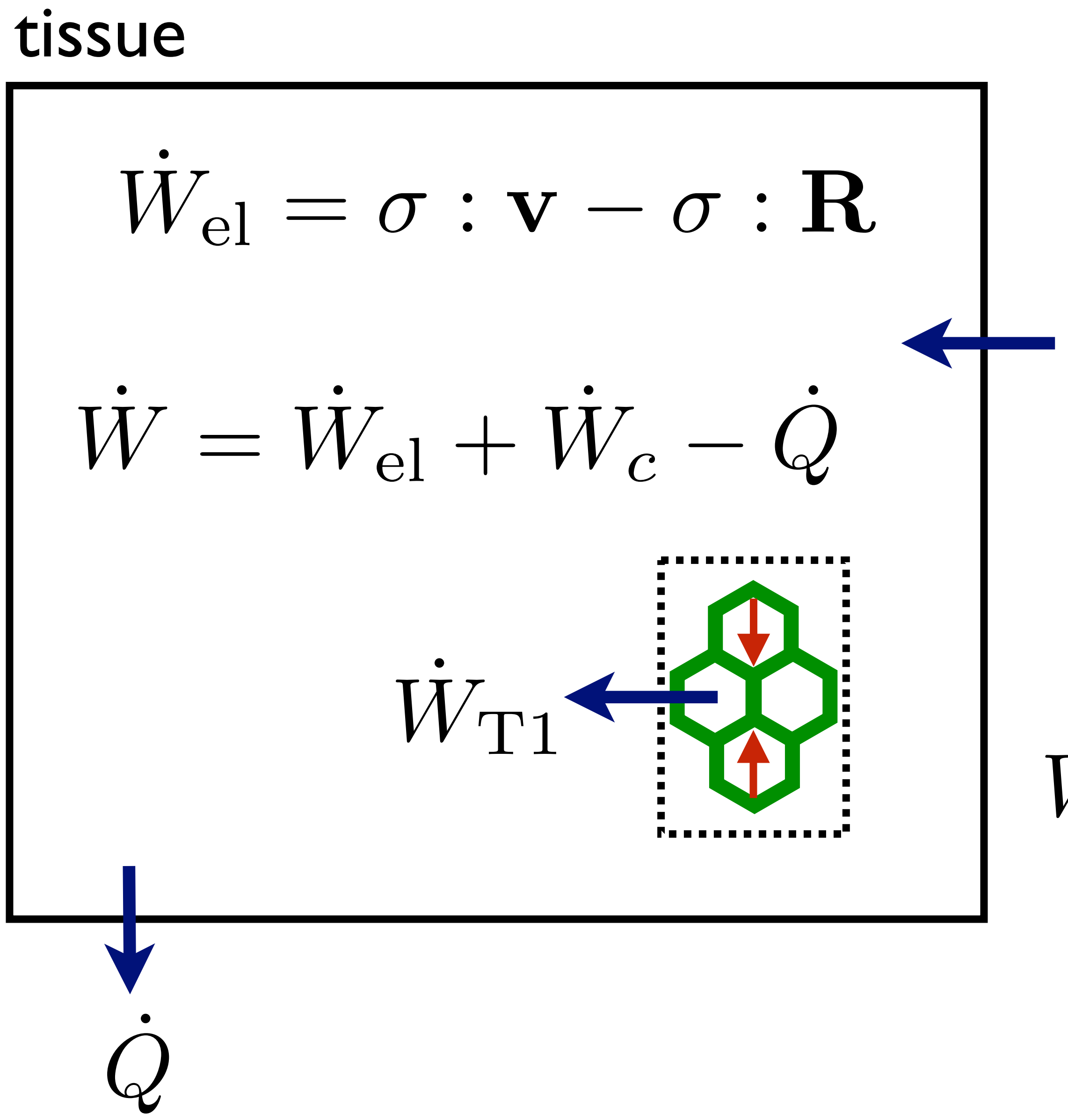
no tissue shear

$$\tilde{\mathbf{v}} = 0$$

$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

$$\lambda < 0$$

Work and energy balance in the tissue



tissue

$$\dot{W}_{\mathrm{el}} = \sigma : \mathbf{v} - \sigma : \mathbf{R}$$

$$\dot{W} = \dot{W}_{\mathrm{el}} + \dot{W}_c - \dot{Q}$$

$$\dot{W}_{\mathrm{T1}}$$

$$\dot{Q}$$

$$\dot{W}_{\mathrm{in}} = \sigma : \mathbf{v}$$

$$\dot{W}_{\mathrm{T1}} = -\sigma : \mathbf{R}$$

passive T1

$$\dot{W}_{T1} < 0$$

active T1

$$\dot{W}_{T1} > 0$$

Work performed on tissue from outside $\dot{W}_{\mathrm{in}}$

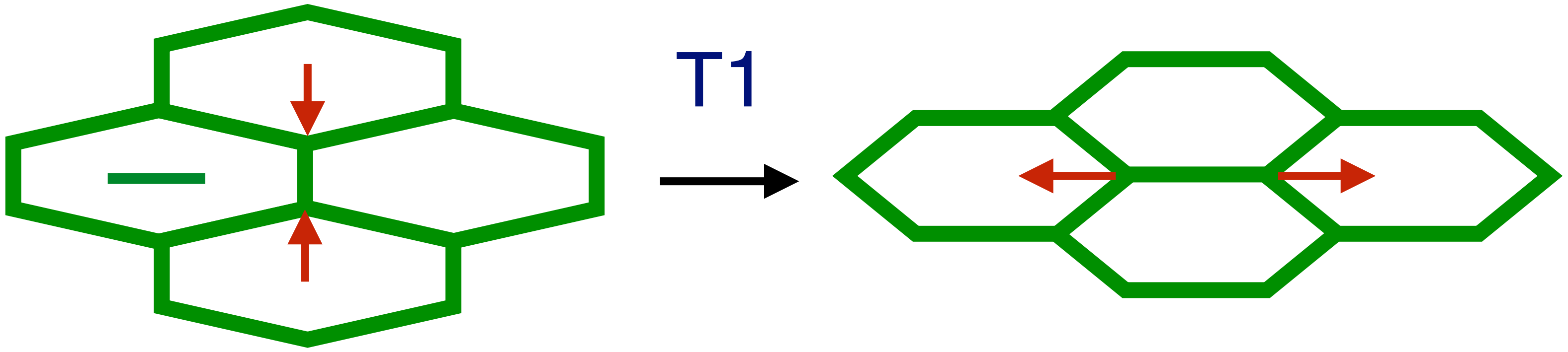
Work performed by T1 on tissue $\dot{W}_{\mathrm{T1}}$

Heat flow $\dot{Q}$ elastic work $\dot{W}_{\mathrm{el}}$ chemical work $\dot{W}_{\mathrm{c}}$

Active and passive T1 transitions

T1 transition biased by cell shape

stress relaxation



$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q}$$

$$\tilde{\sigma} = K\mathbf{Q}$$

$$\dot{W}_{T1} = -\mathbf{R} : \sigma \quad < 0$$

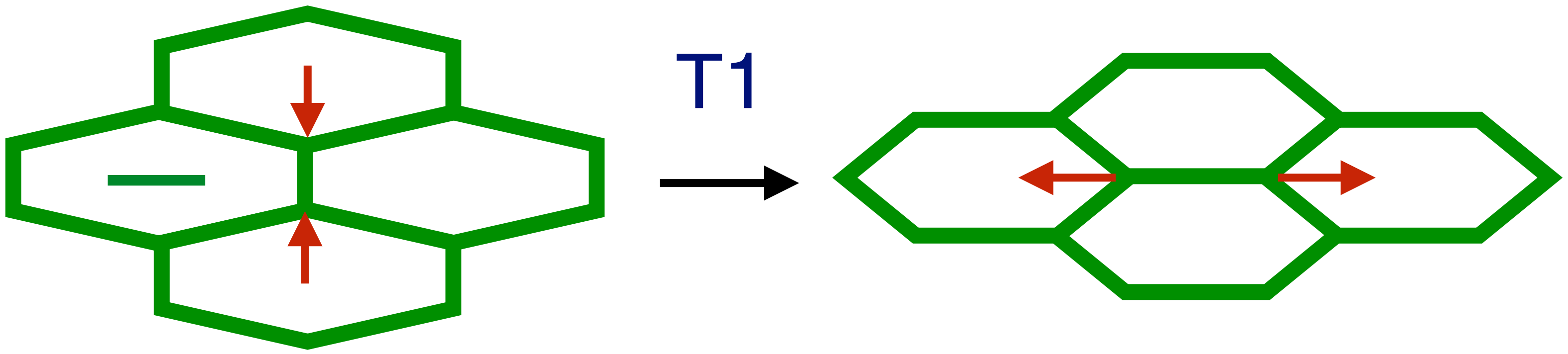
passive T1

$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

Active and passive T1 transitions

T1 transition biased by cell shape

stress relaxation
passive T1

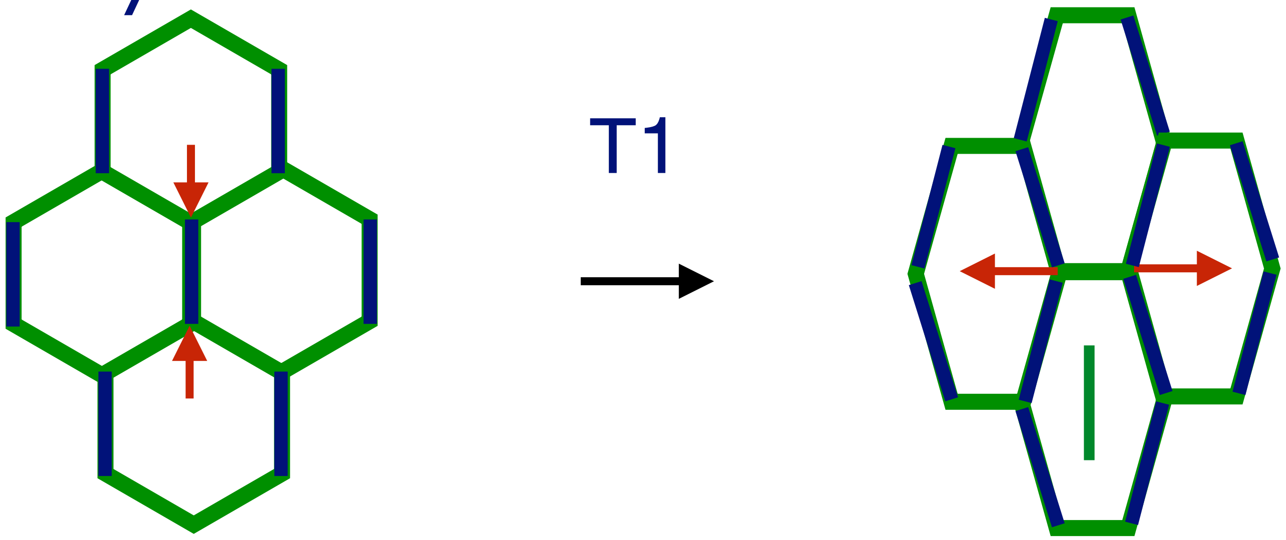


$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q}$$

$$\tilde{\sigma} = K\mathbf{Q}$$

T1 transition driven by bond tension

stress buildup
active T1



$$\mathbf{R} = \lambda\mathbf{q}$$

$$\tilde{\sigma} = \zeta\mathbf{q}$$

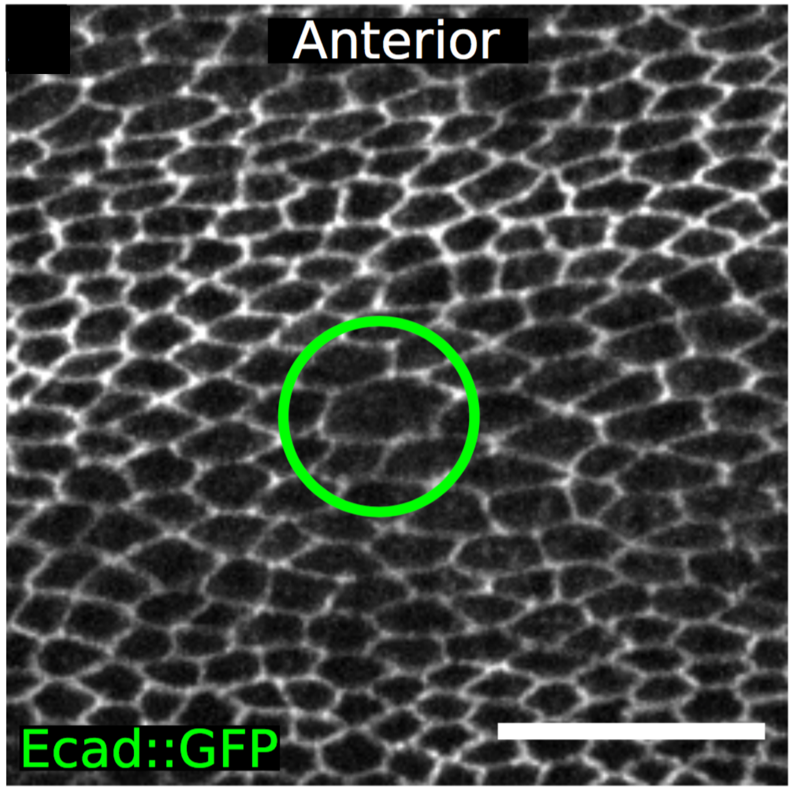
$$\dot{W}_{T1} = -\mathbf{R} : \sigma \ > 0$$

active T1

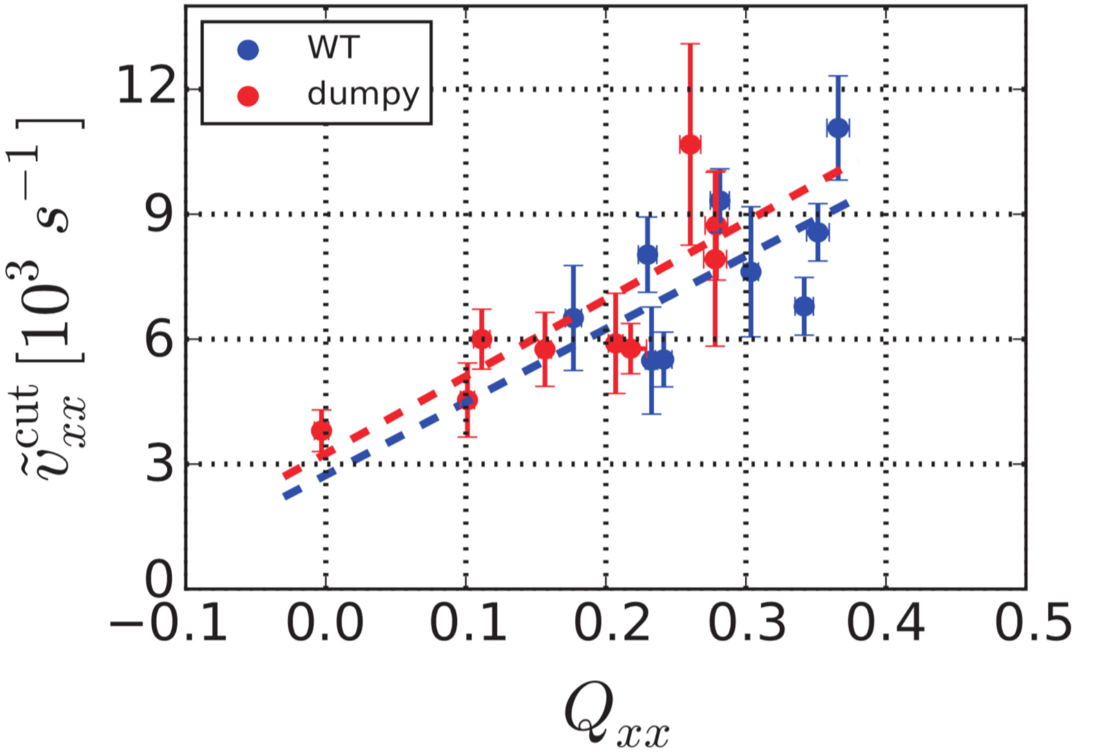
$$\zeta\lambda < 0$$

Tissue stresses

circular laser ablation

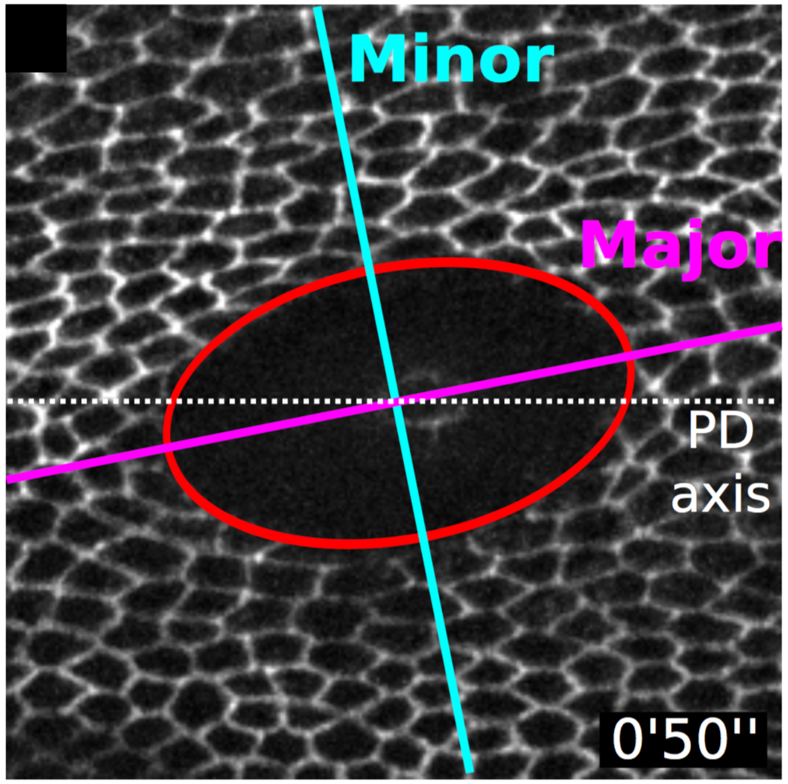


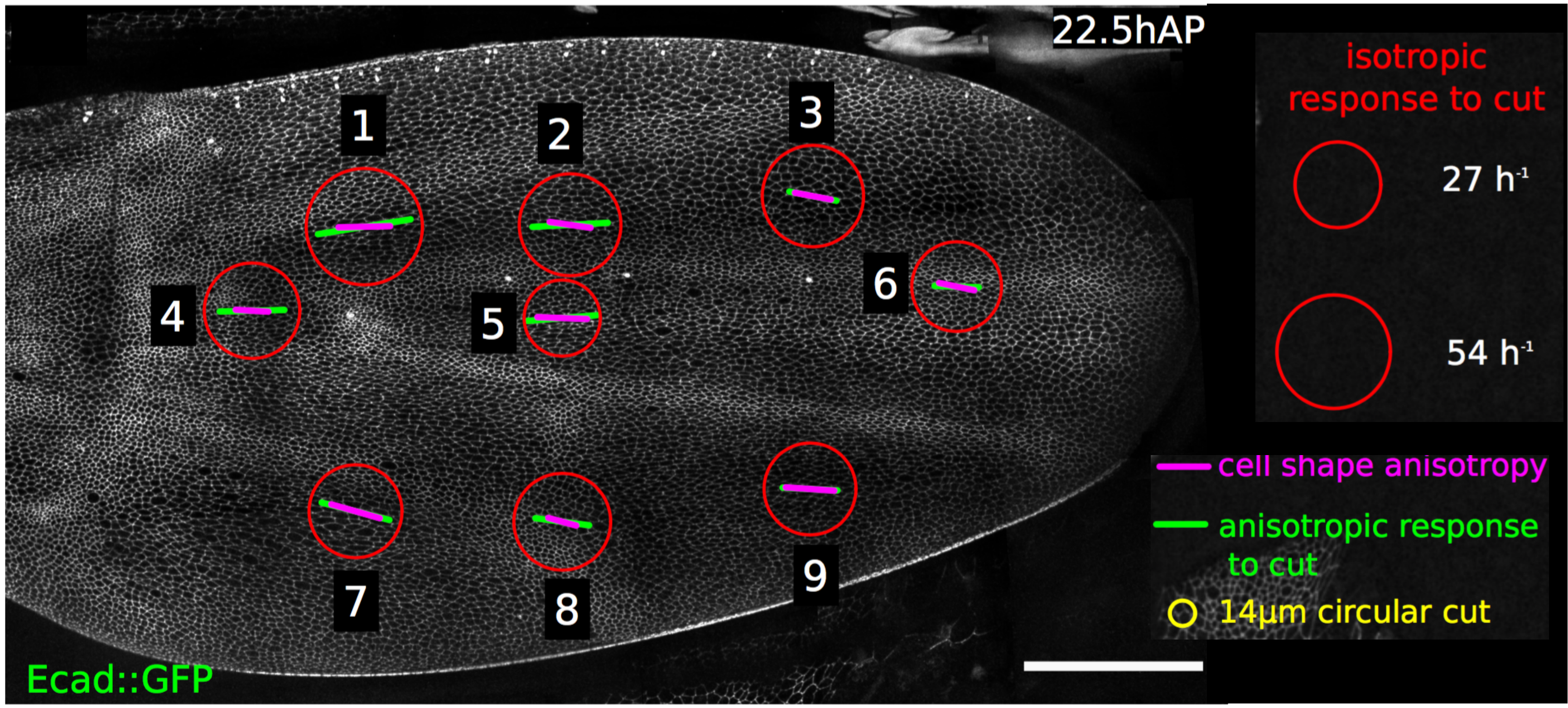
anisotropic velocity component



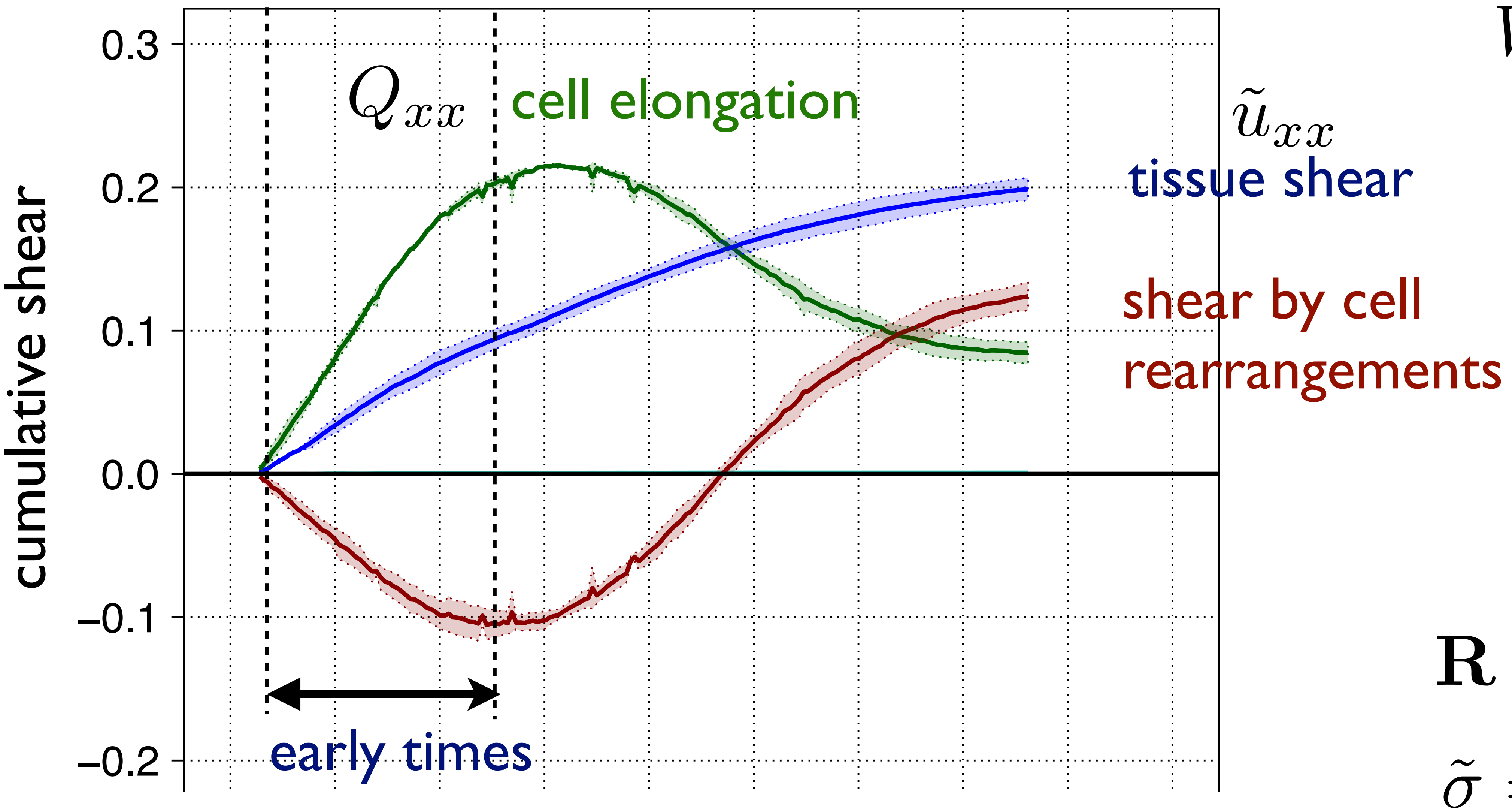
cell shear stress

$$\tilde{\sigma} = K\mathbf{Q} + \zeta\mathbf{q}$$





Early times: active T1 's



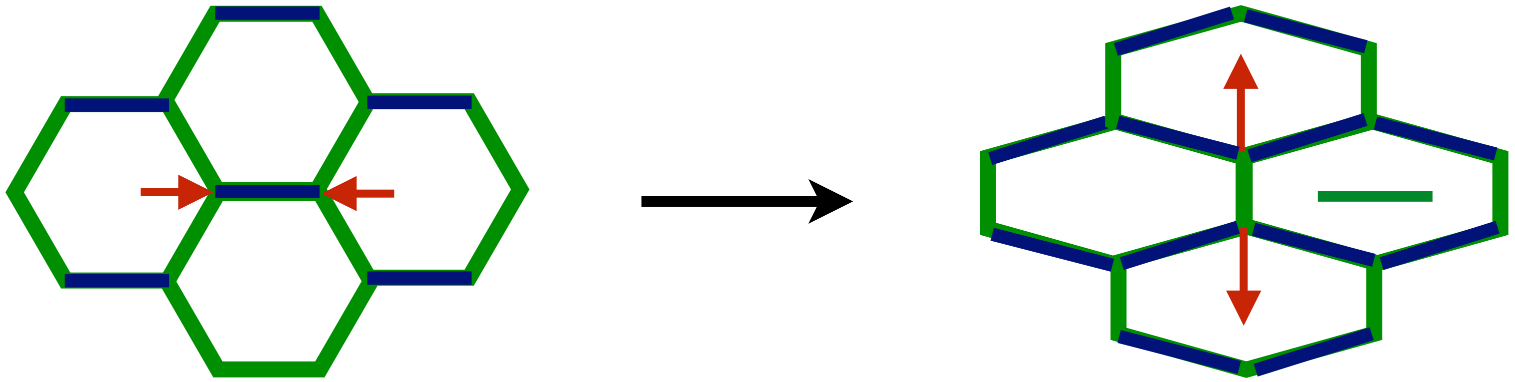
$$\dot{W}_{\mathrm{T1}} = -\sigma : \mathbf{R}$$

$$\dot{W}_{T1} > 0$$

$$\lambda < 0$$

$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q} + \lambda\mathbf{q}$$

$$\tilde{\sigma} = K\mathbf{Q} + \zeta\mathbf{q}$$



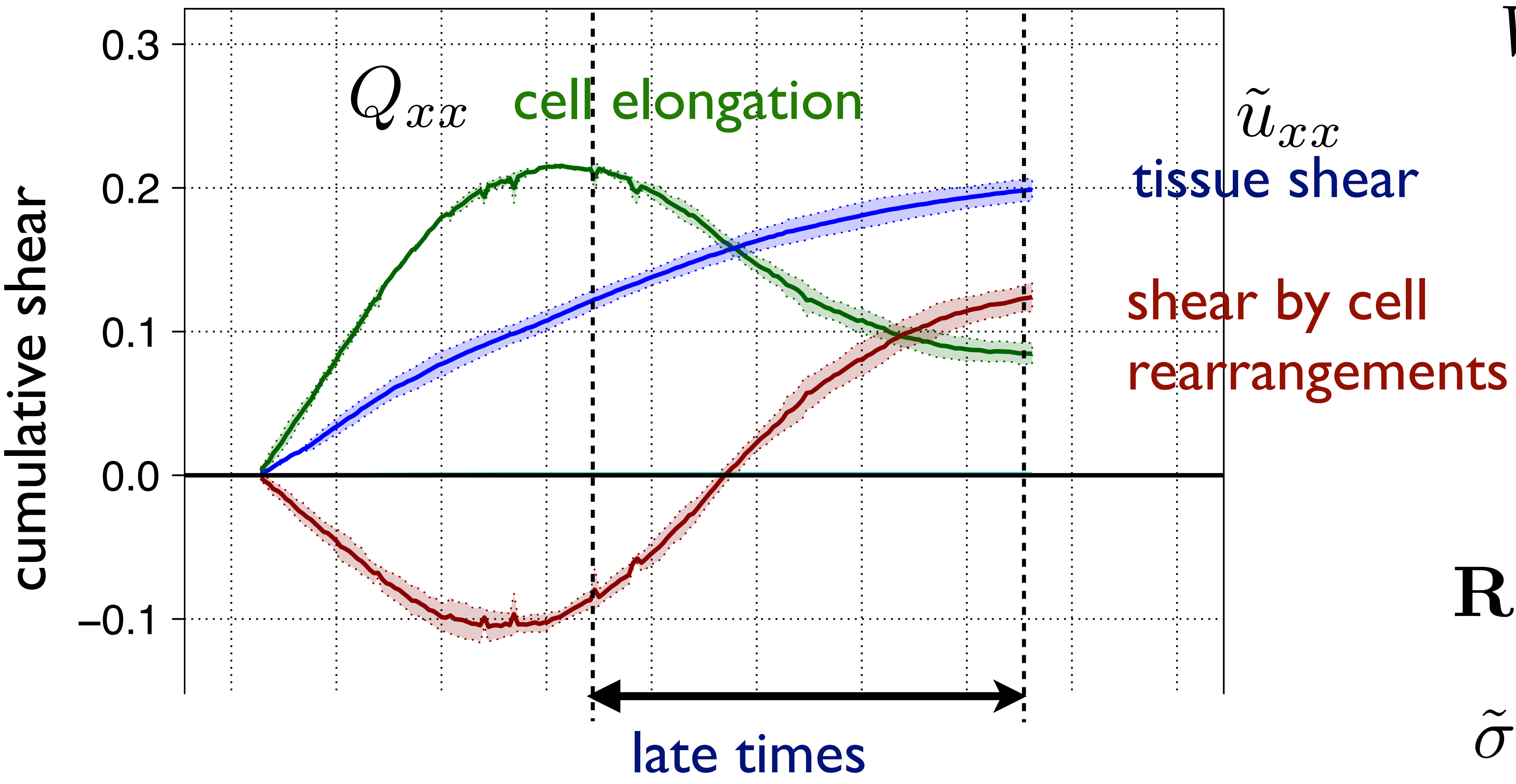
active T1 transitions dominate

$\Delta\mathbf{Q}$ —

$\mathbf{R}$ |

$\mathbf{q}$ —

Later times: passive T1

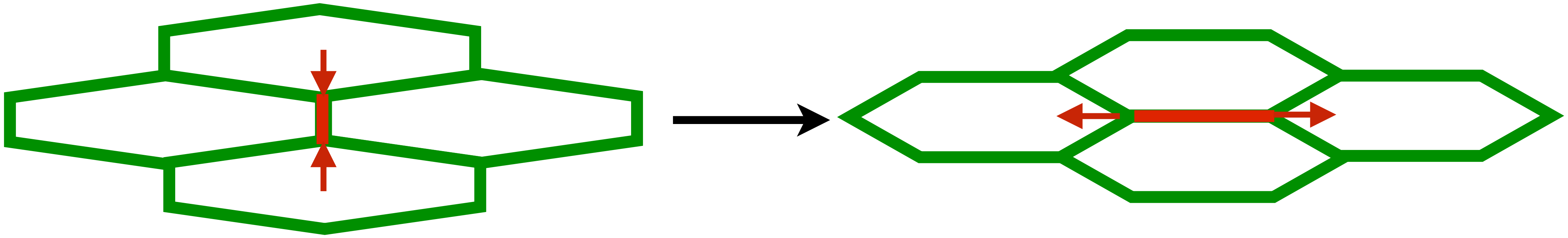


$$\dot{W}_{\mathrm{T1}} = -\sigma : \mathbf{R}$$

$$\dot{W}_{T1} < 0$$

$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q} + \lambda\mathbf{q}$$

$$\tilde{\sigma} = K\mathbf{Q} + \zeta\mathbf{q}$$



T1 relax cell elongation

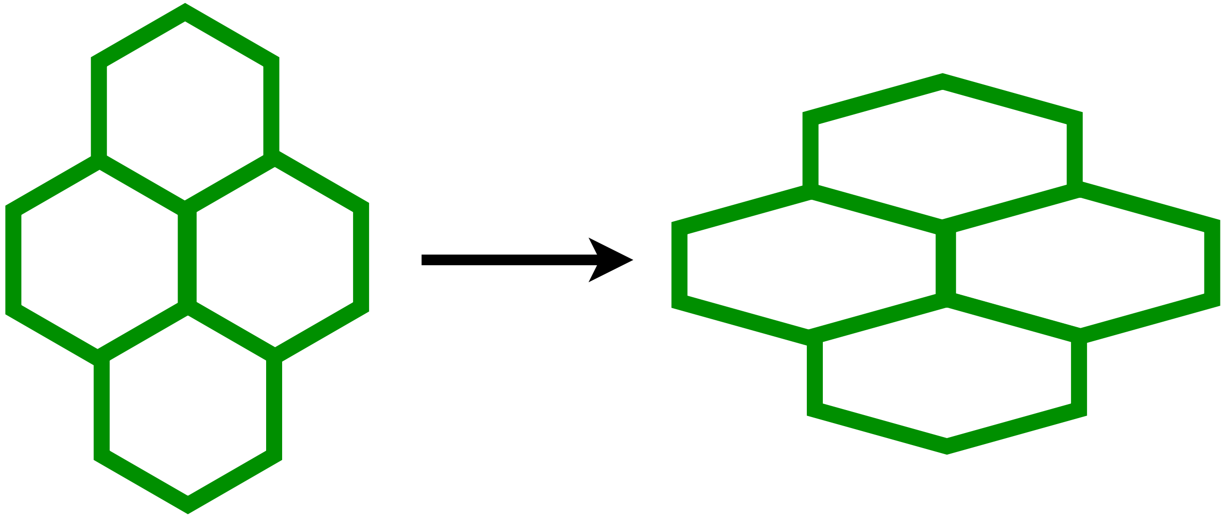
$\mathbf{Q}$ —

$\Delta\mathbf{Q}$ |

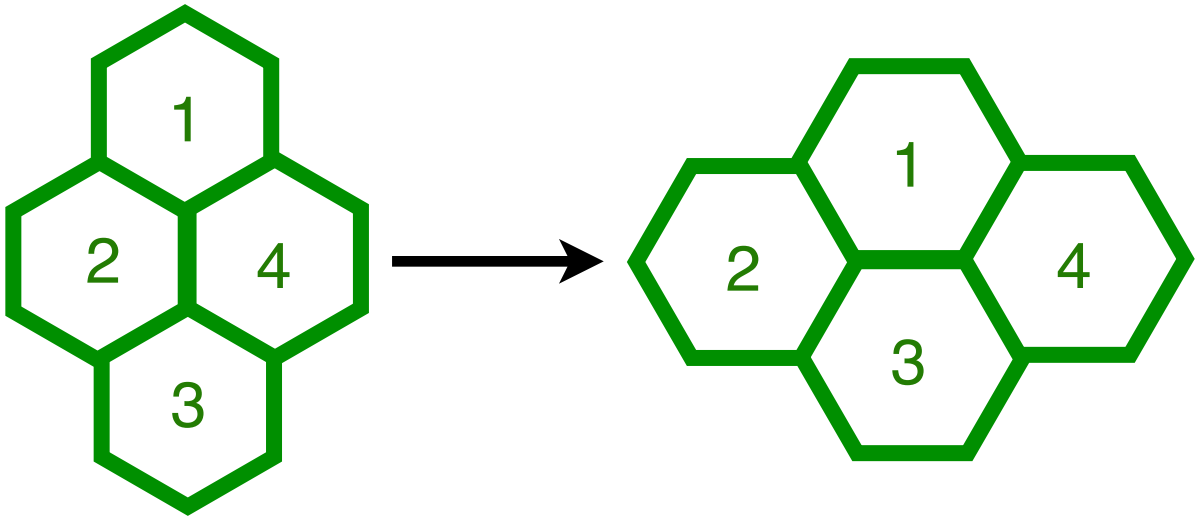
$\mathbf{R}$ —

Theory of tissue mechanics

Cell elongation $\mathbf{Q}$



Cell rearrangements $\mathbf{R}$



tissue pressure

$$P = -\bar{K} \ln \left(\frac{a}{a_0} \right)$$

elastic tissue stress

active stress

$$\tilde{\sigma} = K\mathbf{Q} + \zeta\mathbf{q}$$

elastic stress

tissue shear rate

$$\tilde{\mathbf{v}} = \frac{D\mathbf{Q}}{Dt} + \mathbf{R}$$

shear by cell rearrangements

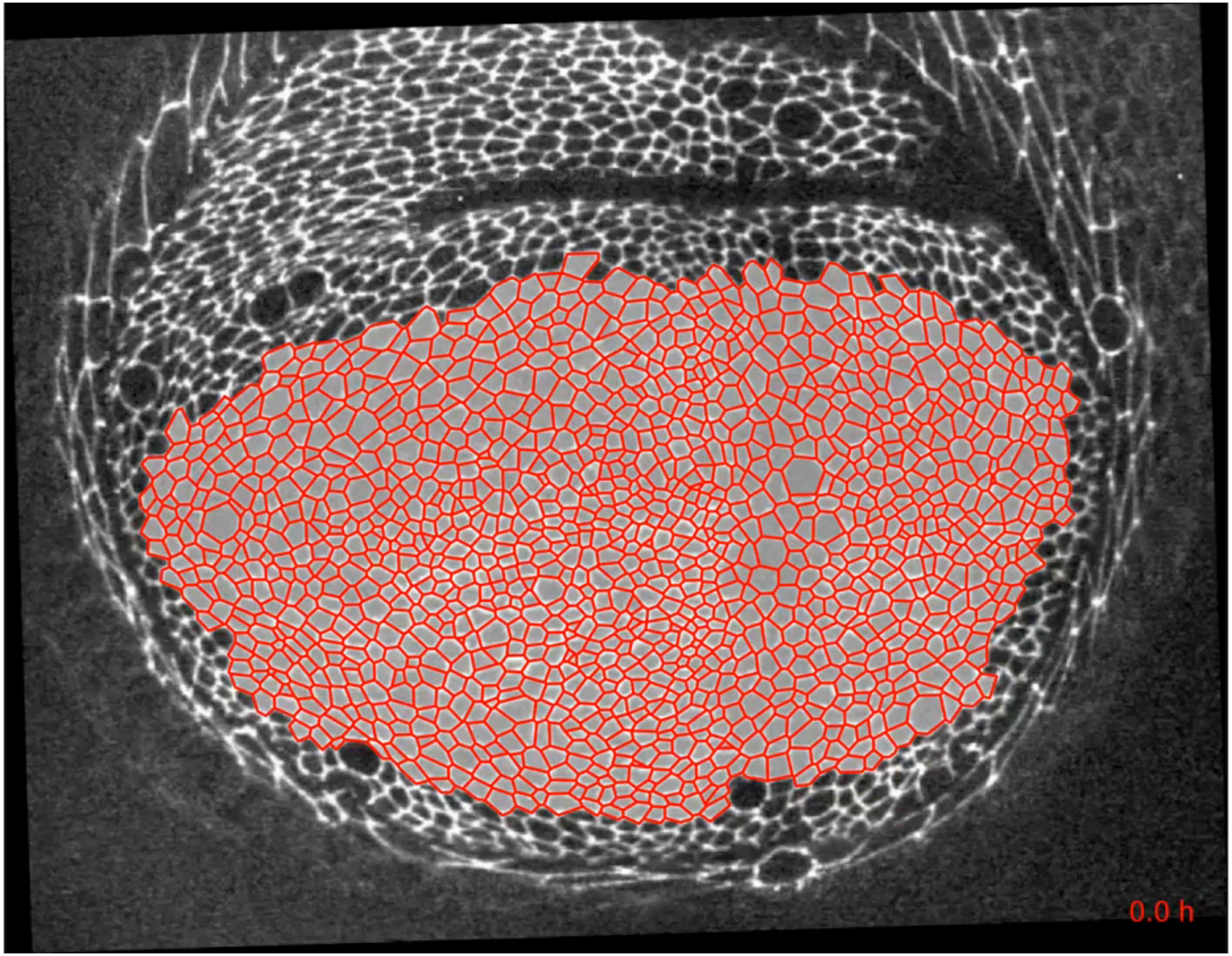
active T1

$$\mathbf{R} = \frac{1}{\tau}\mathbf{Q} + \lambda\mathbf{q}$$

force balance

$$\nabla \cdot (\tilde{\sigma} - P\,\mathbb{I}) = \mathbf{f}_{\mathrm{ext}}$$

Wing imaginal disk dynamics



Natalie Dye

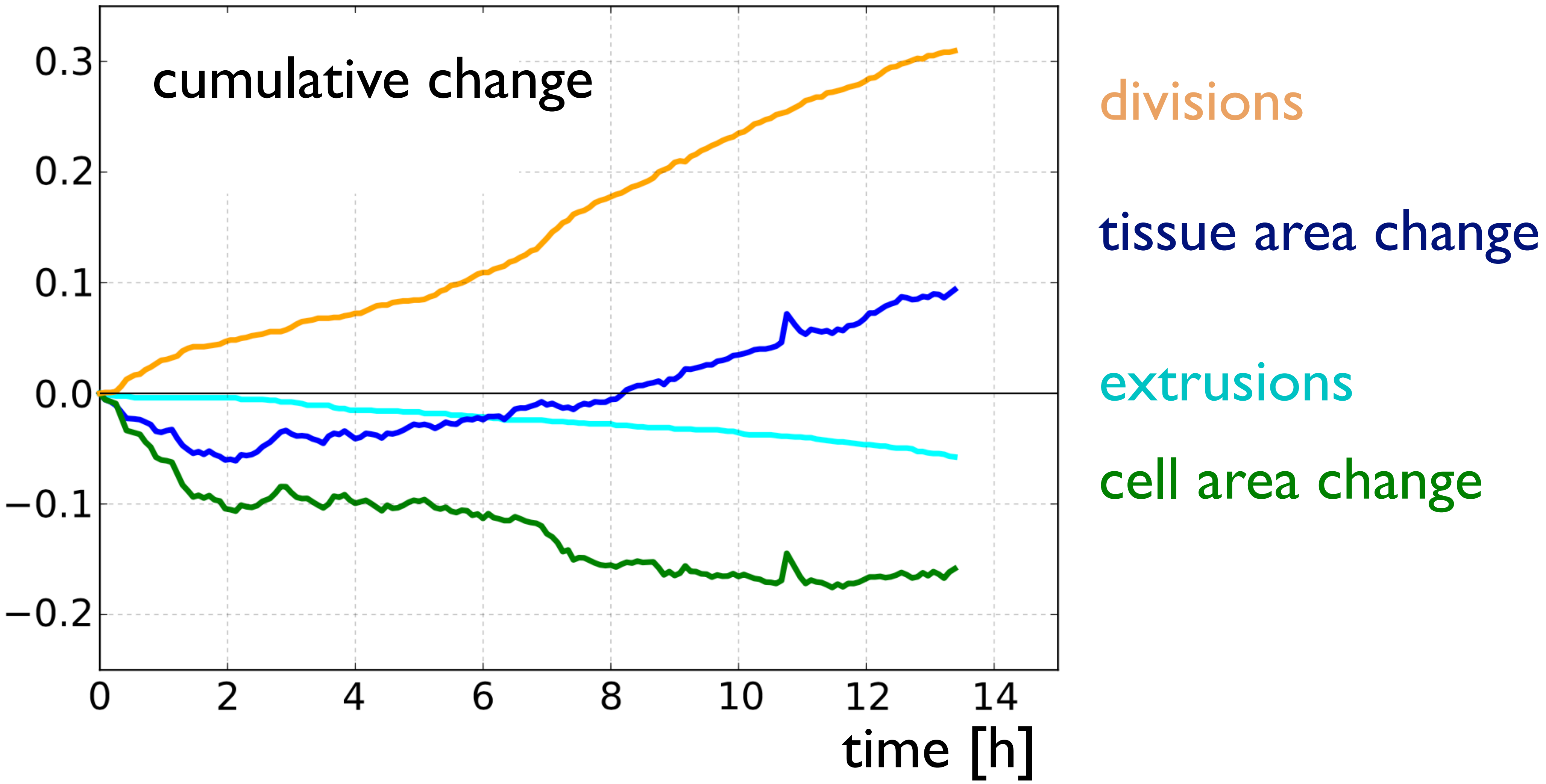
automated image analysis

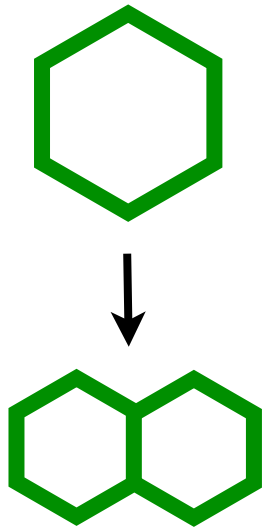
Decomposition of growth

average
area growth

$$\frac{1}{A}\frac{dA}{dt} = -\nabla \cdot \mathbf{v}$$

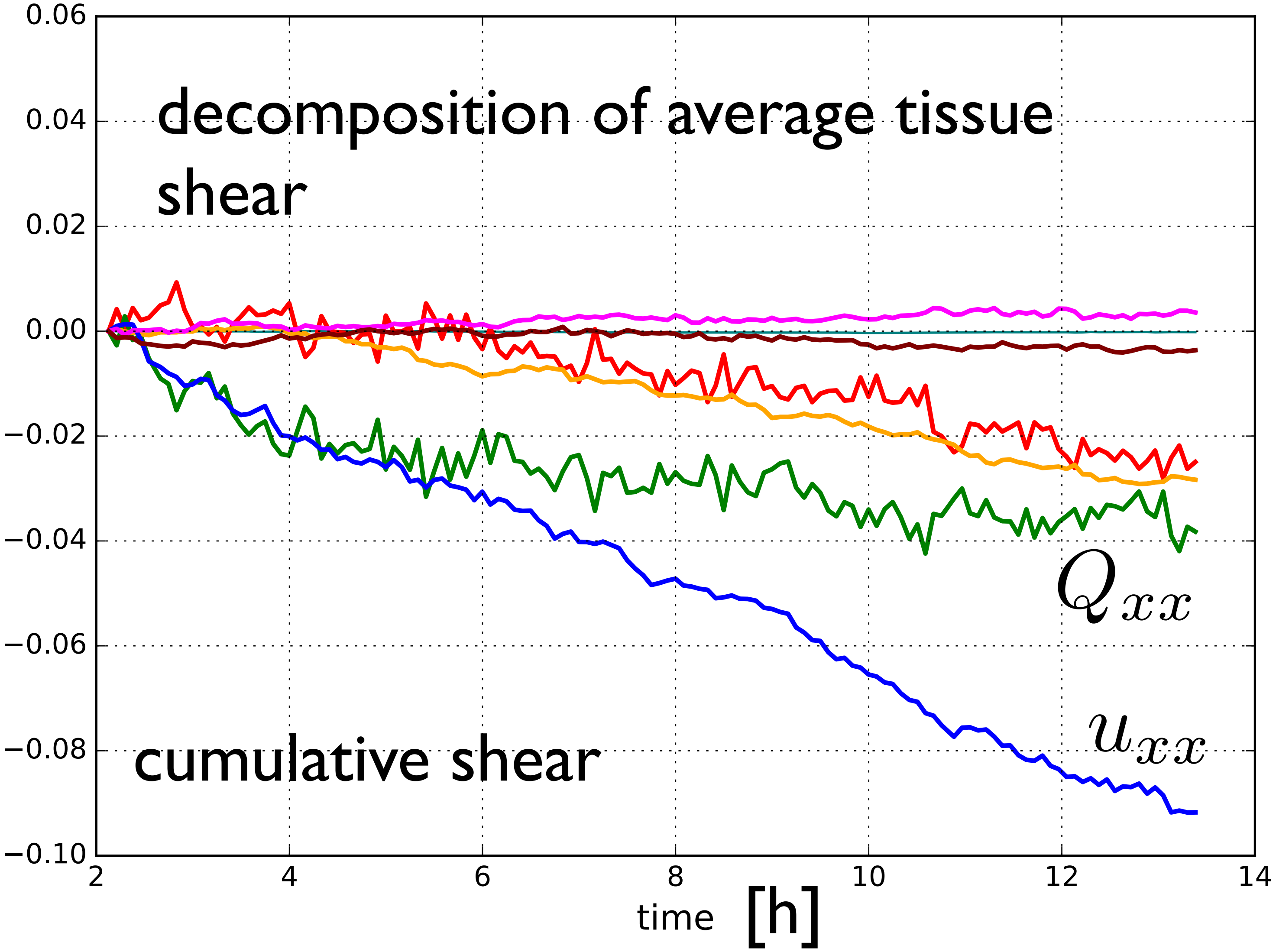
$$g = \dot{A}/A$$

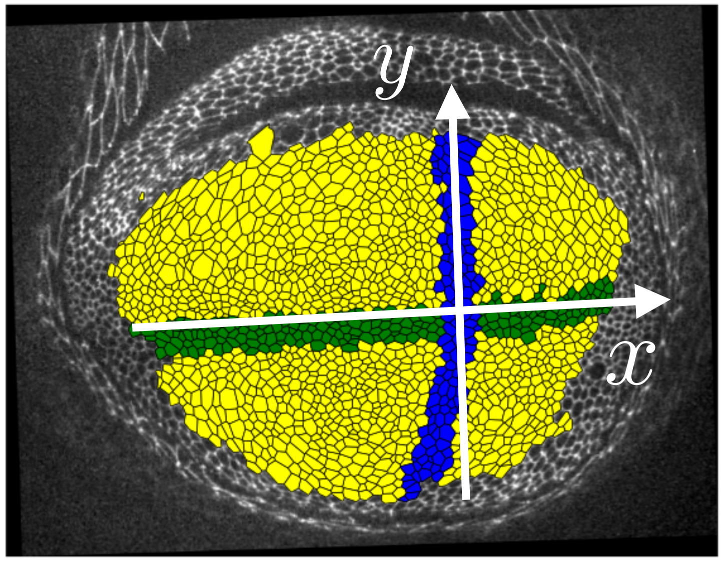




$$\underbrace{\frac{1}{A}\frac{dA}{dt}}_{\text{tissue area change}} = \underbrace{\frac{1}{a}\frac{da}{dt}}_{\text{cell area change}} + \underbrace{k_d}_{\text{division rate}} - \underbrace{k_e}_{\text{extrusion rate}}$$

Average wing disk shear



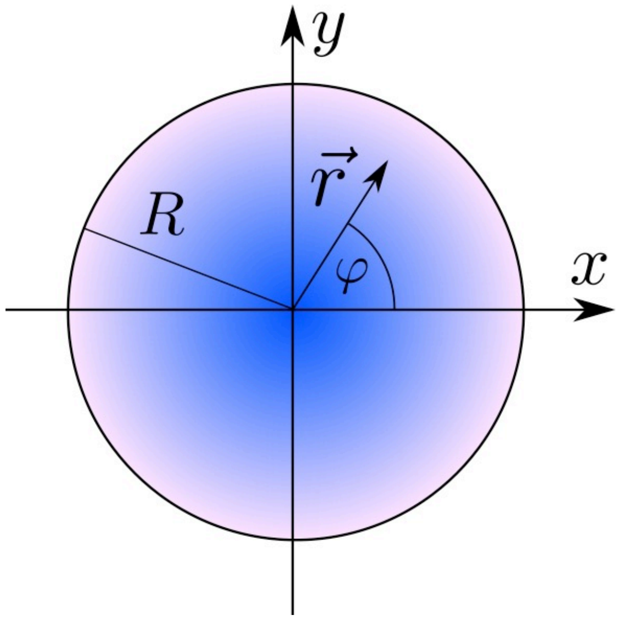


$$\underline{\tilde{v}_{\alpha\beta}} = \frac{DQ_{\alpha\beta}}{\underline{Dt}} + R_{\alpha\beta}$$

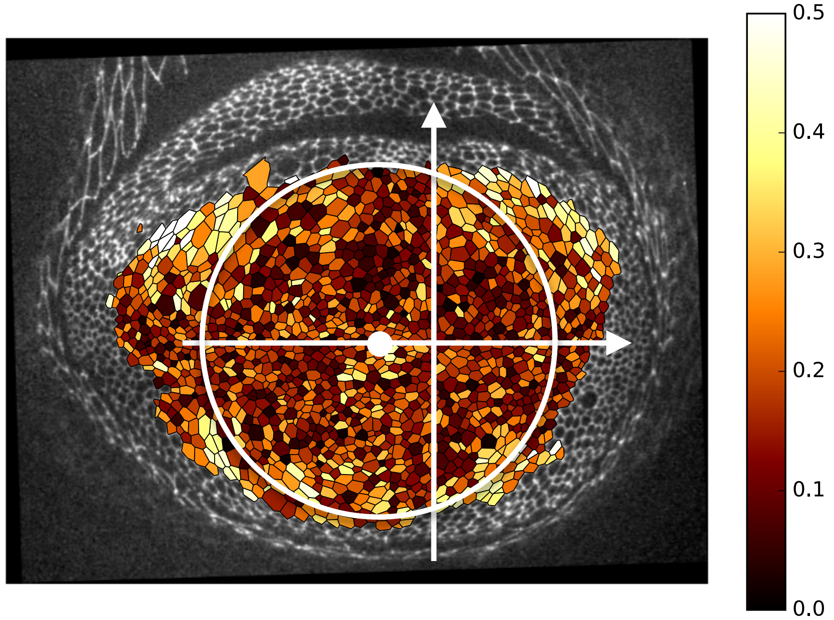
$$R_{\alpha\beta} = \underline{T_{\alpha\beta}} + \underline{C_{\alpha\beta}} + \underline{D_{\alpha\beta}}$$

Radial shear decomposition

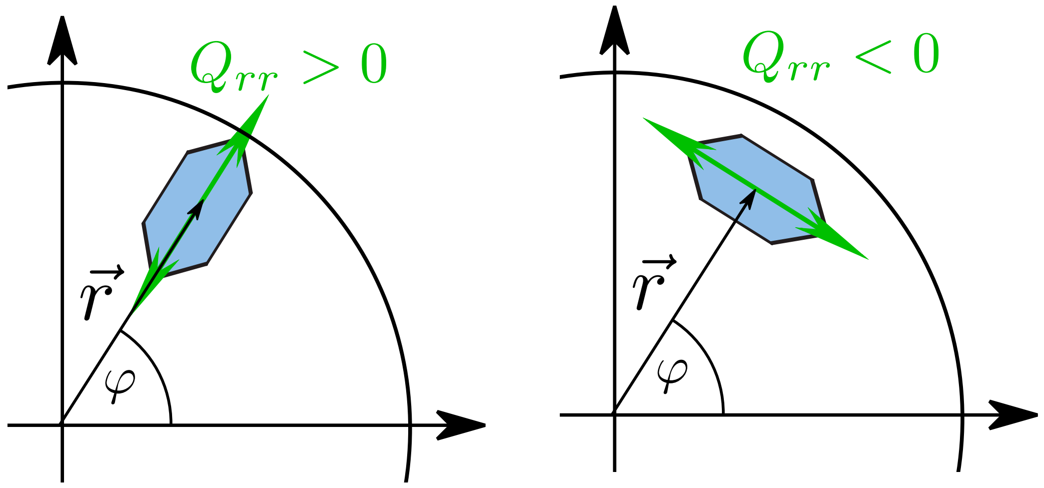
polar coordinates



cell elongation pattern

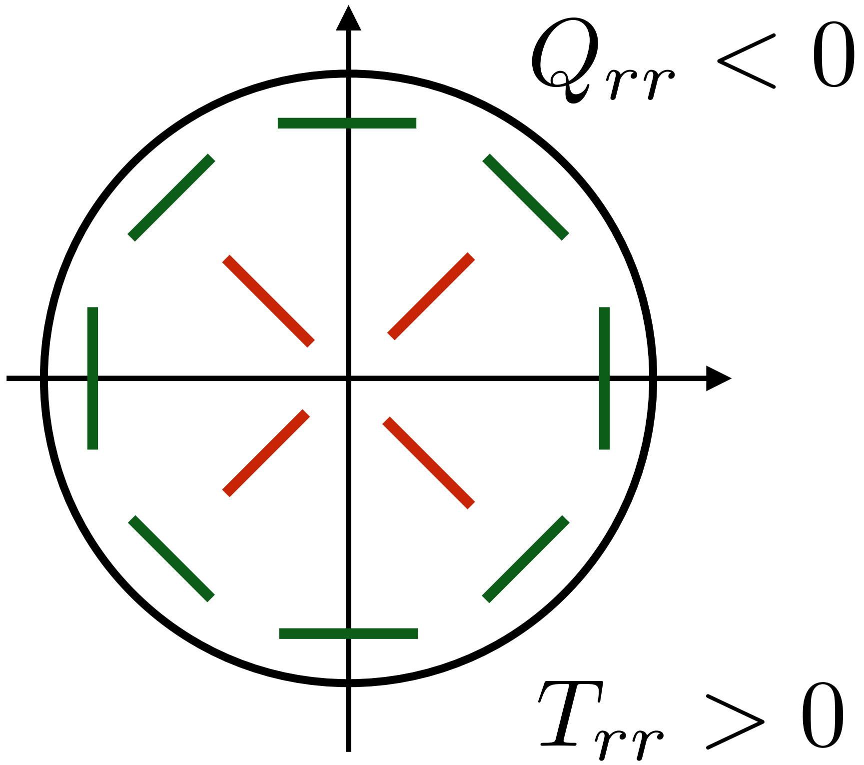


radial cell elongation

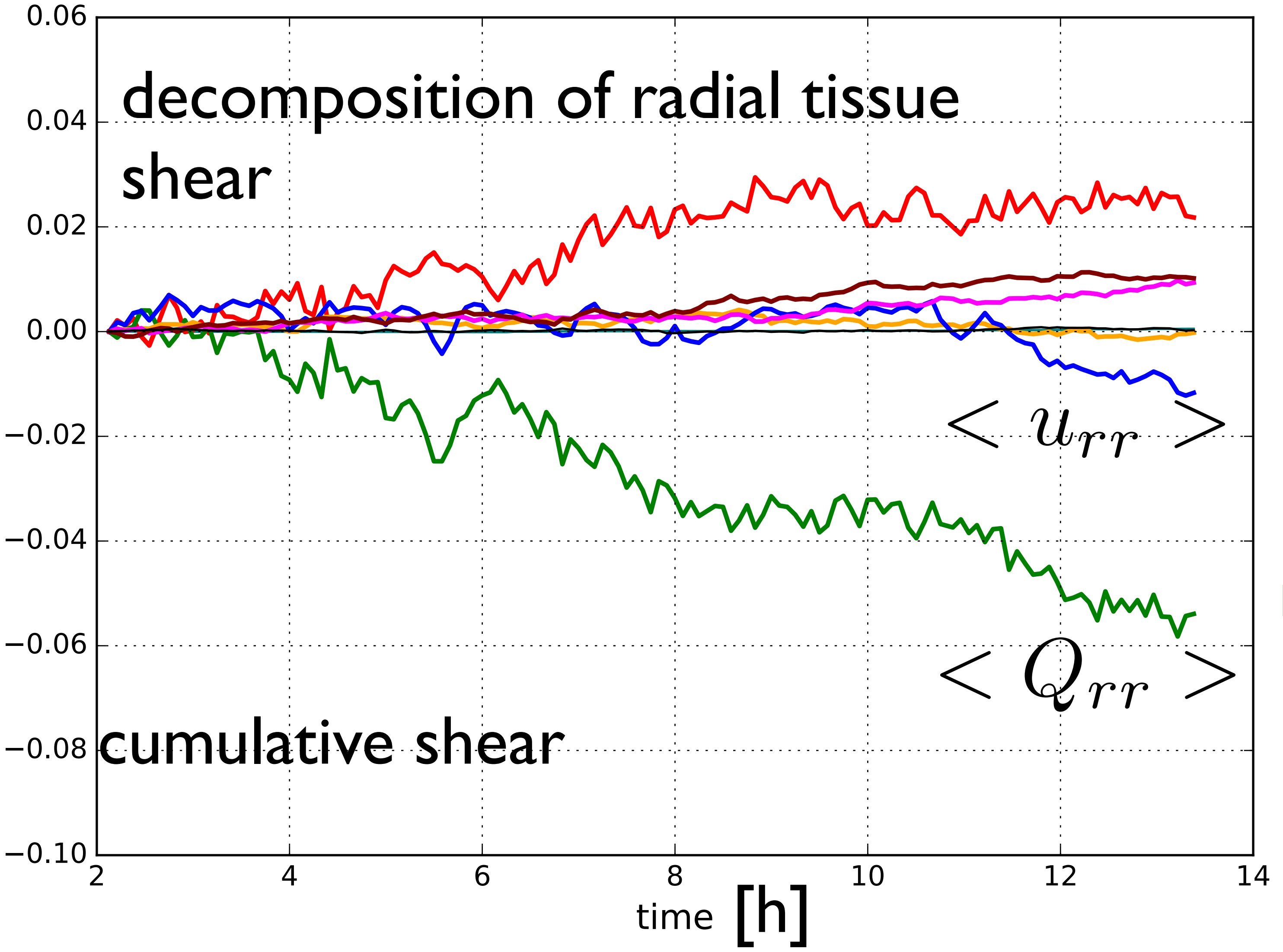


shear decomposition in radial components

$$\tilde{v}_{rr} = \underline{\frac{DQ_{rr}}{Dt}} + \underline{T_{rr}} + C_{rr}$$



Radial shear pattern

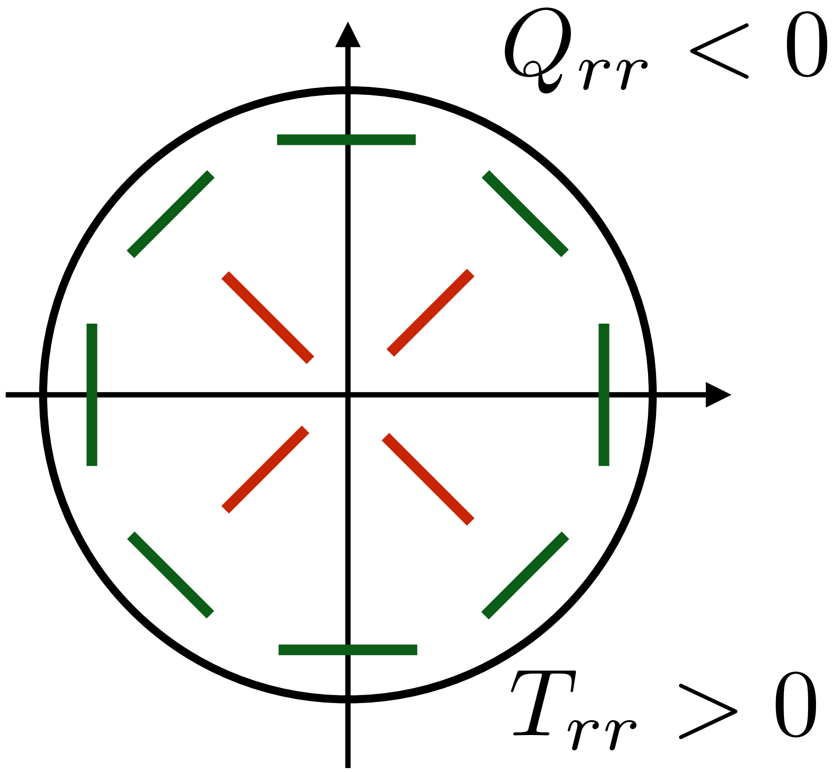


radial T1 transitions

radial shear

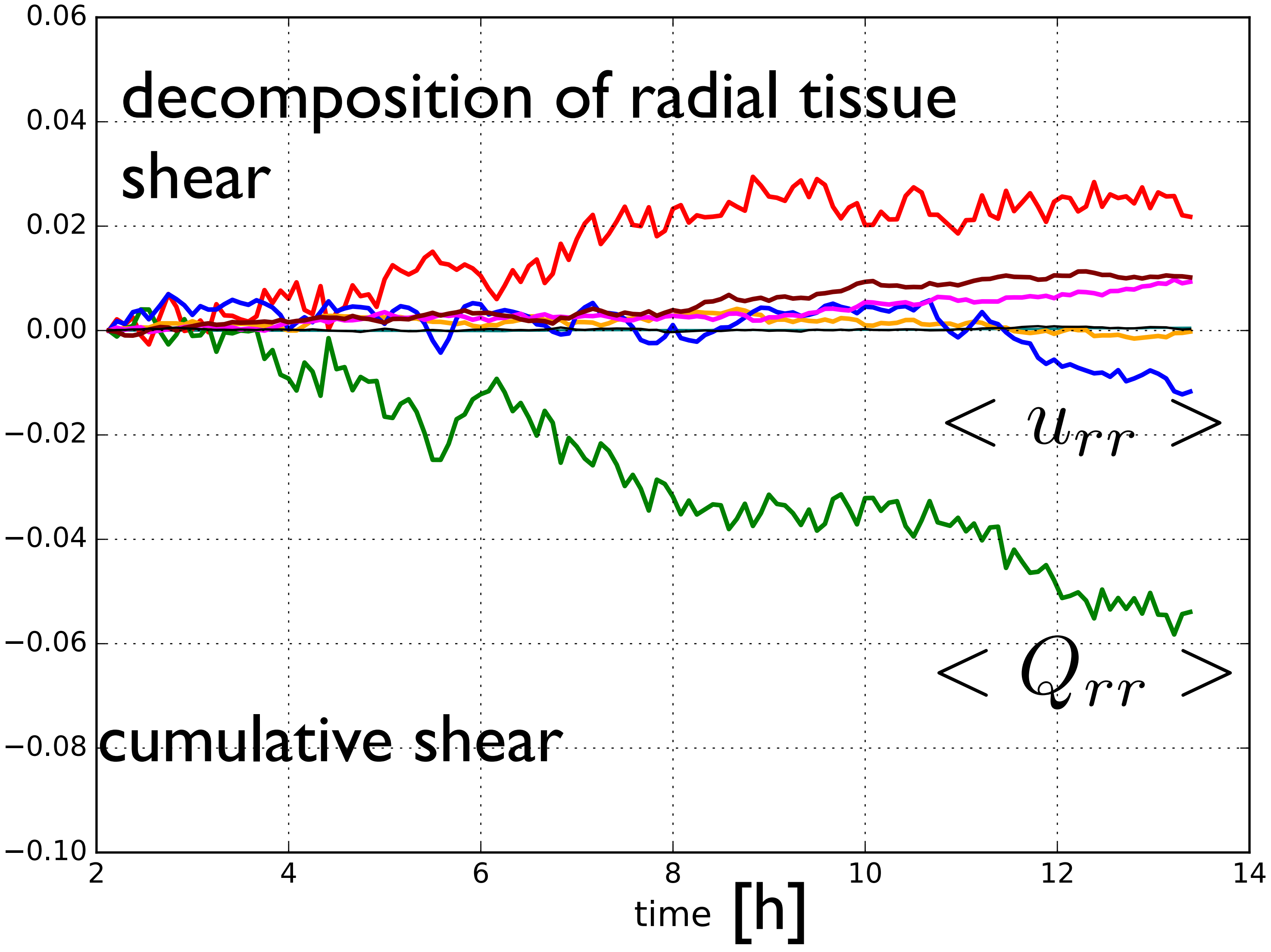
radial cell elongation

$$\tilde{v}_{rr} = \frac{DQ_{rr}}{Dt} + T_{rr} + C_{rr}$$



radially oriented active T1 drive radial pattern of cell elongation

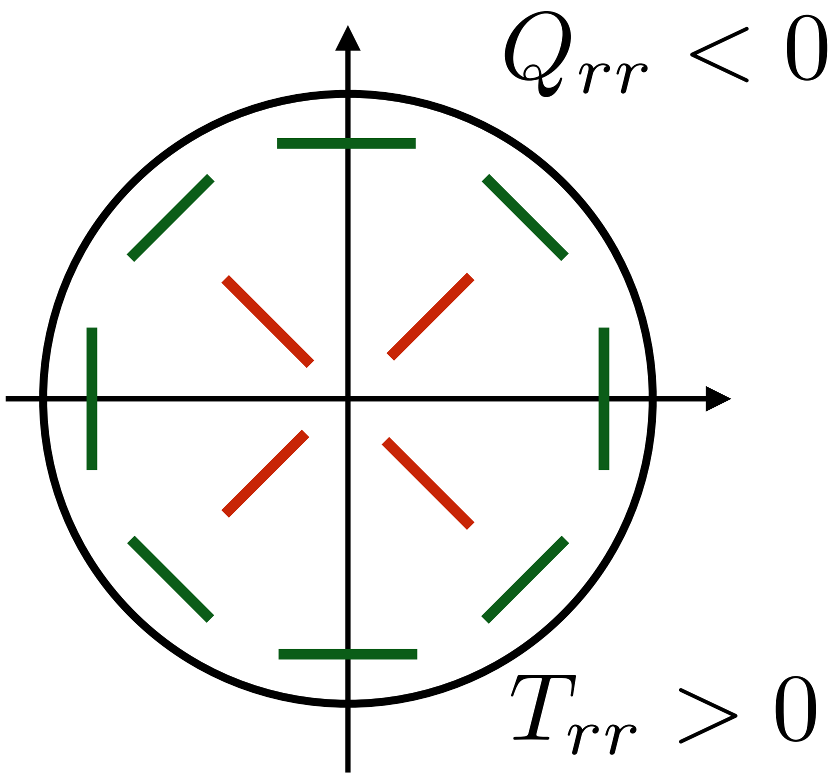
Radial shear pattern

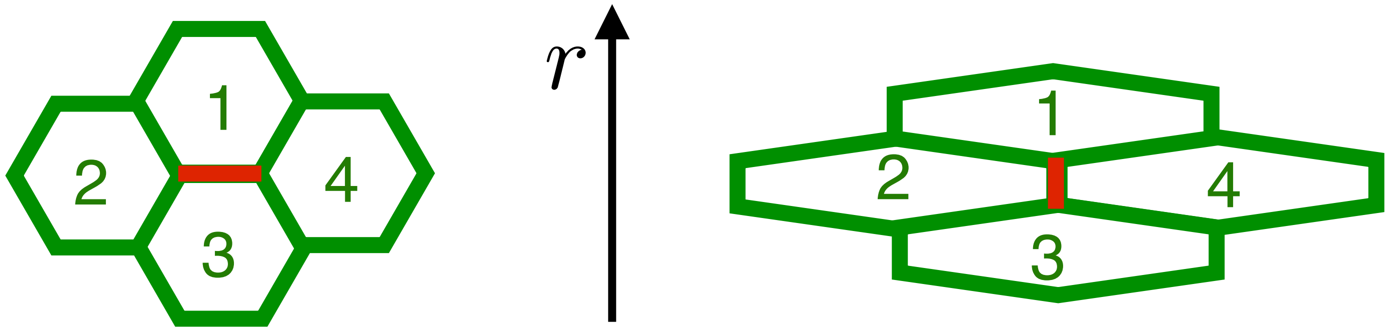


radial T1 transitions

radial shear

radial cell elongation





radially oriented active T1 drive radial pattern of cell elongation

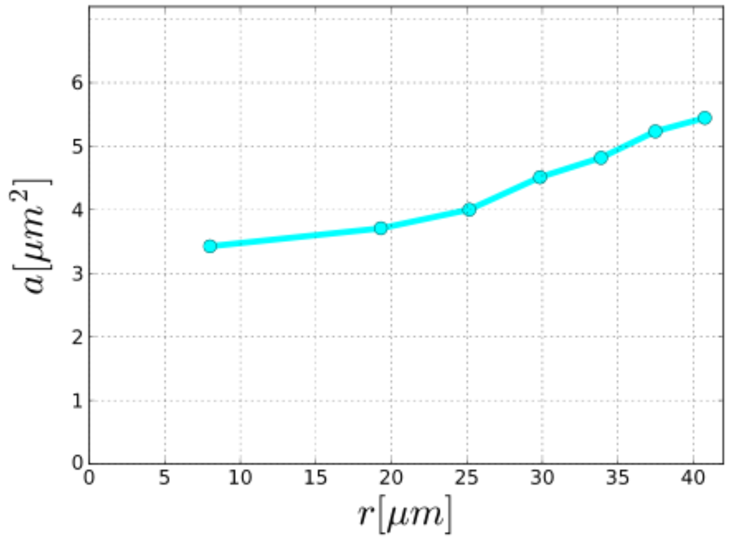
Experiment vs theory

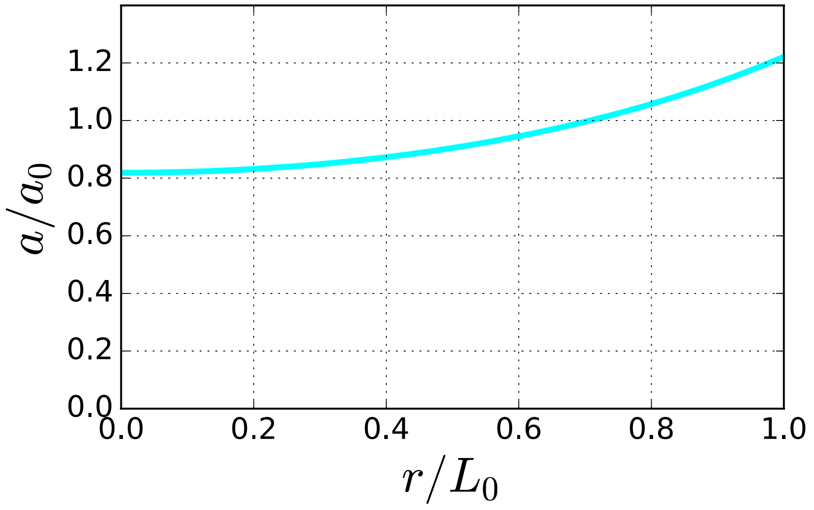
wing imaginal disc

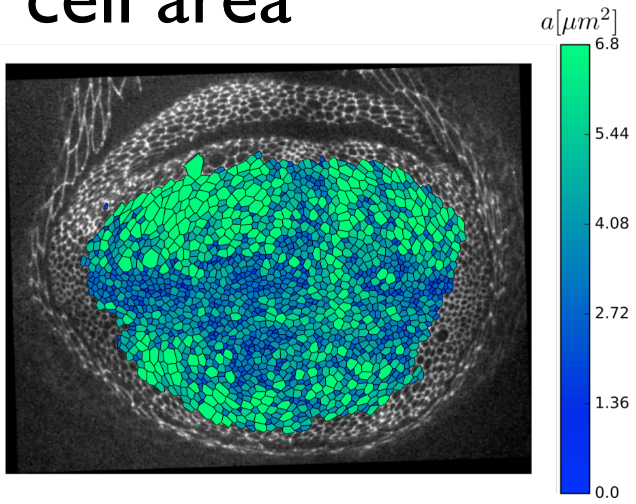
theory

cell area

cell area

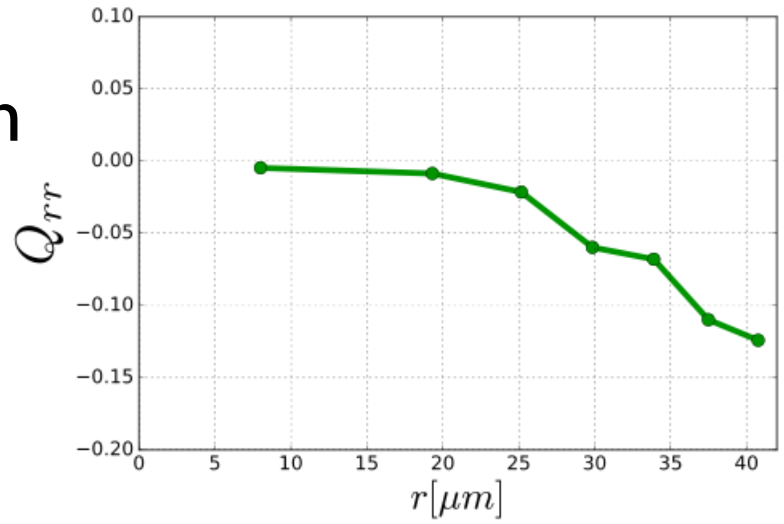


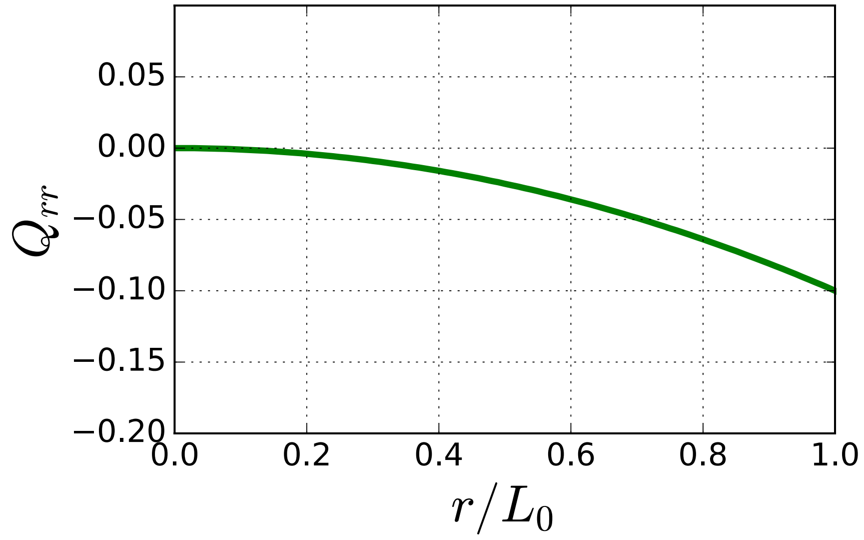


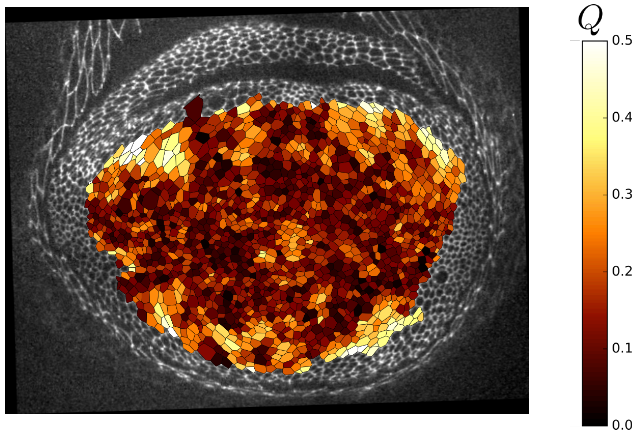


radial cell elongation

cell elongation







$$\lambda_{rr} \sim \frac{r^2}{R^2}$$

← active T1 transitions

Marko Popovich, Natalie Dye

Outline

Role of active tissue material properties in tissue remodeling

Self organization of growth

Self-organization of growth

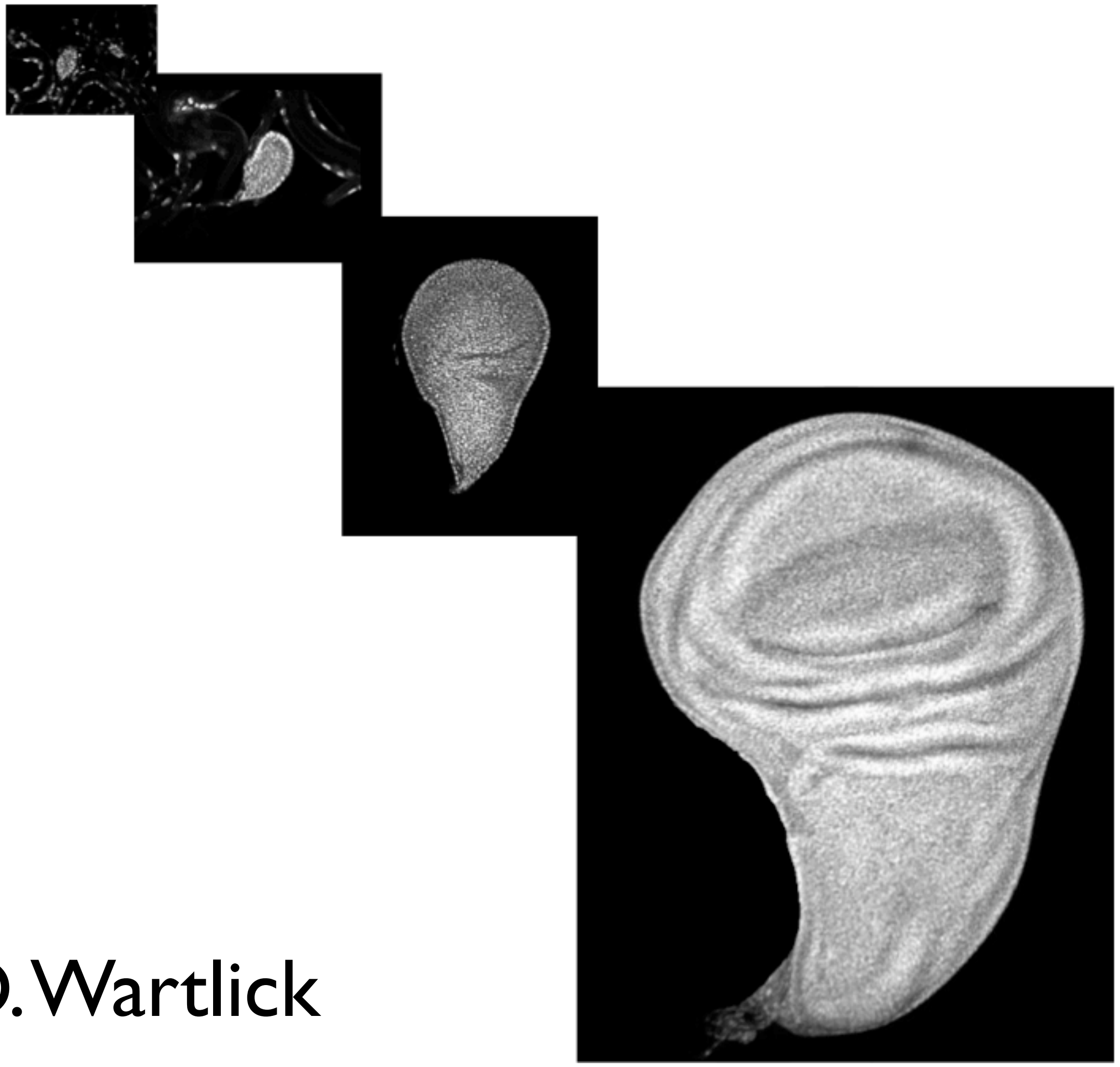
Max Planck Institute for the Physics of Complex Systems, Dresden

Peer Mumcu
Daniel Aguilar-Hidalgo
Steffen Werner
Benjamin Friedrich

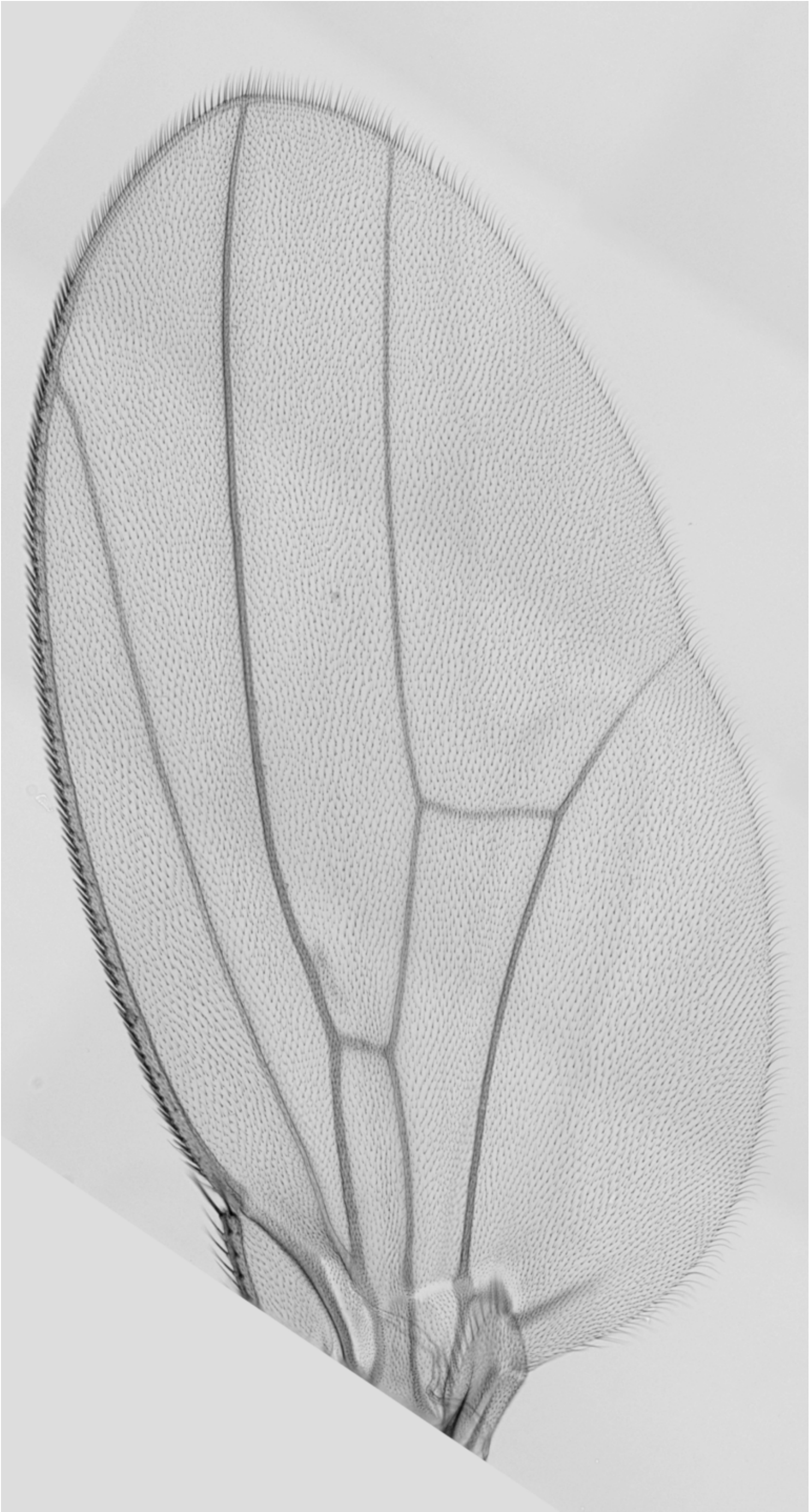
University of Geneva

Ortrud Wartlick
Marcos Gonzalez-Gaitan
Zena Hadjivasiliou
Maria Romanova

Fly wing imaginal disc

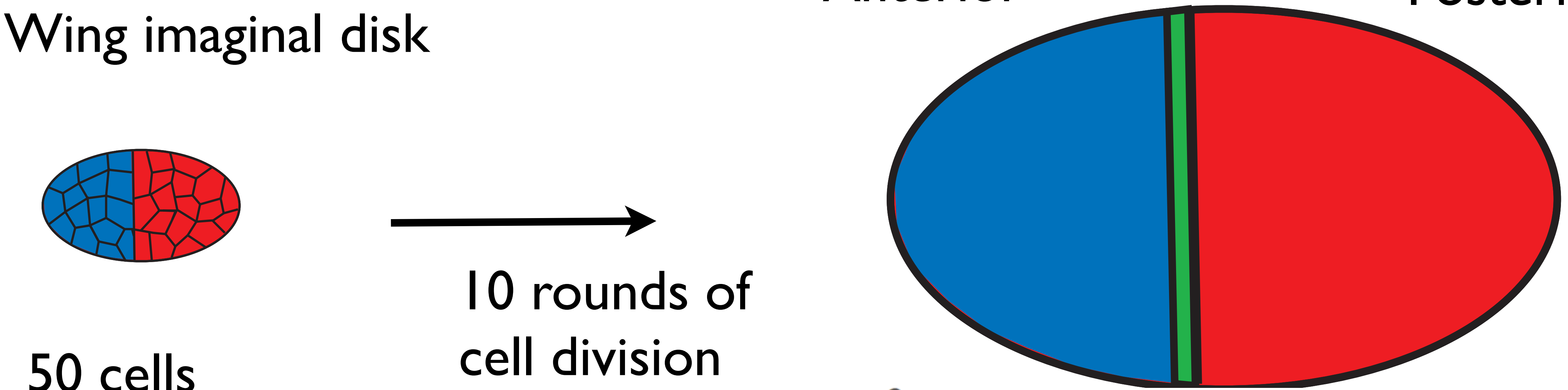


O. Wartlick



From 50 to 50,000 cells within 5 days
(10 rounds of cell division).

Wing disc growth



Wing imaginal disk

50 cells

10 rounds of cell division

Anterior

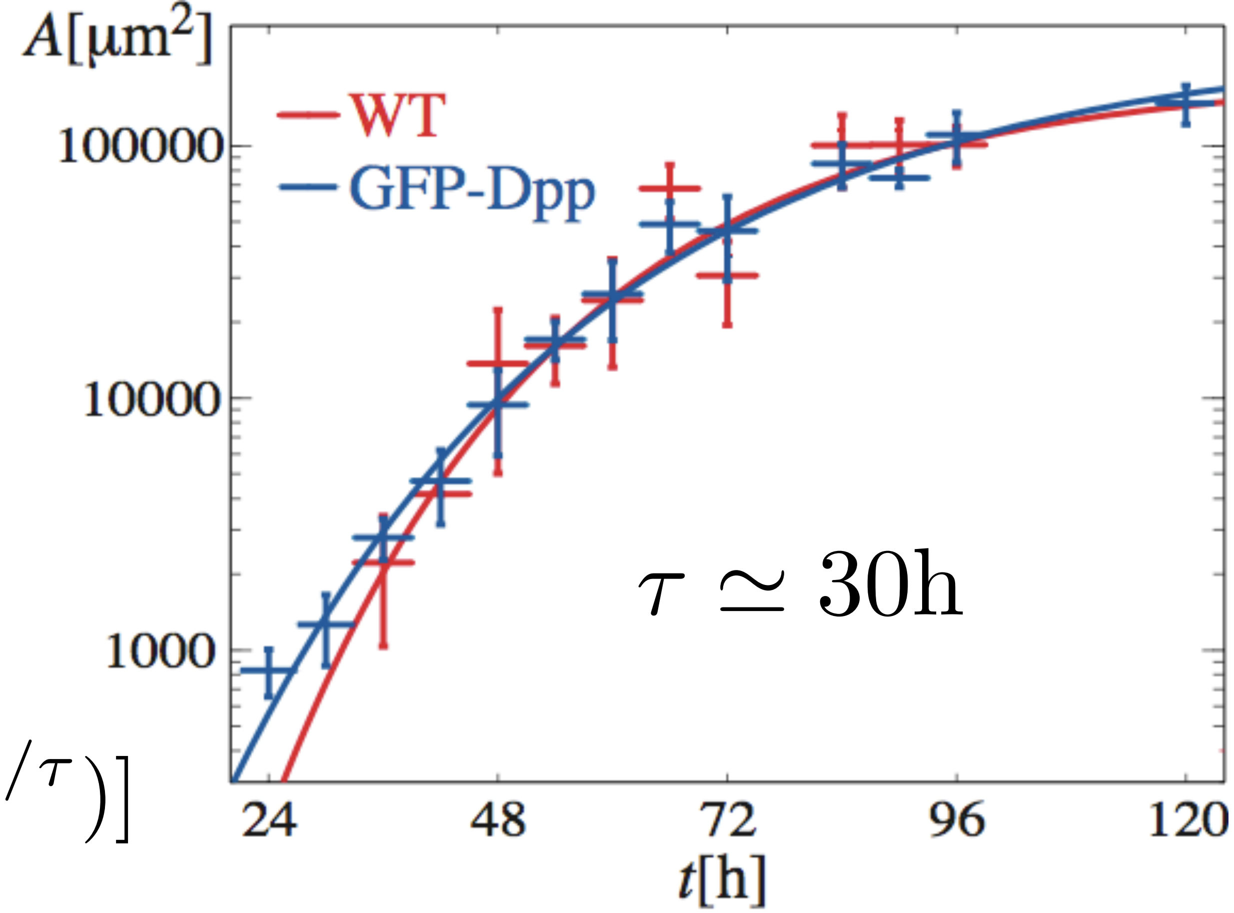
Posterior

Area growth rate $g = \dot{A}/A$

$$g \simeq g_0 \exp\left(-\frac{t-t_0}{\tau}\right)$$

Area growth

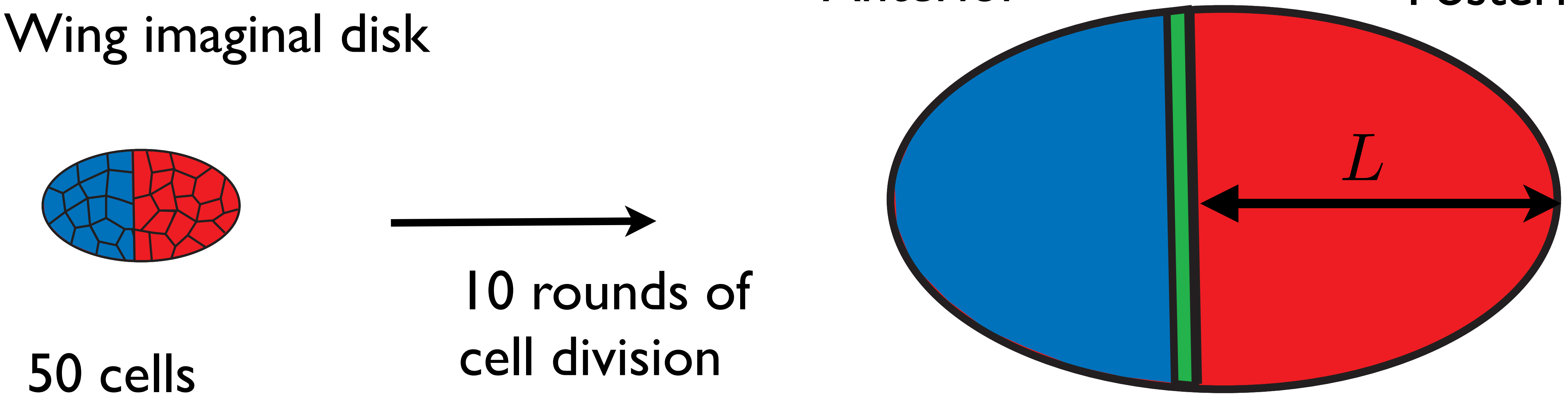
$$A(t) \simeq A_0 \exp[g_0\tau(1-e^{-(t-t_0)/\tau})]$$



Bittig, Wartlick, Gonzalez-Gaitan, Jülicher, EPJE (2009)

Wing disc growth

Wing imaginal disk



50 cells

10 rounds of
cell division

Anterior

Posterior

50000 cells

Area growth rate $g = \dot{A}/A$

$$g \simeq g_0 \exp\left(-\frac{t-t_0}{\tau}\right)$$

Area growth

$$A(t) \simeq A_0 \exp[g_0\tau(1-e^{-(t-t_0)/\tau})]$$

growth anisotropy

$$A \sim L^{1+\epsilon}$$

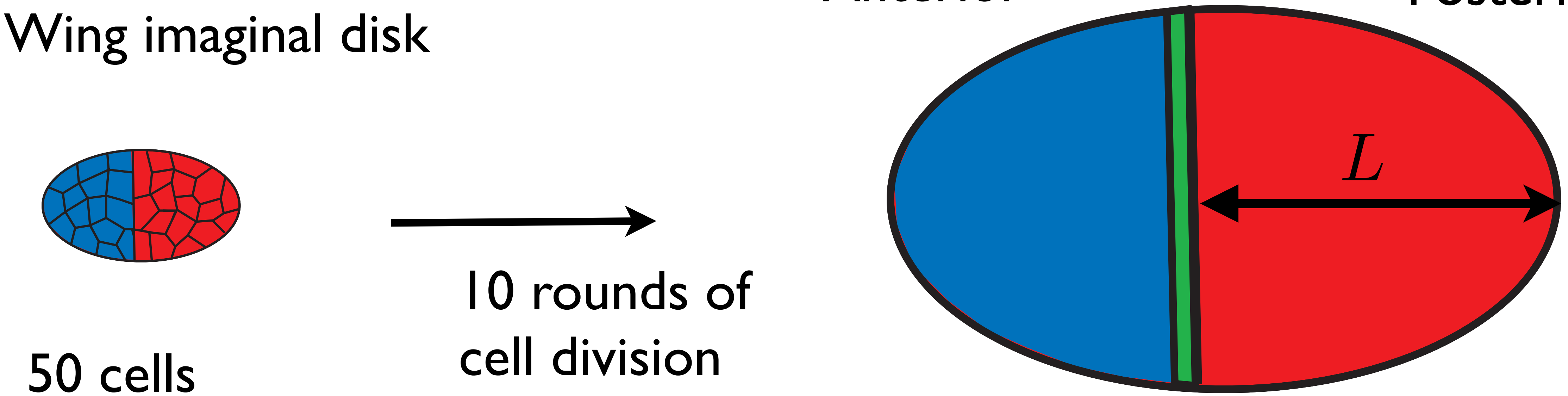
WT $\epsilon \simeq 0.95$

Dpp-GFP $\epsilon \simeq 0.7$

Bittig, Wartlick, Gonzalez-Gaitan, Jülicher, EPJE (2009)

Wing disc growth

Wing imaginal disk



Anterior

Posterior

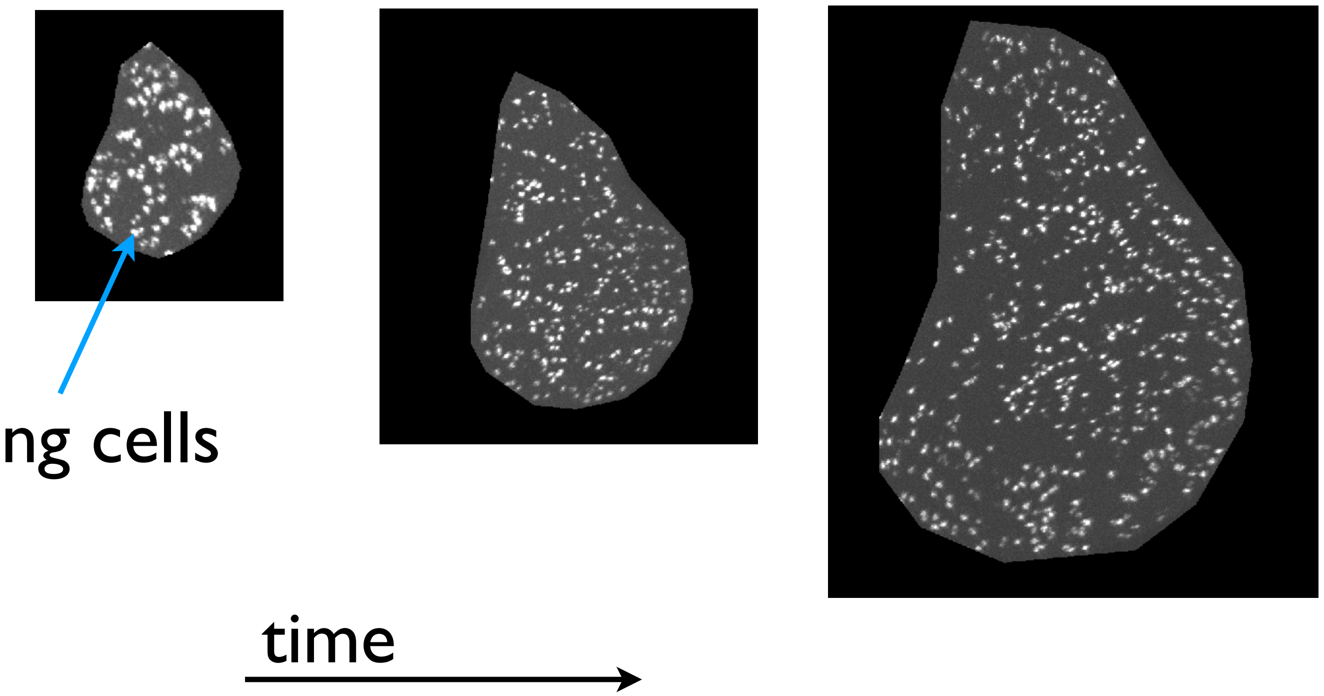
50 cells

10 rounds of cell division

50000 cells

Area growth rate

$$g = \dot{A}/A$$

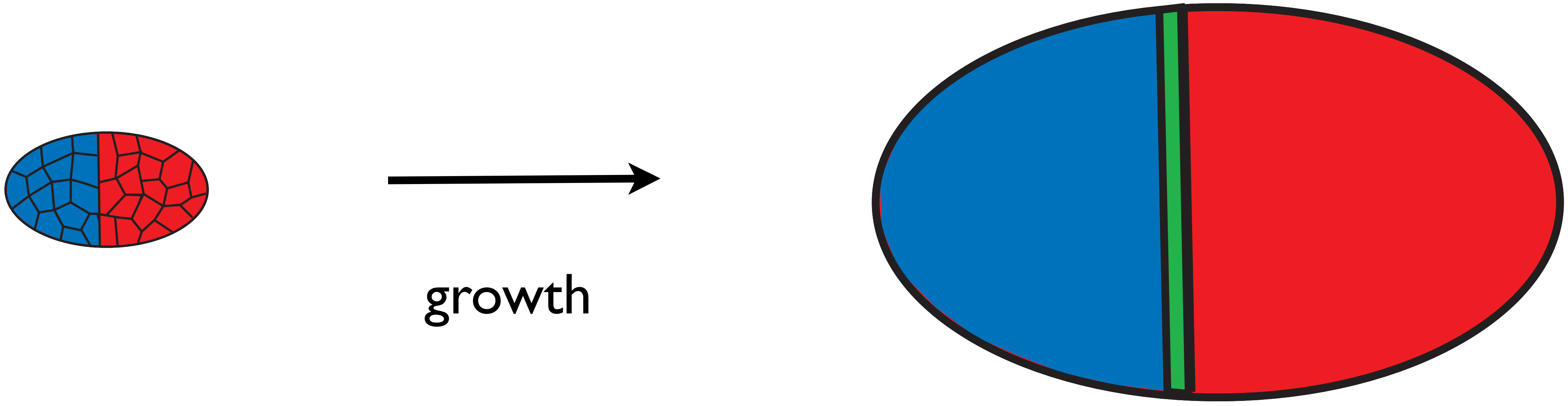


dividing cells

time

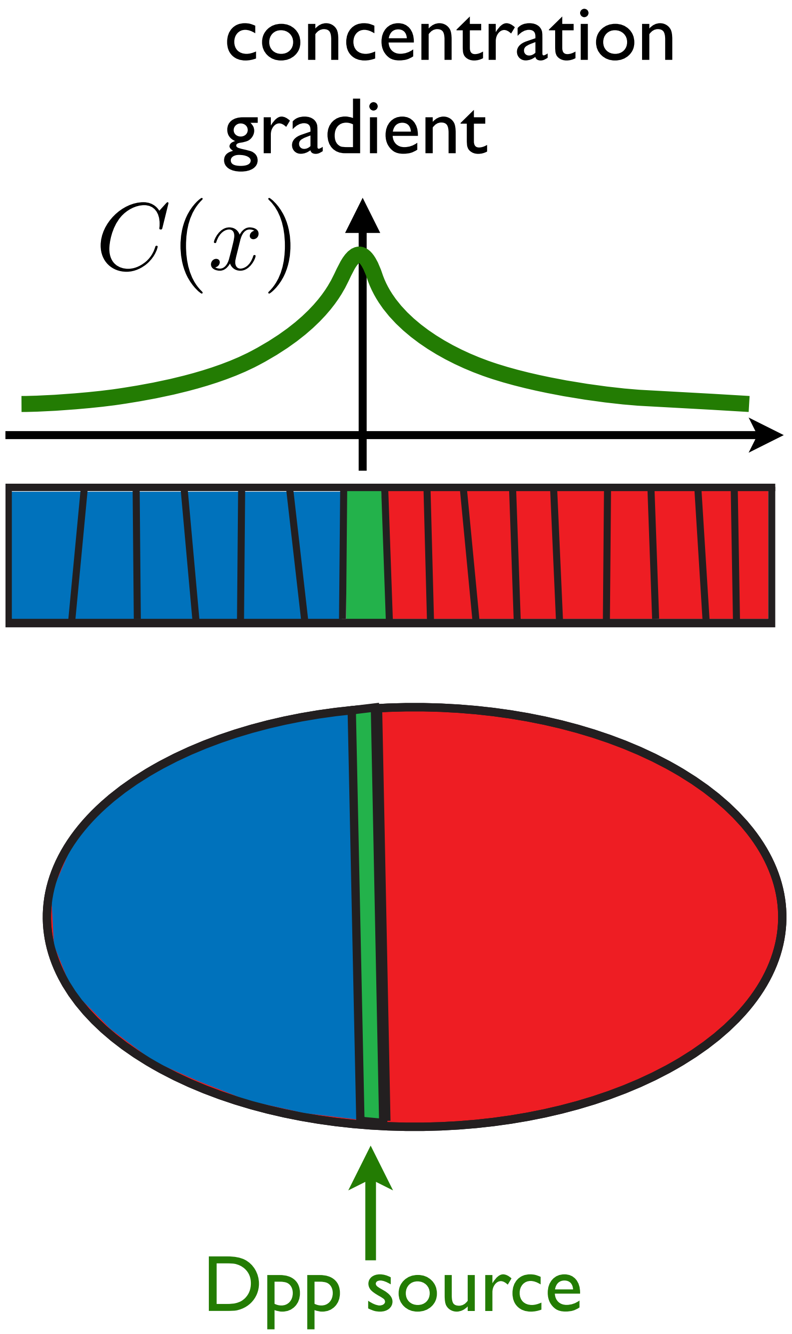
Spatially homogeneous tissue growth

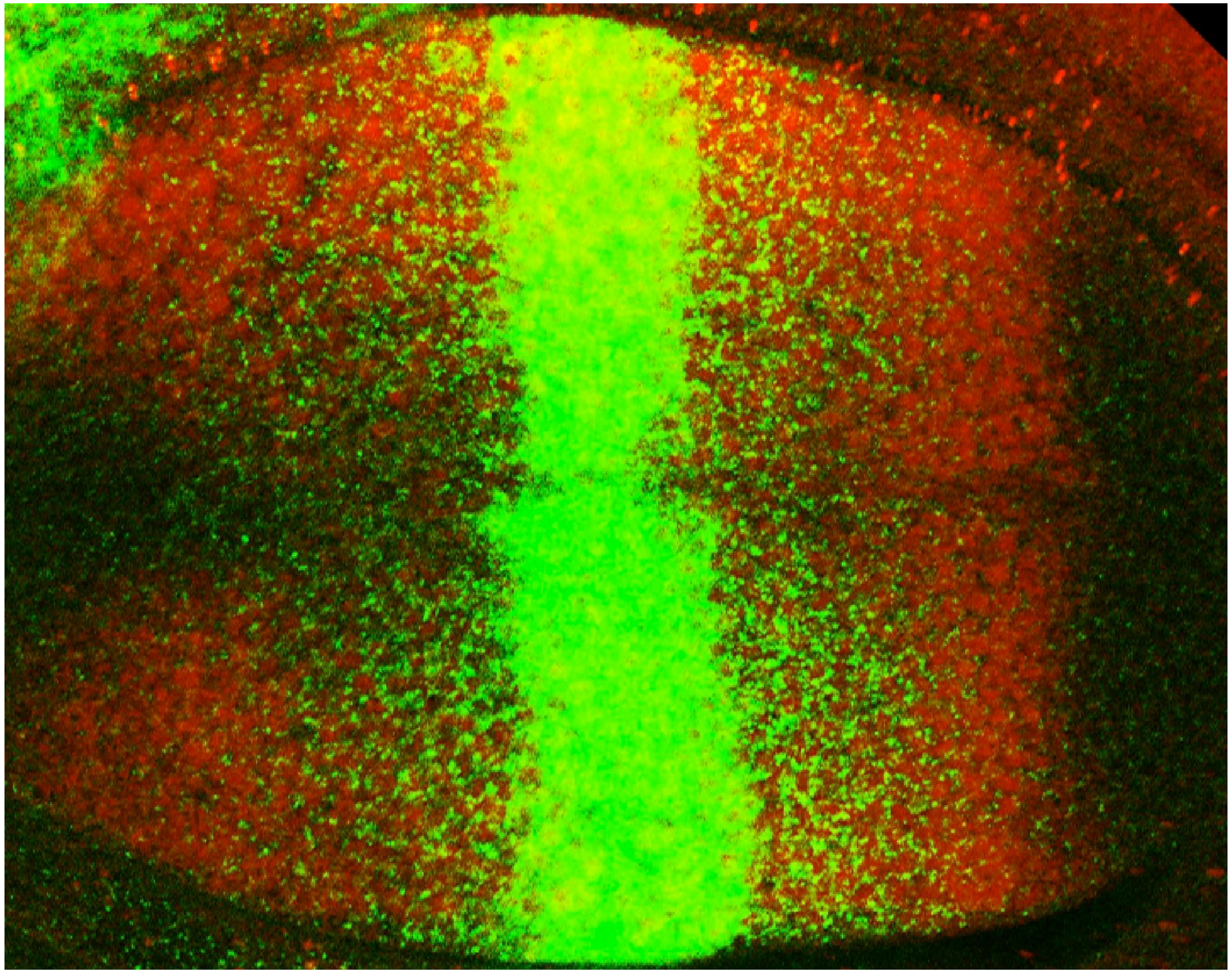
Self-Organisation of tissue growth



How does a collection of cells organize homogeneous tissue growth up to a finite size?

Dpp: graded concentration profiles



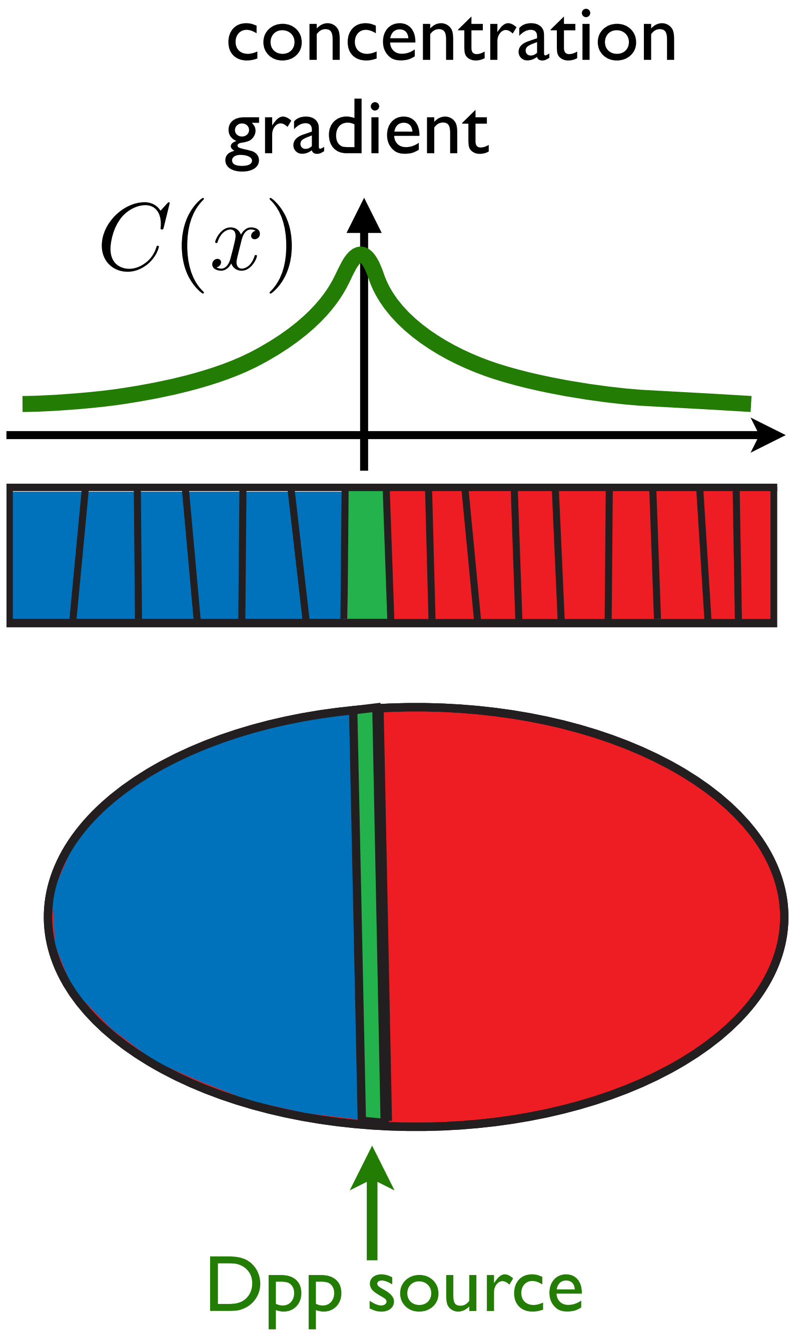


Dpp-GFP

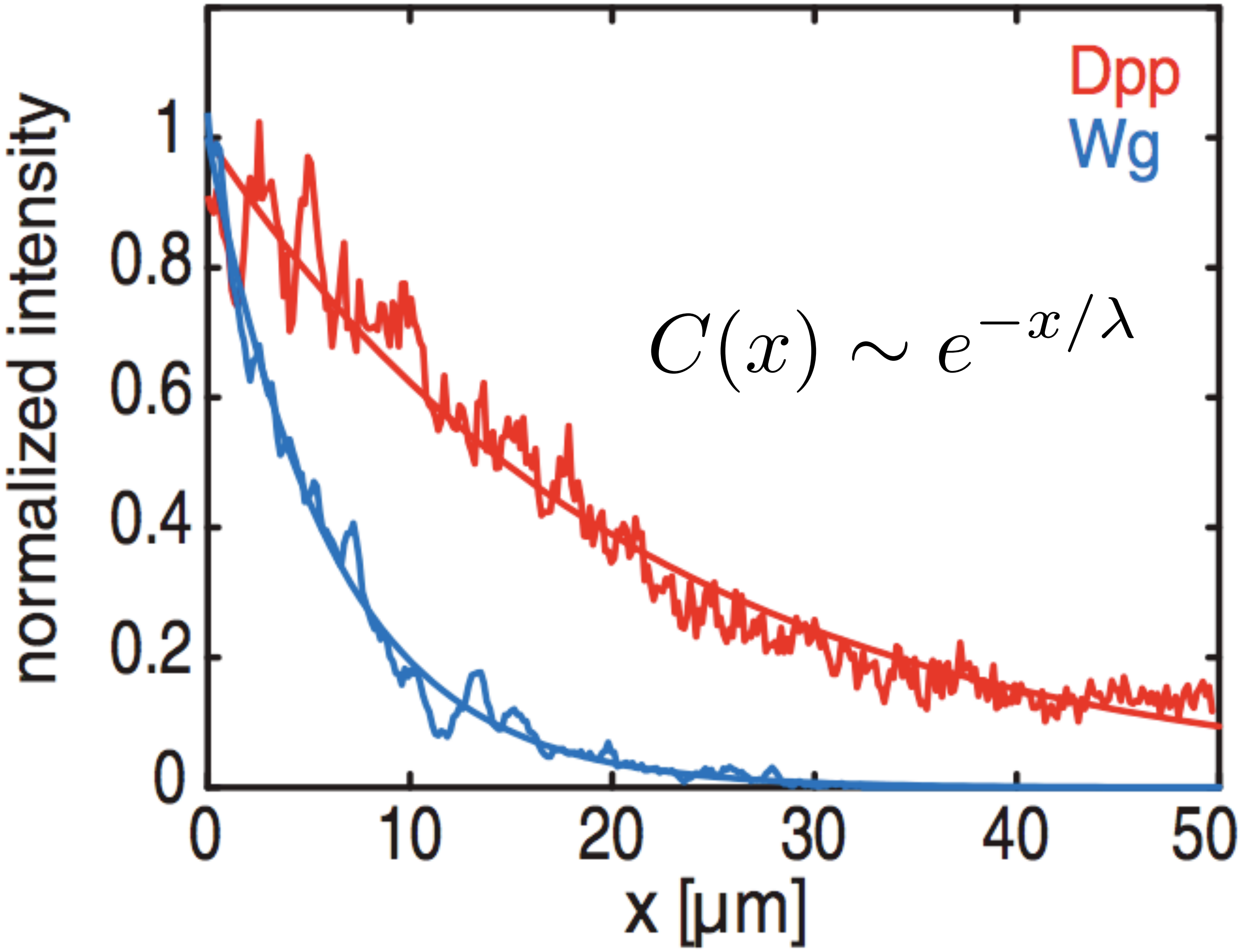
transport, internalization and degradation in target tissue

Kicheva, Pantazis, Bollenbach, Kalaidizis, Bittig, Jülicher, Gonzalez-Gaitan, Science (2007)

Dpp: graded concentration profiles



transport, internalization and degradation in target tissue



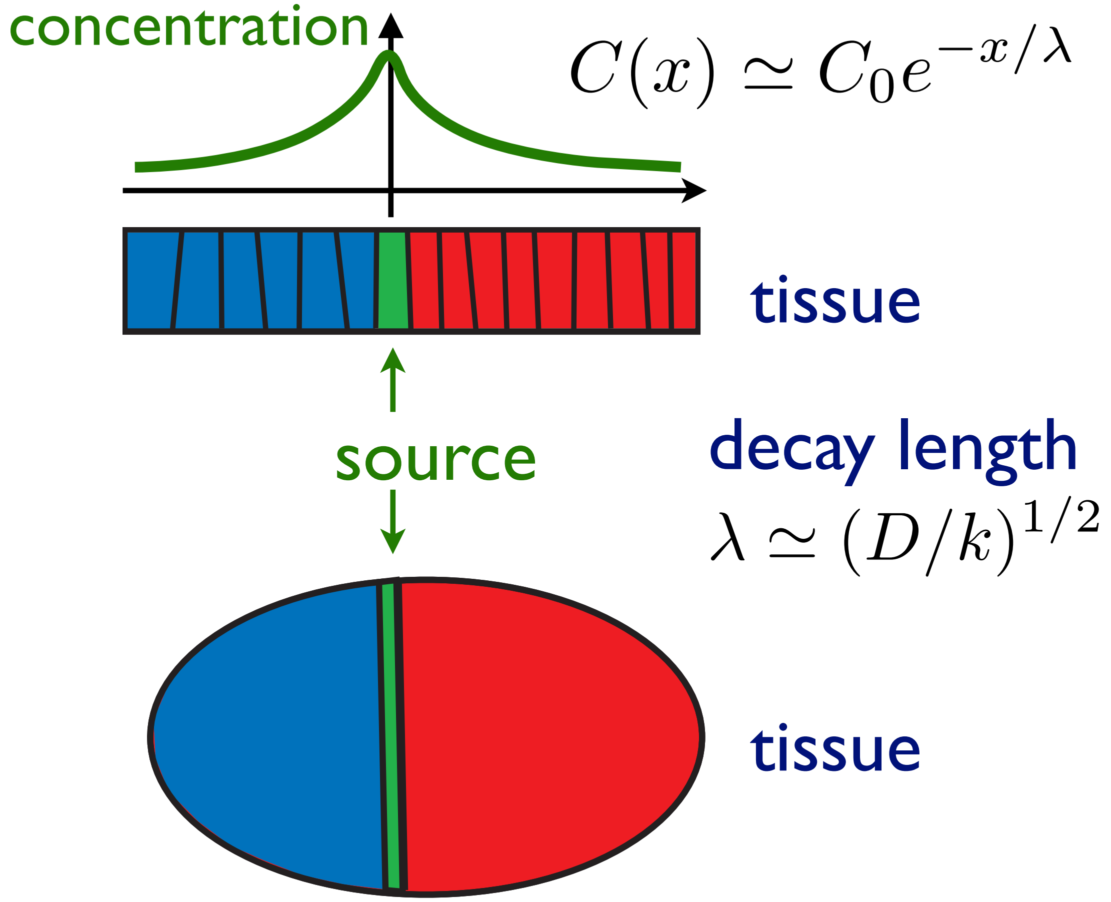
$\lambda \simeq 22\mu\mathrm{m}$ GFP-Dpp

$\lambda \simeq 6\mu\mathrm{m}$ GFP-Wingless

Kicheva, Pantazis, Bollenbach, Kalaidizis, Bittig, Jülicher, Gonzalez-Gaitan, Science (2007)

Growth factors stimulate growth

Secreted growth factors regulate growth



$C(x) \simeq C_0 e^{-x/\lambda}$

decay length
$\lambda \simeq (D/k)^{1/2}$

Diffusion-degradation-convection

effective degradation

$$\partial_t C + \nabla \cdot (\mathbf{v}C) = D\nabla^2 C - kC + \nu(x)$$

cell velocity

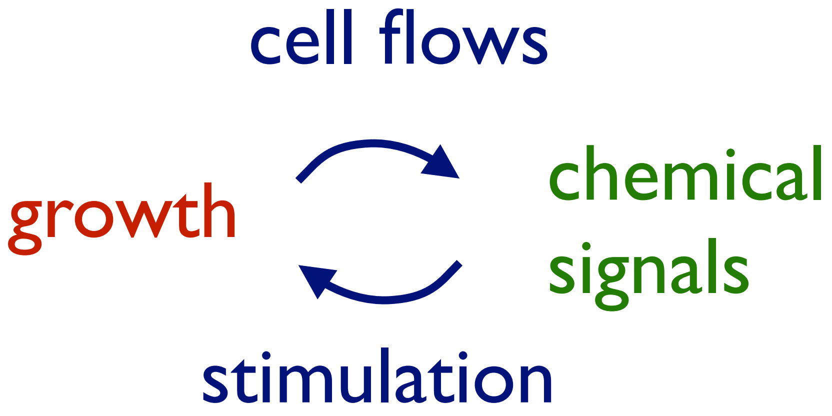
effective diffusion

localized source

Area growth rate generates cell flow

$$\nabla \cdot \mathbf{v} = g$$

Growth control scenarios



cell flows

growth

chemical signals

stimulation

- Dpp gradient slope (spatial control)

  Rogulja and Irvine, Cell (2005)

- Mechanical stress (mechanical control)

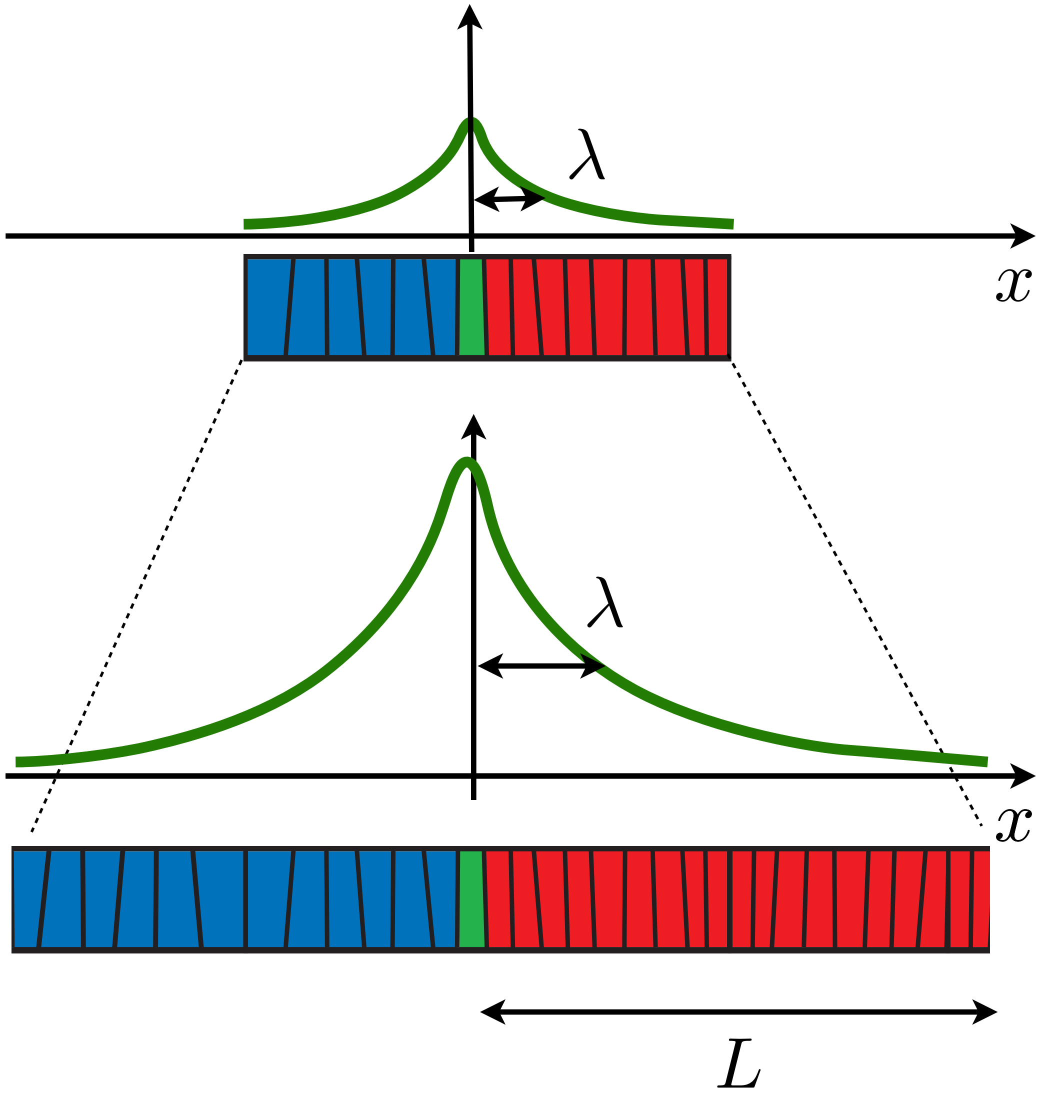
  Hufnagel,...,Cohen, Shraiman, PNAS (2007)

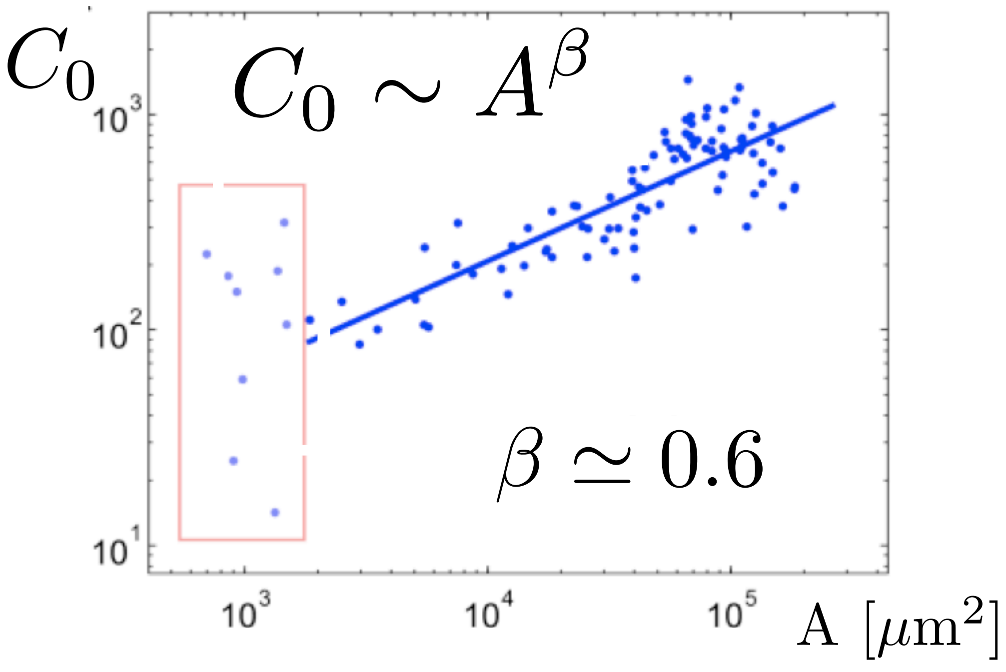
- Relative increase of Dpp levels (temporal control)
  Wartlick et al., Science (2011)

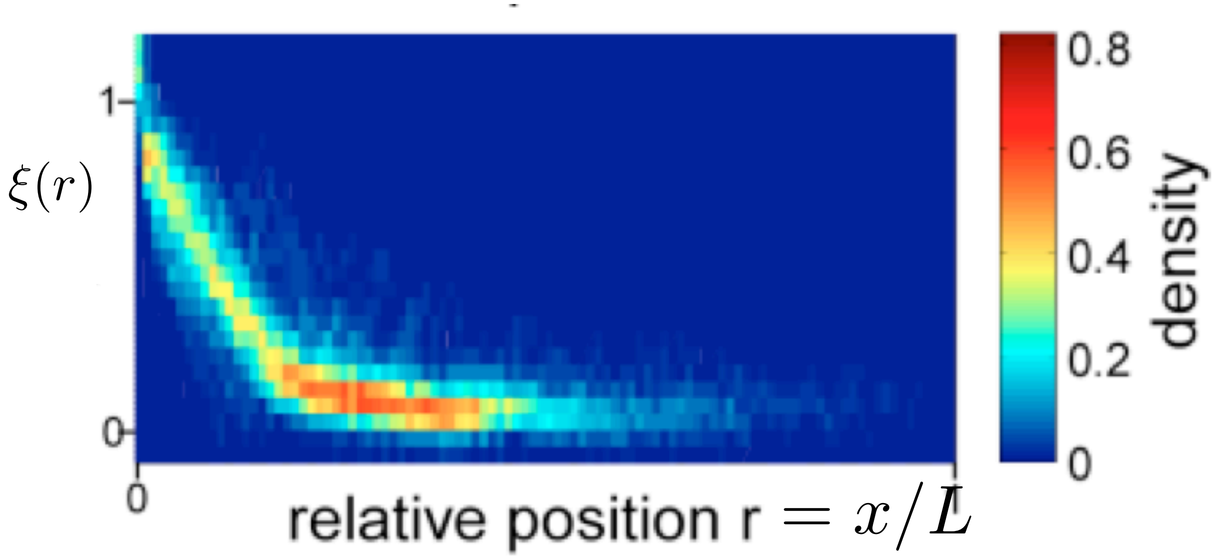
Scaling during tissue growth

scaling of concentration profile

$$C(x,t) = C_0(t)\xi(x/L(t))$$







Ben-Zvi, Shilo, Fainsod, Barkai, Nature (2008)

Ben-Zvi, Pyrowolakis, Barkai, Shilo, Curr. Biol (2011)

Wartlick, Mumcu, Kicheva, Bittig, Seum, Jülicher, Gonzalez-Gaitan, Science (2011)

Scaling during tissue growth

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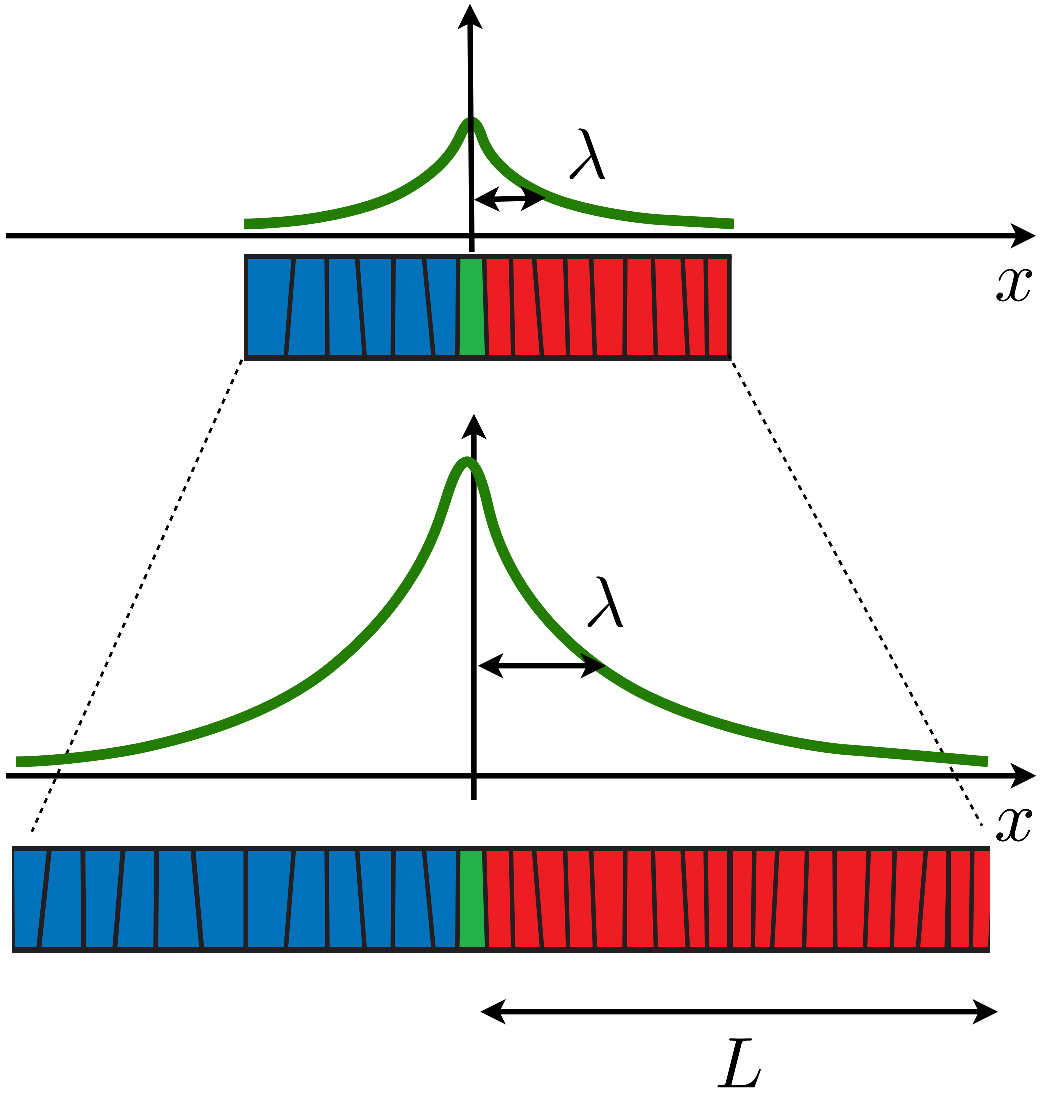
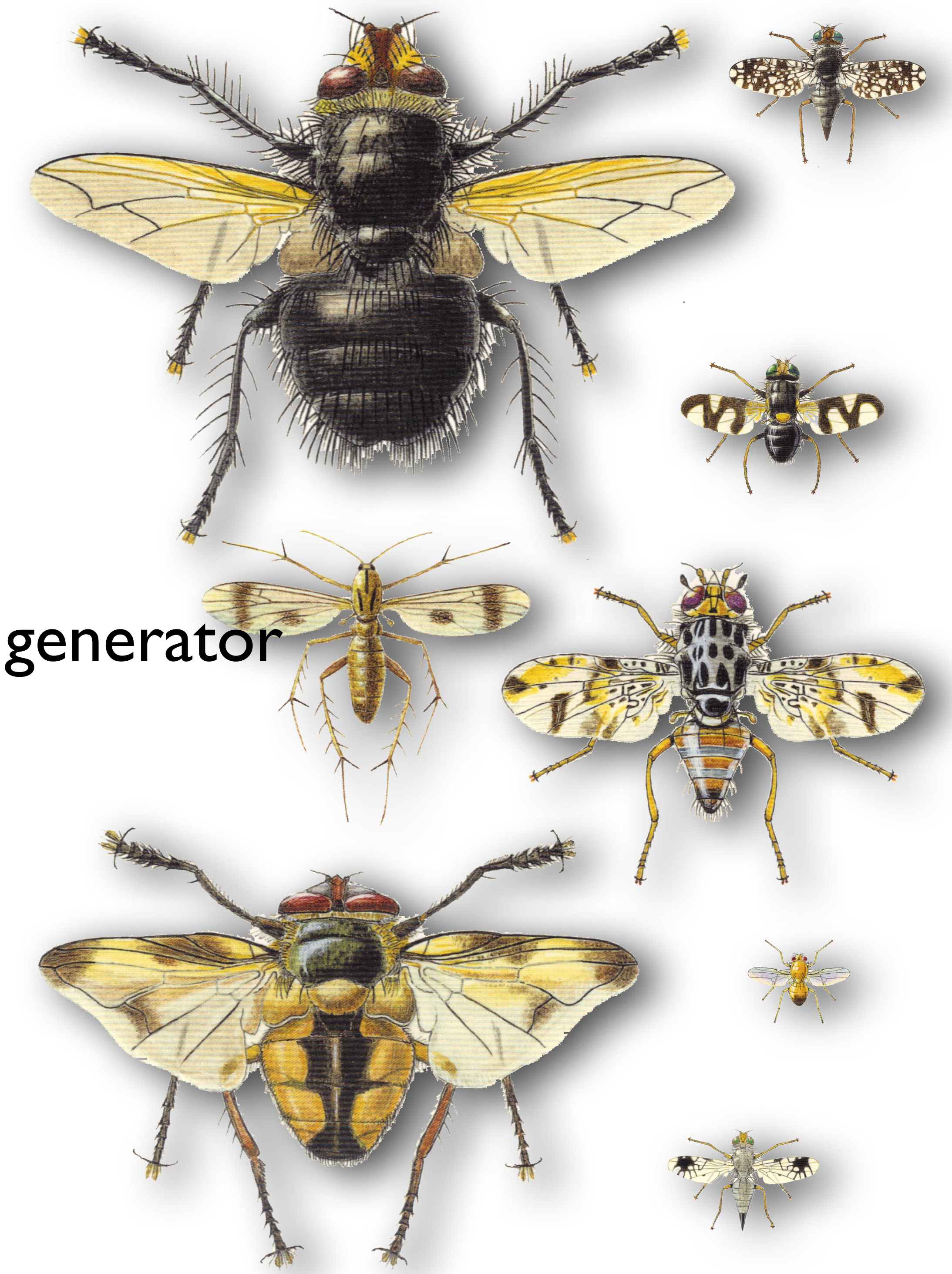




Scalable
pattern generator

Ben-Zvi, Shilo, Fainsod, Barkai, Nature (2008)

Ben-Zvi, Pyrowolakis, Barkai, Shilo, Curr. Biol (2011)

Wartlick, Mumcu, Kicheva, Bittig, Seum, Jülicher, Gonzalez-Gaitan, Science (2011)

Scaling mechanism?

Dynamic regulation of degradation rate

Expansion - repression

Ben-Zvi and Barkai, PNAS 107 (2010)

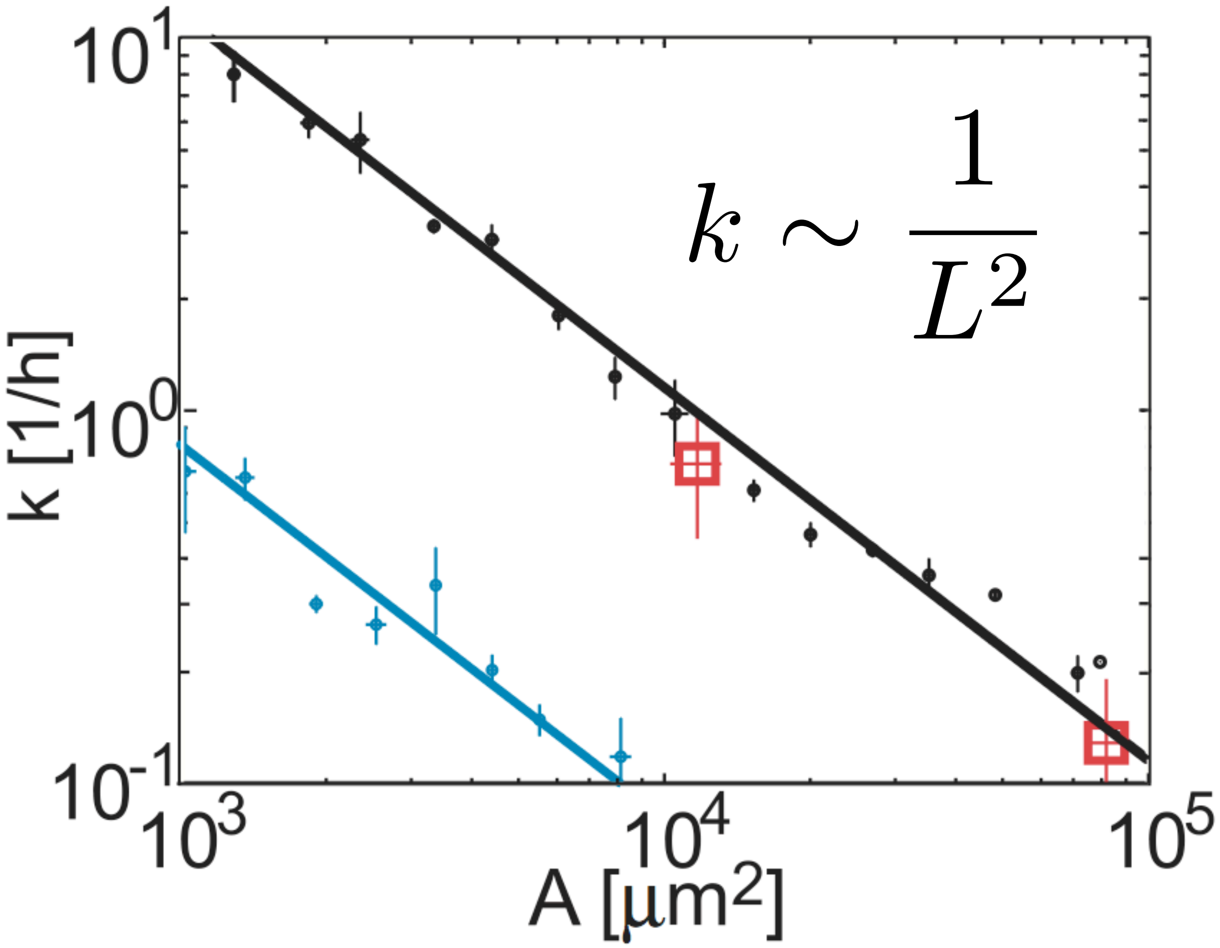
Expander - dilution

Wartlick, Mumcu et al., Science (2011)

Scaling via growth control

Aberbukh, Ben-Zwi, Mishra, Barkai, Development (2014)

$$\lambda = (D/k)^{1/2}$$



$$\lambda \sim L \qquad k \sim \frac{1}{L^2}$$

Key players: Pentagone
HSPG Dally

see also:
Ben-Zvi, Pyrowolakis, Barkai, Shilo, Curr. Biol (2011)
Ben-Zvi and Barkai, PNAS 107 (2010)
Ben-Zvi, Shilo, Fainsod, Barkai, Nature (2008)

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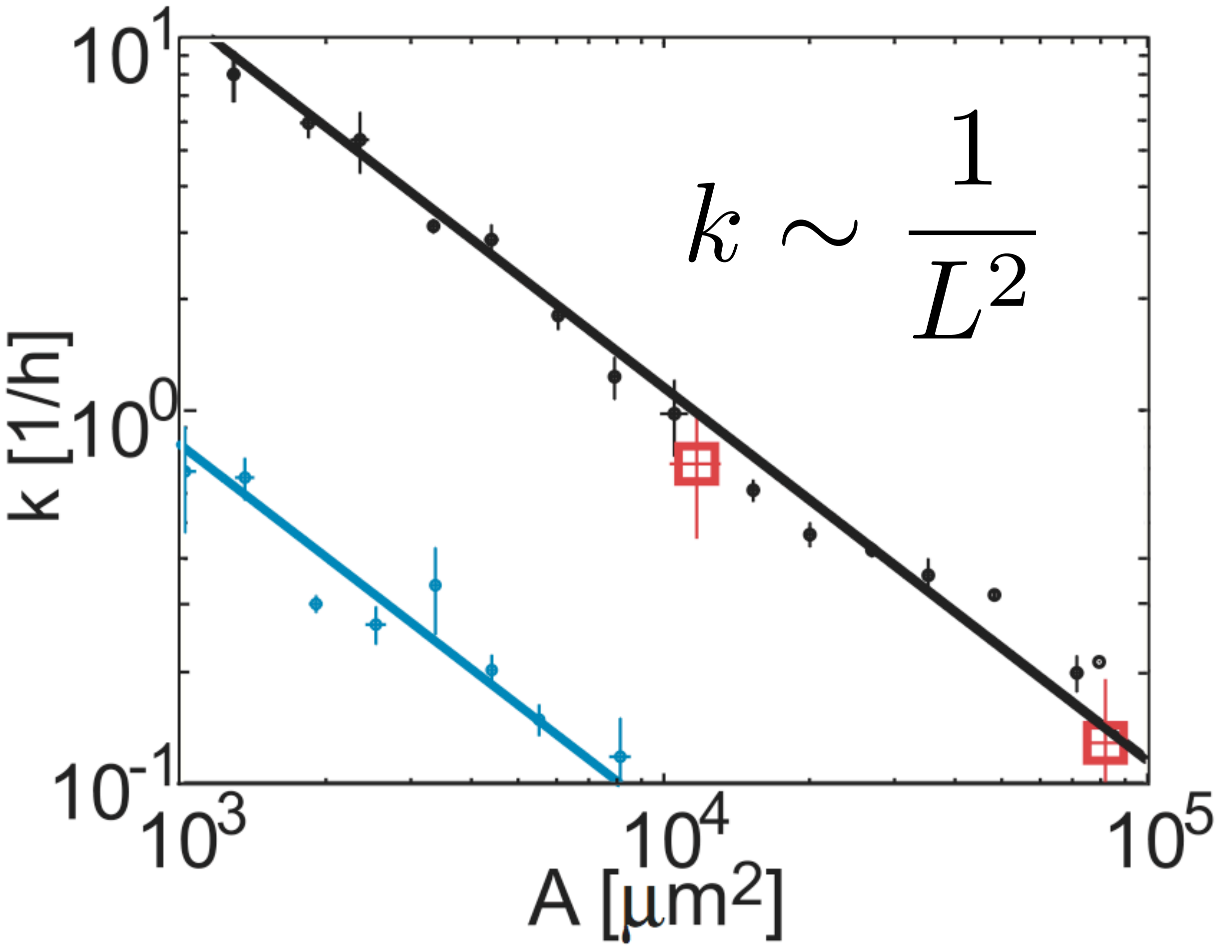

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→ talk by Marcos Gonzalez-Gaitan

Key players: Pentagone
HSPG Dally

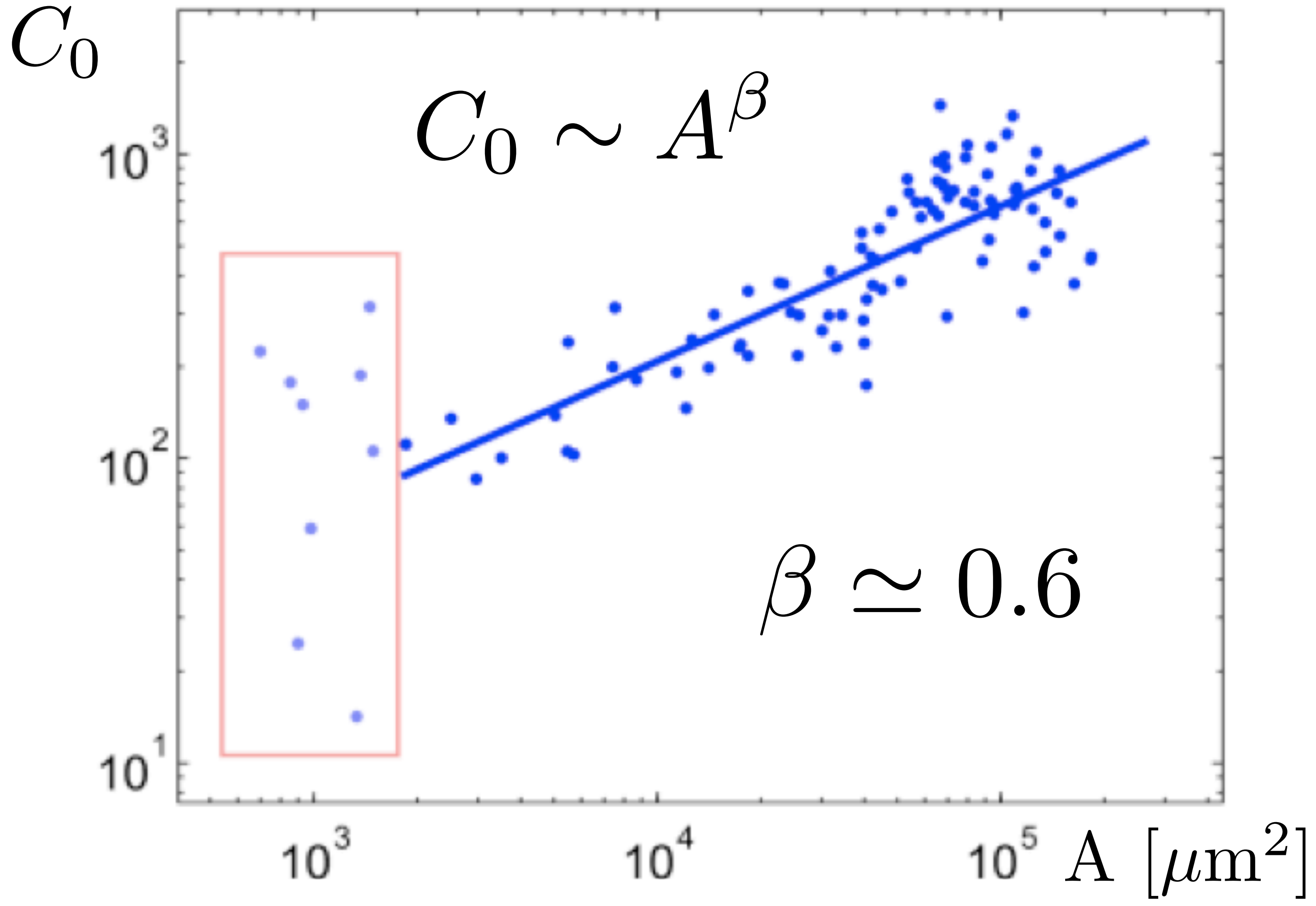
see also:

Ben-Zvi, Pyrowolakis, Barkai, Shilo, Curr. Biol (2011)

Ben-Zvi and Barkai, PNAS 107 (2010)

Ben-Zvi, Shilo, Fainsod, Barkai, Nature (2008)

Scaling and growth



$$C_0 \sim A^\beta$$

$$\frac{\dot{C}_0}{C_0} \simeq \beta \frac{\dot{A}}{A}$$

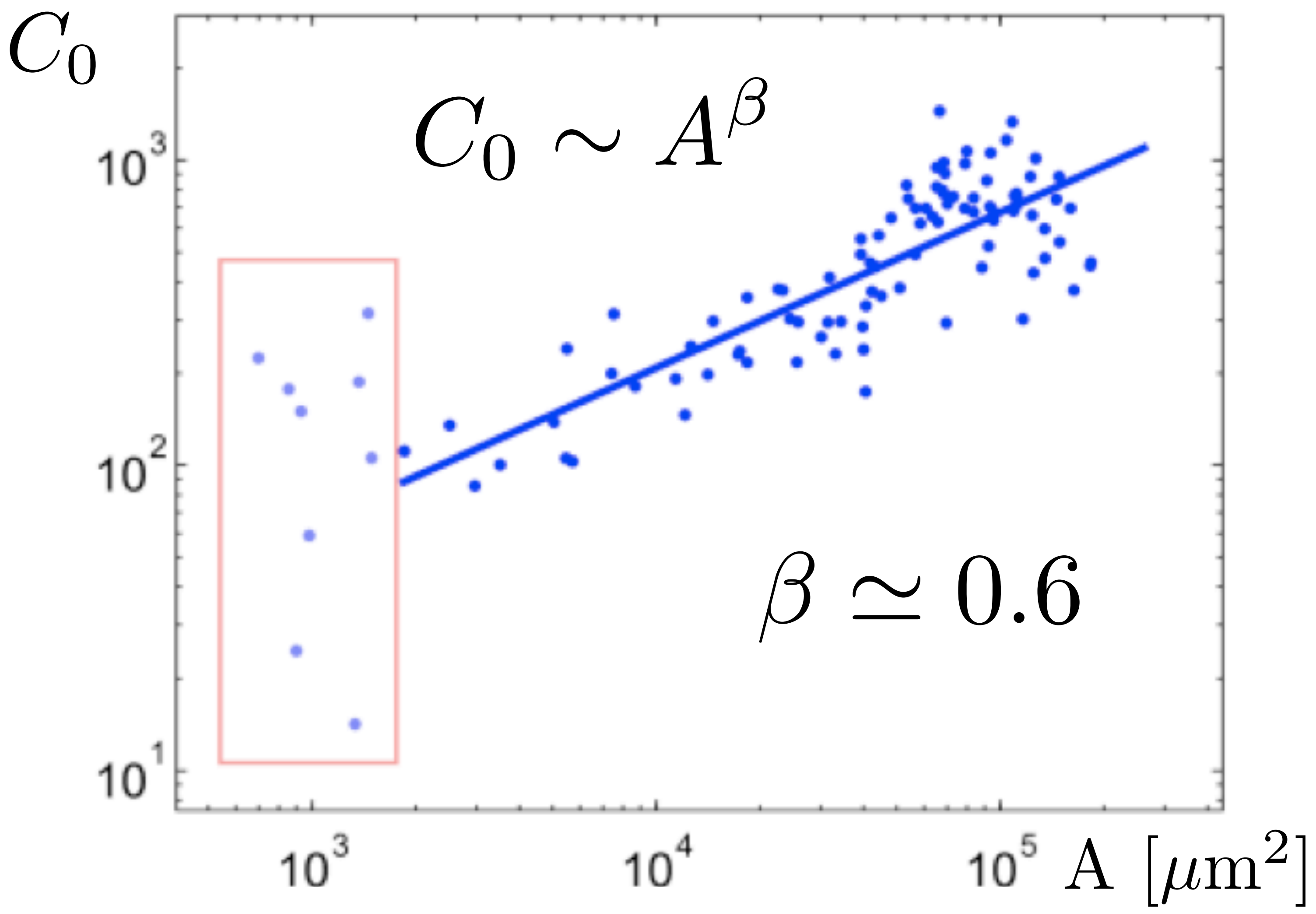
constant during homogeneous growth

Scaling morphogen profile $C = C_0 \xi(x/L)$

Signal received by cell during growth $C(t) = C_0(t)\xi(x(t)/L(t))$

Wartlick, Mumcu, Kicheva, Bittig, Seum, Jülicher, Gonzalez-Gaitan, Science (2011)

Scaling and growth



$$C_0 \sim A^\beta$$

$$\frac{\dot{C}_0}{C_0} \simeq \beta \frac{\dot{A}}{A}$$

$$\frac{\dot{C}}{C} = \frac{\dot{C}_0}{C_0}$$

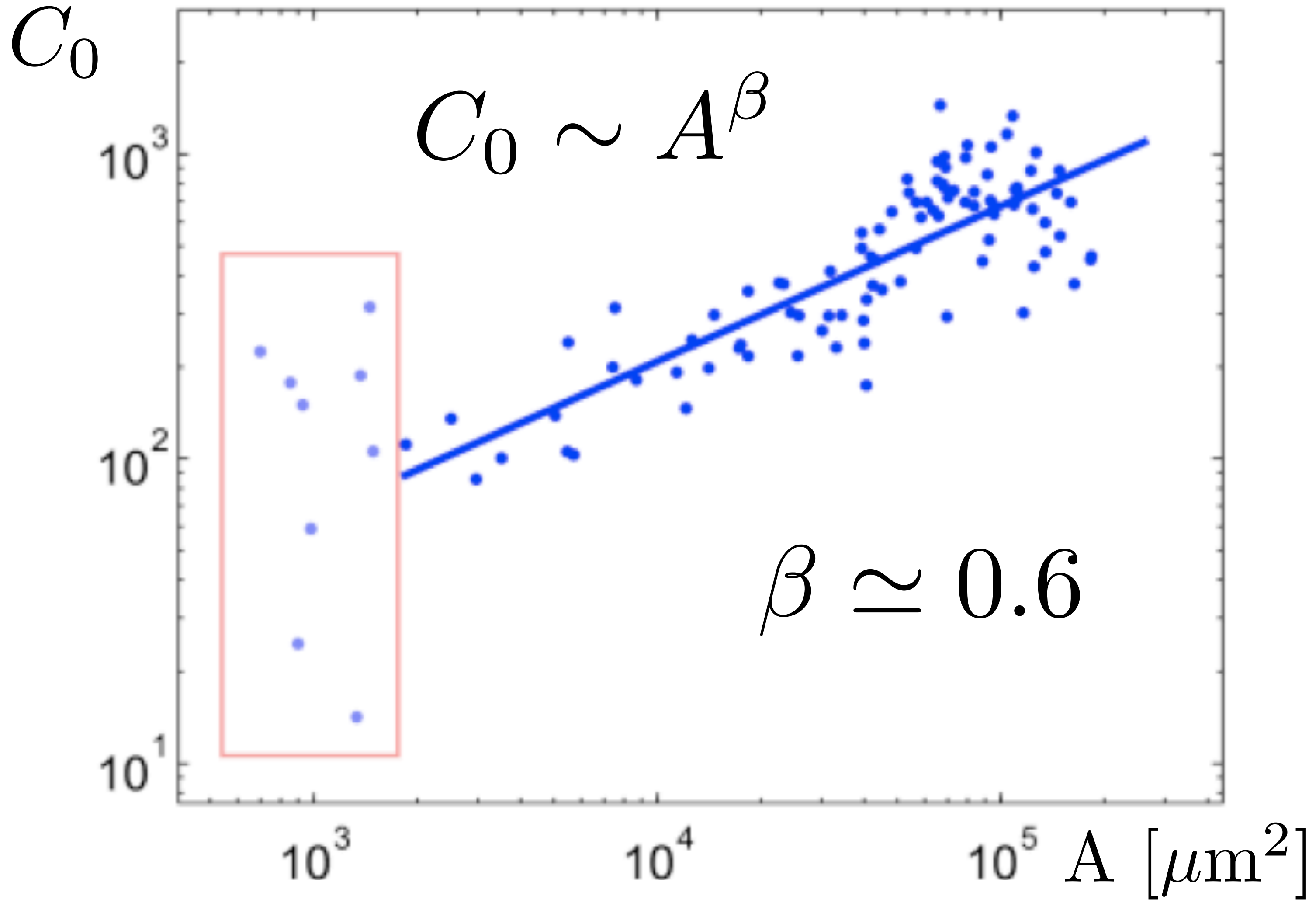
constant during homogeneous growth

Scaling morphogen profile $C = C_0 \xi(x/L)$

Signal received by cell during growth $C(t) = C_0(t) \xi(x(t)/L(t))$

Wartlick, Mumcu, Kicheva, Bittig, Seum, Jülicher, Gonzalez-Gaitan, Science (2011)

Scaling and growth



$$C_0 \sim A^\beta$$

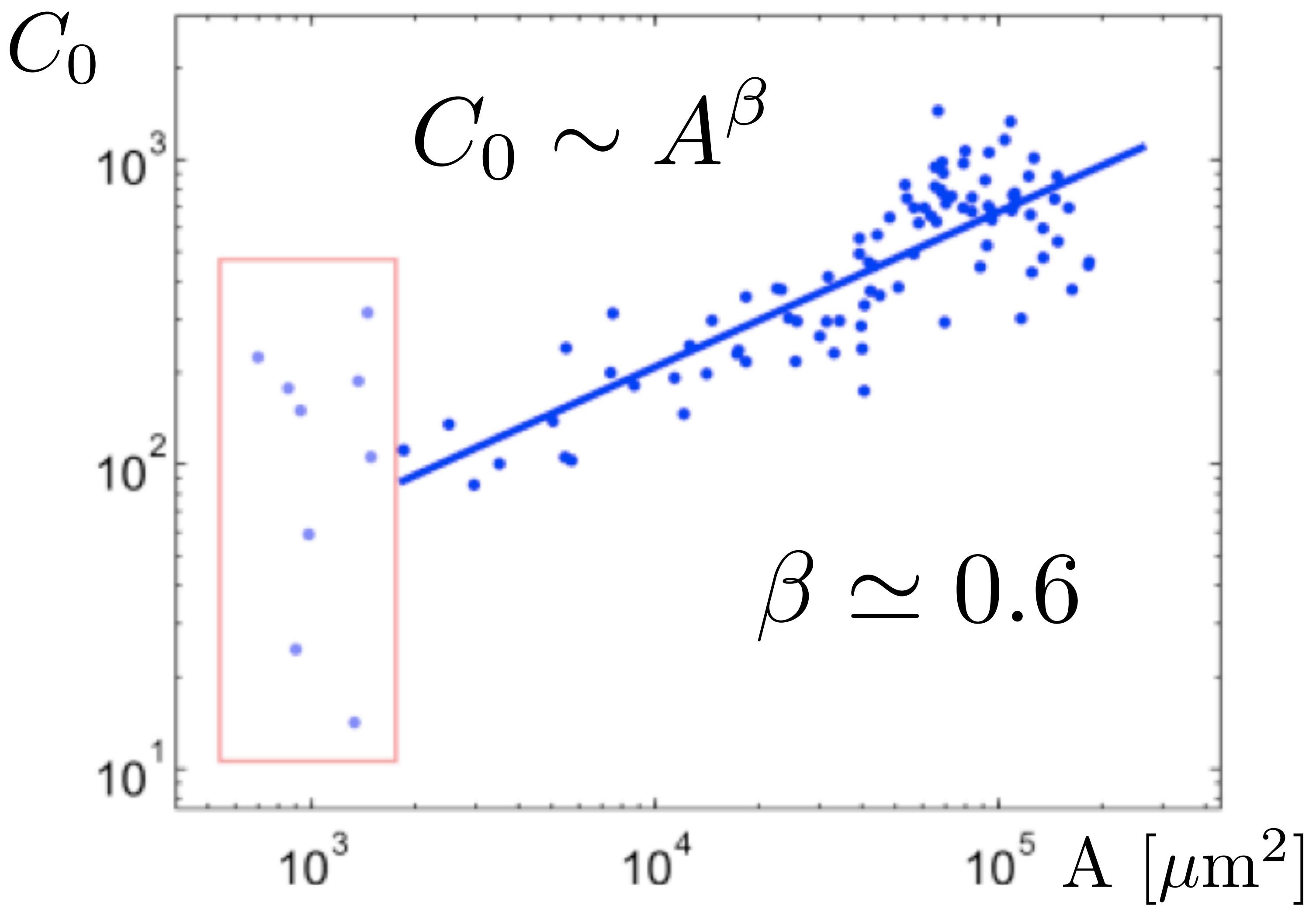
$$\frac{\dot{C}_0}{C_0} \simeq \beta \frac{\dot{A}}{A}$$

$$g = \frac{\dot{A}}{A}$$

$$\boxed{g = \beta^{-1} \frac{\dot{C}}{C}}$$

Wartlick, Mumcu, Kicheva, Bittig, Seum, Jülicher, Gonzalez-Gaitan, Science (2011)

Temporal growth control



$$C_0 \sim A^\beta$$

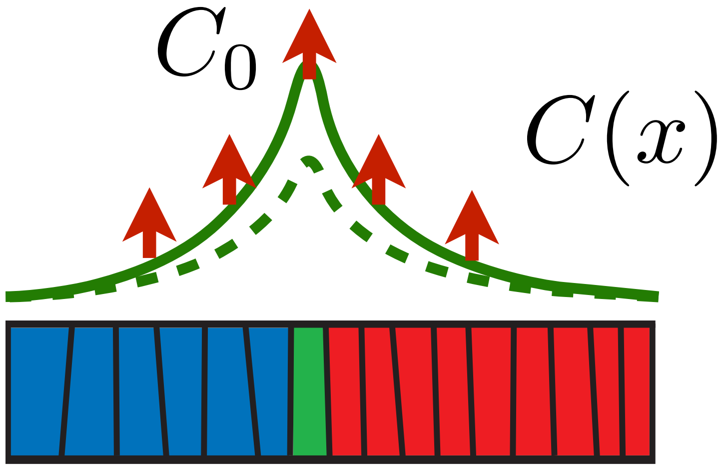
$$\frac{\dot{C}_0}{C_0} \simeq \beta \frac{\dot{A}}{A}$$

$$g = \frac{\dot{A}}{A}$$

growth control by
temporal changes:

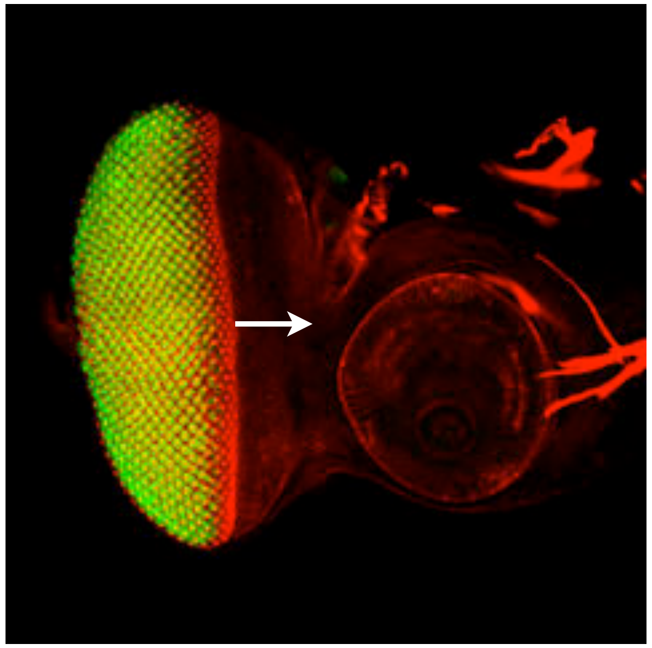
$$\boxed{g = \beta^{-1} \frac{\dot{C}}{C}}$$

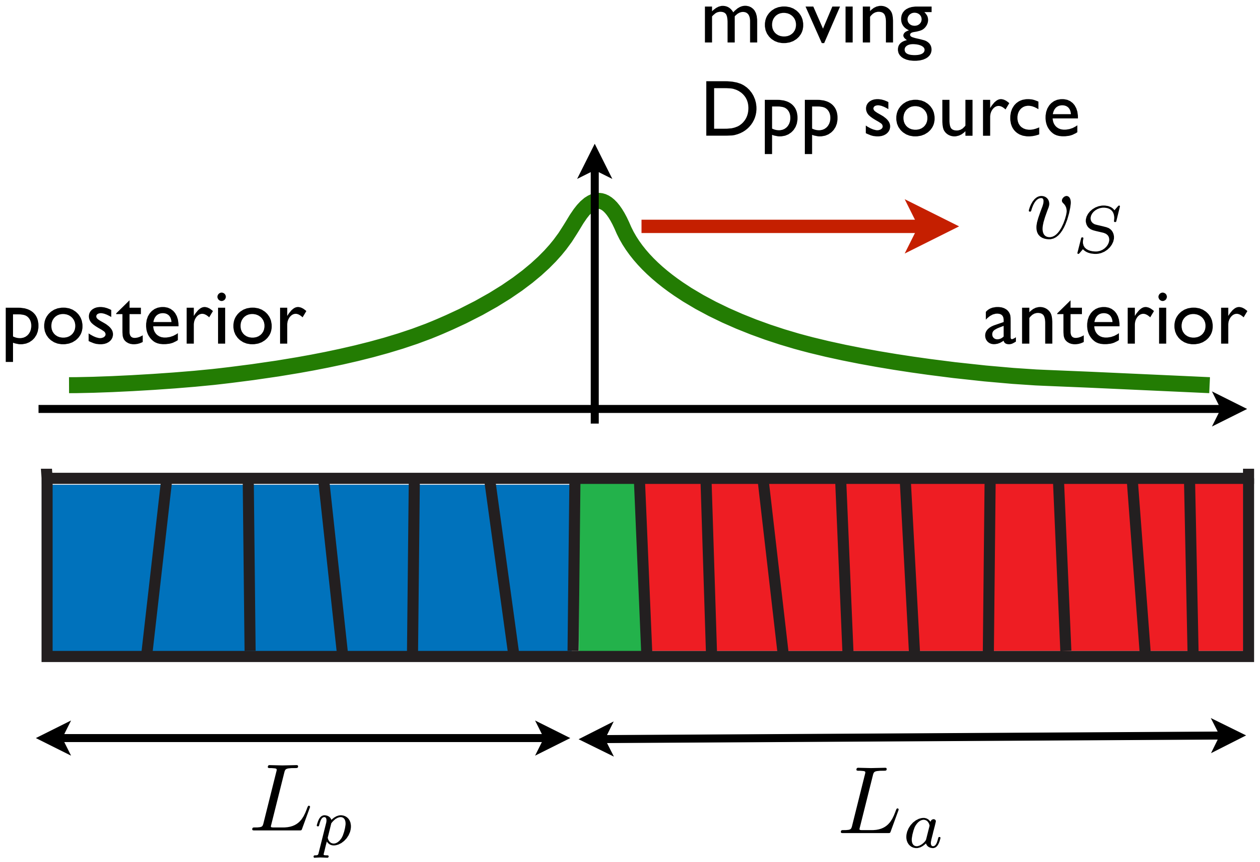
growth control parameter



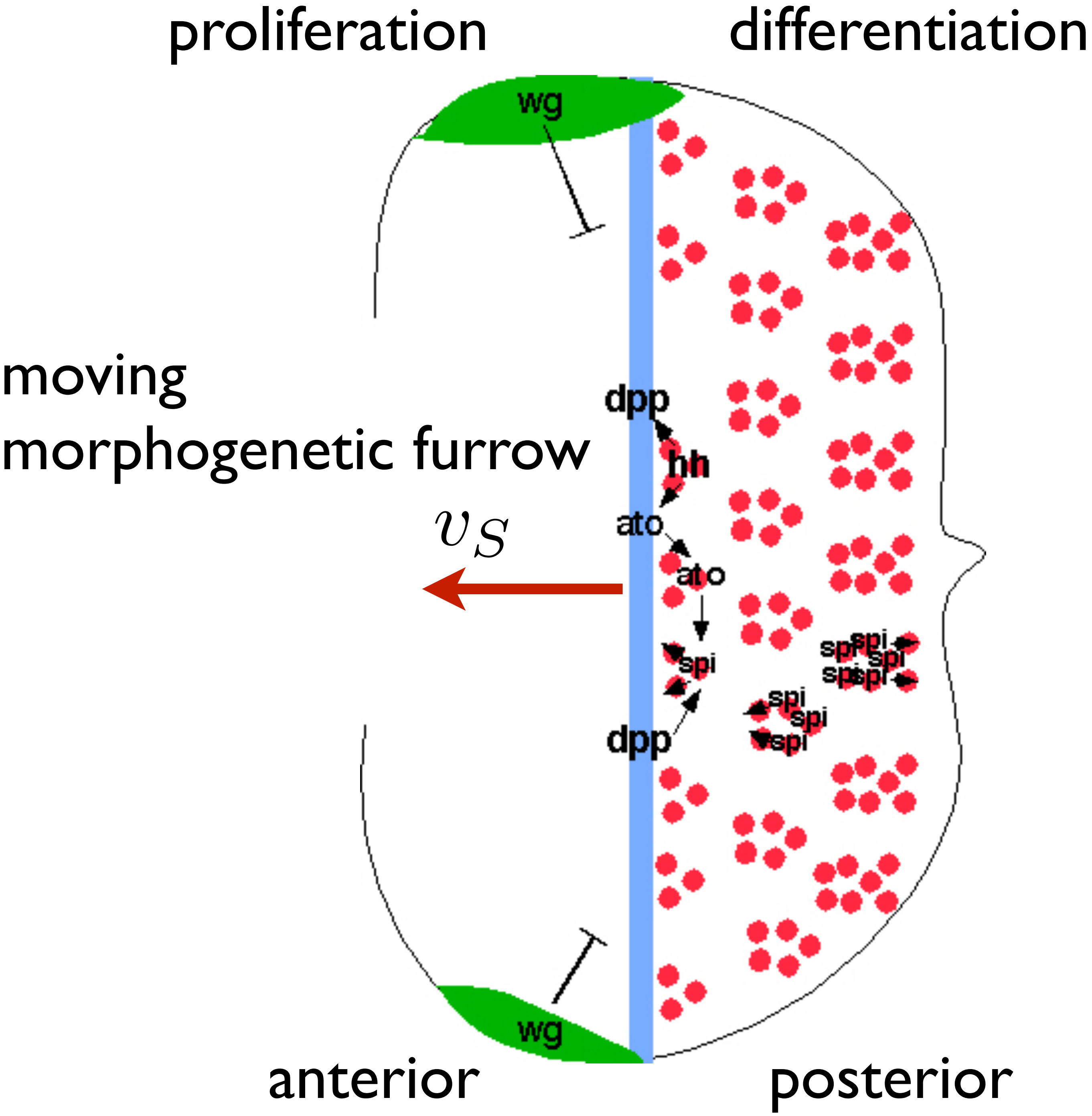
Wartlick, Mumcu, Kicheva, Bittig, Seum, Jülicher, Gonzalez-Gaitan, Science (2011)

Moving furrow in the eye

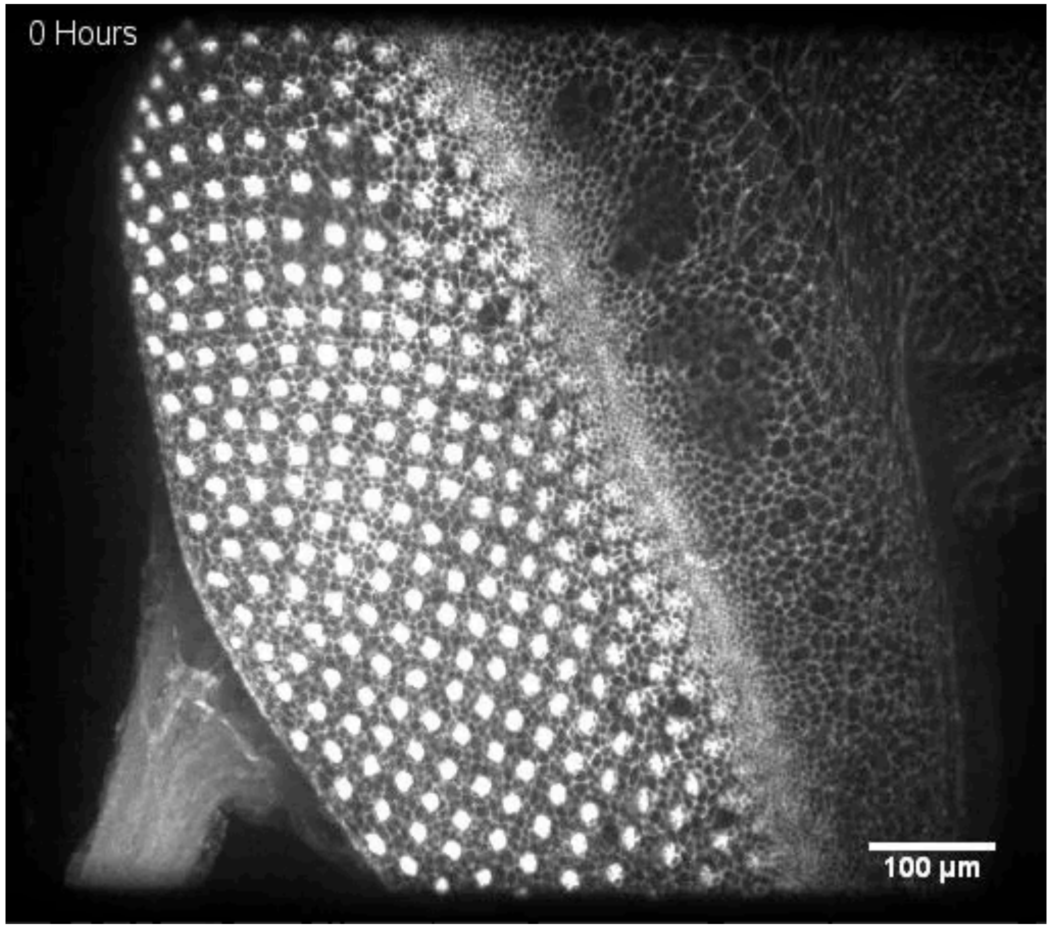


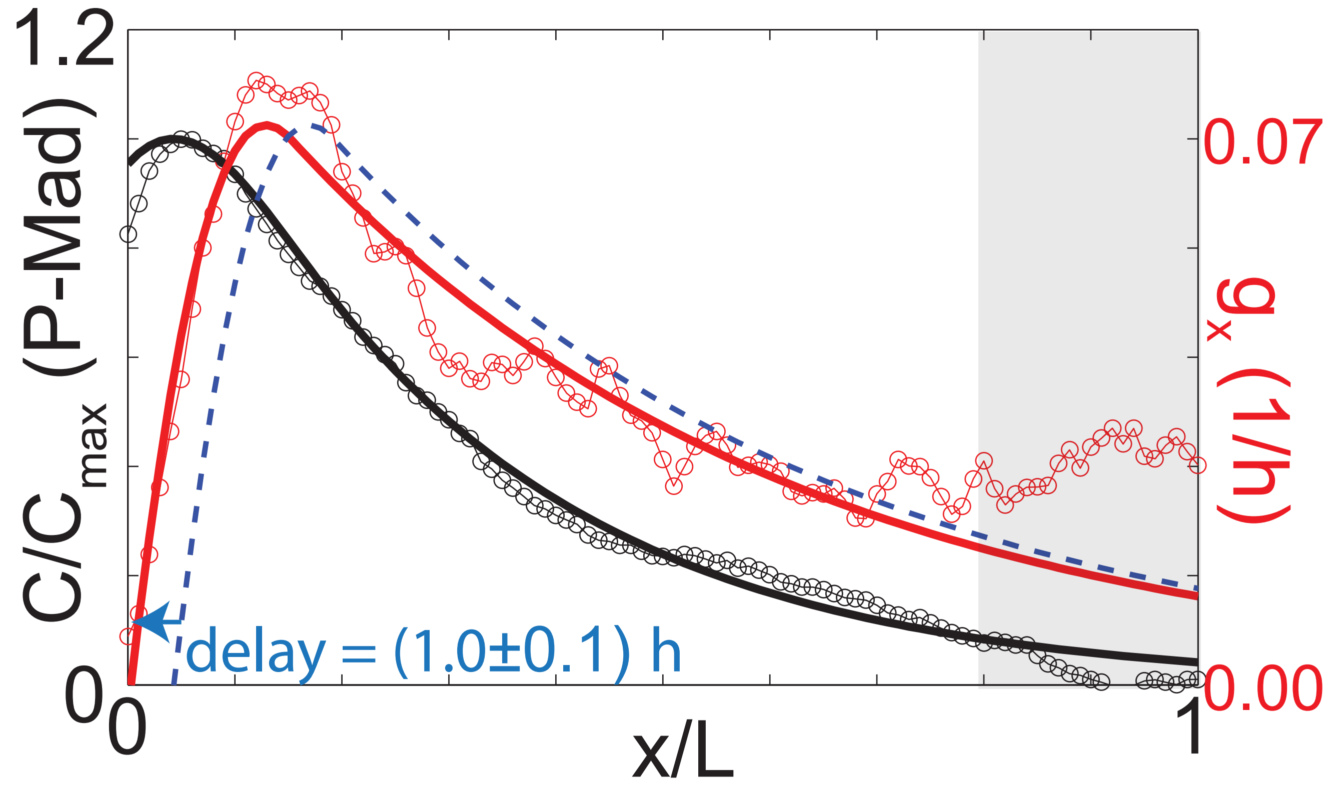


Ma, Zhou, Beachy, Moses, Cell 75 (1993)

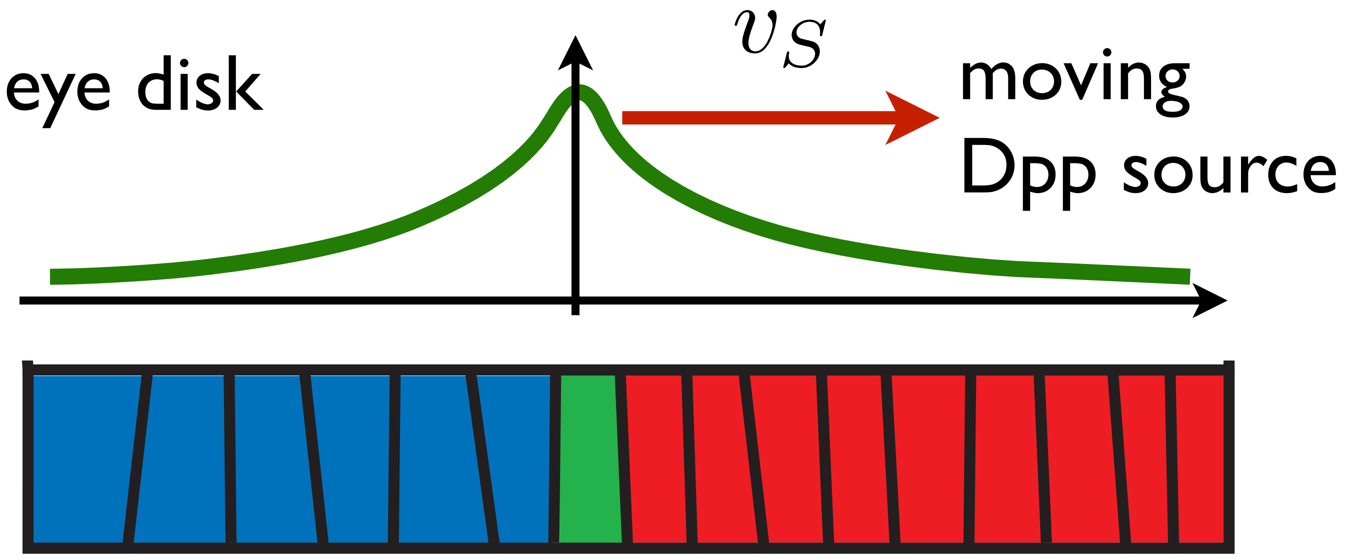


Cell division wave in the eye





$$v_S \simeq 3\mu\mathrm{m}/h$$



eye disk

v_S

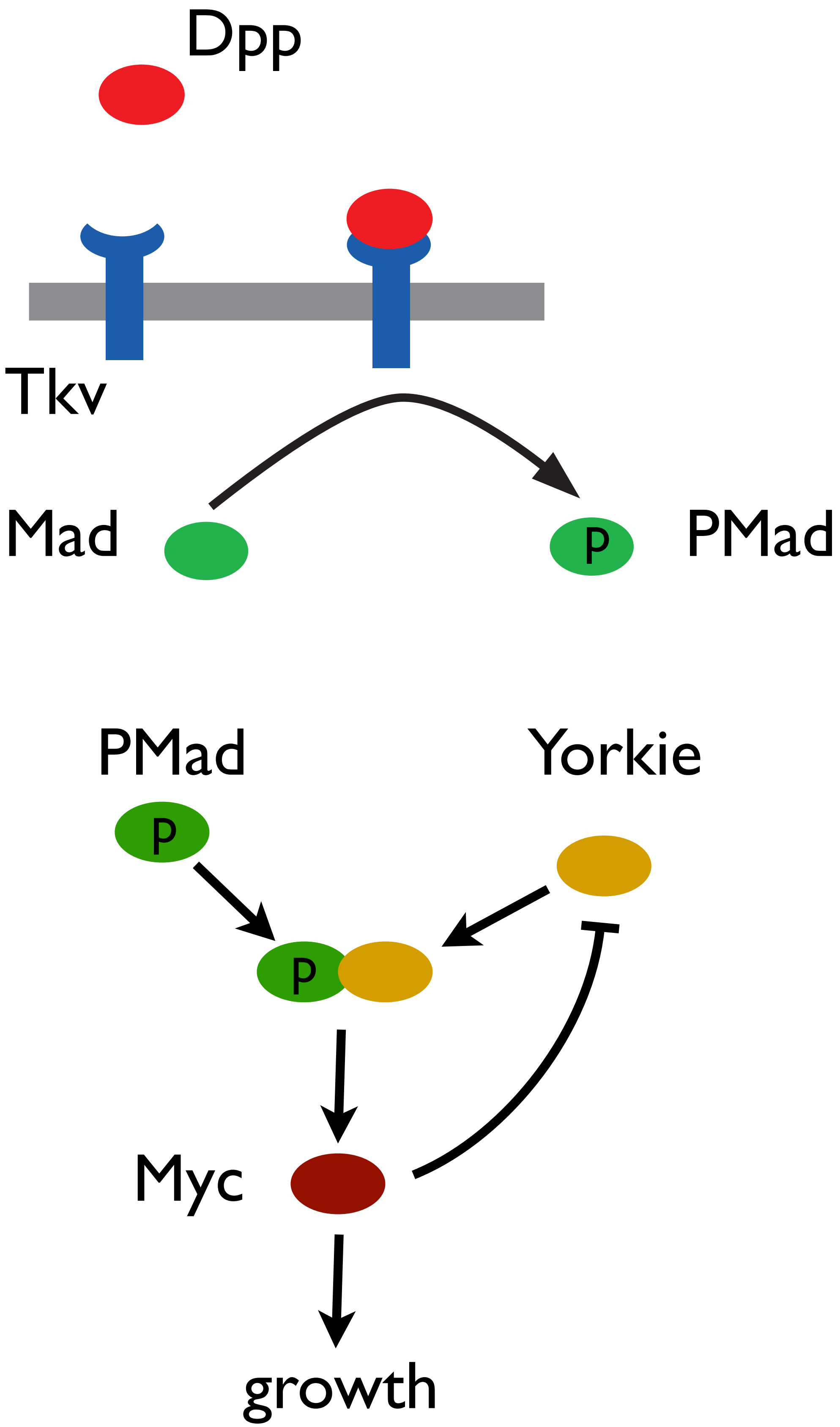
moving
Dpp source

$$g = \beta^{-1}\frac{\dot{C}}{C}$$

$$g_x(x) = -v_s\partial_x\left(\frac{C(x)}{C_{\max}}\right)^{\gamma}$$

Wartlick, Jülicher, Gonzalez-Gaitan, Development 141 (2014)

Adaptive morphogen sensor



Adjust sensitivity by feedback control

fold change detection

Shoval,.., Alon, PNAS 107 (2010)

example: chemotactic signaling

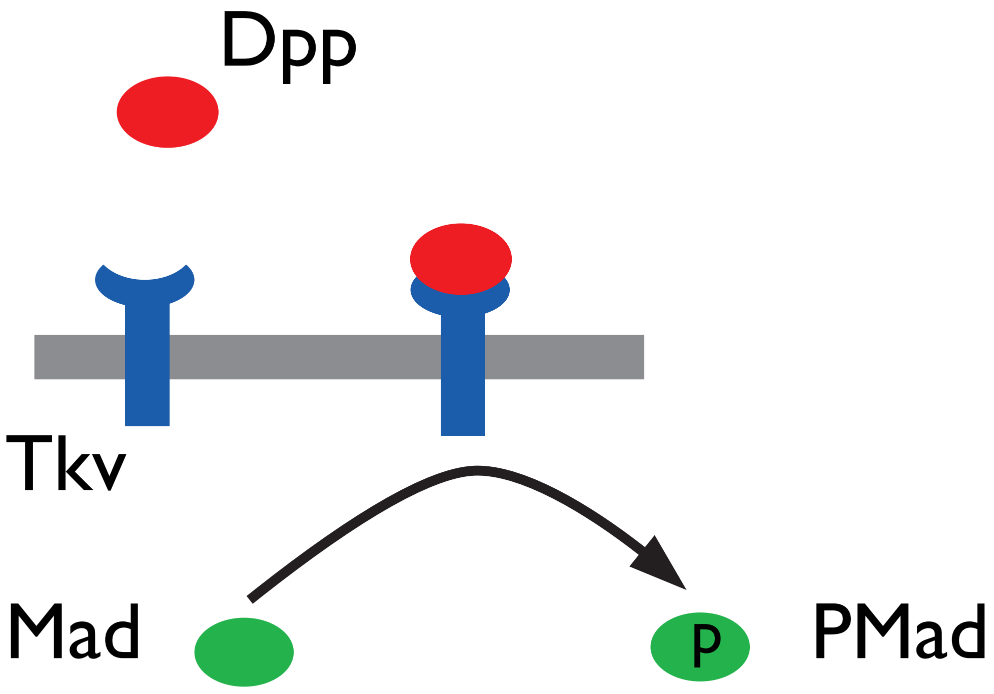
Barkai Leibler, Nature (1997)

Friedrich, Jülicher, PNAS (2007)

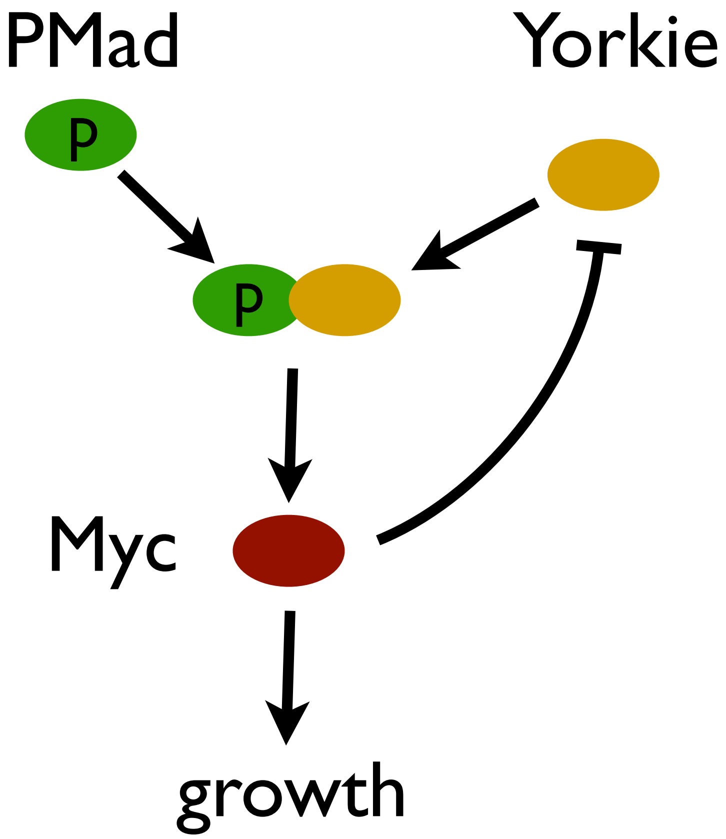
signal output $\propto \frac{1}{\tau}\frac{\Delta C}{C}$

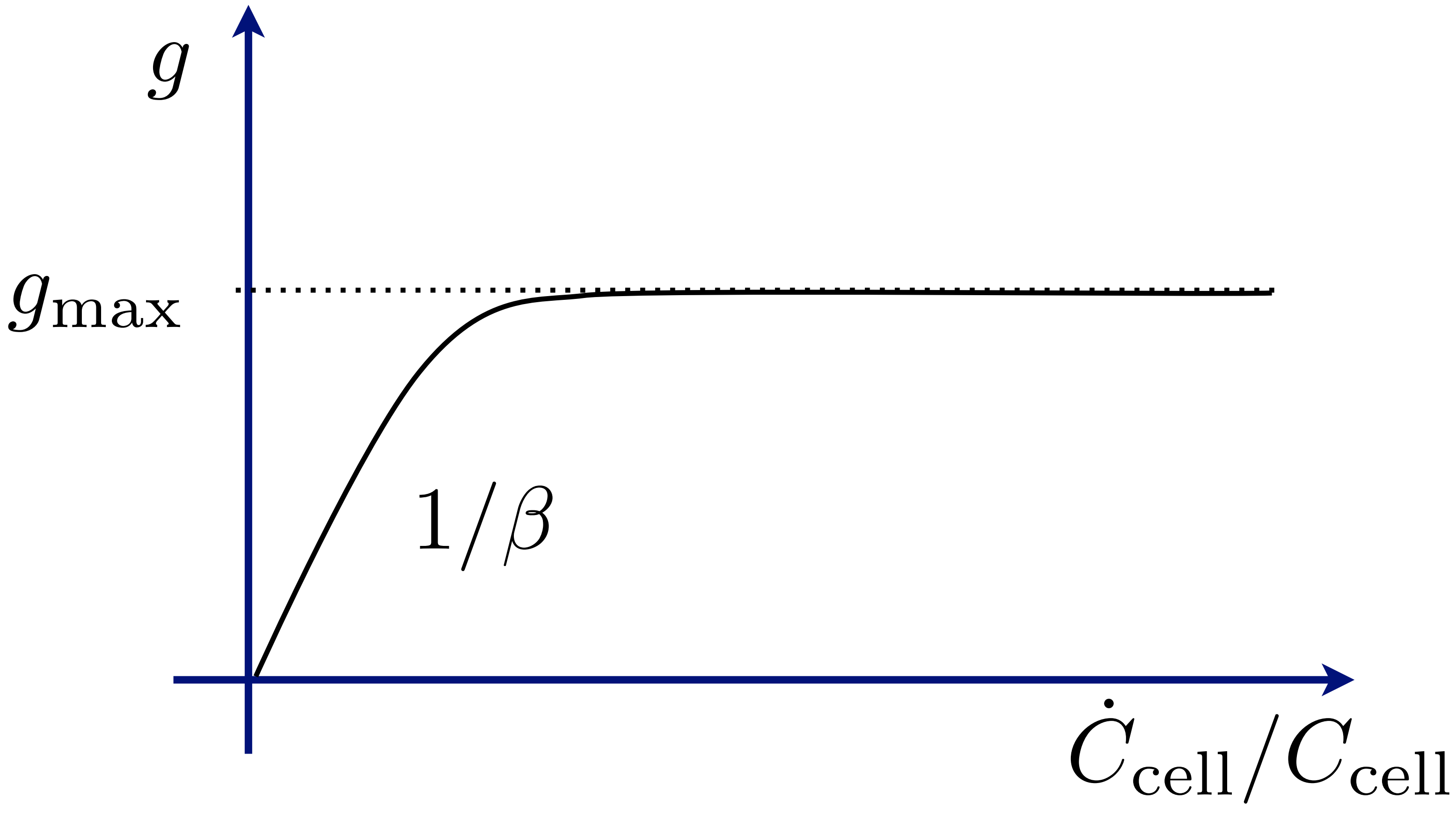
$$\propto \frac{\dot{C}}{C}$$

Adaptive morphogen sensor



$$g \simeq \beta^{-1} \frac{\dot{C}_{\text{cell}}}{C_{\text{cell}}}$$

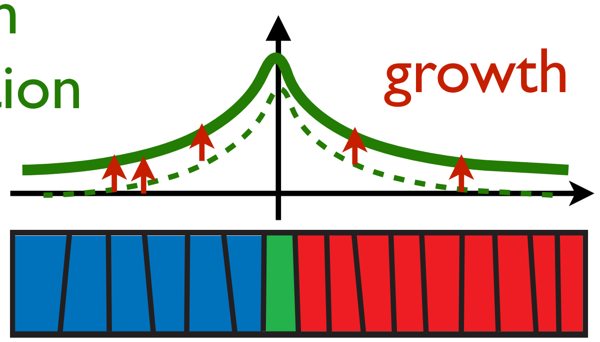




Self-organization of growth

Morphogens regulate growth

morphogen concentration increase



morphogen source

Morphogen dynamics

effective degradation

$$\partial_t C + \nabla \cdot (\mathbf{v}C) = D\nabla^2 C - kC + \nu(x)$$

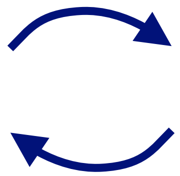
cell velocity

effective diffusion

localized source

cell flows

growth



chemical signals

stimulation

Growth regulation

$$g = \frac{1}{\beta}\frac{\dot{C}}{C}$$

material time derivative

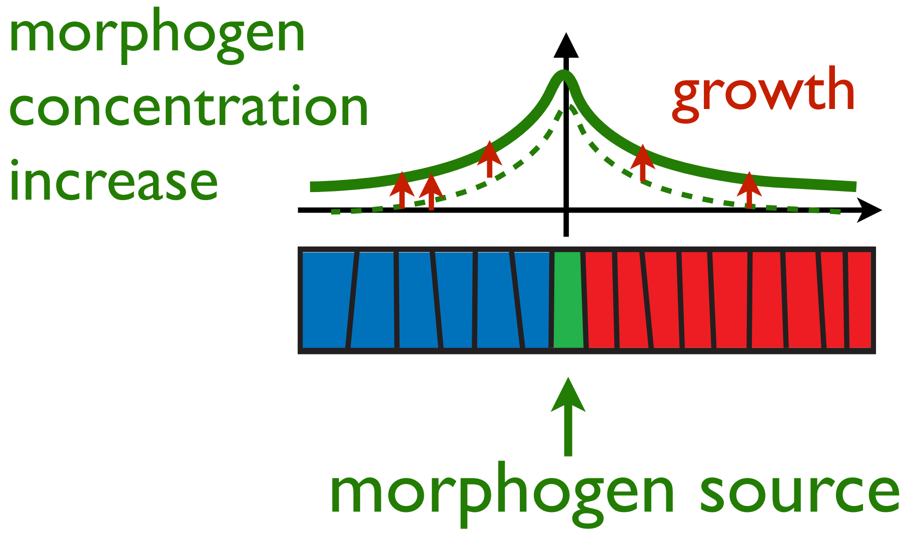
growth control parameter

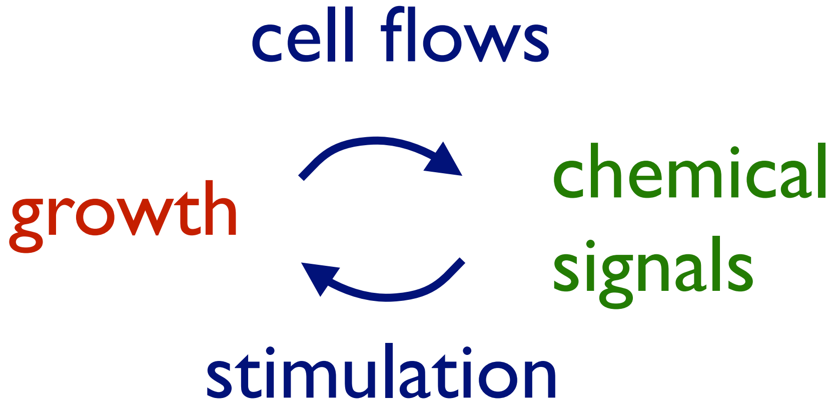
$$\dot{C} = \partial_t C + \mathbf{v} \cdot \nabla C$$

Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

Self-organization of growth

Morphogens regulate growth





Morphogen dynamics

$$\partial_t C + \nabla \cdot (\mathbf{v} C) = D \nabla^2 C - kC + \nu(x)$$

Growth regulation

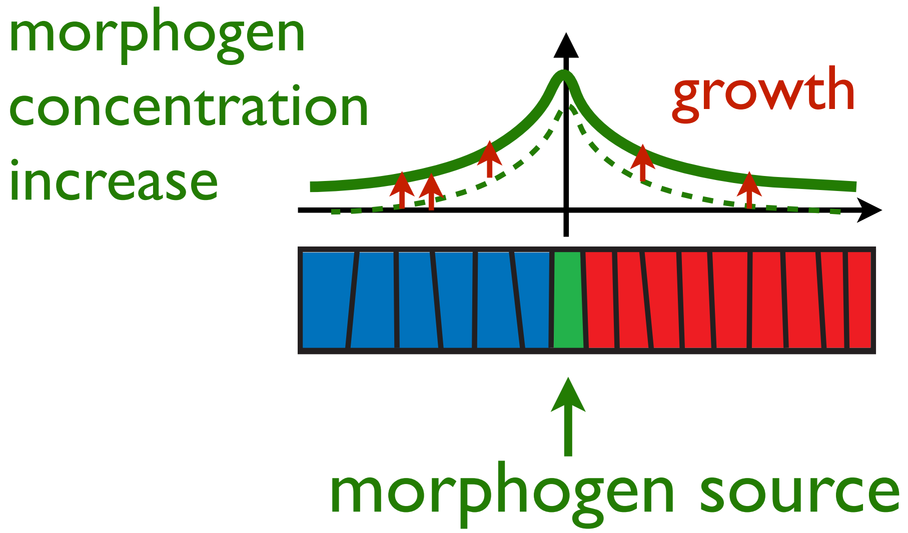
$$g = \frac{1}{\beta} \frac{\dot{C}}{C}$$

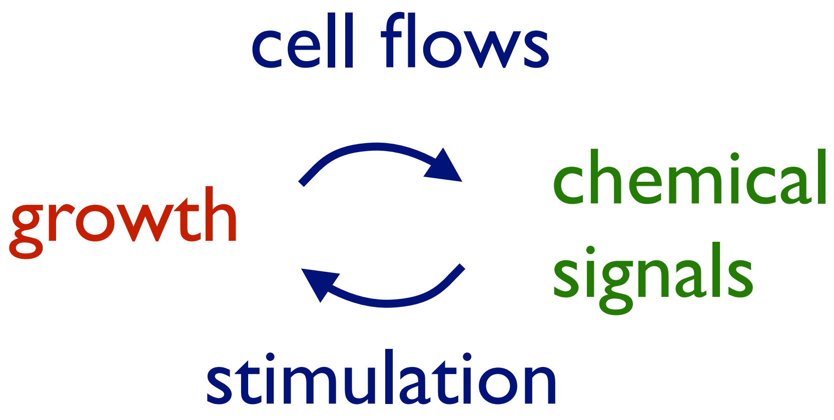
$$\dot{C} = \partial_t C + \mathbf{v} \cdot \nabla C$$

Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

Self-organization of growth

Morphogens regulate growth





cell flows

growth

chemical signals

stimulation

Morphogen dynamics

$$\partial_t C + \mathbf{v} \cdot \nabla C + C \nabla \cdot \mathbf{v} = D \nabla^2 C - kC + \nu(x)$$

Growth regulation

$$g = \frac{1}{\beta} \frac{\dot{C}}{C}$$

$$g = \nabla \cdot \mathbf{v}$$

$$\dot{C} = \partial_t C + \mathbf{v} \cdot \nabla C$$

Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

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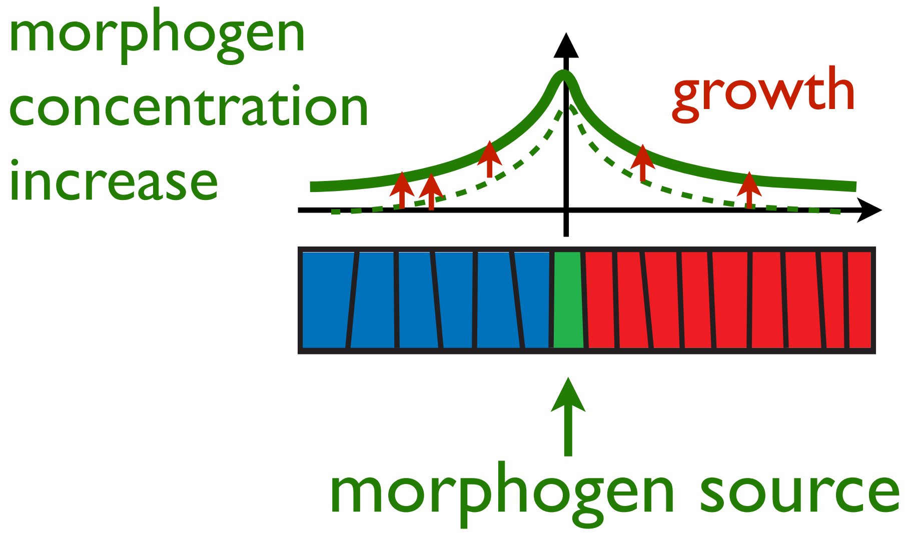

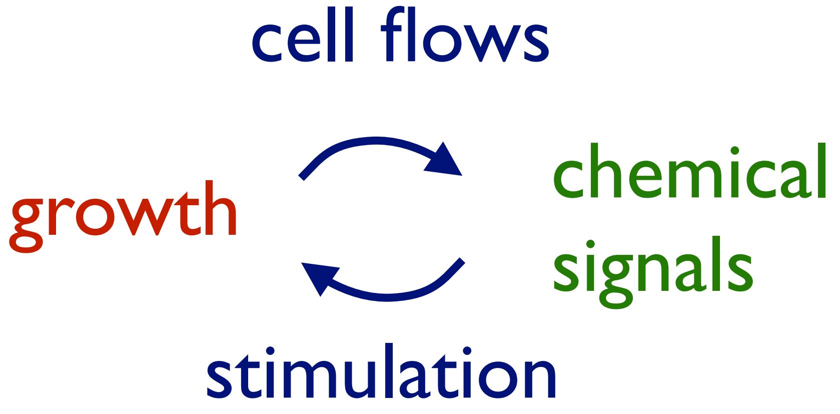

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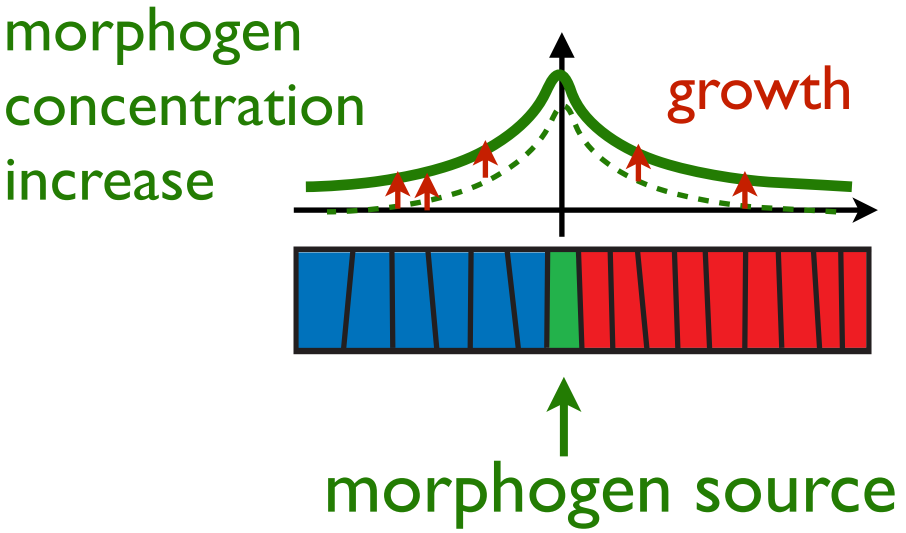

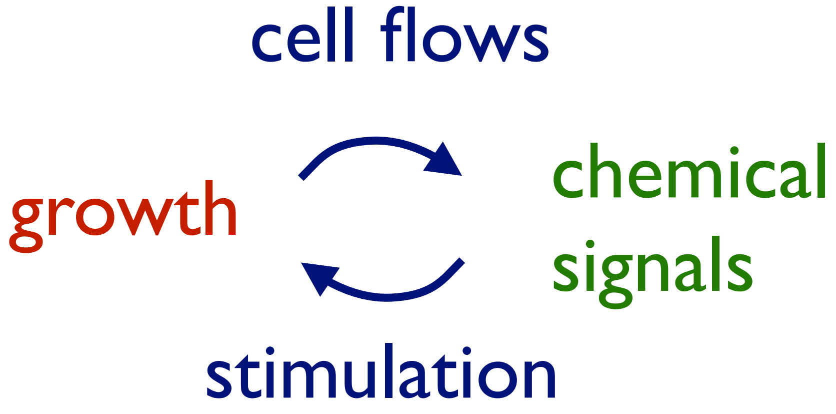

cell flows

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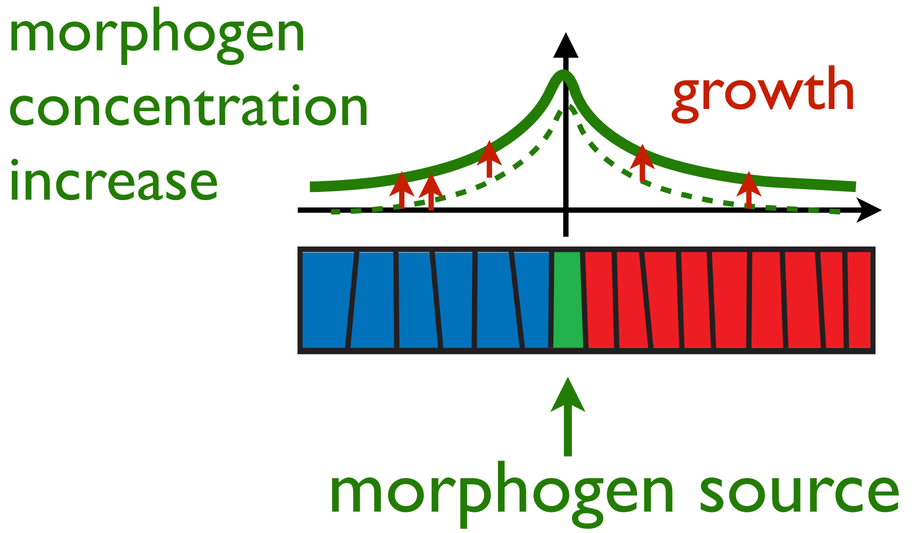

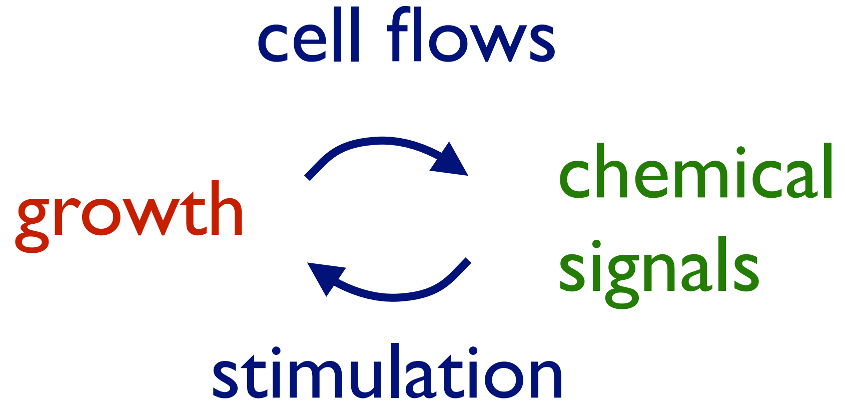

Morphogen dynamics

$$\dot{C} + C\underline{\nabla \cdot \mathbf{v}} = D\nabla^2 C - kC + \nu(x)$$

Growth regulation

$$g = \frac{1}{\beta}\frac{\dot{C}}{C}$$

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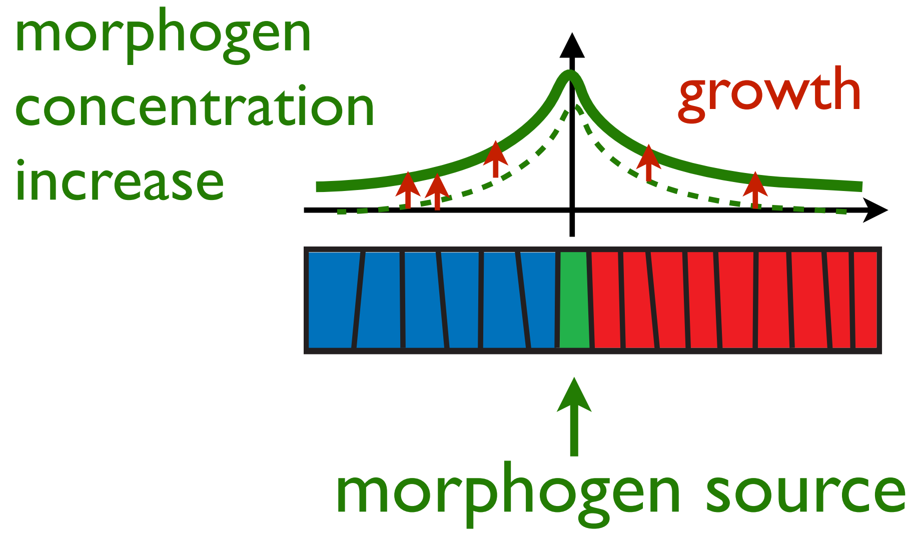

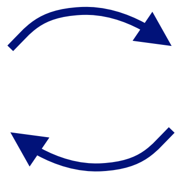

cell flows

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Morphogen dynamics

$$\dot{C} + \underline{gC} = D\nabla^2 C - kC + \nu(x)$$

Growth regulation

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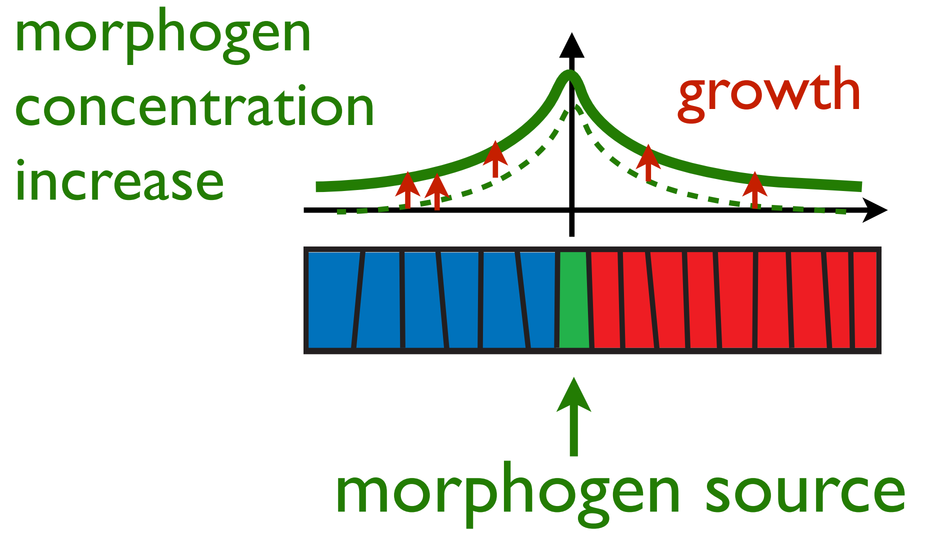

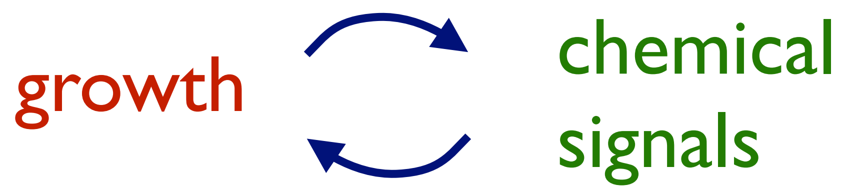
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Morphogen dynamics

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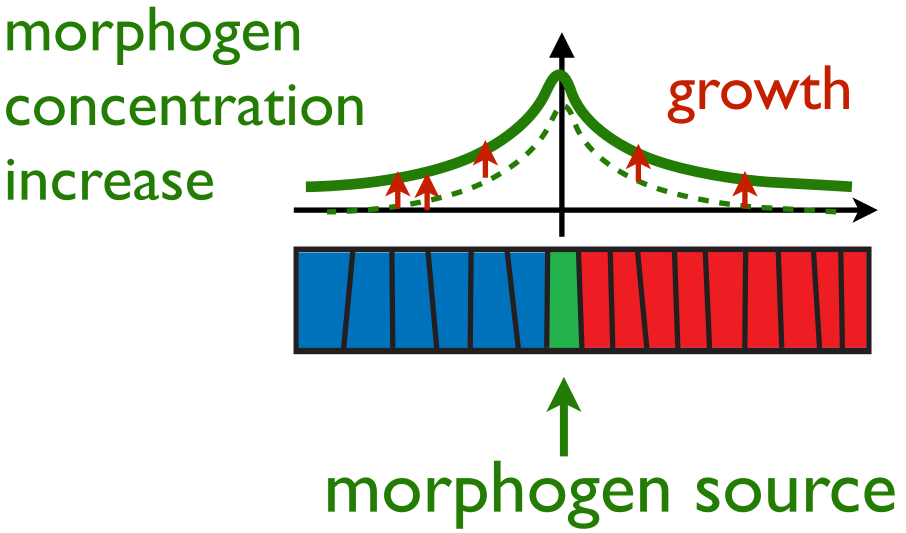

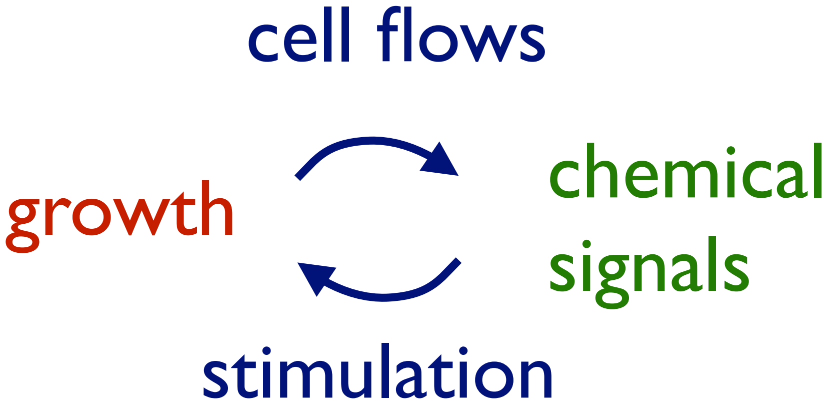
cell flows

growth

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stimulation

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Growth regulation

$$g = \frac{1}{\beta}\frac{\dot{C}}{C}$$

$$g = \frac{D\nabla^2 C - kC + \nu(x)}{(1+\beta)C}$$

$$g = \nabla \cdot \mathbf{v}$$

$$\dot{C} = \partial_t C + \mathbf{v} \cdot \nabla C$$

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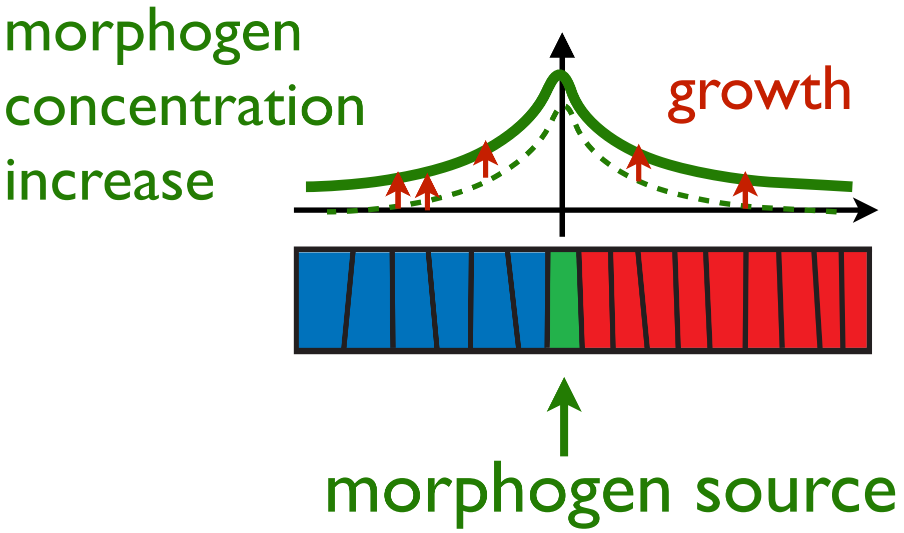
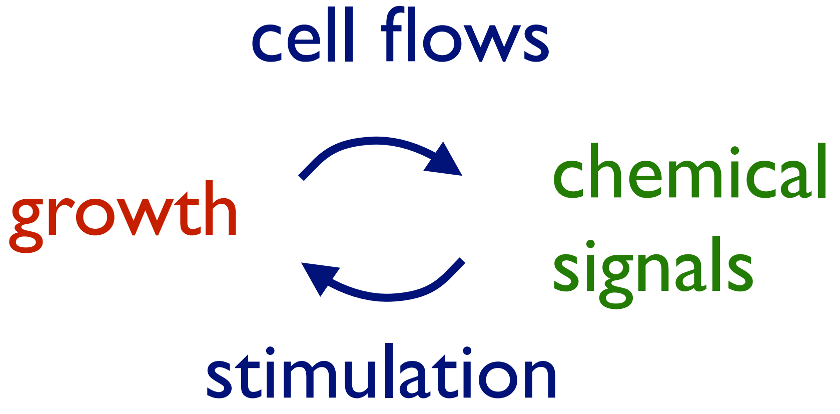




cell flows

growth

chemical signals

stimulation

Morphogen dynamics

$$\dot{C} = \frac{\beta}{1+\beta}(D\nabla^2 C - kC + \nu(x)))$$

Growth profile

$$g = \frac{D\nabla^2 C - kC + \nu(x)}{(1+\beta)C}$$

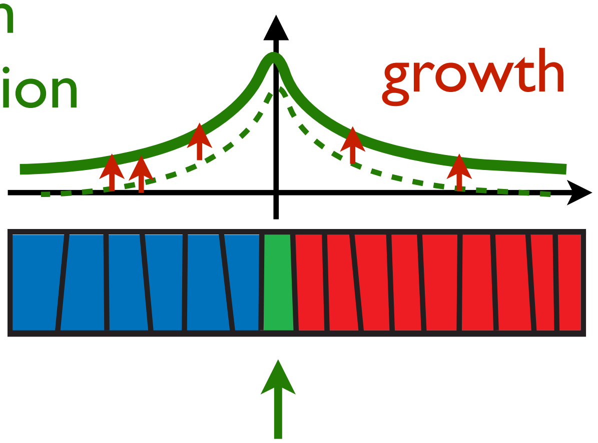
$$g = \nabla \cdot \mathbf{v}$$

$$\dot{C} = \partial_t C + \mathbf{v} \cdot \nabla C$$

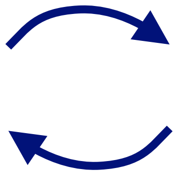
Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

Self-organization of growth

Morphogens regulate growth



cell flows



stimulation

growth anisotropy ϵ

Morphogen dynamics

$$\dot{C} = \frac{\beta}{1+\beta}(D\partial_x^2 C - kC + \nu(x)))$$

Growth profile

$$g = \frac{D\partial_x^2 C - kC + \nu(x)}{(1+\beta)C}$$

one-dimensional gradient

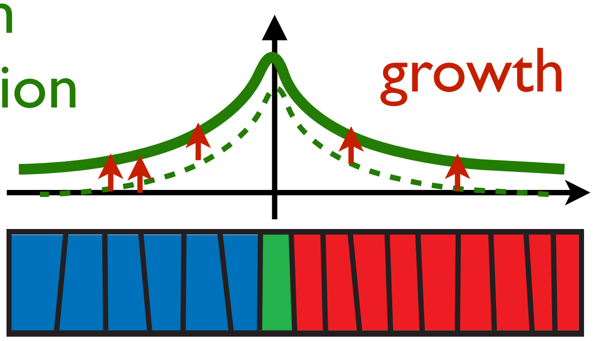
$$g = (1+\epsilon)\partial_x v_x$$

$$\dot{C} = \partial_t C + v_x \partial_x C$$

Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

Homogeneous growth?

Morphogens regulate growth



morphogen concentration increase

growth

morphogen source

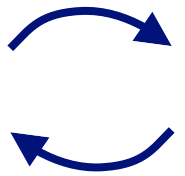
Morphogen dynamics

$$\dot{C} = \frac{\beta}{1+\beta}(D\partial_x^2 C - kC + \nu(x)))$$

Growth profile

$$g = \frac{D\partial_x^2 C - kC + \nu(x)}{(1+\beta)C}$$

$$D\partial_x^2 C - (k + (1+\beta)g)C + \nu(x) = 0$$



cell flows

growth

chemical signals

stimulation

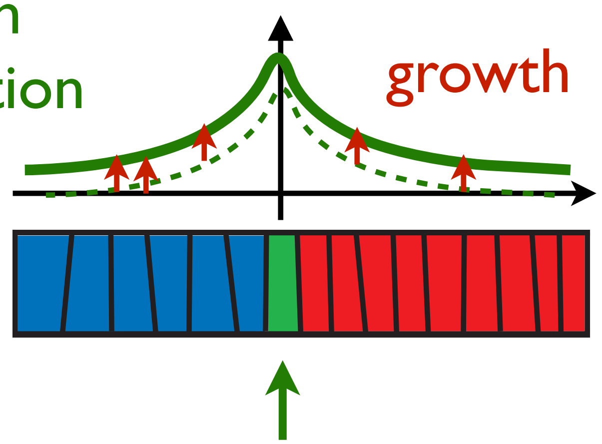
$$C \simeq \frac{\nu\lambda^2}{D} e^{-x/\lambda}$$

$$\lambda^2 = \frac{D}{k + (1+\beta)g}$$

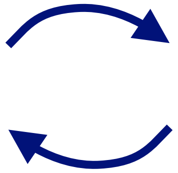
Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

Homogeneous growth?

Morphogens regulate growth



cell flows



growth

chemical
signals

stimulation

Morphogen dynamics

$$\dot{C} = \frac{\beta}{1+\beta}\left(D\partial_x^2 C - kC + \nu(x)\right))$$

Growth profile

$$g = \frac{D\partial_x^2 C - kC + \nu(x)}{(1+\beta)C}$$

Homogeneous growth for $\beta = \beta_c$

Critical value

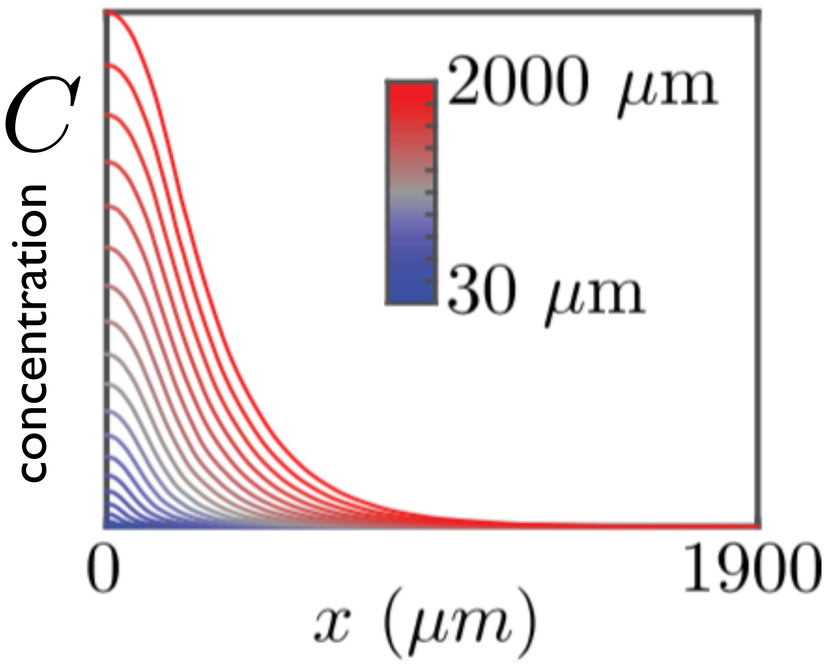
$$\beta_c = \frac{2}{1+\epsilon}$$

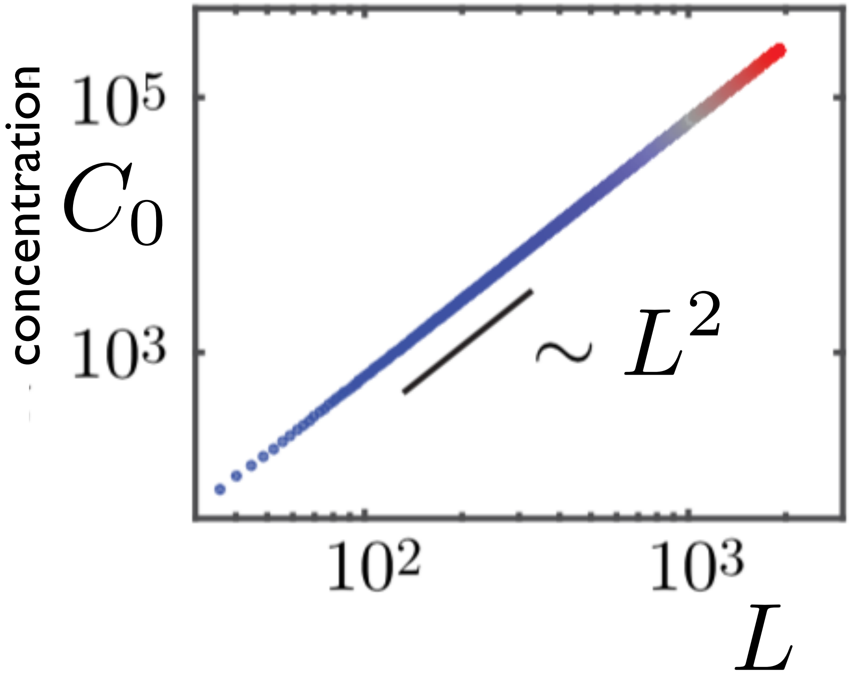
$$C \simeq \frac{\nu\lambda^2}{D} e^{-x/\lambda}$$

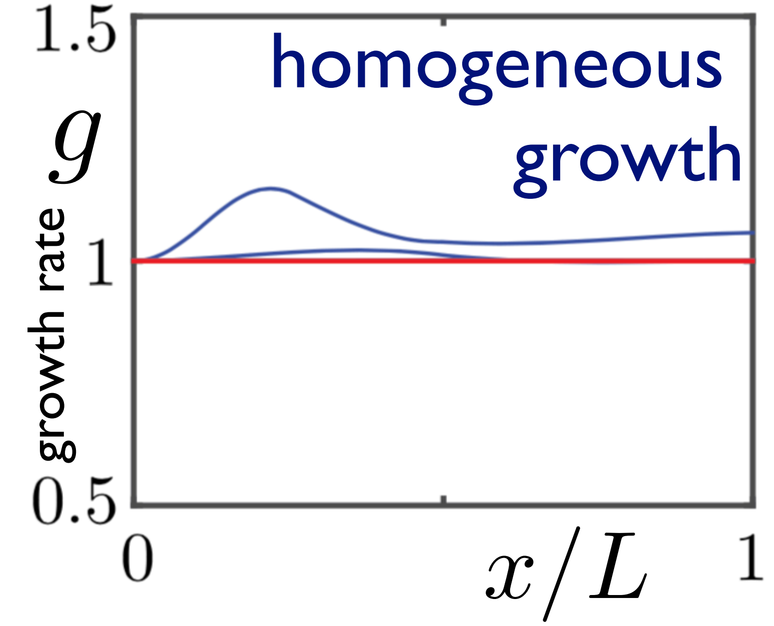
$$\lambda^2 = \frac{D}{k + (1+\beta)g}$$

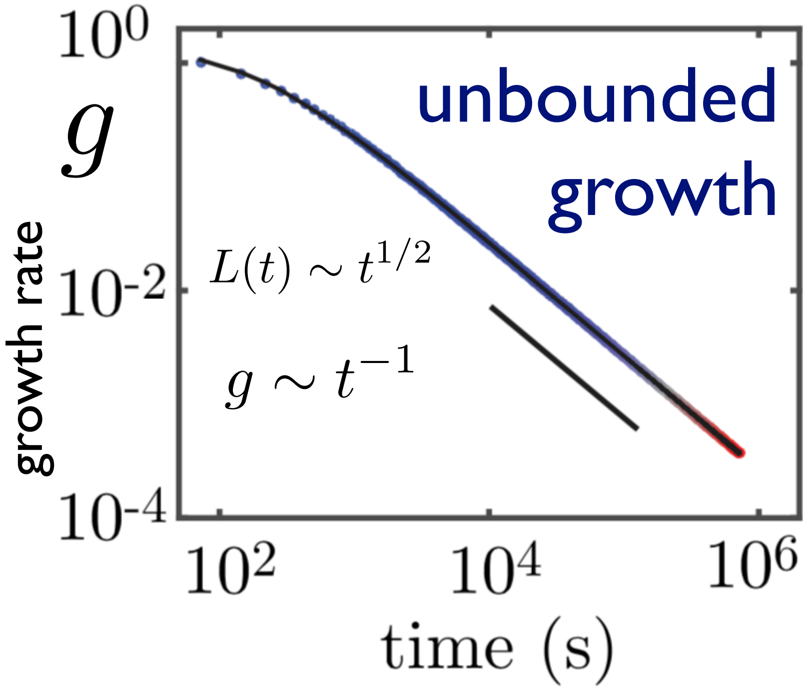
Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

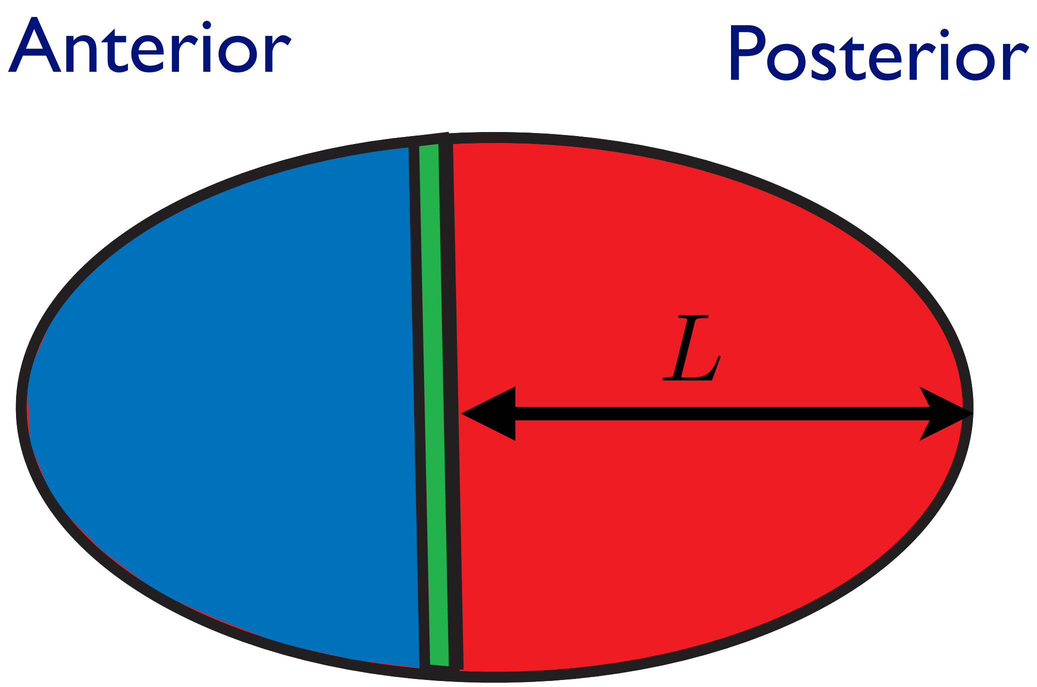
Growth dynamics $k = 0$











$$\partial_t C + \nabla \cdot (\mathbf{v}C) = D\nabla^2 C - kC + \nu(x)$$

$$g = \frac{1}{\beta}\frac{\dot{C}}{C}$$

Critical value

$$\beta_c = \frac{2}{1+\epsilon}$$

$$\beta = \beta_c$$

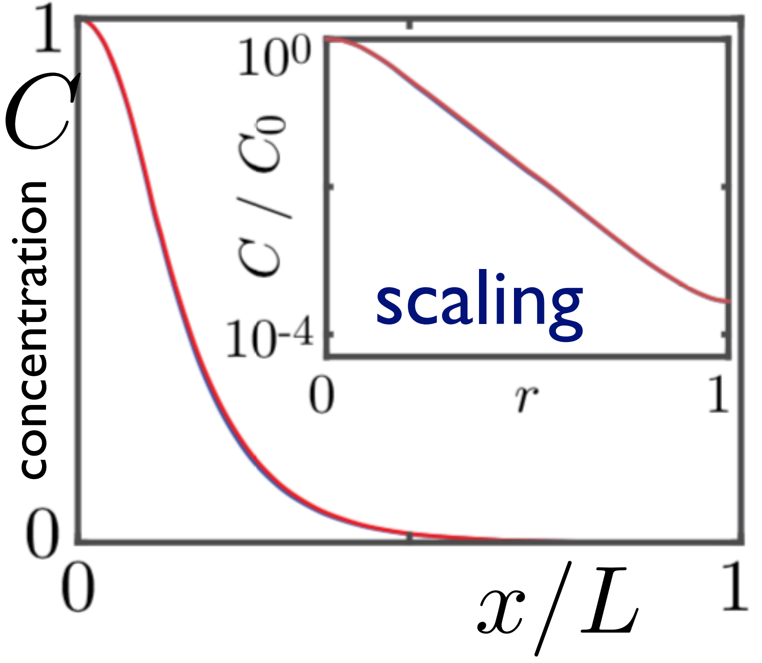
$$k = 0$$

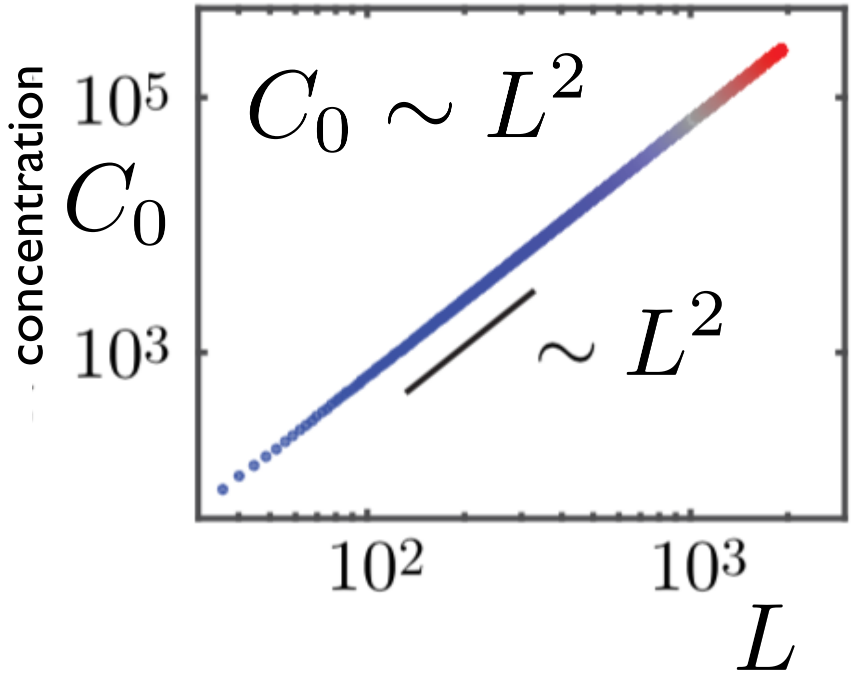
$$C \simeq \frac{\nu\lambda^2}{D} e^{-x/\lambda}$$

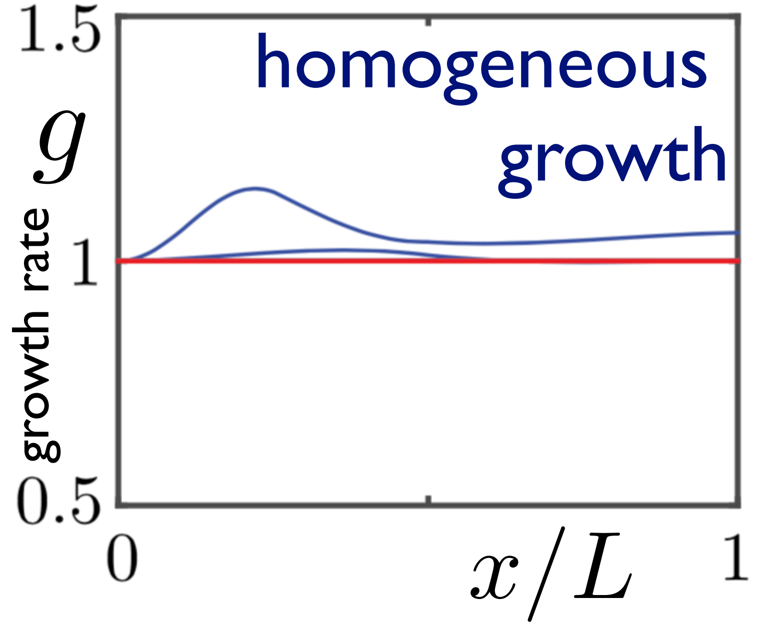
$$\lambda^2 = \frac{D}{(1+\beta)g}$$

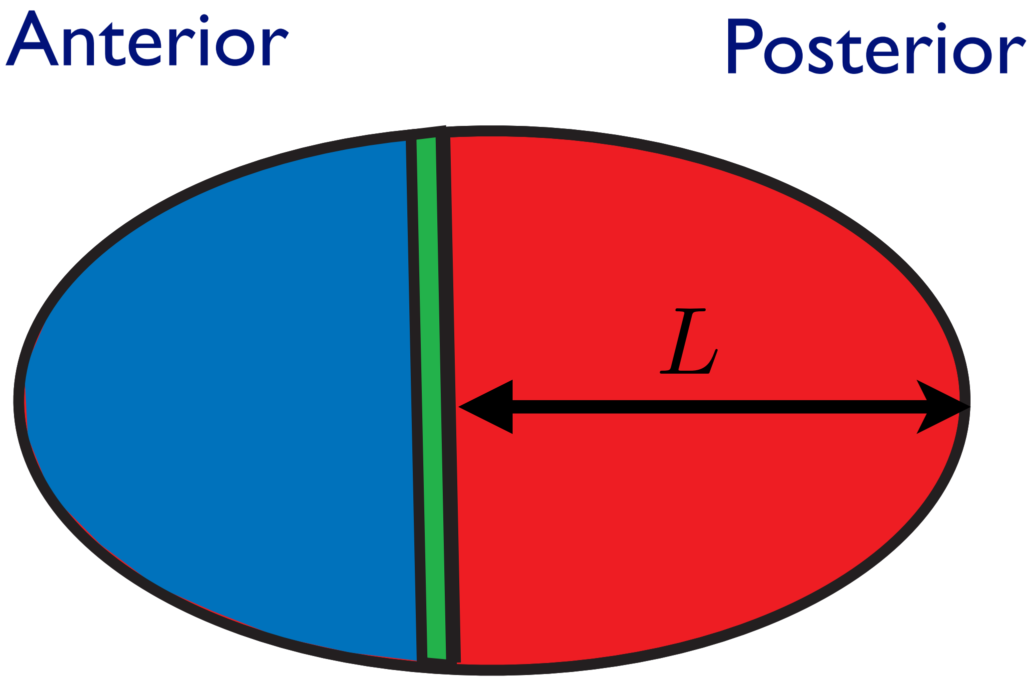
Gradient scaling $k = 0$

$$C(x,t) = C_0(t)\xi(x/L(t))$$









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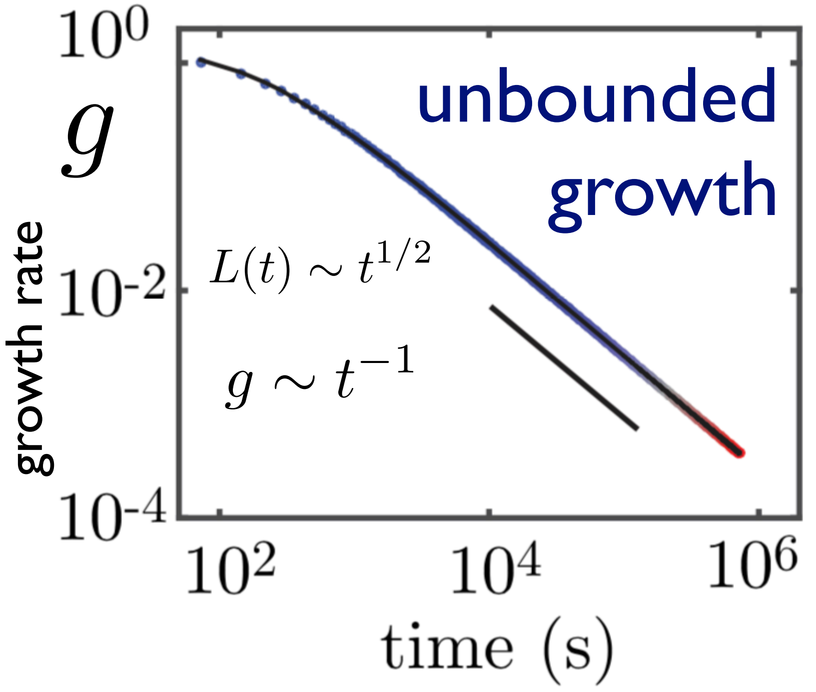


$$C \simeq \frac{\nu\lambda^2}{D} e^{-x/\lambda}$$

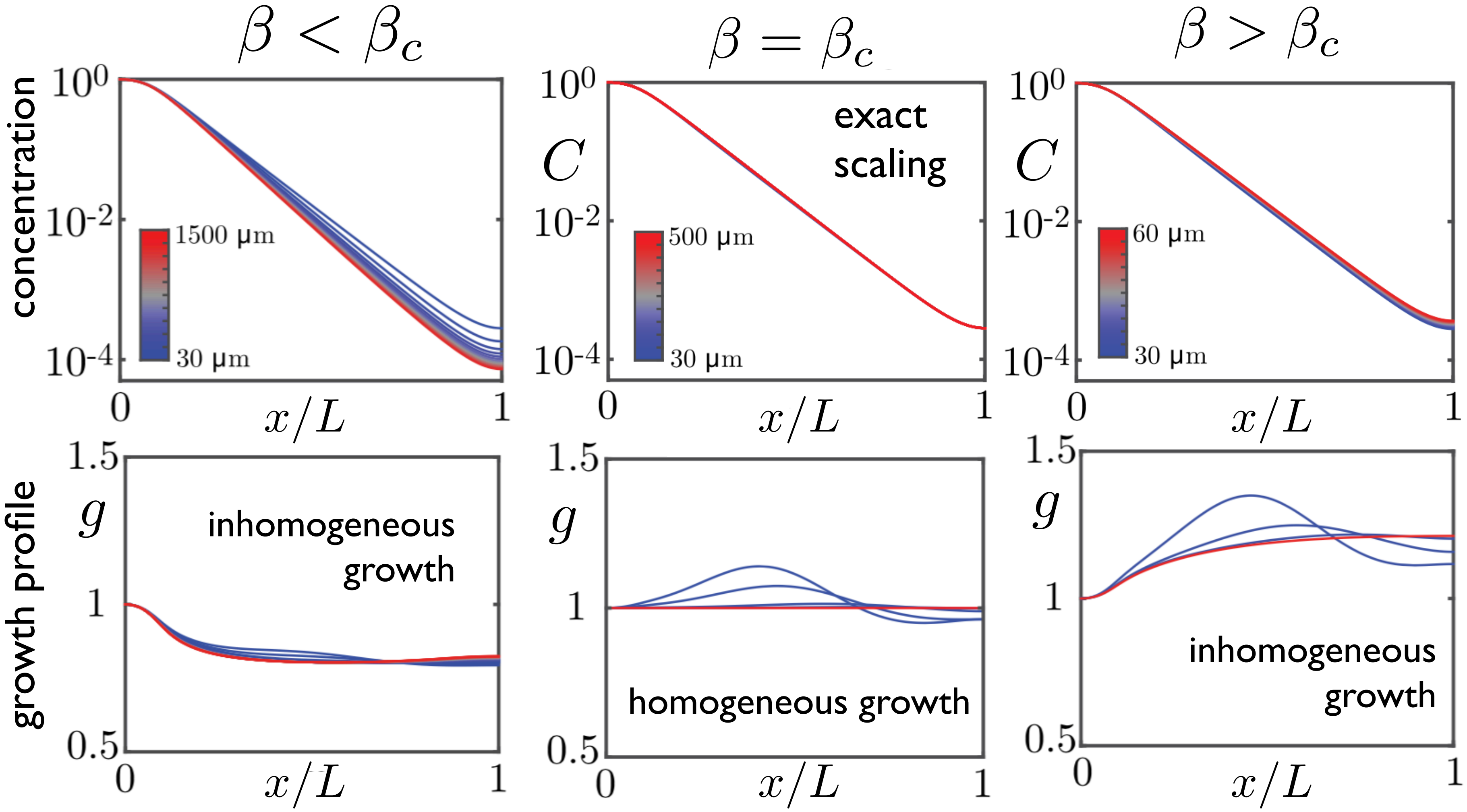
$$\lambda^2 = \frac{D}{(1+\beta)g}$$

Expander feedback

$$C \simeq \frac{\nu\lambda^2}{D} e^{-x/\lambda}$$

$$\lambda^2 = \frac{D}{k + (1+\beta)g}$$

$$k \sim \frac{1}{L^2}$$



$$\dot{C} = D\nabla^2 C - (k+g)C + \nu(x)$$

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$$\dot{C} = \partial_t C + v_x \partial_x C$$

Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher, Phys. Rev. Lett. (2018)

Expander feedback

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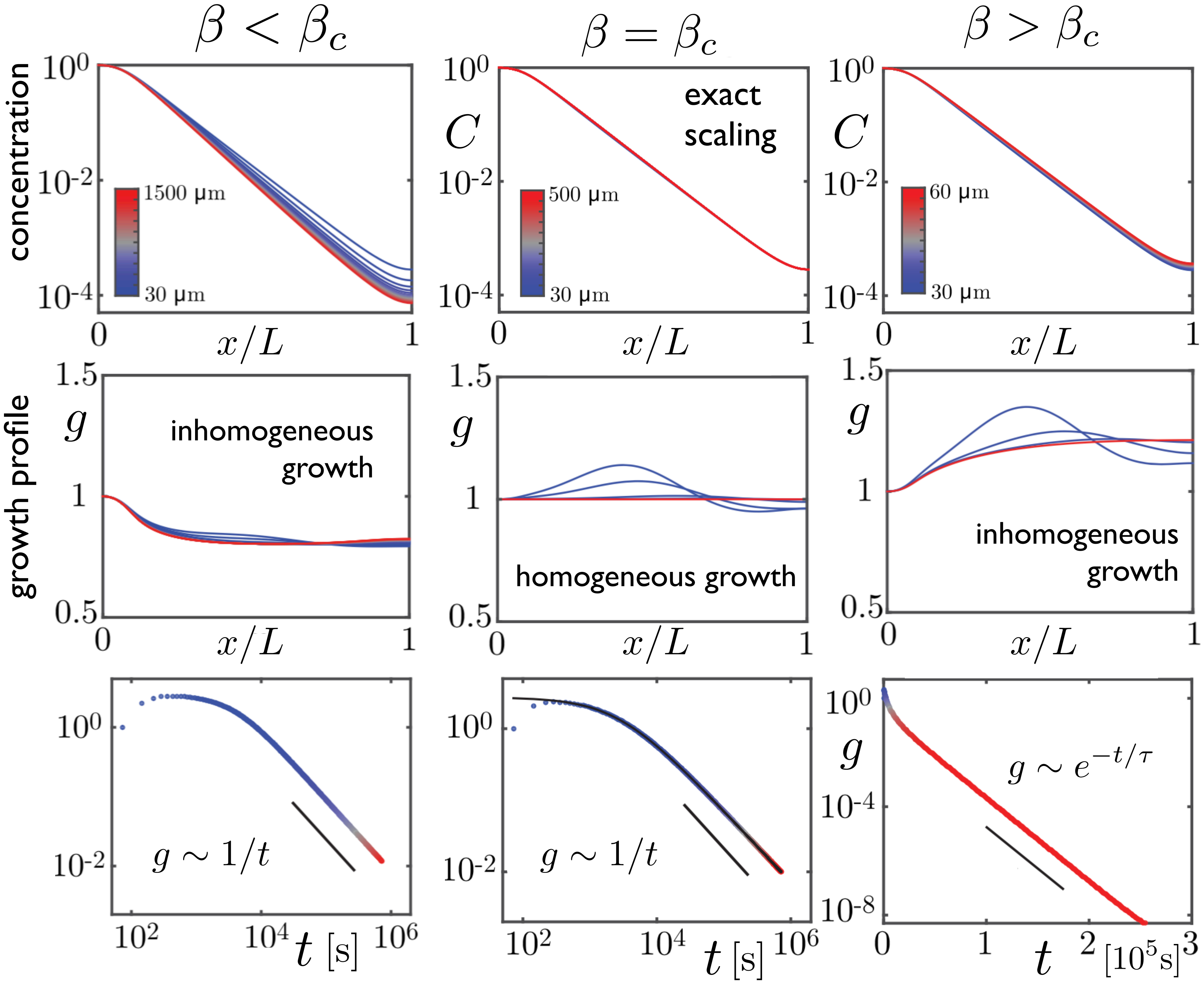


unbounded growth $L(t) \sim t^{1/2}$

unbounded growth $L(t) \sim t^{1/2}$

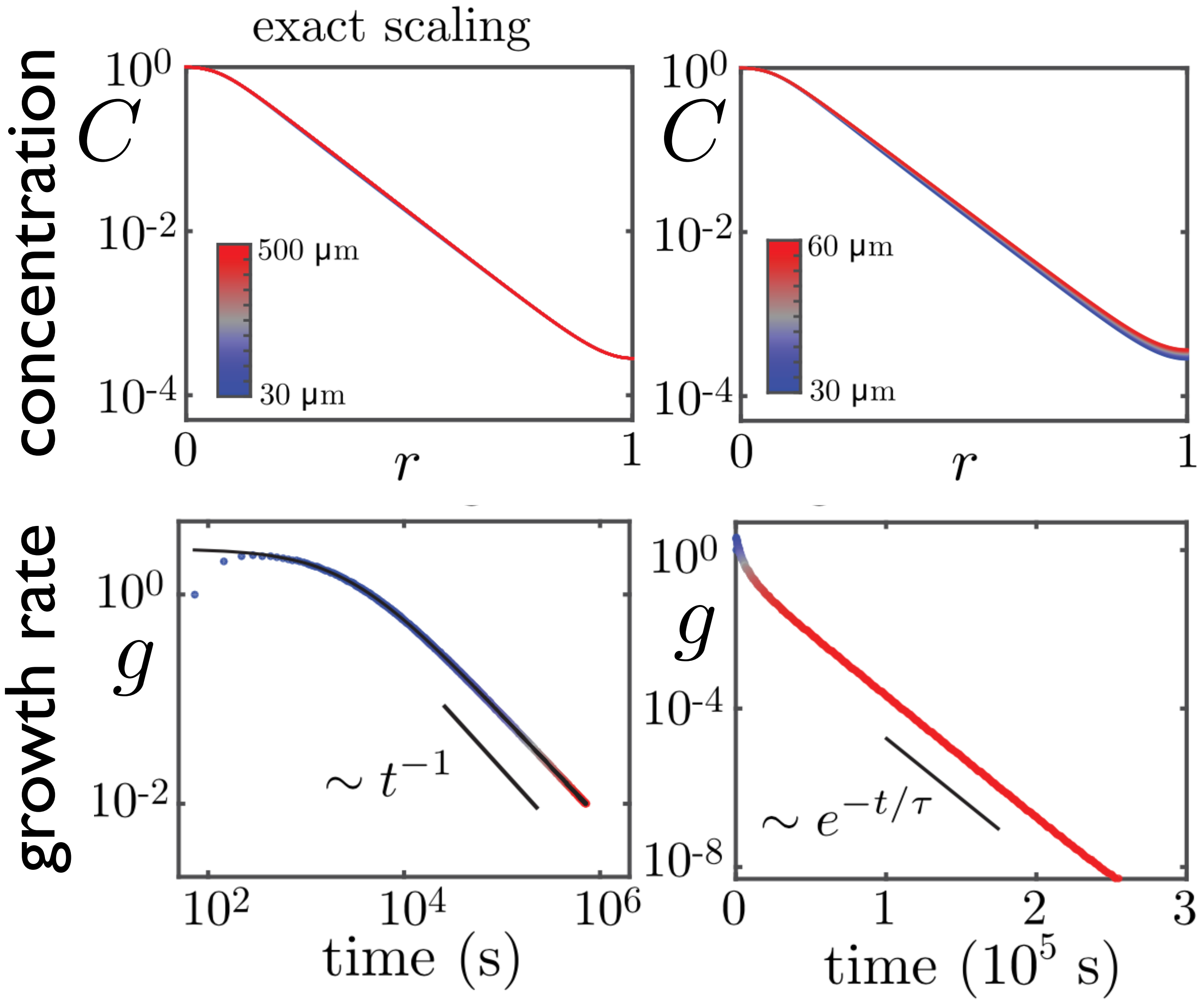
growth arrest $L(t) \to L_{\max}$

Critical point

critical point

$\beta = \beta_c$

$\beta > \beta_c$

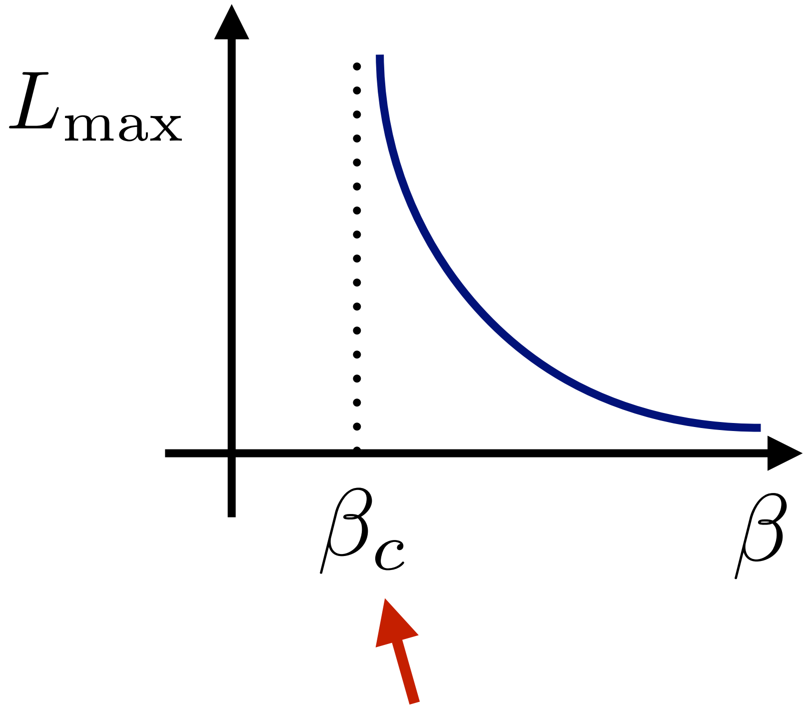


$$L(t) \sim t^{1/2}$$

$$L(t) \to L_{\max}$$

$$\beta_c = \frac{2}{1+\epsilon}$$

final size



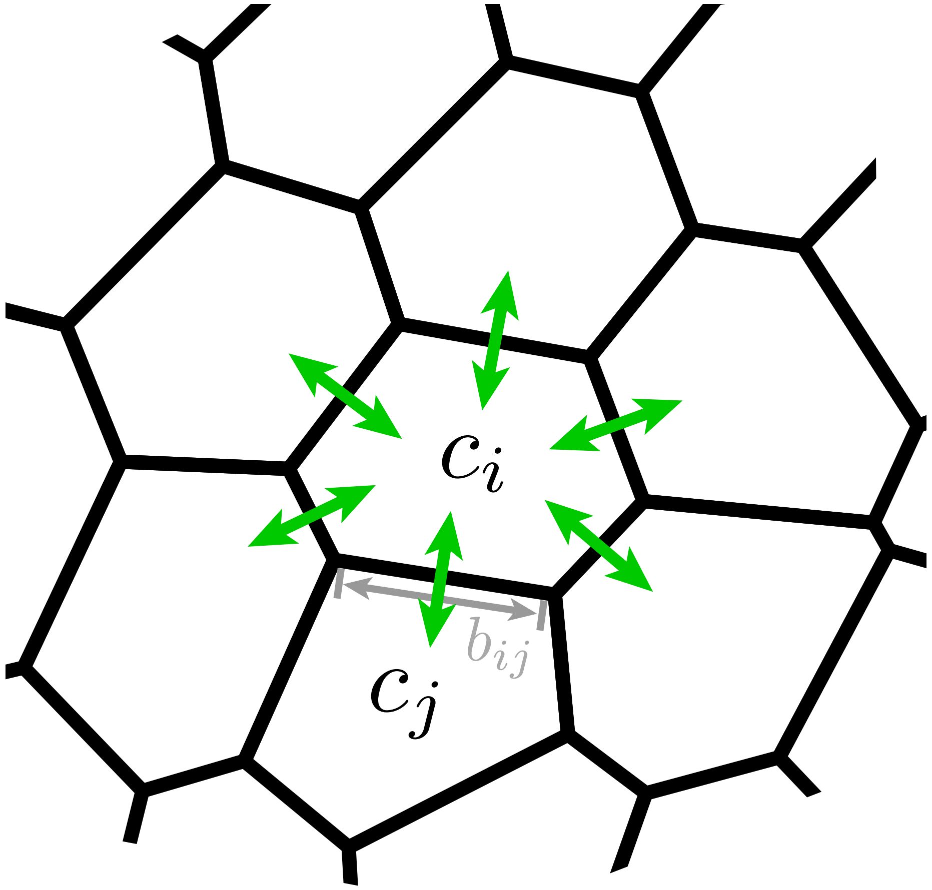
critical point

scaling
power law growth

$$L(t) = L_0 \exp\left(\int_0^t \frac{\bar{g}}{1+\epsilon} dt'\right)$$

Auguilar-Hidalgo, Werner, Wartlick, Gonzalez-Gaitan, Friedrich, Jülicher Phys. Rev. Lett. (2018)

Vertex model



source

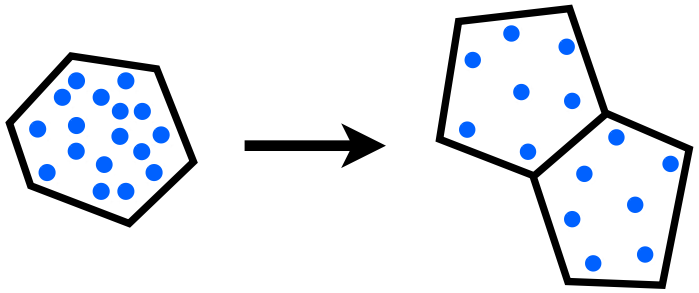
degradation $k_i = a e_i$

diffusion

Dpp $\dot{c}_i = \nu_i + k_i c_i + d \sum_j b_{ij}(c_j - c_i)$

Hh $\dot{h}_i = \ldots$

expander $\dot{e}_i = d^{(e)} \sum_j b_{ij}(e_j - e_i)$

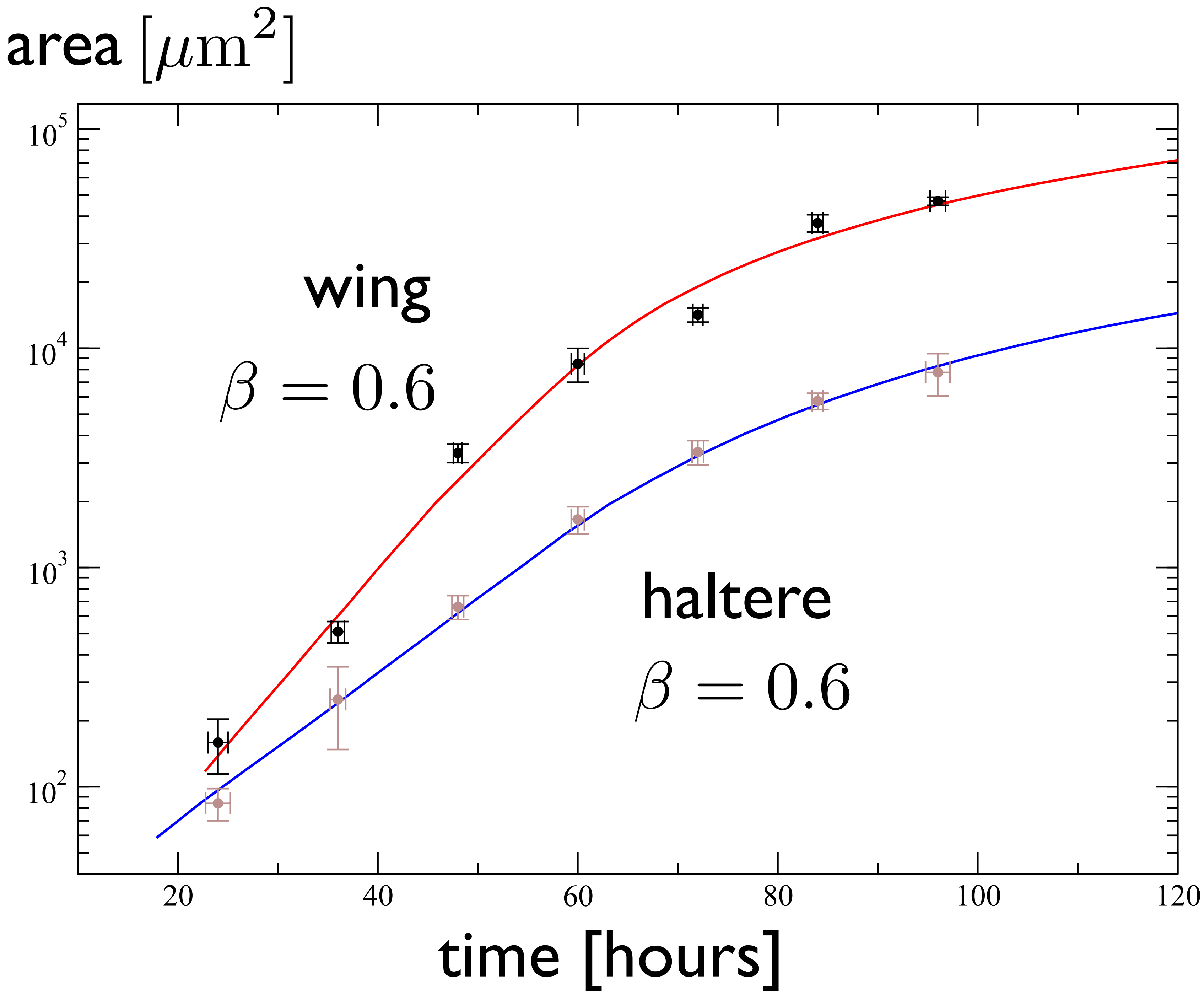


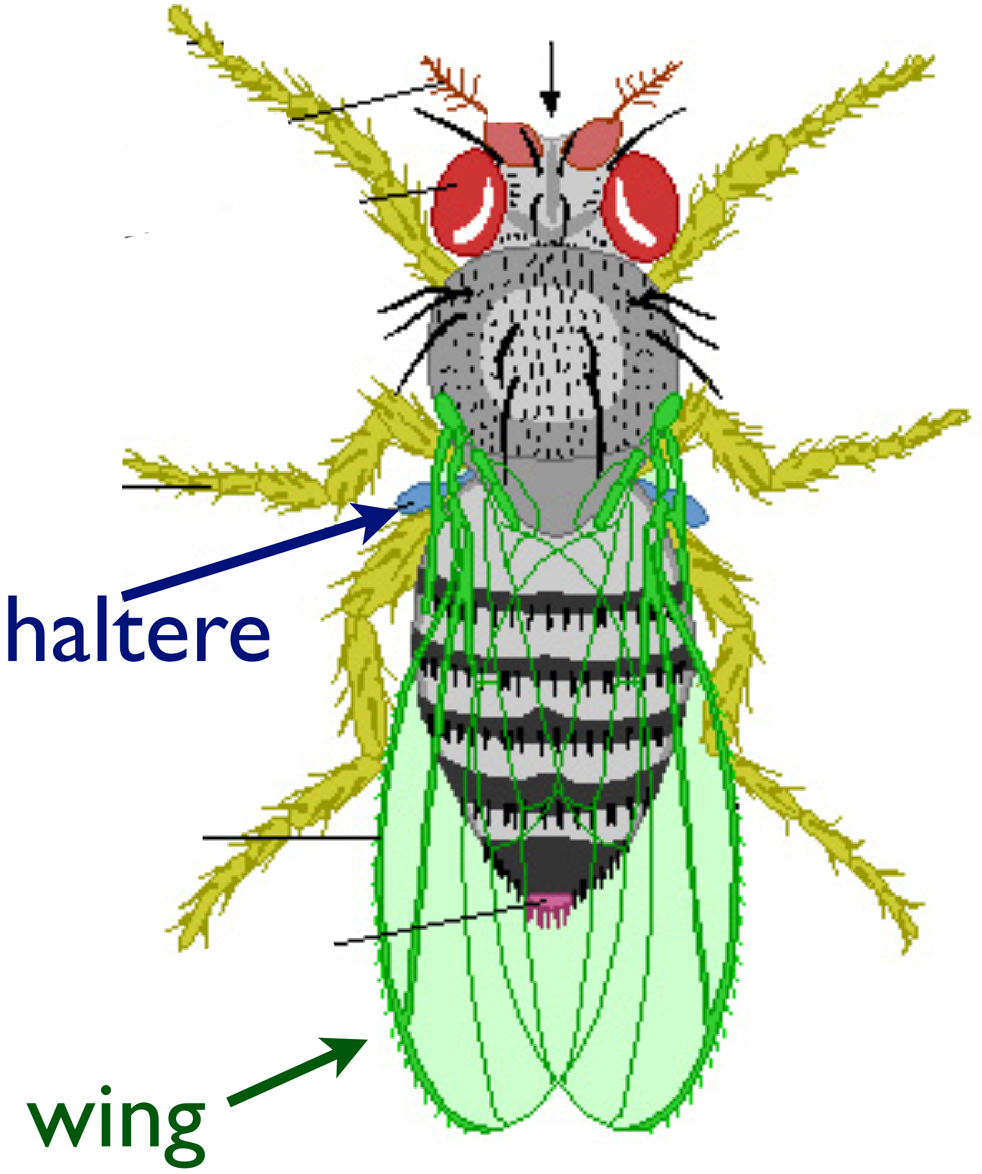
dilution

cell growth $\dot{A}_i = A_i g(\dot{c}_i / c_i)$

Peer Mumcu

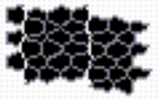
Comparison to experiments





Wartlick, Mumcu, Kicheva, Bittig, Seum,Jülicher, Gonzalez-Gaitan, Science (2011)

Temporal growth rule



Cell growth

$$g \simeq \beta^{-1} \frac{\dot{C}}{C}$$

Cell division when cell area doubled

$$\beta = 0.6$$

Posterior

Anterior

morphogens

Hedgehog

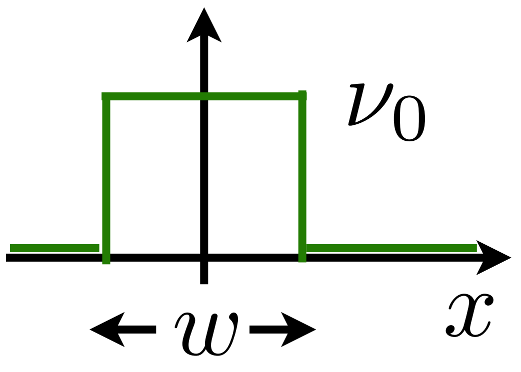
Dpp

regulation of
Dpp degradation

$$k \sim 1/L^2$$

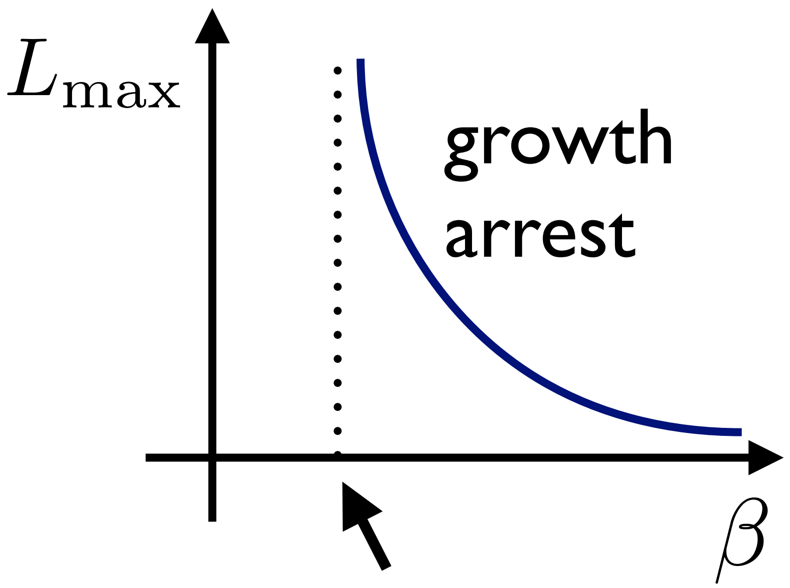
Growth diagram

source width growth



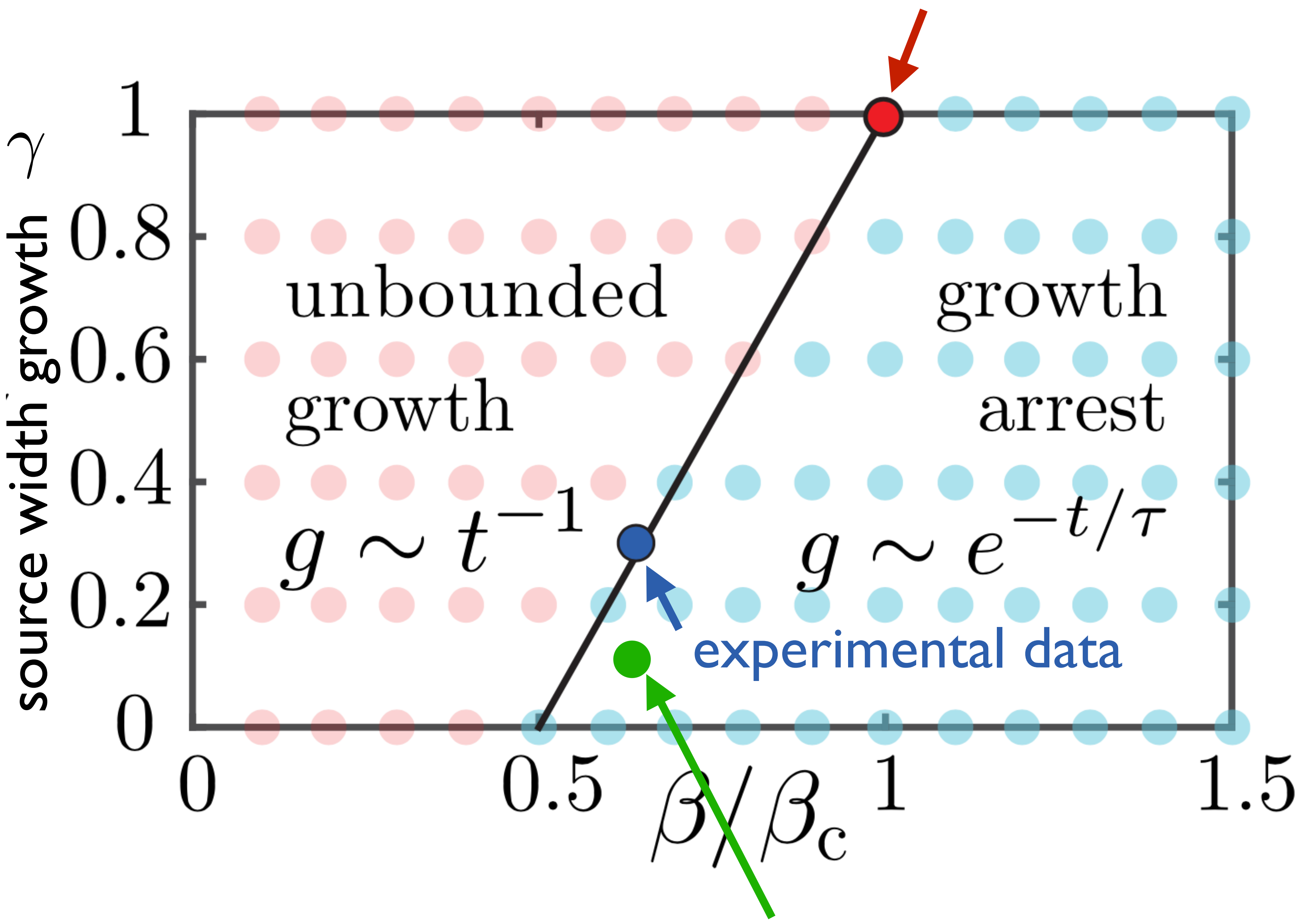
$w \sim L^\gamma$

final size



transition bounded-unbounded growth $\beta = \beta_c(\gamma + 1)/2$

critical point



experimental data

simulation