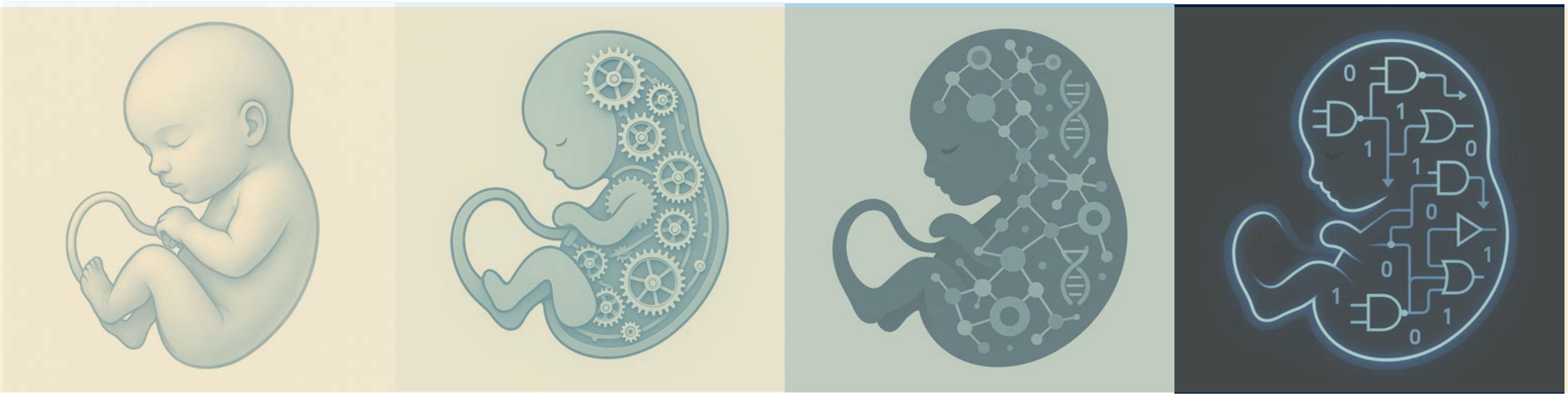
What is biological information? (II)



Course 5: Biological tuning, adaptation and learning

Thomas Lecuit
chaire: Dynamiques du vivant
COLLÈGE DE FRANCE 1530

Summary of previous course: Geometric models

- Compare logic view and dynamic view of information processing

- Geometric landscape models do not account for existence of different states
  The model predicts transition steps between states and how signals exert a force that steers cells in the landscape

- The exact dynamics and path followed by cells is not yet captured but can be.
So far, use of « flat » representations for cell states with gradient field.
Signals globally tilt the landscape and cause bifurcations.

- Questions: are all dynamics gradient-like? The answer is no (eg. oscillations).
- Dynamics also emerge in a rotational field (with non zero curl, ie. non-equilibrium dynamics).
- Consider local curvature to modify the dynamics.

More general framework

- When the dynamics is not simply dictated by a gradient (eg. non-zero curl of vector field, non-equilibrium dynamics etc)
- Consider the local curvature (ie. metric)

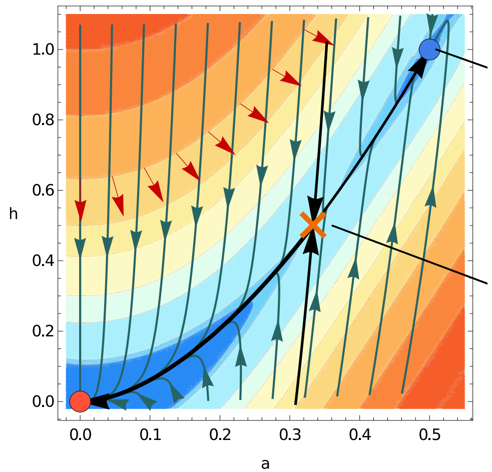
$$\dot{x}_i = -\sum_j g^{ij} \frac{\partial f}{\partial x_j}$$

Inverse of metric tensor: Local distortion of landscape

Gradient-like dynamics

f encodes attractors and saddles, while
g⁻¹ encodes **state- and signal-dependent mobility** – *direction-dependent speed and steering*.

Signals have two levers: (i) reshape the landscape (the potential) and (ii) change how "easy" it is to move in different directions (the metric/mobility).



"the metric… rotates and stretches the potential gradient so it coincides with the vector field… the model with its metric abstractly represents how signals distort the landscape and direct cells to the available fates."

D. A. Rand, A. Raju, M. Sáez, F. Corson, and E. D. Siggia, Geometry of gene regulatory dynamics, *PNAS*. 118, e2109729118 (2021).

More general framework

PNAS RESEARCH ARTICLE | BIOPHYSICS AND COMPUTATIONAL BIOLOGY
DEVELOPMENTAL BIOLOGY

Generative epigenetic landscapes map the topology and topography of cell fates

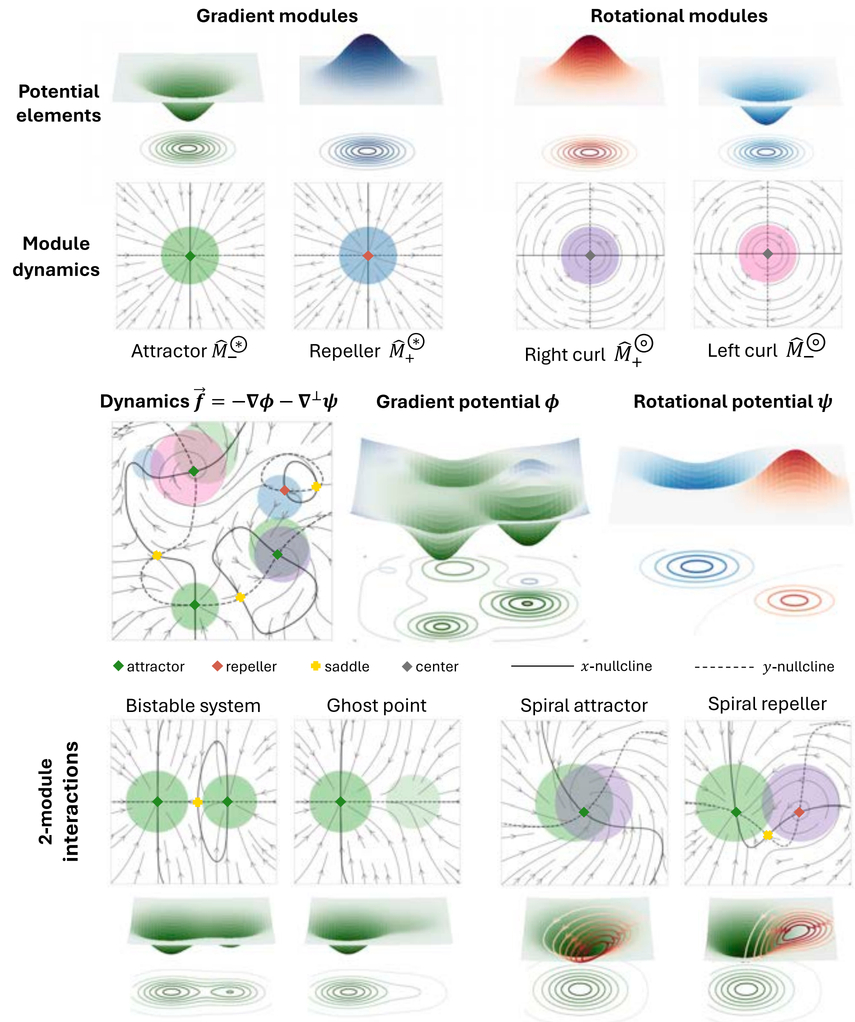
Victoria Mochulska[a] and Paul François[b,c,1]

- The landscape is built from gradient and rotational vector fields composed of locally weighted elements that encode "valleys" of the Waddington landscape
- Landscapes are optimised through computational evolution.

$$\frac{d\vec{q}}{dt} = \vec{f}(\vec{q}) + \vec{\eta}(t), \qquad \vec{f}(\vec{q}) = -\nabla\phi_0(\vec{q}) - \nabla\phi(\vec{q}) - \nabla^{\perp}\psi(\vec{q}).$$

- The vector field consists in the sum of local linear dynamics modules $\hat{M}_i$

$$\vec{f}(\vec{q}) = -f_0(\vec{q}) + \sum_{i=1}^{n+m} a_i \exp\left(-\frac{|\vec{q}-\vec{q}_i|^2}{2\sigma_i^2}\right)\hat{M}_i\,(\vec{q}-\vec{q}_i)\,.$$



Victoria Mochulska and Paul François *PNAS*, *122*, *50:* e2514508122 (2025)

Tuning, Adaptation and Learning

- *Pre-conditionned and determined* state:
  - Heredity of genome, chemistry, structures, cellular algorithmic processes.
  - Dynamics of cells and embryos follows a rule-based sequence of steps in a set order.

- *Propensity to respond to « environment » and reset* state:
  - Interaction with the environment, update and tuning of internal state variables.
  - *Tuning:* internal variables are updated
  - *Adaptation:* return to initial configuration following perturbation and deviation
  - *Learning:* update with memory (of varying time scale), as internal representation of environment (training data set), to *increase* performance or *acquire* new state.

- General properties of living system, from cells to embryos and organisms. The nervous system is an advanced version of these universal properties.

What is biological learning?

Novelty: new information, new state and memory.

Examples: Reading a book, talking to someone

Nervous system, Immune system

Cell decision: evolution to a new state

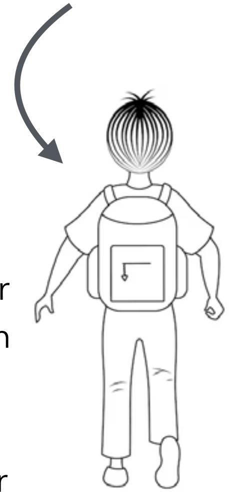
Improved performance

Examples: practicing instrument, sport, doing an experiment.

Nervous system, Immune system

Faster response, increased specificity, increased persistence of a cell behaviour

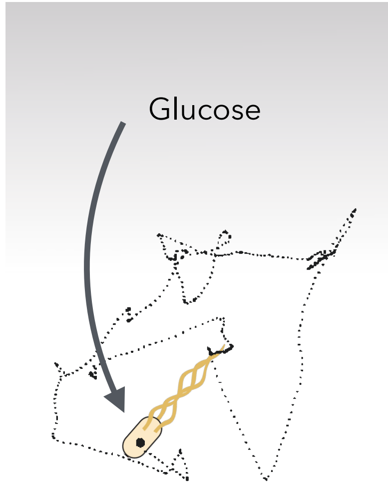
- *Learning*: acquisition of new information from outside that leaves a transient or permanent trace or memory or engram or retention in the organisation/ dynamics/behavior of the system.

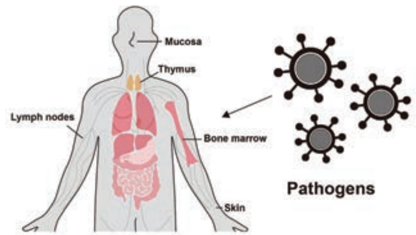


Learning and Memory

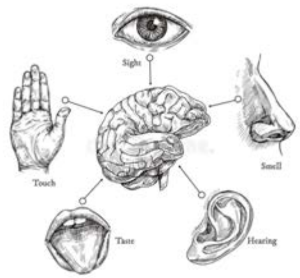
- *Learning*: sensing and decoding *external* information with memory

- *Memory*: transient or long term storage or representation of external information





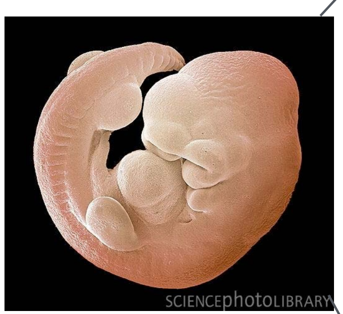
- **Sensory systems:** Bacteria chemotaxis, photon detection, acoustic pressure etc
- **Nervous sytem:** Internal representations of past experience
- **Immune system:** « adaptive » immunity, memory B cells

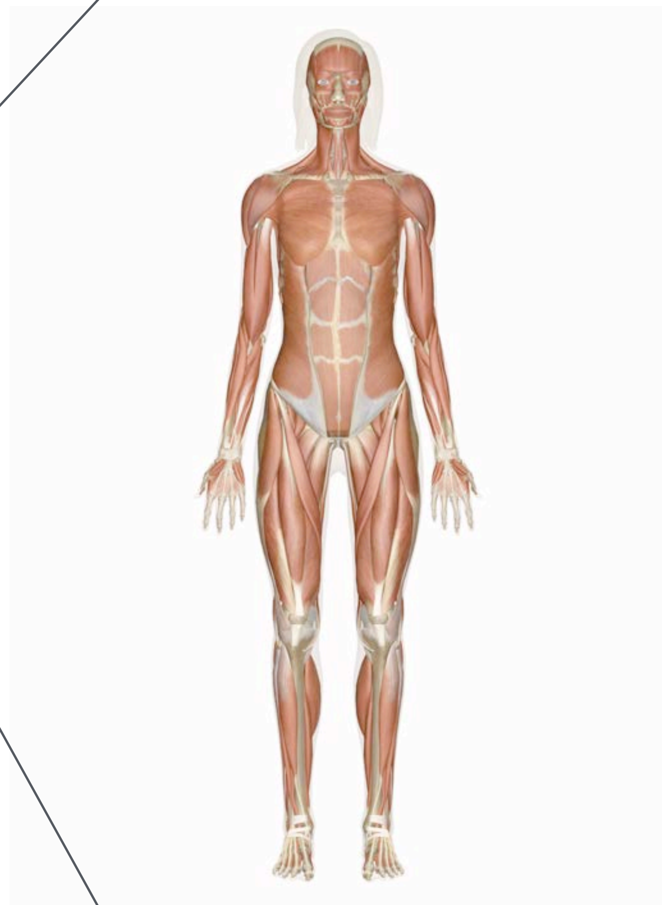


- **Evolution:** internal representation (via selection) of external world inside cells/organisms:
  - the circadian clock network is an internal representation of external diurnal cycle,
  - the chemotactic network of *E. coli* is an internal representation of the functionally meaningful chemical world for *E. coli*.

Self-tuning, -adaptation and -learning during development?

D. Phillips/SCIENCE PHOTO LIBRARY

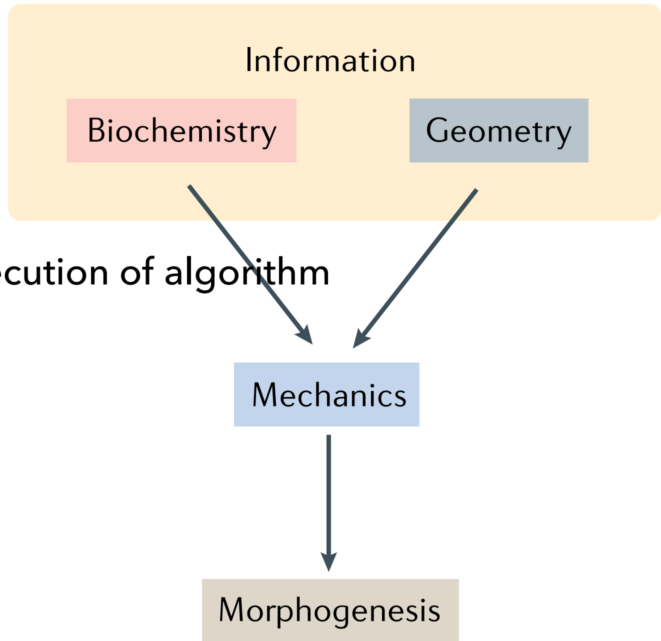




Self-tuning, -adaptation and -learning during development?

PROGRAM

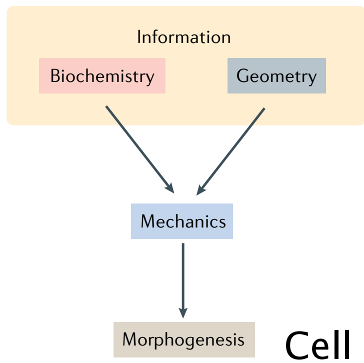
- Initial conditions



- Execution of algorithm

Pre-determinism/Prewiring

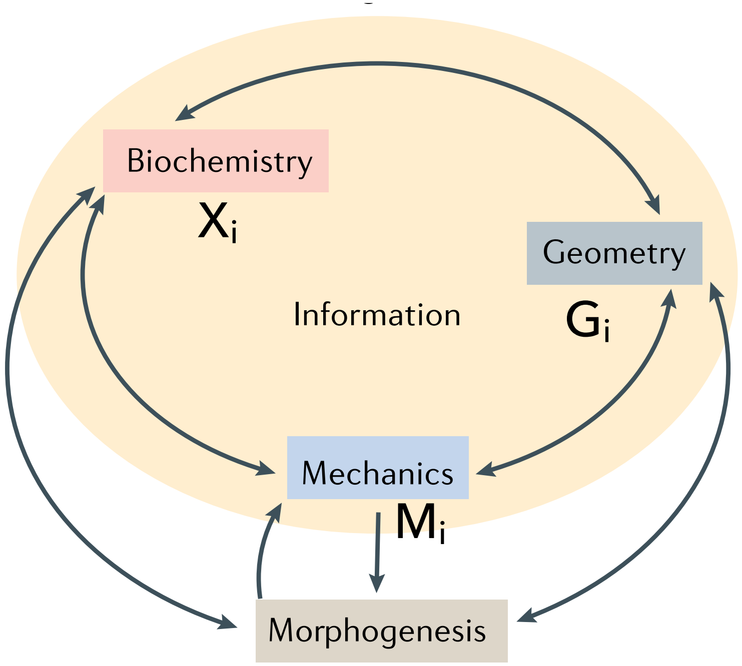
- Top down
- Inheritance, Initial conditions
- Pre-programmed: encoded algorithm in genome and cells state



Cell state

Self-tuning, -adaptation and -learning during development?

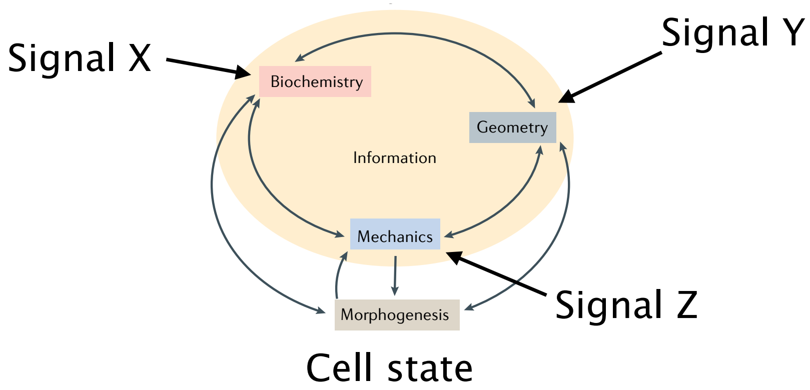
SELF-ORGANIZATION



- Recursive algorithm with update rules

Developmental Tuning and Learning

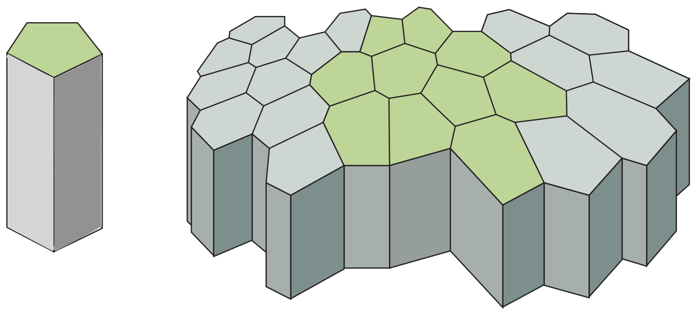
- Bottom up
- External stimuli and signals lead to a new state
- Cell inherits a capacity to update its states as it is exposed to signals
- Sequentiality of cell decision reflects permanent changes (memory), ie. Learning.
- Not all information available at the onset, it manifests sequentially in a changing environment



Self-tuning, -adaptation and -learning during development?

- Learning: new information
- From the embryo point of view, no new information from outside (except for mammals)
- **But from the cellular point of view**, each cell receives new information as a result of sequential events in their embryonic environments (ie. other cells and fluids).

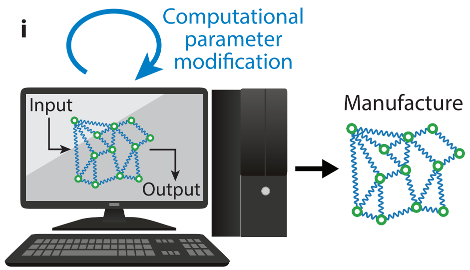
- Reference state encoded in algorithm
- Self-tuning
- Learning algorithm: update rules with memory
- Permanent change in state: memory (ie. cell decision)
- **Cellular learning from within the organism**



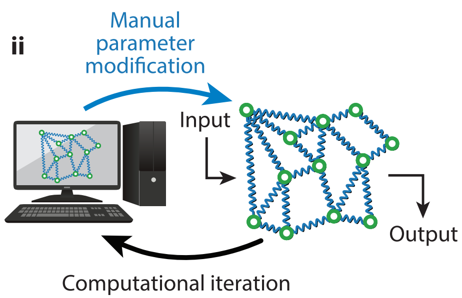
Properties of a learning material

Top down approach

COMPUTATIONAL DESIGN



ITERATIVE DESIGN



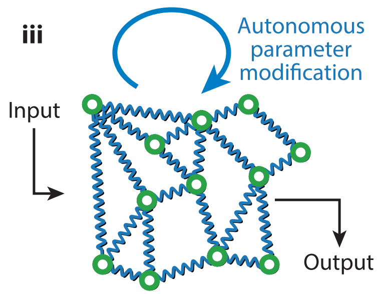
Top down approach to design degrees of freedom (d.o.f)

iterative design-build-test process.

- Materials are often computationally designed for particular properties or responses, either (i) entirely on a computer or through (ii) an iterative design-build-test process.

Bottom up approach

PHYSICAL LEARNING



- Given external stimuli, materials autonomously modify their parameters to adopt desired properties or functions.
- Such autonomous learning machines modify themselves based on their response to stimuli according to physical “learning rules” .

Biological adaptation vs learning

Adaptation

- Cells respond to a stimulus (signal) and respond by changing their state
- They subsequently return to the initial state

Ingredients:

- Physical degrees of freedom (d.o.f):

s, respond to input signal/stimulus f, $s(f)$, and define the output configuration/state.

Learning

- Cells respond to a stimulus (signal) and respond by changing their state
- They adjust their response property such that exposure to a subsequent stimulus leads to a *different* or *improved* state.

Ingredients:

- Physical degrees of freedom (d.o.f): s, respond to input signal/stimulus f, $s(f)$, and define the output configuration/state.
- Learning degrees of freedom (d.o.f): θ_i, modify how the physical d.o.f $s(f\,;\{\theta_i\})$ respond to external signal f.
- Learning rule: $\mathrm{d}\theta_i/\mathrm{d}t = h(s(f\,;\{\theta_i\}))$ modifies the learning d.o.f based on how the physical d.o.f respond to signal f.

Biological tuning and adaptation

Examples: all sensory systems

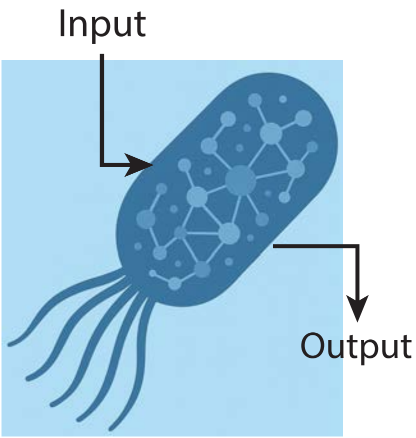
- Response to a cue and restoration of state after perturbation
- Homeostatic function
- Exploration of large amplitude of signals: chemical and mechanical

- Vision
- Audition
- Cell motility: chemical gradient, mechanical cues, durotaxis

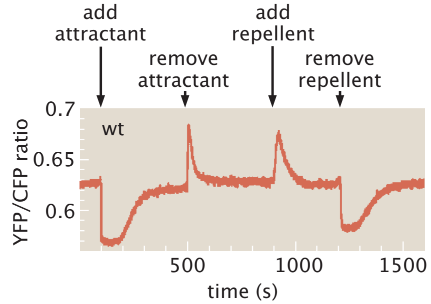
Biochemical adaptation - bacterial chemotaxis

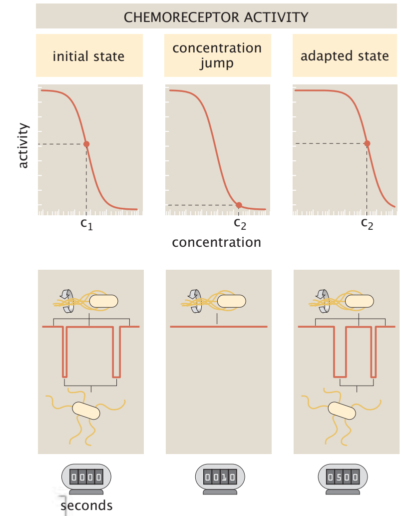
A bacterium self-adapts to an external chemical stimulus

- Cells chemically adapt to a change in chemoattractant concentration
- This allows cells to move over a wide range of concentration

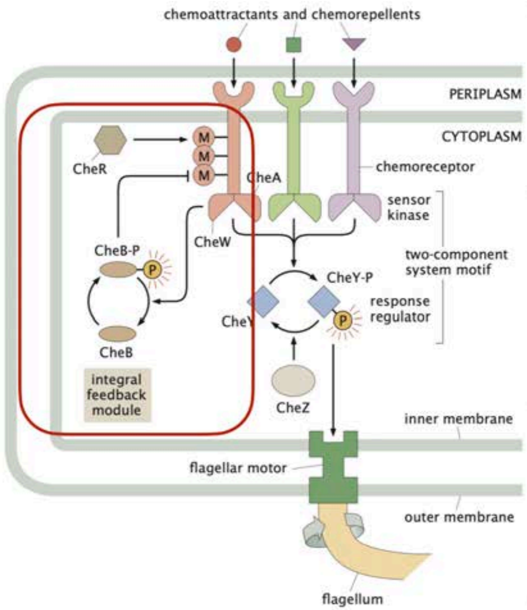


- Adaptation





INPUT



Activity of receptor (R and CheA)

$a(t) = f[L(t), m(t)]$

L : Ligand

m: methylation state

More methylation → higher CheA autophosphorylation rate

OUTPUT

Alon, U, Surette, MG, Barkai, N, & Leibler, S *Nature* 397, 168. (1999)

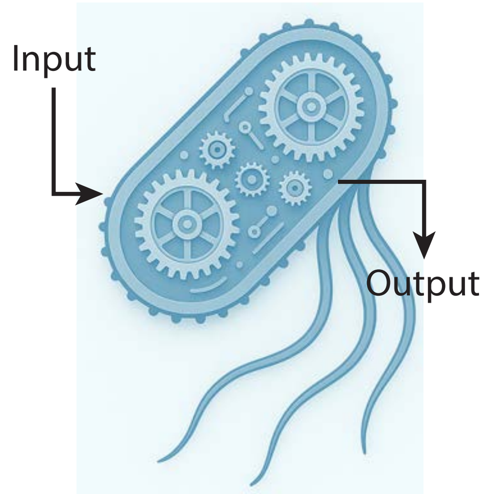
Sourjik, V. & Berg, H. C. *Proc. Natl Acad. Sci. USA* 99, 123–127 (2002).

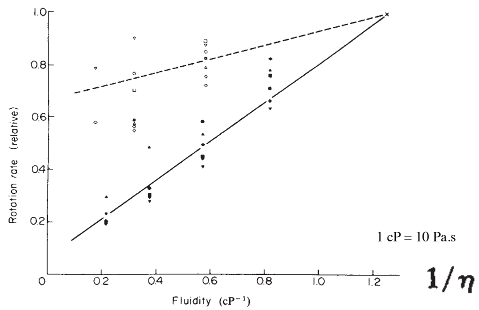
R. Phillips, The Molecular Switch. *Princeton Univ. Press*. 2020

Mechanical adaptation - bacterial swimming

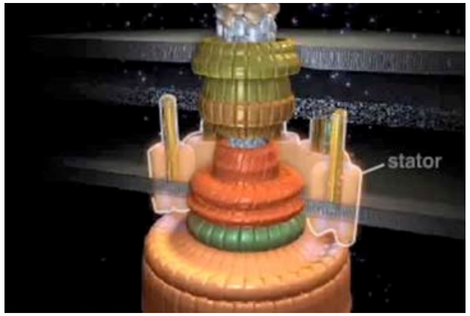
A bacterium self-adapts to an external mechanical stimulus

- Cells mechanically adapt to a change in load on flagellum, e.g. due to change in fluid viscosity
- This allows cells to adjust the torque in the flagellum and restore the rotation speed

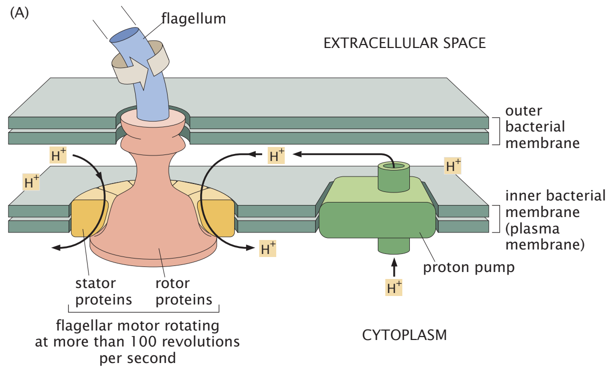


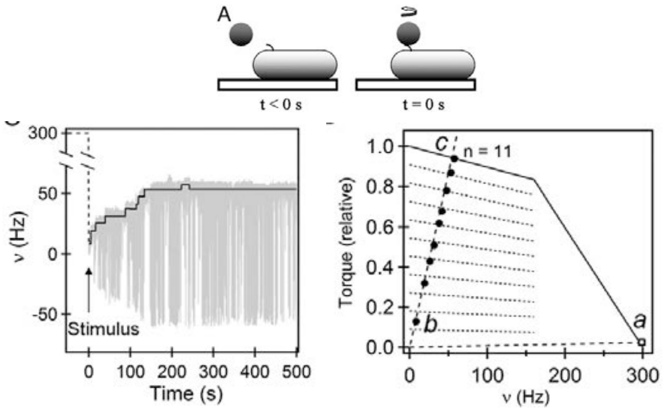


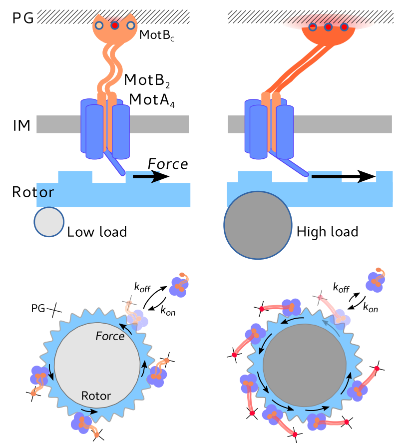
HC Berg *Nature* 278:349-351 (1979)



https://m.youtube.com/watch?v=B7PMf7bBczQ



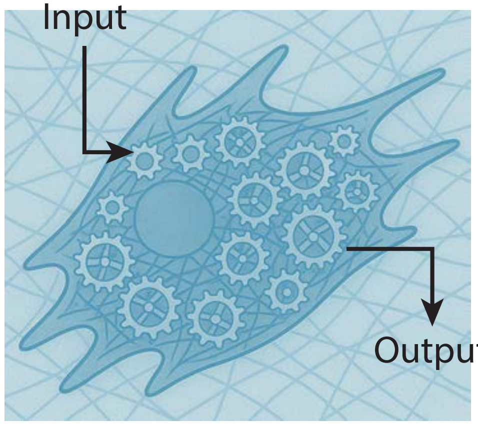




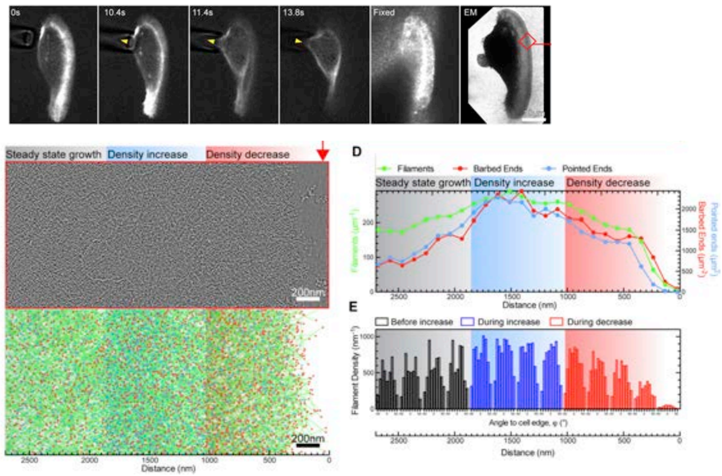
P. Lele, B Hosu and HC Berg *PNAS* 110:11839-11844 (2013)

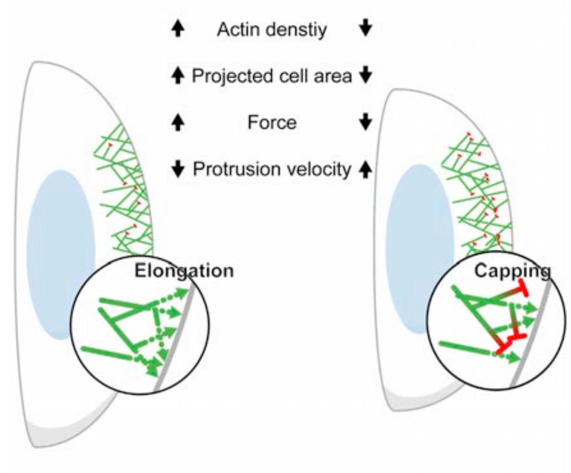
Mechanical adaptation - eukaryotic cell motility

A cell self-adapts to an external mechanical stimulus



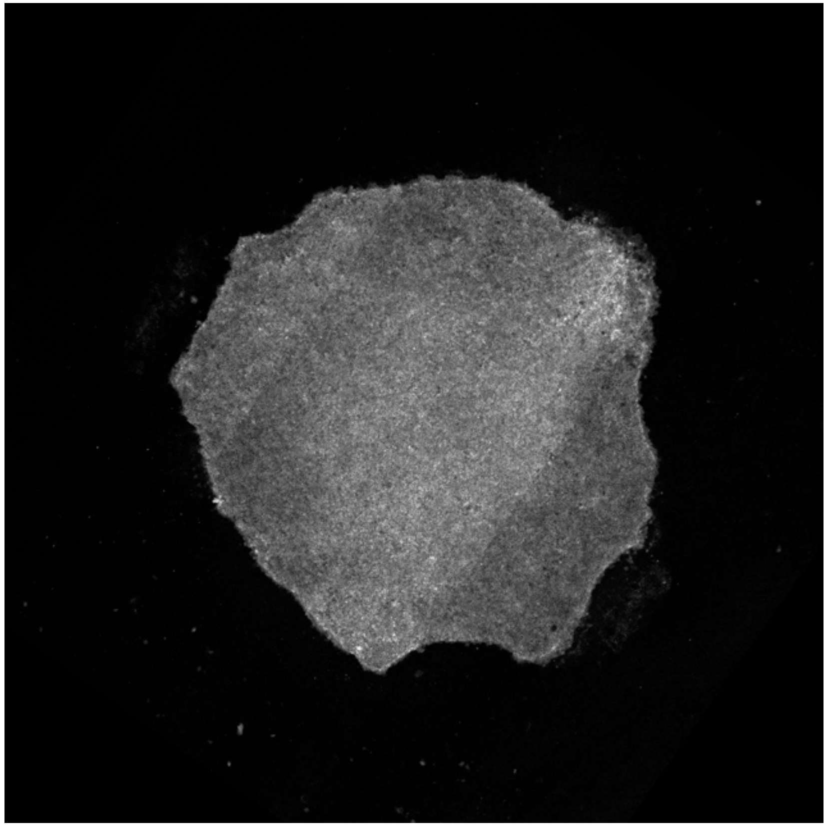
- **Cell motility: mechanical environmental sensing: geometry, adhesion & stiffness**
- Matrix stiffness dependent modification of Focal adhesion and Actomyosin network contraction.
  Reconfiguration of cell state through mechanical feedbacks.
- Protrusive force tuning in response to mechanical load (increased membrane tension)
  Update of actin network geometry as a function of membrane tension. Network-intrinsic geometrical adaptation mechanism.

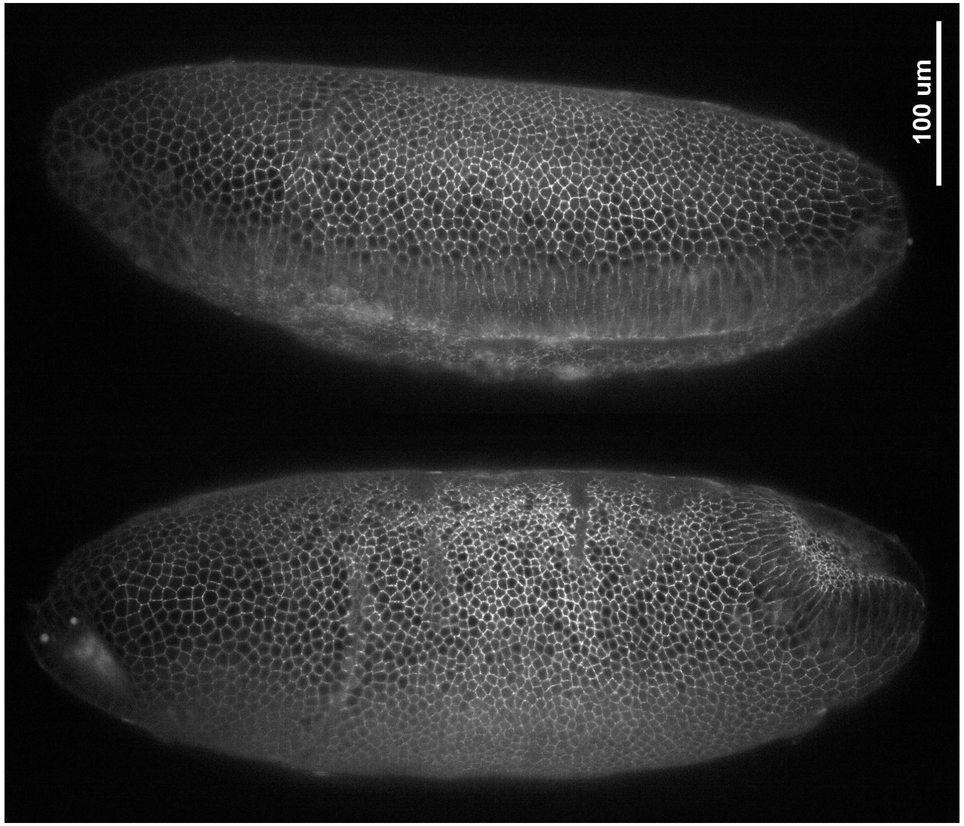




J. Mueller et al., and M. Sixt *Cell* 171, 188–200 (2017)

Mechanical tuning during tissue morphogenesis

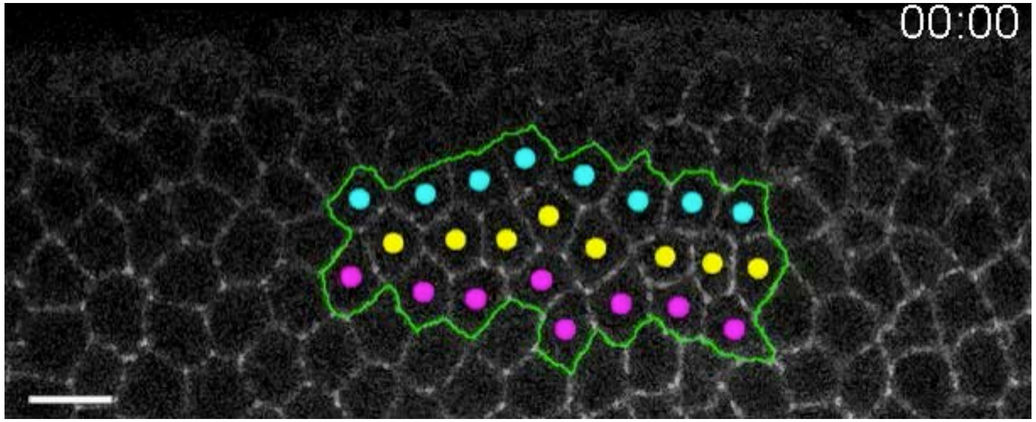


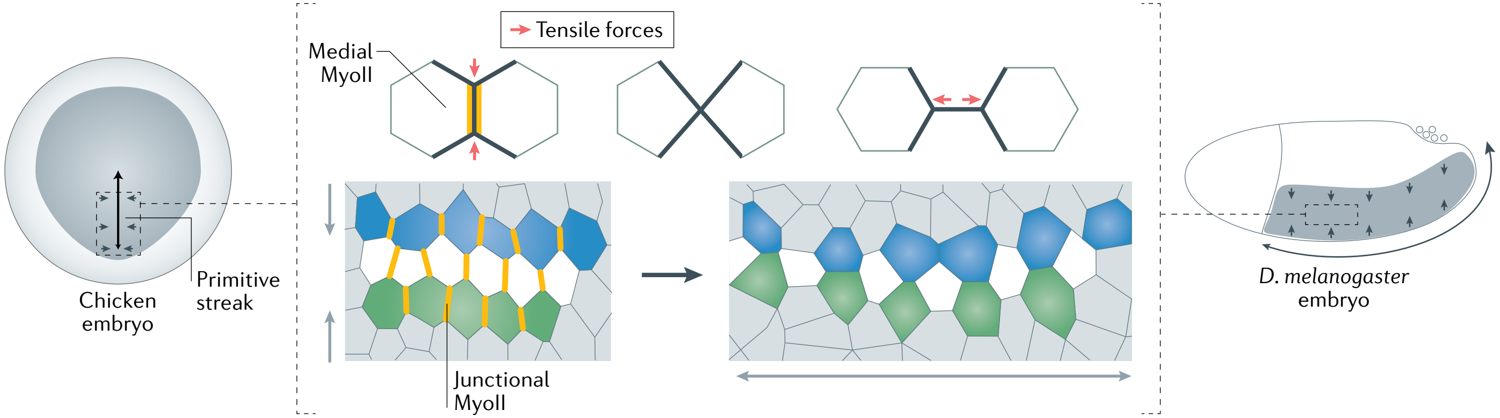


Mechanics of convergence extension

- Tissue flow is driven by cell intercalation and anisotropic tension

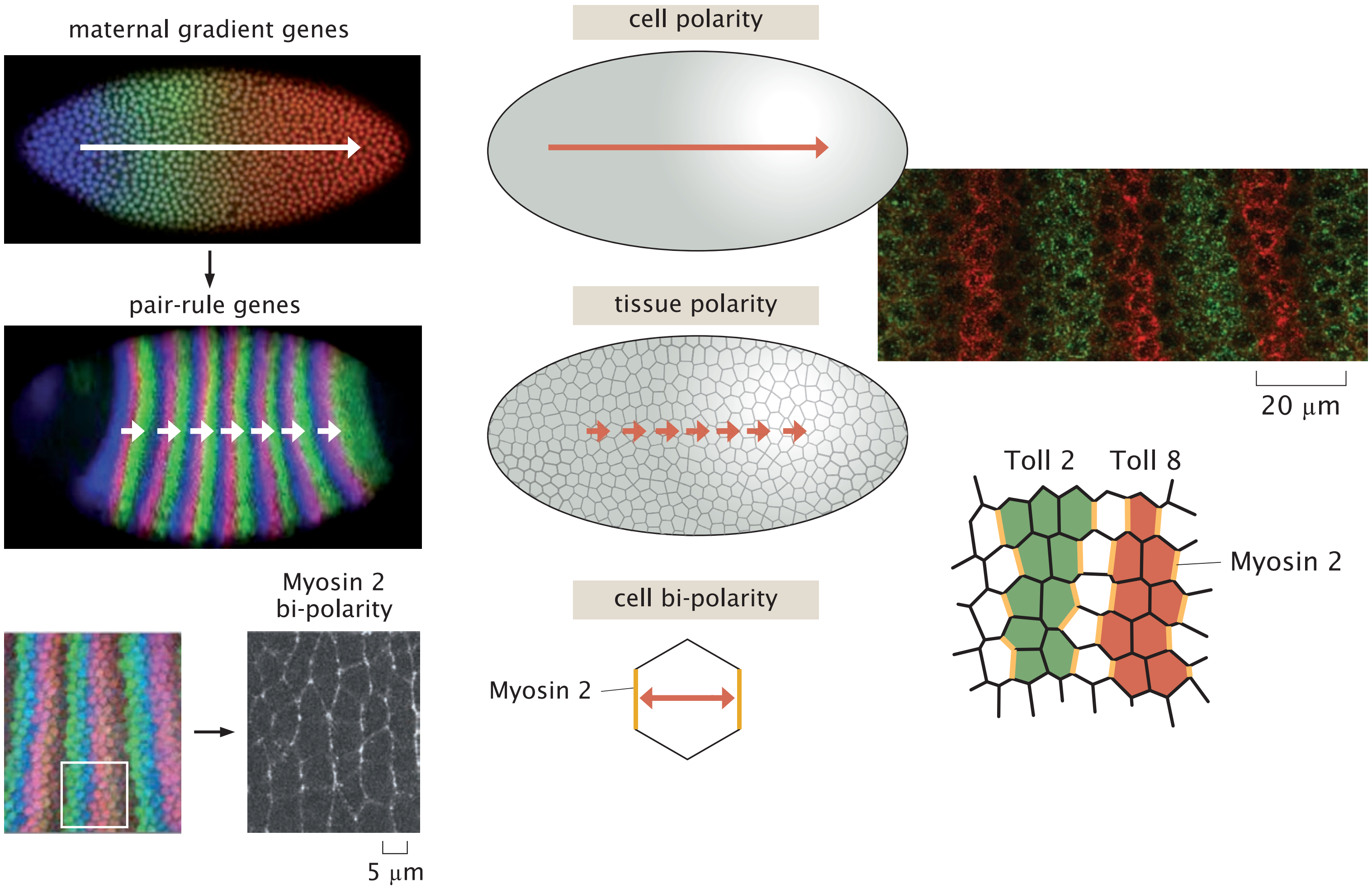
- Irreversible and planar polarised changes in the topology of cell interfaces drive cell intercalation and tissue flow in vertebrate and invertebrate embryos.
- Similar to T1 transition in foams.
- This emerges from anisotropic contractile forces at cell junctions.





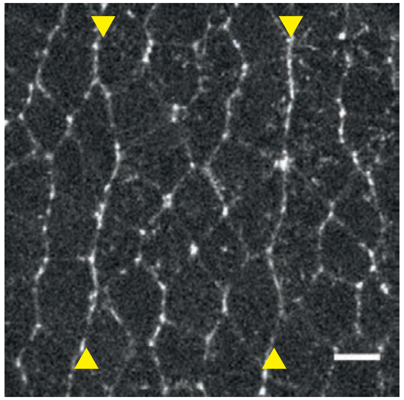
Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, (2021)
C. Bertet, L. Sulak and T. Lecuit. *Nature* 429(6992):667-71. (2004)

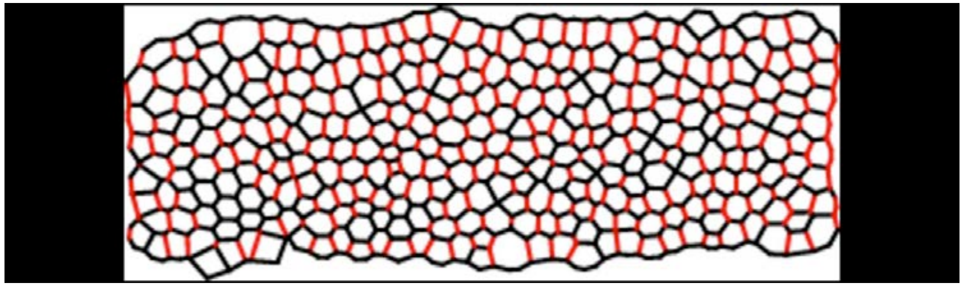
Global contractile patterns are directed by spatial patterning



Guided morphogenesis: deterministic pattern of contractility

MyoII::mCherry





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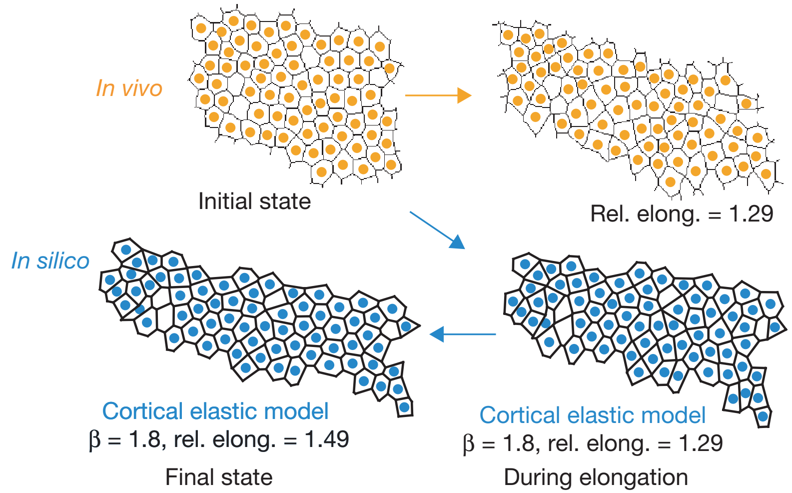
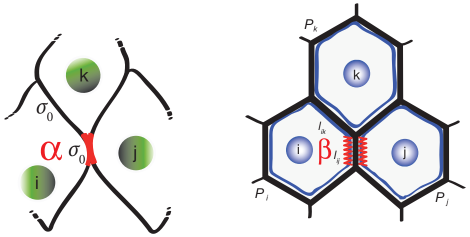




$$E = \underbrace{\sum_{\text{junctions }(ij)} \sigma(\theta_{ij})\, l_{ij}}_{\text{line energy}} + \underbrace{\frac{1}{2}\sum_{\text{cells } i} k_i^P \left(\sum_{\text{cells } j \text{ neighbours of } i} \beta(\theta_{ij})\, l_{ij} - P_i^0\right)^2}_{\text{cortical elastic energy}} + \underbrace{\frac{1}{2}\sum_{\text{cells } i} k_i^A \left(A_i - A_i^0\right)^2}_{\text{area elastic energy}}$$

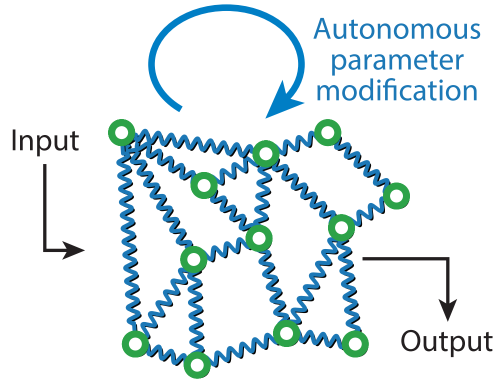
Rauzi, M, et al, T. Lecuit and PF Lenne, *Nat. Cell Biol.* **10**, 1401-1410 (2008)

Garcia De Las Bayonas et al., *Current Biology* 29, 1–16 (2019)

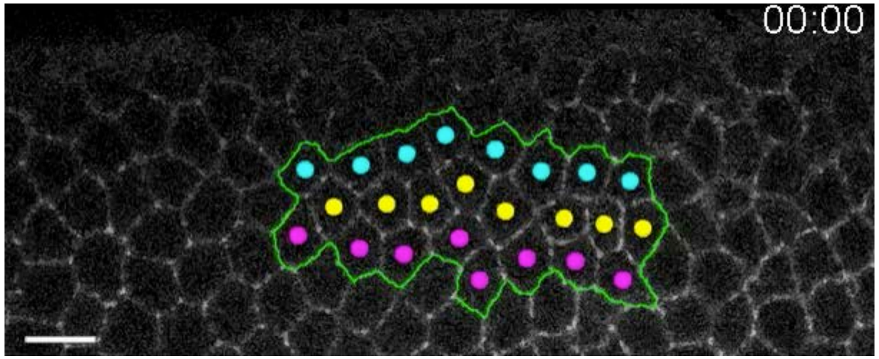
Convergence extension as a self-tuning process

Initial conditions set anisotropic pattern of cell contractility
Update rules modify this pattern of contractility as the tissue deforms.

Cell junctions constantly change length and angles.
Embryos reorganise their internal mechanics to achieve targeted deformations.



Question 1: what is the best pattern of contraction to yield CE?
Ie. what is the best algorithm?
Question 2: is the pattern of contraction tuned to sustain CE?
Is it fixed or self-tuned or self-learning?



S. Arzash, A.J. Liu and L. Manning, *biorxiv* (2025)

Convergence extension as a self-tuning process

$$E = \sum_{i=1}^{N} \left[K_A(A_i - A_0)^2 + K_P(P_i - P_0)^2\right] + \sum_{\langle ij \rangle} \Lambda_{ij}\, \ell_{ij}, \quad [1]$$

- *Global* rule – gradient descent: instantaneous update of all Λ_{ij} (not biologically realistic)

  Λ_{ij} are tunable degrees of freedom
  that actively drive tissue remodelling. Cost function $C = \left(L_y^{\text{current}} - L_y^{\text{target}}\right)^2, \qquad \frac{d\Lambda_{ij}}{dt} = -\gamma \frac{\partial C}{\partial \Lambda_{ij}},$

- *Local* tuning rules: $\mathrm{d}T_{ij}/\mathrm{d}t = F(\textit{local geometry}, T_{ij}))$
  - Orientation rule $\frac{dT_{ij}}{dt} = -\gamma T_{ij} \cos(2\theta_{ij}).$
  - Length-Orientation rule $\frac{dT_{ij}}{dt} = -\gamma T_{ij} \ell_{ij} \cos(2\theta_{ij}),$

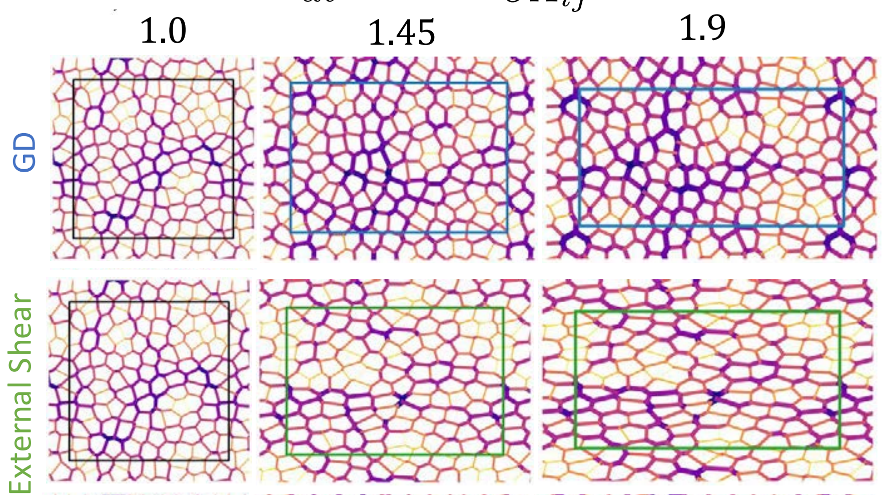
- Update of the edge tensions T_{ij} at each time step according to the specified local feedback mechanism.
- Minimize the mechanical energy E with respect to both the vertex positions and the global pure shear degree of freedom.

S. Arzash, A.J. Liu and L. Manning, *biorxiv* (2025)

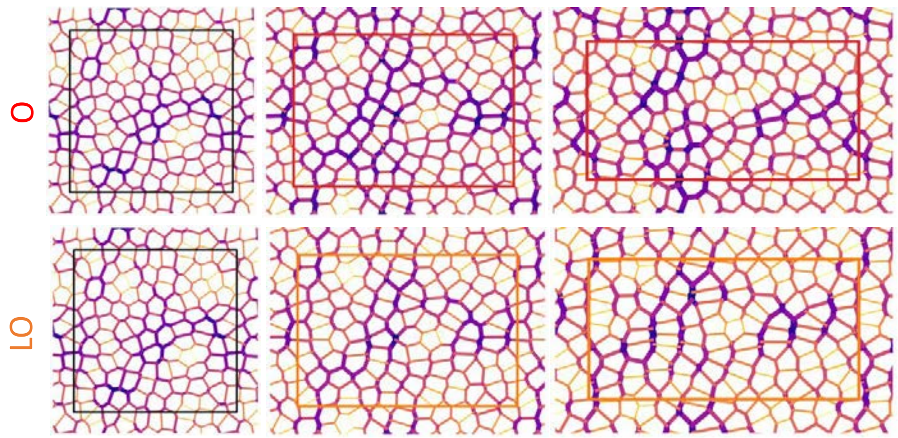
Convergence extension as a self-tuning process

- The local LO learning rule is the one that best recapitulates planar polarised patterns of tension (MyosinII)

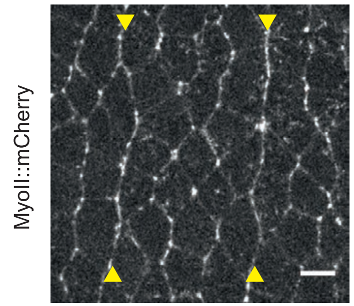
$$\frac{d\Lambda_{ij}}{dt} = -\gamma \, \frac{\partial C}{\partial \Lambda_{ij}},$$



$$\frac{dT_{ij}}{dt} = -\gamma T_{ij} \cos(2\theta_{ij}).$$



$$\frac{dT_{ij}}{dt} = -\gamma T_{ij} \ell_{ij} \cos(2\theta_{ij}),$$

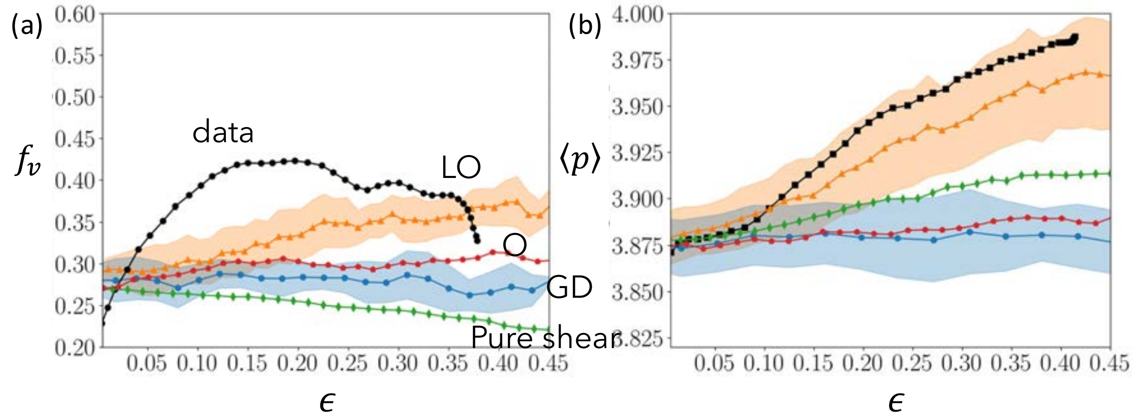


S. Arzash, A.J. Liu and L. Manning, *biorxiv* (2025)

Convergence extension as a self-tuning process

- The LO rule best fits with junction orientation and cell shape

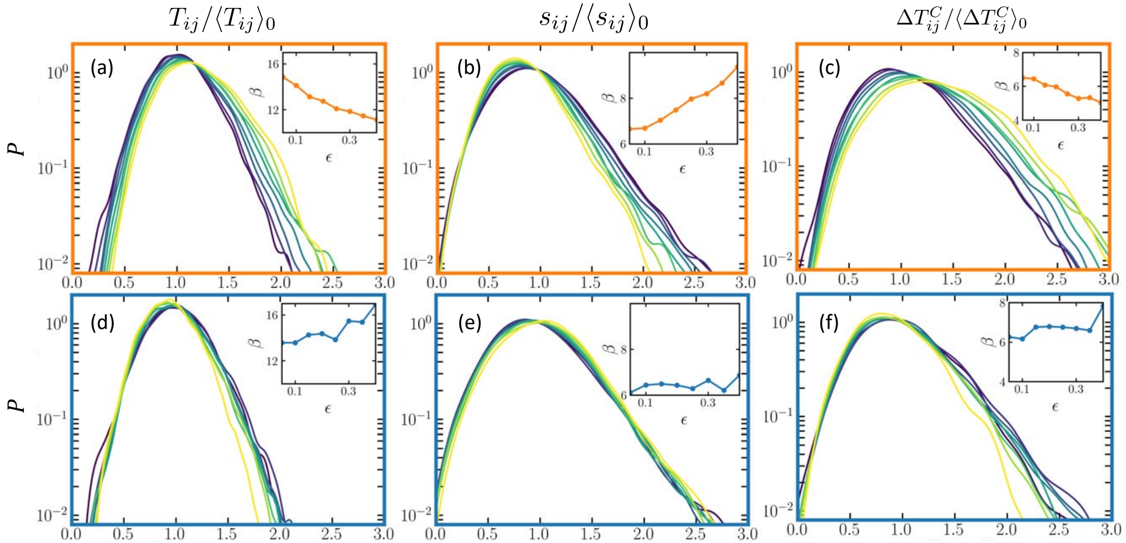
- Fraction of vertically oriented edges, f_v , defined as the fraction of edges with orientation angle θ (75° <θ<105°), where θ is measured with respect to the AP (x-) axis.
- Average cell shape index $p= P/\sqrt{A}$



- Edge tension $T_{ij}/\langle T_{ij}\rangle_0$
- Susceptibility (how sensitively the length of an edge changes in response to infinitesimal forces applied at tissue vertices). $s_{ij}/\langle s_{ij}\rangle_0$
- Cellular tension anisotropy. $\Delta T^C_{ij}/\langle \Delta T^C_{ij}\rangle_0$

$$\Delta T^C_{ij} = \max(T_{ij}) - \min(T_{ij})$$

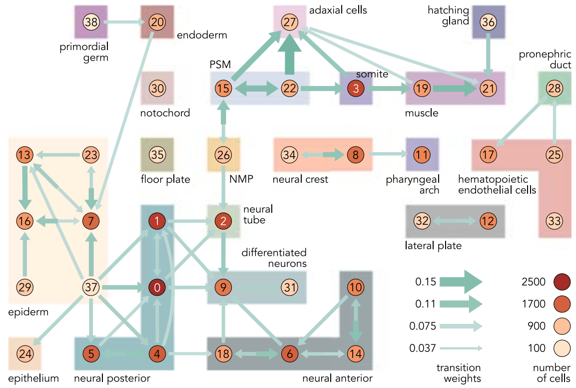
- LO: heterogenous, robust
- GD: homogenous, susceptible

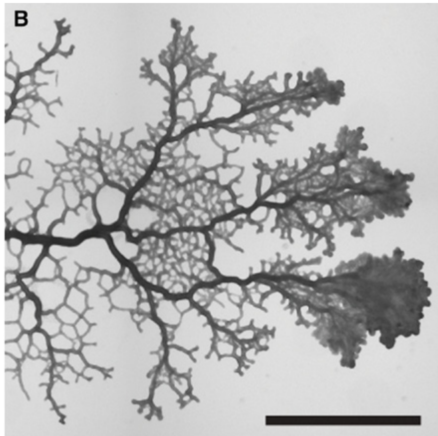


S. Arzash, A.J. Liu and L. Manning, *biorxiv* (2025)

Biological learning

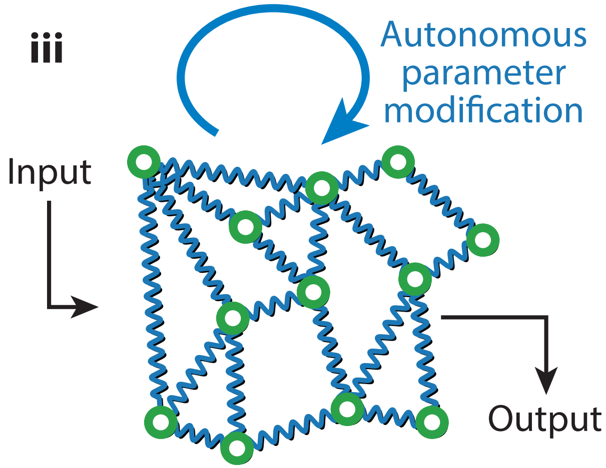
- Cell decision during development
- Cell motility





Properties of a learning material

PHYSICAL LEARNING



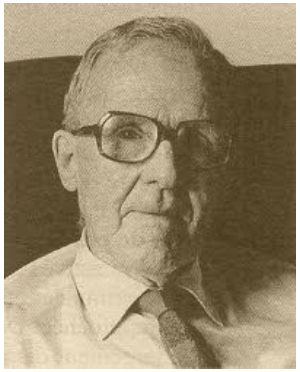
Learning is not centralised (ie. computer) but distributed in the many components of the system.

Definition: Learning degrees of freedom:
Elements of the material that change as described by a system-dependent dynamical process called a learning rule

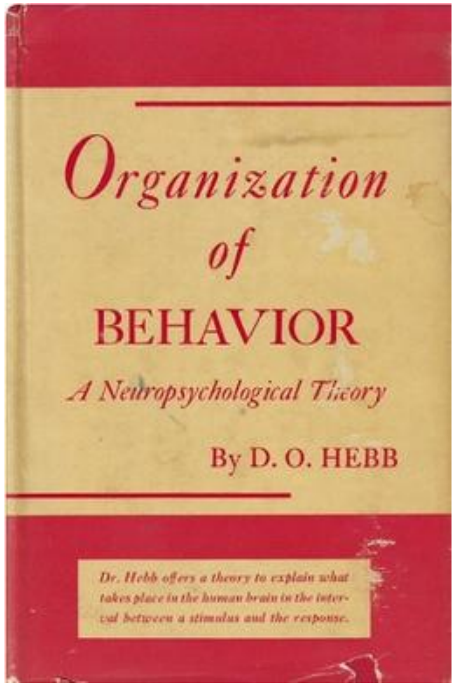
Ingredients:

- **Physical degrees of freedom (d.o.f):** s, respond to input signal/ stimulus f, $s(f)$, and defines the output configuration/state.
- **Learning degrees of freedom (d.o.f):** θ_i, modify how the physical d.o.f $s(f;\{\theta_i\})$ respond to external signal f.
- **Learning rule:** $\mathrm{d}\theta_i = h(s(f;\{\theta_i\}))\mathrm{d}t$ modifies the learning d.o.f based on how the physical d.o.d respond to signal f.
- The physical d.o.f evolve on shorter time scale than learning d.o.f
- **A learning cost function is used to quantify learning** $C(s(f;\{\theta_i\}))$

Hebbian learning - lessons from neuroscience



Donald E. Hebb (1904-1985)



1949

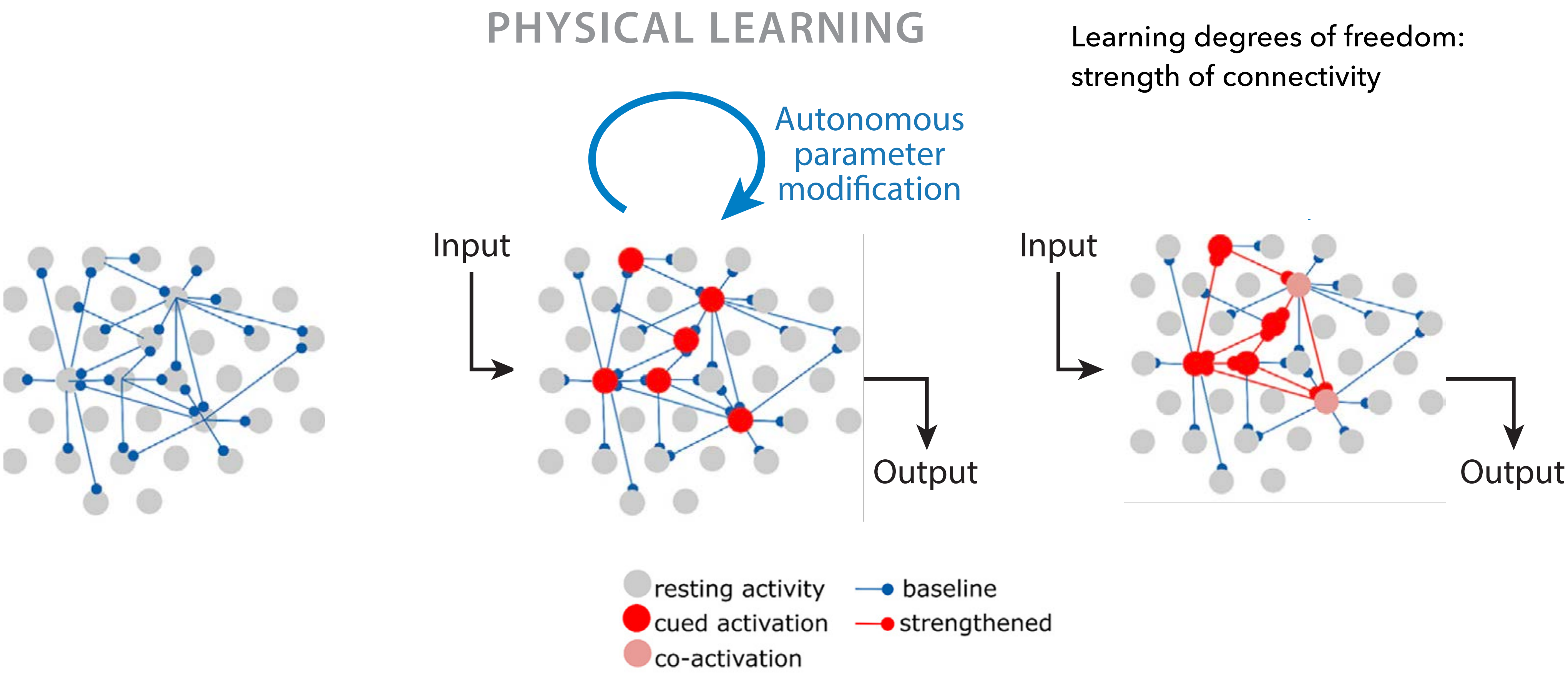
« Neurons wire together if they fire together »

« Let us assume that the persistence or repetition of a reverberatory activity (or "trace") tends to induce lasting cellular changes that add to its stability. ... When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased ».

« **If the inputs to a system cause the same pattern of activity to occur repeatedly, the set of active elements constituting that pattern will become increasingly strongly inter-associated. That is, each element will tend to turn on every other element and (with negative weights) to turn off the elements that do not form part of the pattern. To put it another way, the pattern as a whole will become 'auto-associated'. We may call a learned (auto-associated) pattern an engram** »

D. O. Hebb, *The Organization of Behavior; a Neuropsychological Theory* (Wiley, New York, 1949)

Biological learning - neural network



Learning degrees of freedom: strength of connectivity

Lansner et al. *Current Opinion in Neurobiology* (2023), 83:102809

Time scales in biological learning

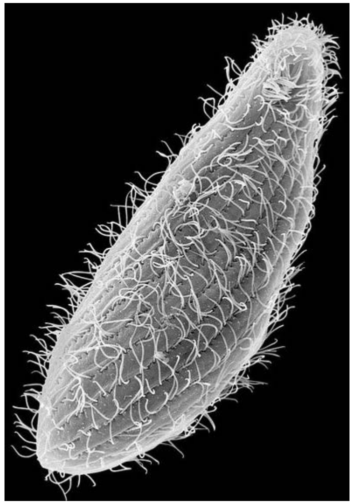
- State depends on history due to memory of past stimuli in the system

- Physical degrees of freedom: Fast response variable $s(f)$
- Learning degrees of freedom: Slow evolving variable $s(f\,;\,\{\theta_i\})$

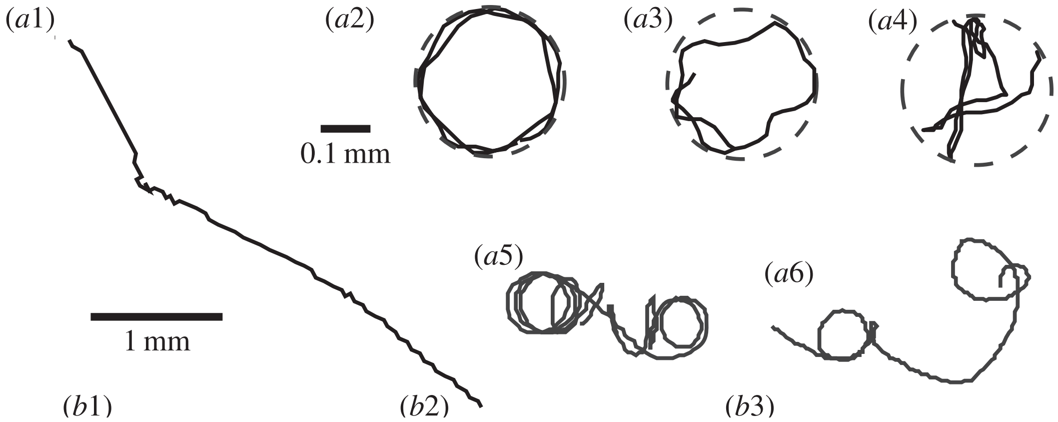
$$d\theta_i = h(s(\underset{\text{Fast}}{f}\,;\,\{\underset{\text{Slow}}{\theta_i}\}))dt$$

- *Global* vs *Local* sensing and tuning/update

Learning the geometry of the environment in Ciliates



Tetrahymena thermophila

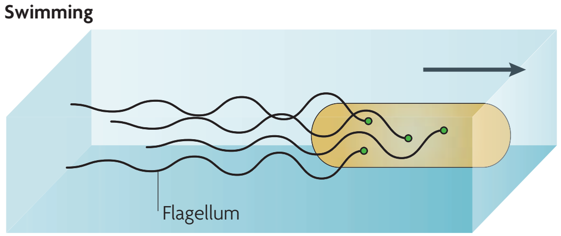


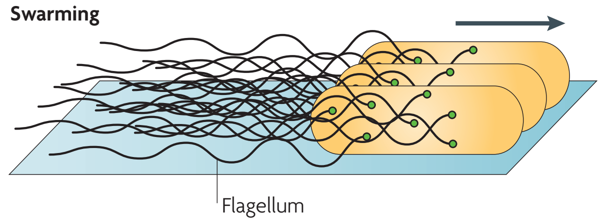
Swimming trajectories (–) of *Tetrahymena* before and after confinement:
(a1) in an open space
(a2 – a4) in the confined space of a spherical droplet (- - -) D=0.3 mm
(a5, a6) in an open space *after confinement*.

Kunita et al *J. R. Soc. Interface* 13: 20160155 (2015)

Biological learning – cell motility in bacteria

$$\mathrm{d}\theta_i = h(s(\underbrace{f}_{\text{Fast}} ; \underbrace{\{\theta_i\}}_{\text{Slow: gene expression }(Laf)}))\mathrm{d}t$$

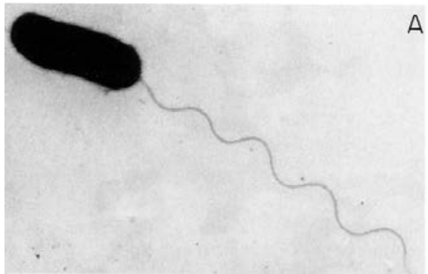




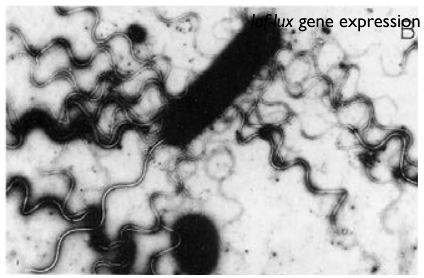
Kearns DB (2010) A field guide to bacterial swarming motility. *Nat Rev Microbiol* 8(9): 634–644. (2010)

- Induction of flagellar genes and increase in number of flagella per cell
- Flagella cover the entire cell
- Flagella bundle together when they rotate to increase the effective flagellar stiffness and make force generation more efficient in viscous liquids

- Synthesis of new flagella (lateral flagella) in *Vibrio parahaemolyticus*: flagellar dynamometer

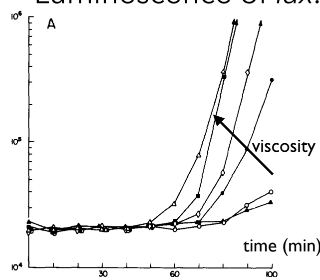


swimming
polar flagellum (Fla genes)



swarming
lateral flagella (Laf genes)

Laf expression
Luminescence of *lax::lux*



L. McCarter et al. *Cell* 54: 345-351 (1988)

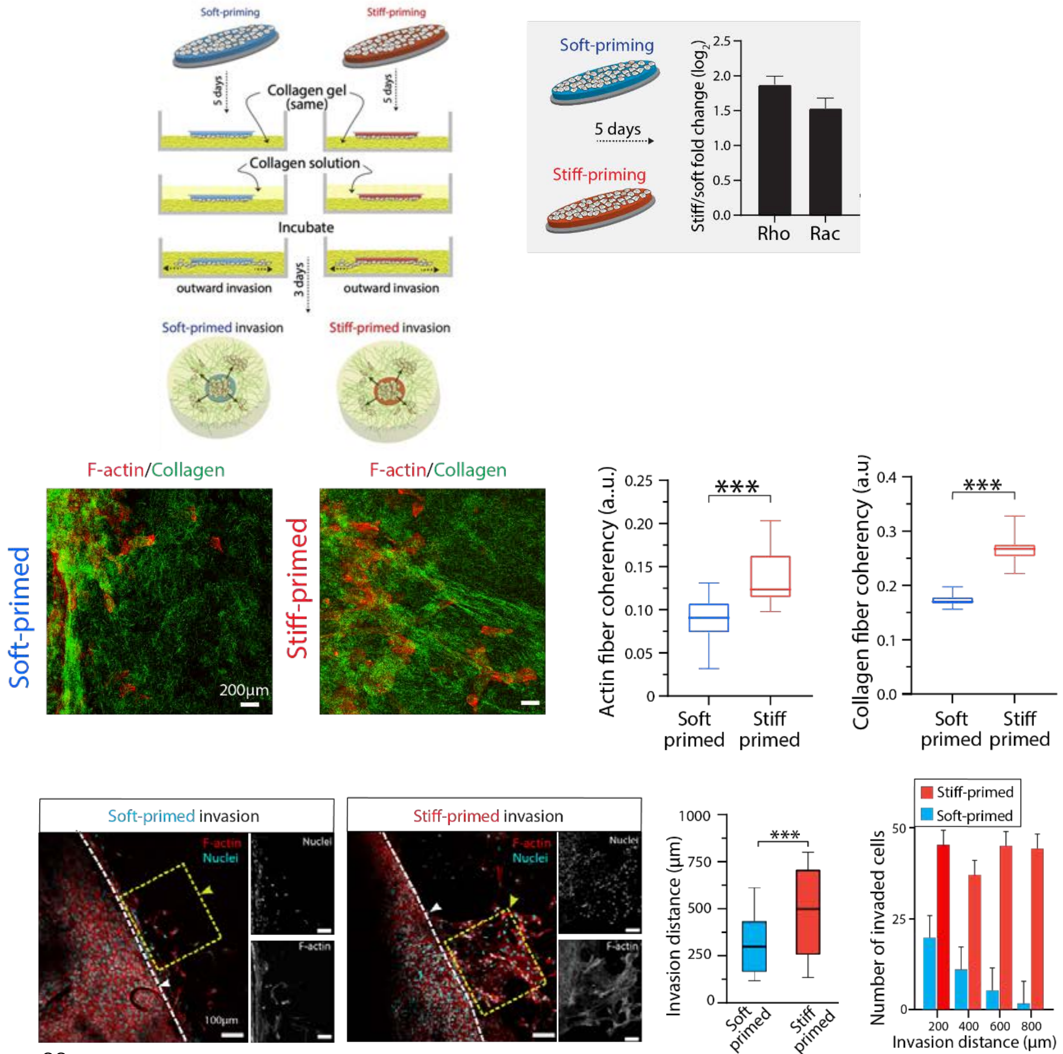
Mechanical learning – cell motility in eukaryotes

- Cell priming over 5 days on a soft or stiff collagen substrate
- Cell invasion on soft substrate subsequently
- **Stiff-primed cells have long lasting modifications of state: actin alignement, Rho1 and Rac activity and cell invasiveness, deformation of collagen substrate**
- YAP is required for cell memory and memory transfer on collagen substrate
- Collagen remodelling is required for stiff-primed cell invasion.

$$\mathrm{d}\theta_i = h(s(f\,;\,\{\theta_i\}))\mathrm{d}t$$

Fast   Slow: YAP expression
+ memory transfer to substrate

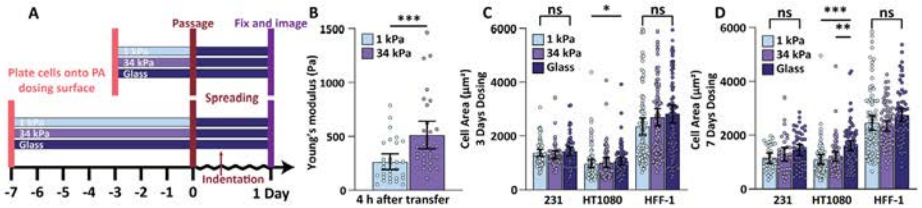
J. Almeida et al, A. Pathak *Molecular Biology of the Cell* • 34:ar54, 1–17 (2023)

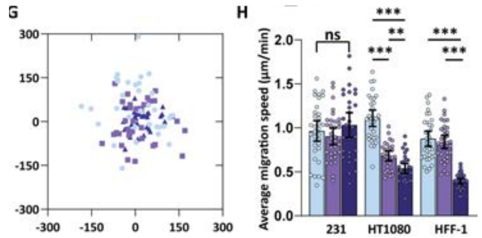


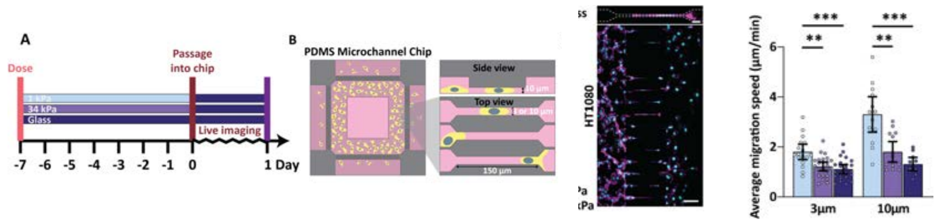
Mechanical learning – cell motility in eukaryotes

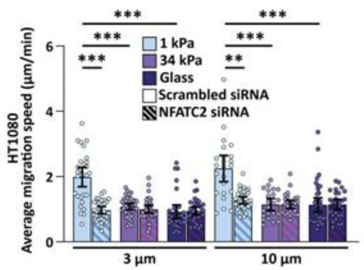
- Cell priming over 3-7 days on a soft or stiff polyacrylamid gel or glass.
- Cells change morphology
- **Cells primed on soft substrates are more invasive that if primed on stiff substrates (capillary channels and in gel)**
- NFATC2 is required for cell mechanical memory (cell migration speed)
- NFATC2: calcineurin-responsive transcription factor implicated in cell migration and cancer progression (nuclear translocation).

$$d\theta_i = h(s(\underbrace{f}_{\text{Fast}}\,;\,\underbrace{\{\theta_i\}}_{\text{Slow: NFATC2 expression}}))dt$$









Jia Wen Nicole Lee et al, A.W. Holle, *biorxiv* (2025)

https://doi.org/10.1101/2025.09.07.674701

Biological learning – Mechanical learning and memory

- The timescale of memory retention is orders of magnitude larger than the timescale of mechanosensitive signaling.
- Memory retention time changes with priming time.
- **Positive reinforcement in mechanical signalling underlies memory.**

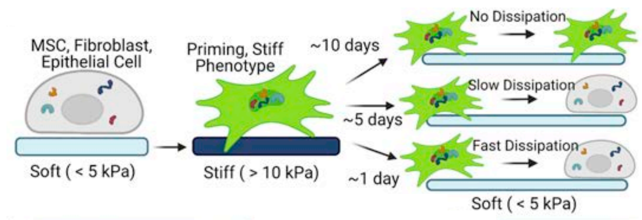
$$\mathrm{d}\theta_i = h(s(f\,;\,\{\theta_i\}))\mathrm{d}t$$

Fast   Slow: Reinforcement

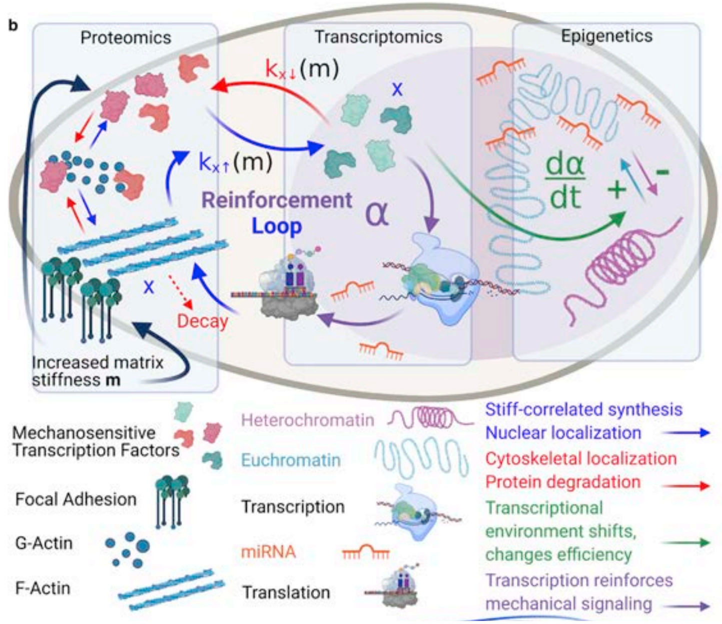
x measures the net mechanoactivation of the cell induced by increased ECM stiffness

x **represents the average functional concentration of all the stiff-activated proteins** (eg. F-actin, vinculin, & integrins) and **TFs** (eg. YAP, MKL-1 & RUNX2) and **chromatin modification** (HDAC and HAT)

$$\frac{dx}{dt} = \underbrace{k_{x\uparrow}(m)\left(x_{ref} - x\right) - k_{x\downarrow}(m)x}_{\text{Mechanosensitive adaptation}} + \underbrace{\alpha\frac{x^{\beta}}{x^{\beta}+1}}_{\text{Reinforcement, ie memory/learning}}$$



adaptation   learning   learning

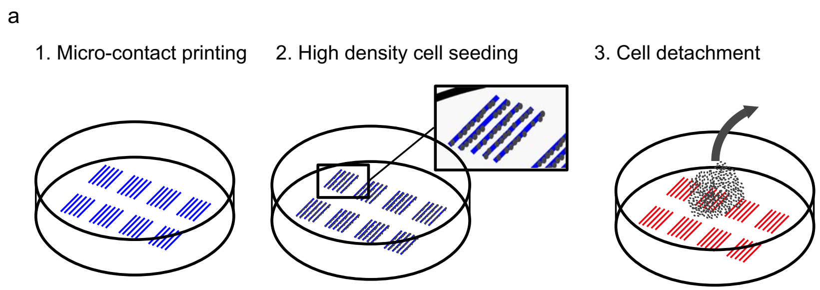


C. Price et al and V.B. Shenoy. *Biophysical Journal* 120, 5074–5089

Transfer of memory onto substrate/environment

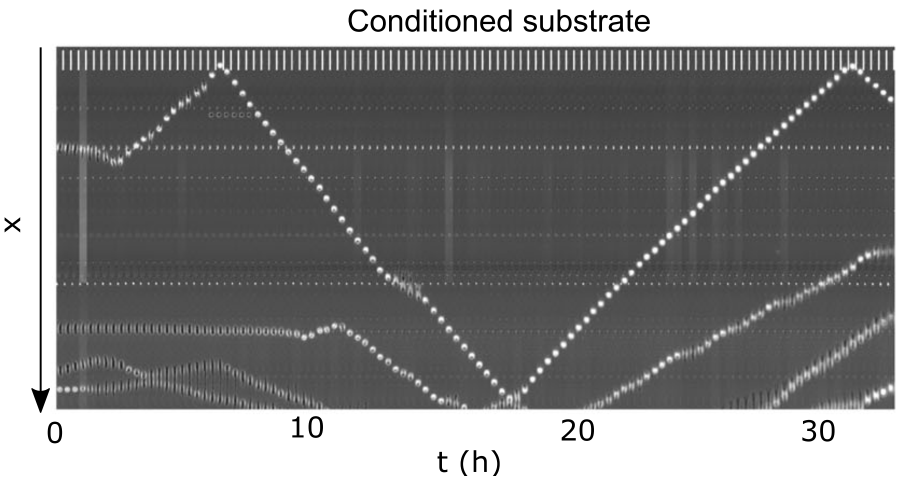
Learning and modification of environment to stabilise the memory

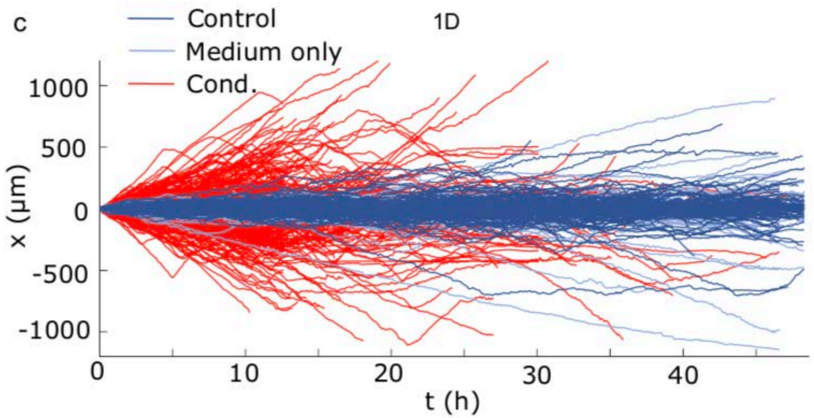
Reinforcement of guidance landscape by cells: spatial memory (akin to stigmergia)



Conditioned substrate enhances cell motility
Oscillatory migration in 1D channels

Kymograph of a cell moving along a conditioned 20 µm track with high persistence

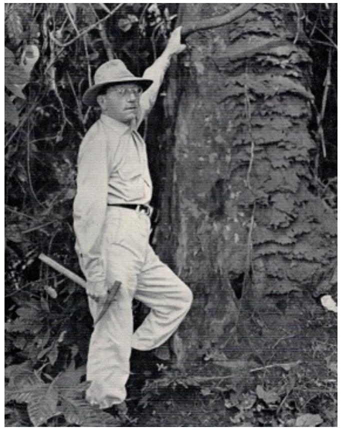




d'Alessandro et al. RM Mège R. Voituriez and B. Ladoux *Nature Communications* 12:4118 (2021)
https://doi.org/10.1038/s41467-021-24249-8

Transfer of memory onto substrate/environment

Stigmergy: the construction guides the behaviour of workers



LA RECONSTRUCTION DU NID
ET LES COORDINATIONS INTERINDIVIDUELLES
CHEZ *BELLICOSITERMES NATALENSIS*
ET *CUBITERMES SP.*
LA THÉORIE DE LA STIGMERGIE :
ESSAI D'INTERPRÉTATION
DU COMPORTEMENT DES TERMITES CONSTRUCTEURS.

par Pierre-P. GRASSÉ

La conséquence de ce type de stimulation est de régler automatiquement la marche de l'ouvrage.

La coordination des tâches, la régulation des constructions ne dépendent pas directement des ouvriers, mais des constructions elles-mêmes. *L'ouvrier ne dirige pas son travail, il est guidé par lui.* C'est à cette stimulation d'un type particulier que nous donnons le nom de STIGMERGIE (*stigma*, piqûre ; *ergon*, travail, œuvre=œuvre stimulante).

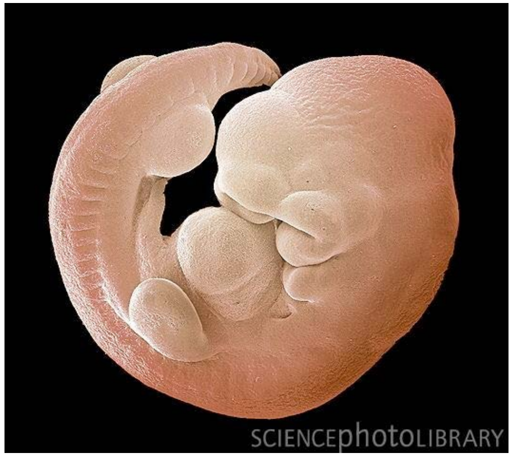
B. — ***La stigmergie et les stimulations simultanées.*** — Mais il y a plus encore. Selon que les boulettes sont rassemblées en tas ou disposées en ligne, elles ne déclenchent pas la même réponse. La forme du stimulus acquiert le pouvoir, significatif, d'orienter la construction. Elle tient donc un rôle capital pour le devenir de l'édifice.

INSECTES SOCIAUX, TOME VI, N° 1, 1959.

Learning during embryonic development?

- **Cellular decisions and differentiation:** sudden and irreversible dynamics
  - Mostly chemical learning (sometimes mechanical as well)

- Morphogenesis: irreversible changes in shape
  - Mechano-chemical learning

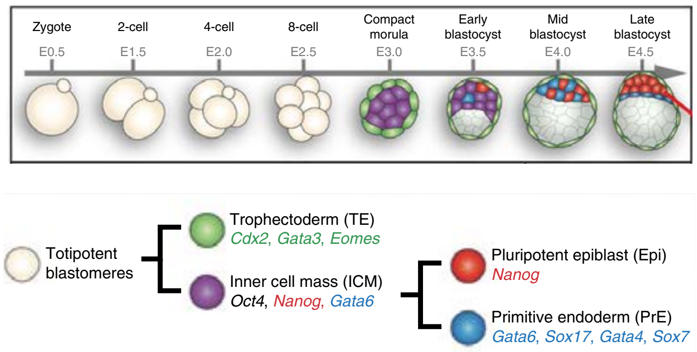


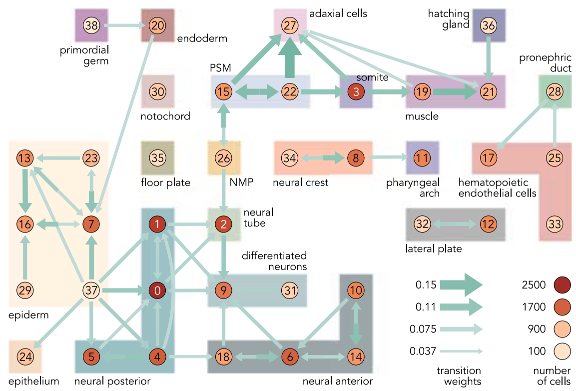
Dynamics of developmental cellular decisions

Basic phenomenology

- *Fate*: cell fates are discrete
- *Competence*: cells are competent to respond to signals in a temporal window
- *Commitment/specification*: cells are committed when they no longer need signals
- *Determination*: other signals can no longer deviate the assigned cell fate.

- Proliferating pool of progenitor cells gives rise to two mutually exclusive states by different signals





 A. Czechanski et al. *Nature Protocols* 9:559 (2014) Merlin Lange et al. and Loic Royer, *Cell* 187, 6742–6759 (2024)

Learning during embryonic development

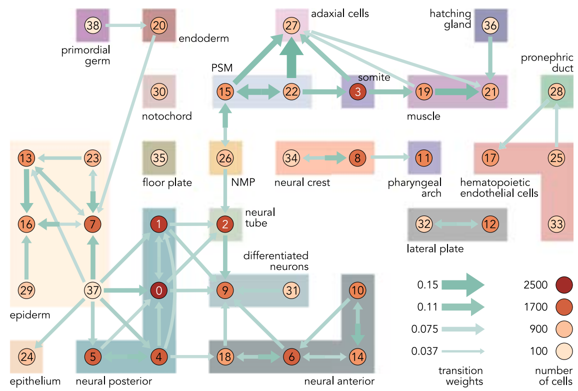
- Encoding of ensemble of possible cellular states in a cell type
  ie. in genome /cell, GRN, geometric landscapes as representation.

- Cells evolve sequentially by learning transition to new states.
  This is not readily available to it at the onset

- This requires new signals, or ensemble of signals that trigger cell decisions (paths to new states)

- The cells keep a *memory*, sometimes permanently.
  Inducing signals may be removed without any consequence once decision has been made (commitment).

- A cellular decision as a learning process.



Learning in the context of Marr’s level of analysis

A framework to disentangle:

- Purpose(why): computation
- Strategy (how): algorithm
- Biology/physics (what):   implementation

1982, Vision, David Marr
W. H. Freeman and Company
2010: *MIT press* (re-published)

- **Computational level: making predictions in a changing environment**

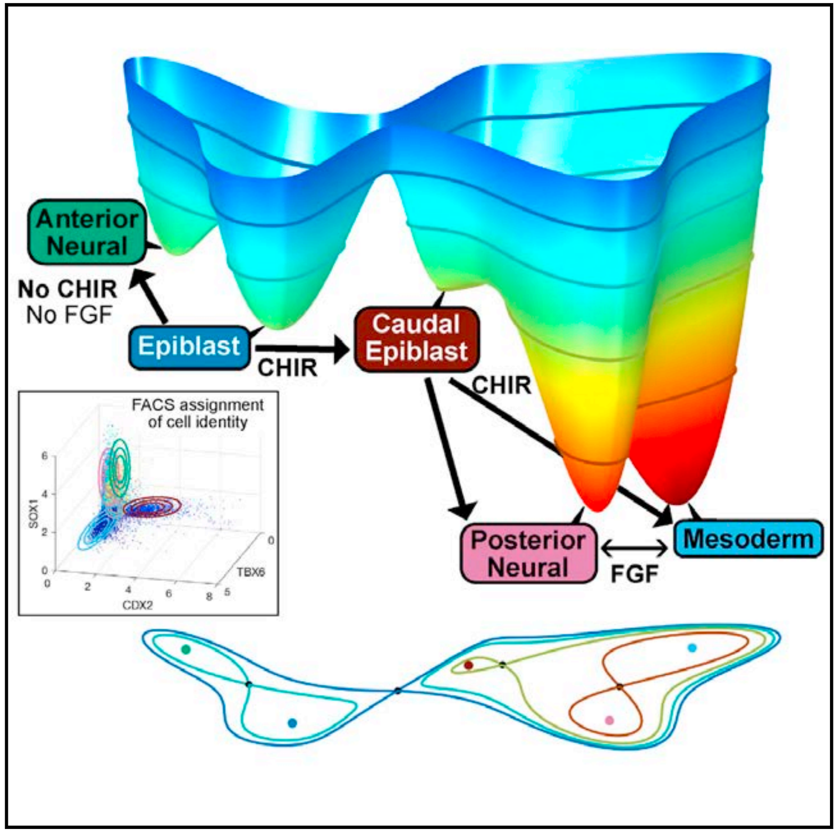
Learning systems build internal models of regularities.
These models are compressed representations of their environment (ex. signals as in chemotaxis).
The external environment of an embryonic cell is the internal environment of the embryo.
This environment is not constant: there are regularities and stochastic fluctuations.

- **Algorithmic level: making algorithms learnable.**
- **The algorithm is modified by experience (the changing environment):**
  - Learning parameters

Geometric landscape and cell decision

- A geometric representation of cellular devisions.
- Landscape for Binary choice

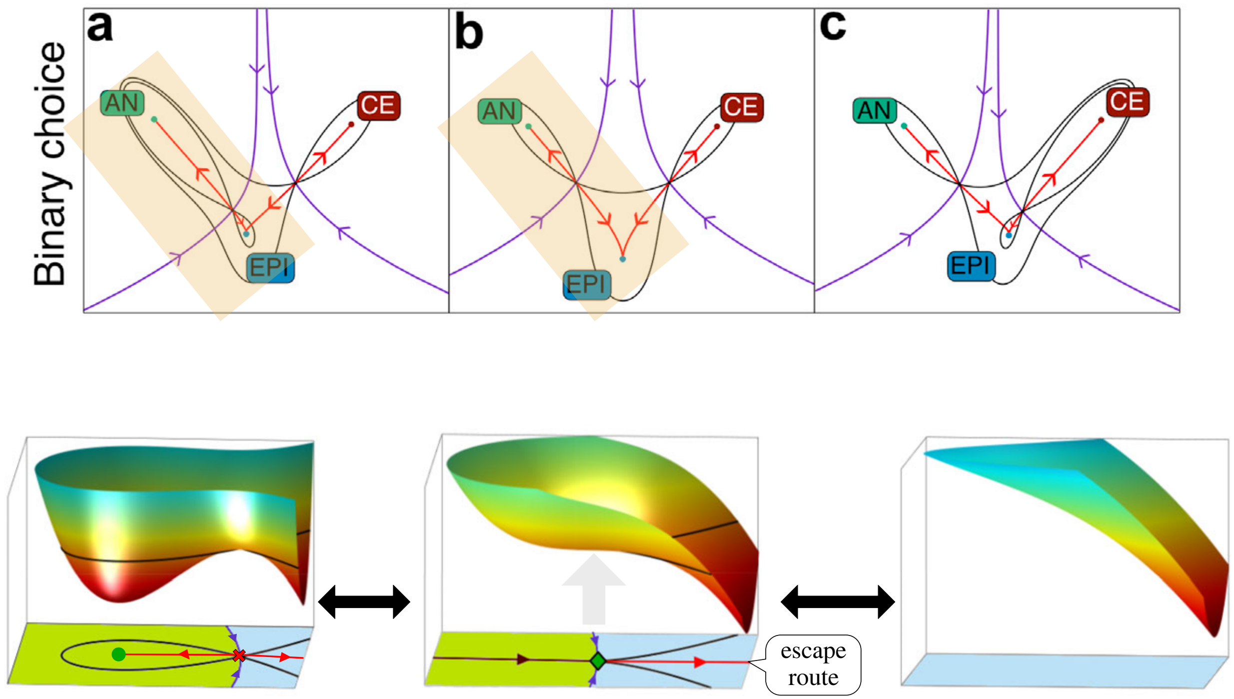
Epiblast cells (EPI) can become Anterior Neural or Caudal Epiblast cells depending on signals received (Wnt).
3 attractors with 2 saddle points, 1 attractor in the middle.



M. Saez et al. E. Siggia, D. Rand and J. Briscoe, 2022, *Cell Systems* 12, 12–28

Landscape for *Binary choice*

- Saddle node or fold bifurcation:
- Bifurcation between EPI and either of 2 saddle points.
- Peripheral attractors never connect directly



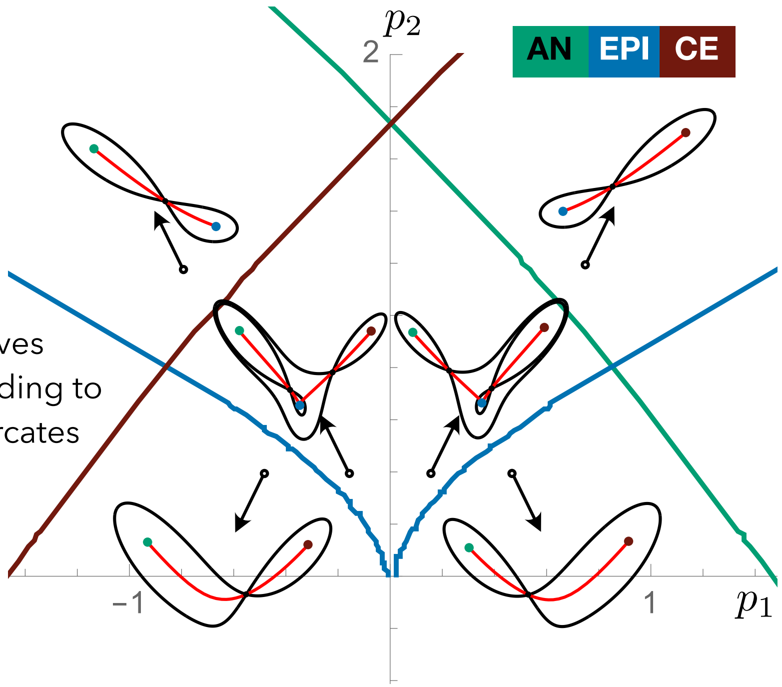
M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)

Sáez M, Briscoe J, Rand DA. Dynamical landscapes of cell fate decisions. *Interface Focus* 12: 20220002. (2022)

Parametrisation of the geometric decision landscape

Landscape for *Binary Choice*

Saddle-node bifurcation diagram



Fold bifurcation curves colour coded according to which attractor bifurcates

M. Saez et al. E. Siggia, D. Rand and J. Briscoe, 2022, *Cell Systems* 12, 12–28

The potential defines attractors and saddle points, unstable manifolds that connect the saddle points and attractors

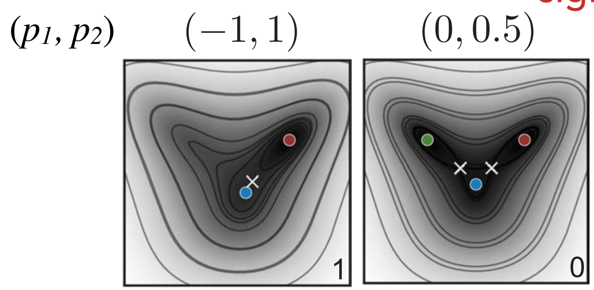
Potential function defined by a polynomial:

$$F_1(x, y; p) = x^4 + y^4 + y^3 - 4x^2y + y^2 - p_1\,x + p_2\,y.$$

Non linear part defines the number and position of attractors

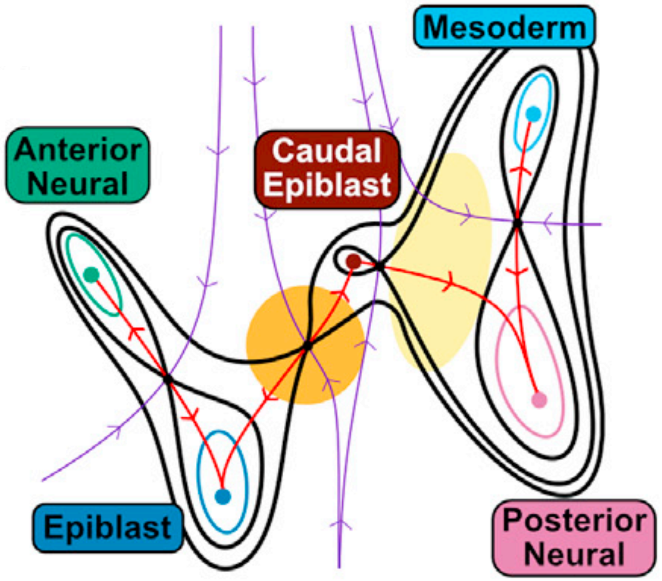
Parametrised linear part akin to a global tilt

Model the effect of signalling

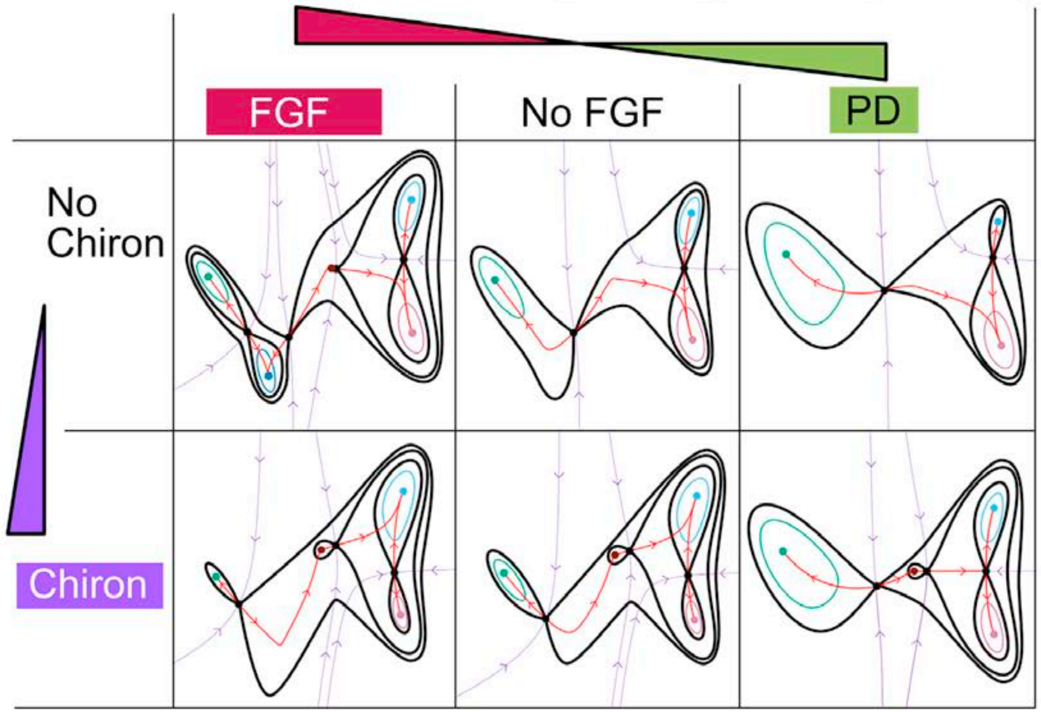


A. Howe and M. Mani. *Phys. Rev. X* 15, 031070 (2025)

Evolution of landscape geometry as a function of signals



Wnt signalling



M. Saez et al. E. Siggia, D. Rand and J. Briscoe, 2022, *Cell Systems* 12, 12–28

Geometric landscape and learning rule

Geometric landscape framework: $\mathrm{d}x/\mathrm{d}t = \partial V(x, \theta)/\partial x$

Learning algorithm in the egg:

- Potential with time evolving parametrisation: $V(x;\, \theta(t, u))$ that determines the dynamics. V is tuned by signals.
- Learning function (or update rule):
  $$\mathrm{d}\theta/\mathrm{d}t = F(\theta(t), x, u(t))$$

History of signals: $u(t)$

- Landscape parameters are learned as they depend on history of signals and memory.
- Internal memory: past signals permanently change the state of cells.

The genome encodes:

- A space of possible landscapes $V(x;\theta)$,
- And a rule F that says how θ should be updated given local signals and internal states.

Proposal:

- What is encoded in the egg is not simply a fixed programme of landscapes, but a learning rule for the landscape parameters.
- The learning rule says how chemical and mechanical signals update the effective landscape in development.
- The developmental history of signals, morphogens, mechanics, cell-cell contacts etc is the "training data set".
- The evolved rule F compresses environmental regularities (ie. signals in the embryo) into the landscape geometry.
- Development as learning the correct landscape for a particular environment and history, starting from a genetically specified prior.

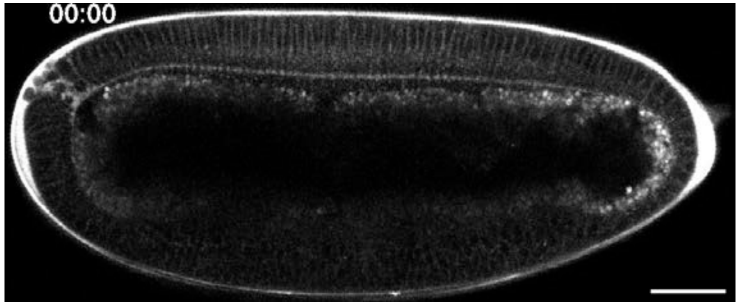
Learning during embryonic development

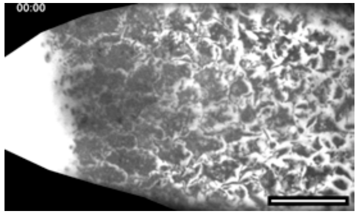
What is the environment? Internal or external.

- **The external environment of an embryonic cell is the internal environment of the embryo.**
- This environment is not constant: there are regularities and stochastic fluctuations.
- Cells tune the environment composition, volume.

- **Many local cell learners coupled to an environment they collectively generate**
- **The patterns of signals that a cell learns from are produced by the collective behaviour of the cells themselves.**

Protein diffusion in vitelline fluid

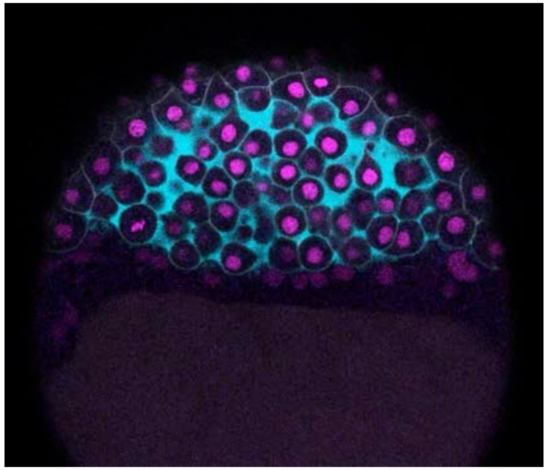




Secreted protein in vitelline fluid in *Drosophila* embryo

G. Mundhe et al, and T. Lecuit *bioRxiv* 2025.04.11.648359

Vitelline fluid in zebrafish embryo



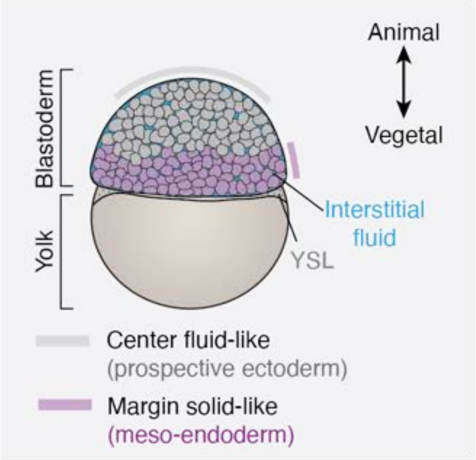
C. Autorino et al, and N. Petridou, *bioRxiv* 2025 https://doi.org/10.1101/2025.06.06.658228

Learning during embryonic development

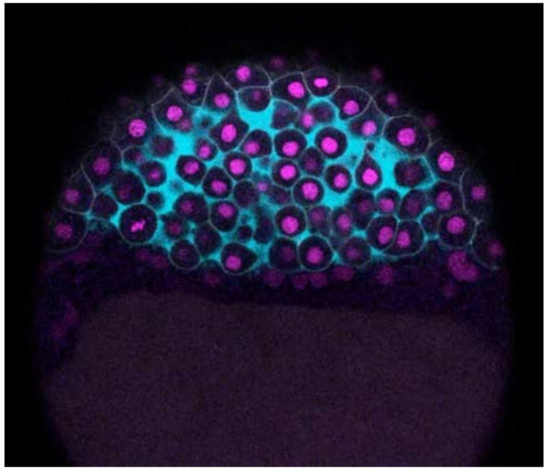
- The patterns of signals that a cell learns from are produced by the collective behaviour of the cells themselves.

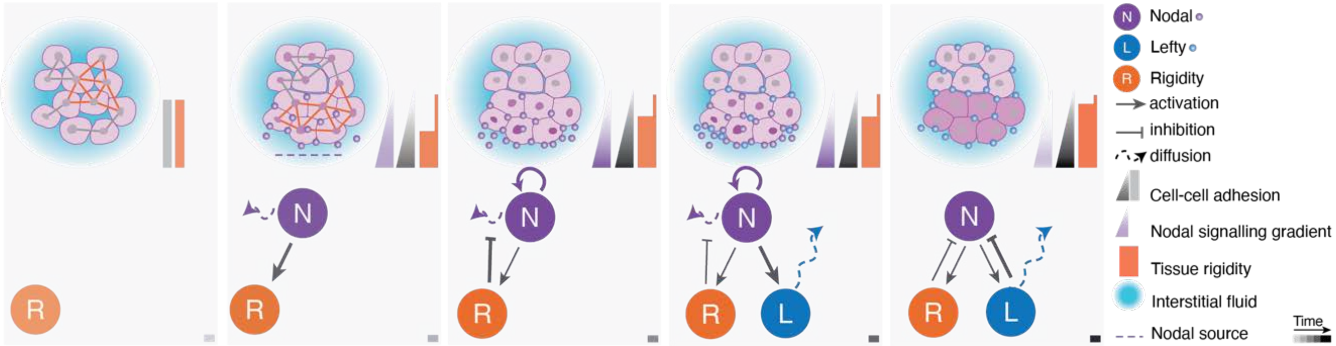
- tissue rigidity phase transition guides patterning by tuning the length-scales and time-scales of morphogen (Nodal) signalling.

- Co-regulation between the tissue material state and cell fate decisions.



Vitelline fluid in zebrafish embryo





C. Autorino et al, and N. Petridou, *biorxiv* 2025
https://doi.org/10.1101/2025.06.06.658228

Multi-agent learning in a self-generated environment

Ants and pheromone trails
- Each ant is an "agent".
- Environment = pheromone concentration on the ground.
- That environment is the result of ants' past actions (where they walked, how much they deposited).
- Each ant learns a foraging behaviour from this environment.

Cells and chemical gradients
- Each cell is an "agent".
- Environment = chemical concentration of signals, e.g. a morphogen
- The environment is the result of total cells past activities (production, diffusion, advection, sequestration etc)
- Each cell learns a new cell state from this environment

Internal mechanochemical environment $E(t)$:
Is the result of the past history of the embryo
- morphogen and signalling fields,
- local mechanical stresses and strains,
- ECM composition and topology,
- geometry of the tissue (cell neighbours, orientation, etc.).

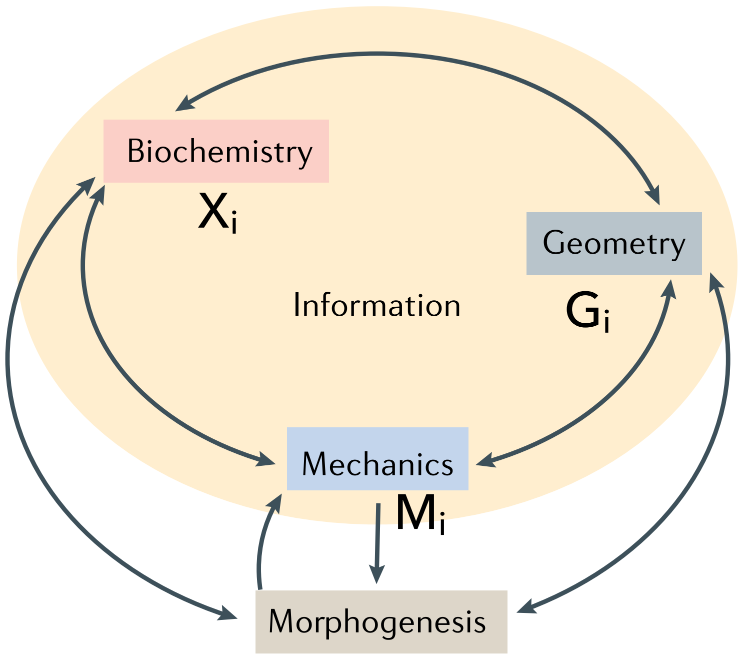
- Learning function (or update rule function):
  $\mathrm{d}\theta_i/\mathrm{d}t = F(\theta_i(t), x, E_i(t))$ where $E_i(t)$ is the local environment the cell i sees.

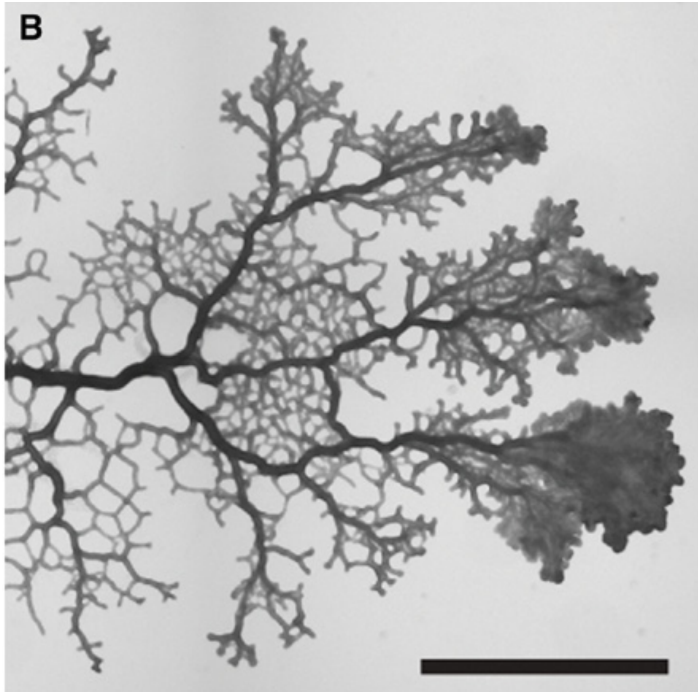
Learning during development

Conclusion

- Instead of saying that all the information for development is « already in the egg », we propose that the egg contains a learning algorithm for the epigenetic landscape.
- As cells experience sequences of chemical and mechanical signals, these signals do not just drive them down a fixed landscape, they re-shape the landscape itself.
- The evolving landscape encodes a memory of developmental history and environmental context.
- In that precise sense, development is a form of learning.

Case study: Structural and mechanical learning: *Physarum*



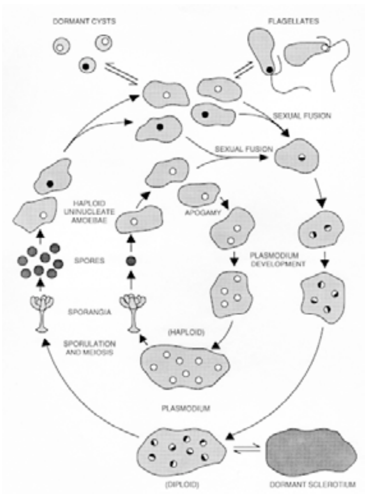


Alim K. *Phil. Trans. R. Soc.* B 373: 20170112. (2018)

Structural and mechanical learning: *Physarum*

Physarum polycephalum: an acellular self-organised optimal transport system

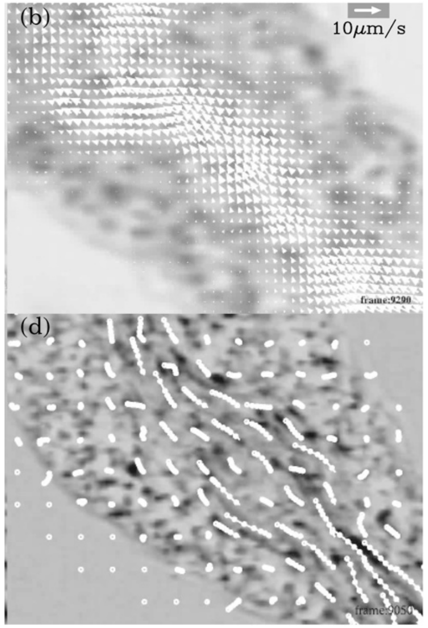
- A plasmodial myxomycete (Protist, Amoebozoa)
- Contains 1000s to millions of nuclei in a syncytium called plasmodium
- **Grows and migrates towards food source**
- Self-organizes a hydrodynamic network to distribute food to the entire cell/organism and promote its growth

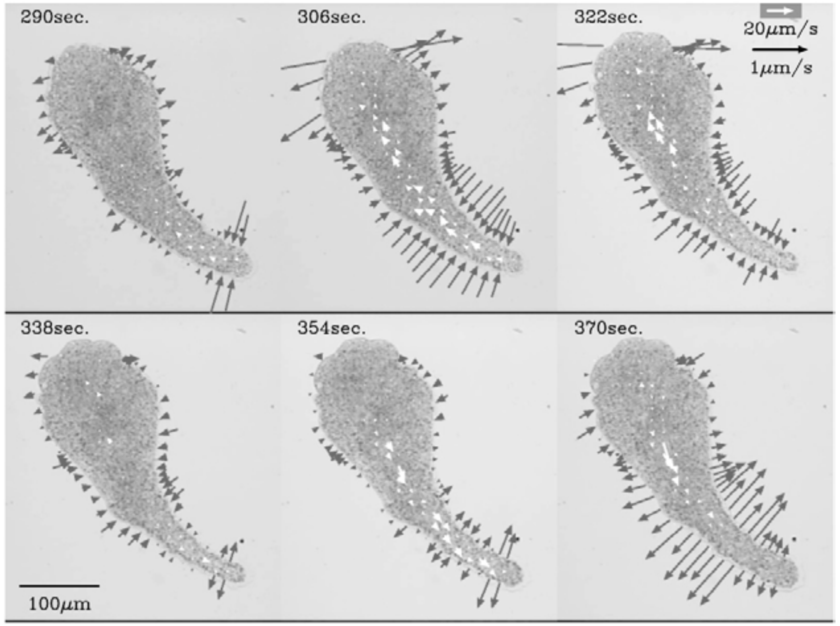


Peristaltic contraction and internal fluid flow

- Motility of small fragments plasmodia

- Particle imaging velocimetry of cytosolic structures: cytosolic flow.
- **Cytosolic flow** towards the anterior or posterior.
- **Peristaltic wave** of contraction from Posterior to Anterior: cortical contraction + shape change (width and thickness variation).





Matsumoto et al *Biophysical Journal* 94:2492–2504 (2008)

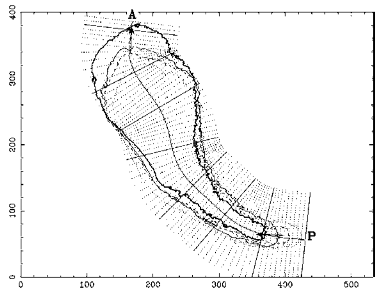
Peristaltic contraction, internal fluid flow and motility

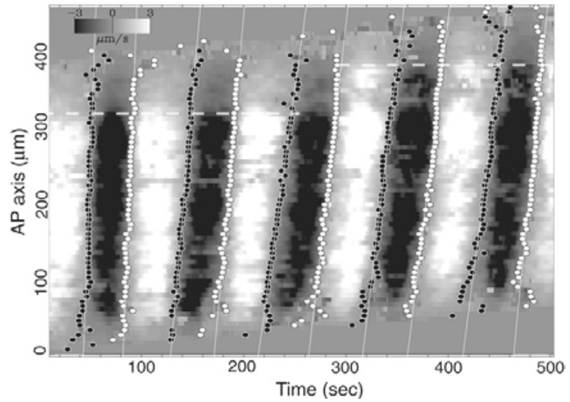
- Motility of small fragments plasmodia

period of ~100 s

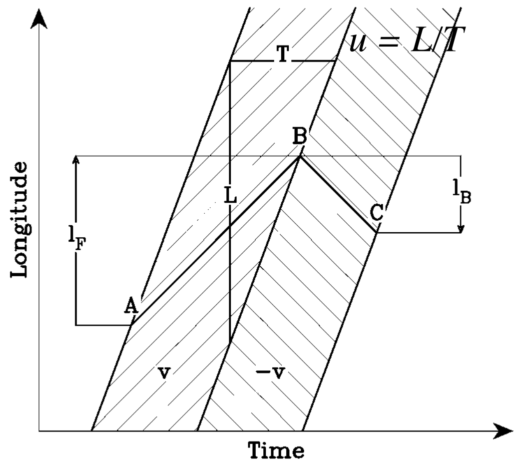
- **Shifting velocity field**

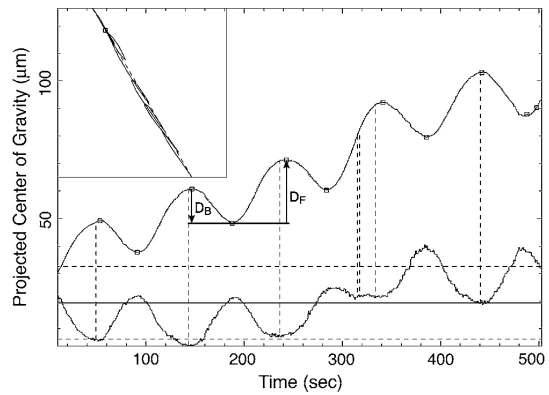
- The forward flows are represented by the lighter shade, and the backward flows are represented by the darker shade.
- Each straight line defines a velocity with which the vector field moves from the posterior to the anterior part of the plasmodium.





- Forward peristaltic movement (velocity u) = a traveling wave of cortical contraction + shape change (width and thickness variation)
- Flow at velocity $+v$ or $-v$.
- The peristaltic wave advects the flow velocity
- This creates an intrinsic asymmetry in the flow and cell center during motility.

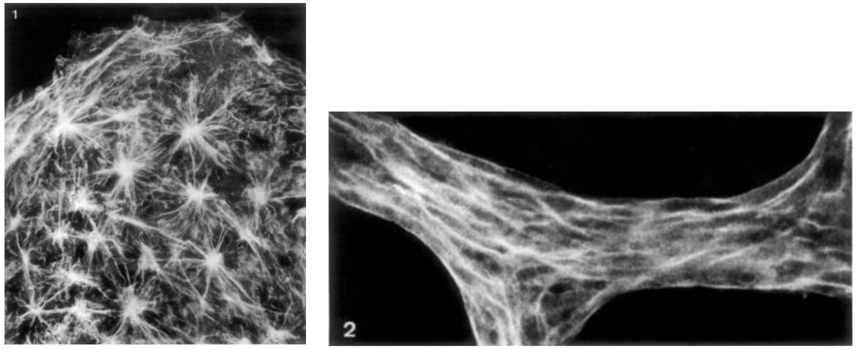




Matsumoto et al *Biophysical Journal* 94:2492–2504 (2008)

Origin and evidence of contraction

- Presence of a contractile actin cortex.

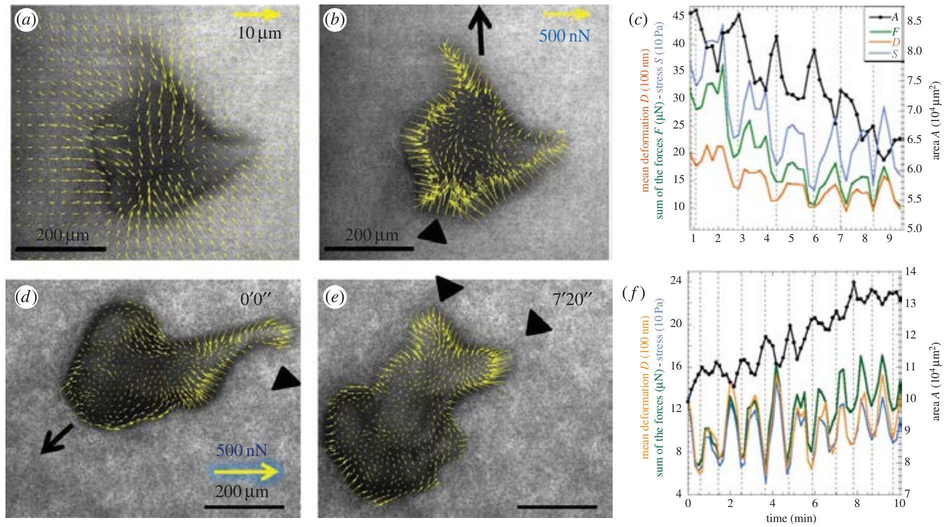


Naib-Majani W, et al Wohlfarth-Bottermann KE. *Cell Biol. Int.* 7, 637 – 640 (1983)

- Periodic contraction and traction in micro plasmodia (fragments)
- Motility when there is an asymmetry in traction force pattern

Substrate deformation field

Traction force field

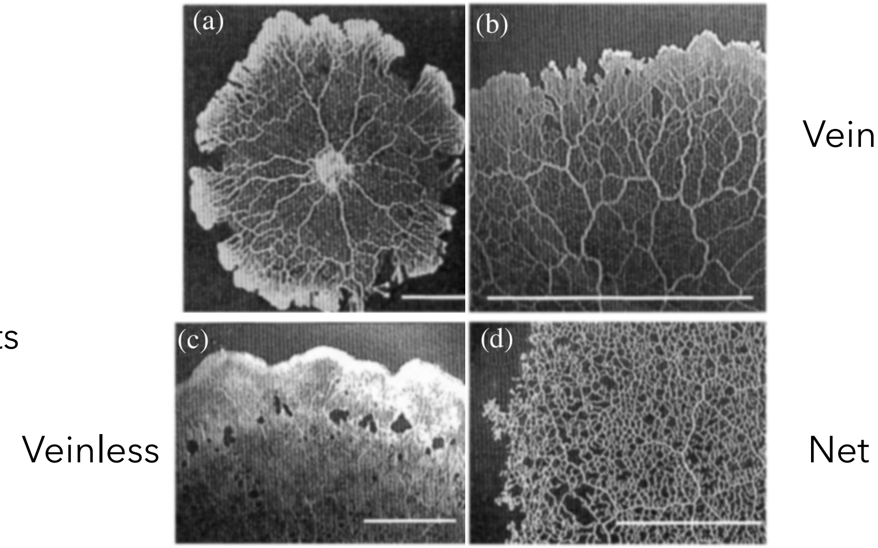


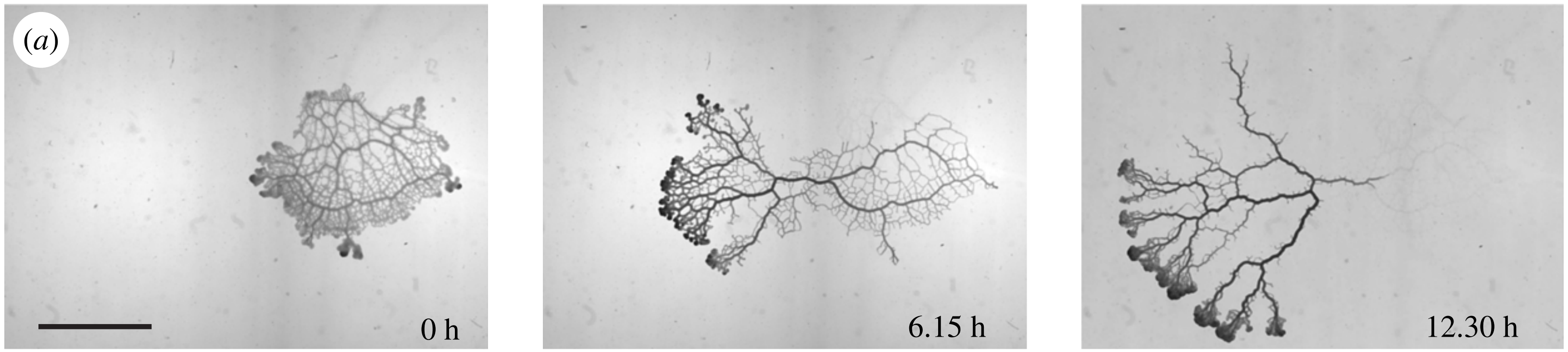
Rieu J-P, et al. Nakagaki T. J. R. Soc. Interface 12: 20150099 (2015)

Plasmodium architectures are flexible and tuned by the environment

- Different structures form in isotropic plasmodia (absence of food):
  Vein, veinless and net structures

- In presence of food the network reorients in the direction of the food source.
- The network becomes anisotropic.

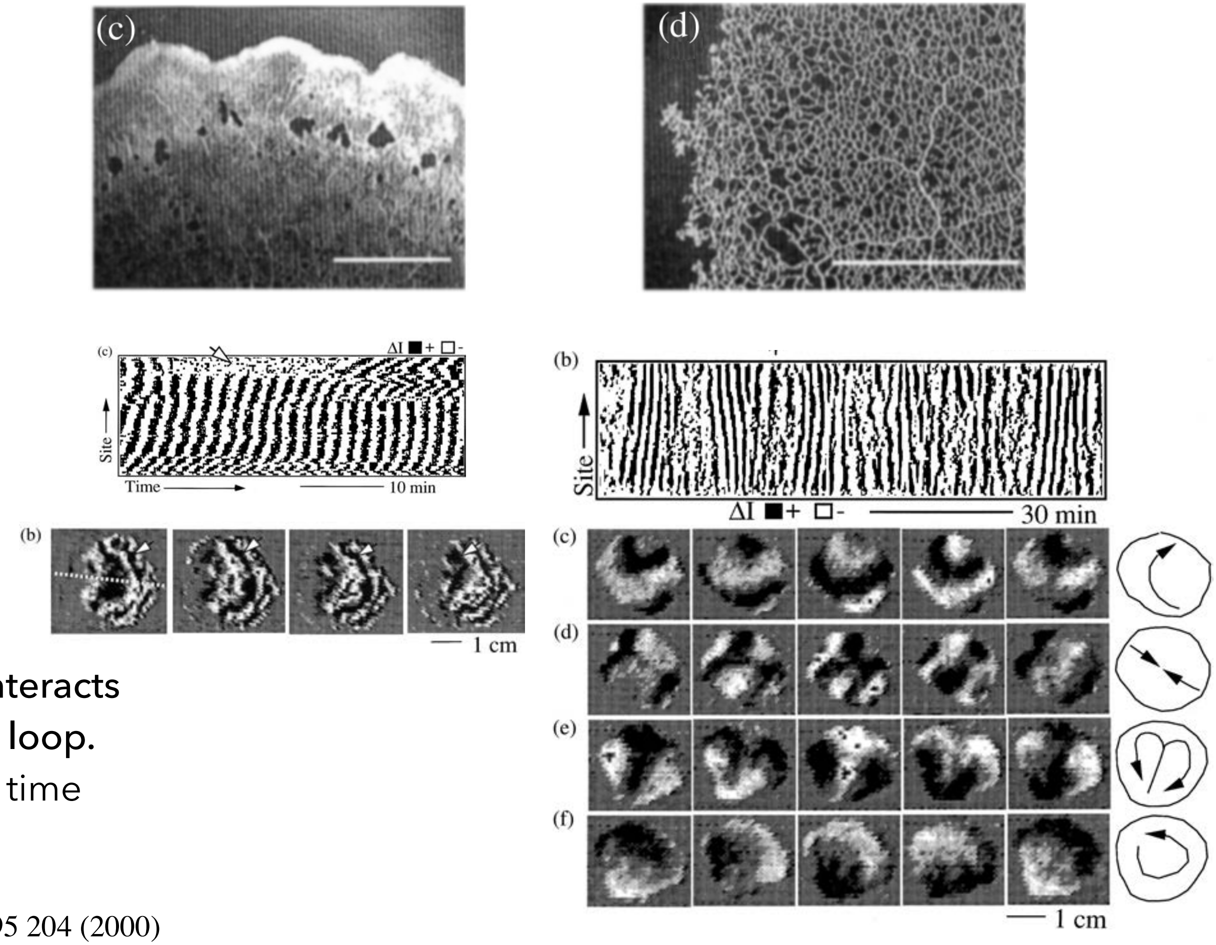




Network architecture and contraction patterns

- Contraction patterns are characterised by measuring the time difference in brightness of transilluminated plasmodia: contracting tubes are narrower and thicker and transmit less light.

- **Contraction patterns are different in plasmodia with different architectures:** veinless and vein-net structures.
- **Change in contraction patterns induced by temperature affects network architecture.**

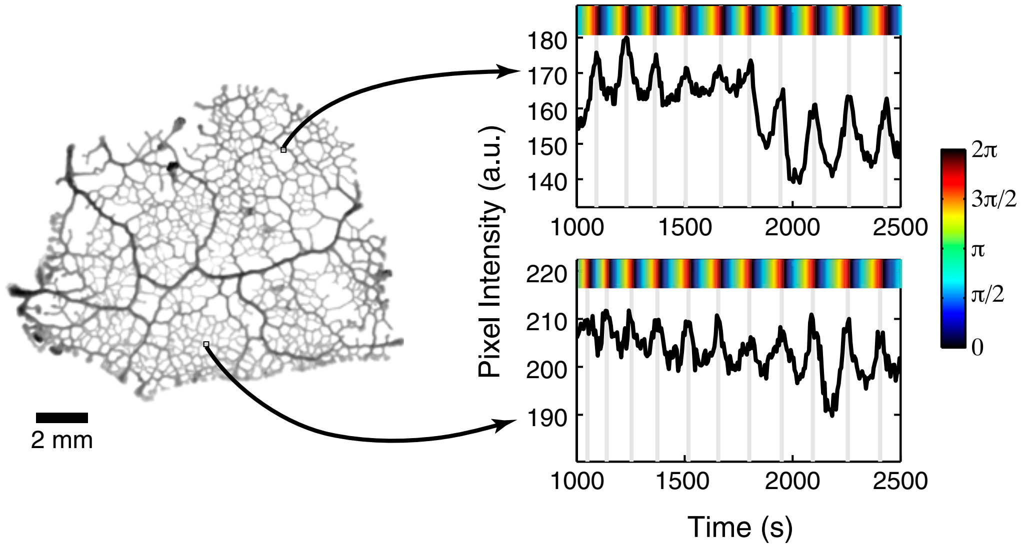


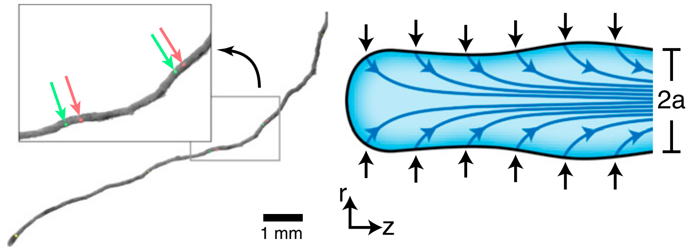
Hypothesis: The vein organization of the cell interacts with the contractile activity to form a feedback loop.
Note: morphological changes occur on longer time scale (45 min) than flow (100s).

T. Nakagaki et al. *Biophysical Chemistry* 84:195 204 (2000)

Fluid flow in a random network in *Physarum*

- Cross-sectional contractions of tubes drive fluid flows
- Observations:
  - contraction oscillations (transmitted light), frequency and amplitudes.
  - Phase (color coded)
- **Model:** solve equation of incompressible fluid flow in a tube, using measurement of time variation of tube radius.
- Results of simulated flow in a closed tube agree with experiments.

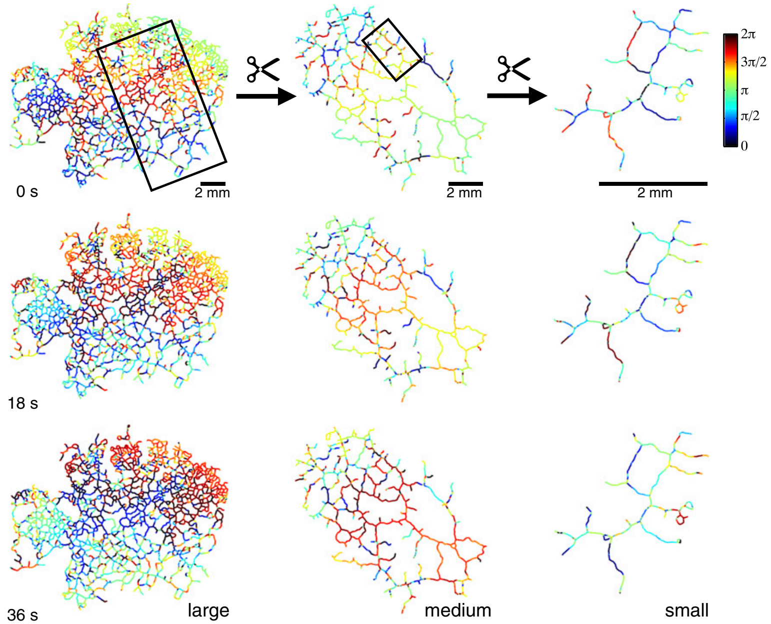




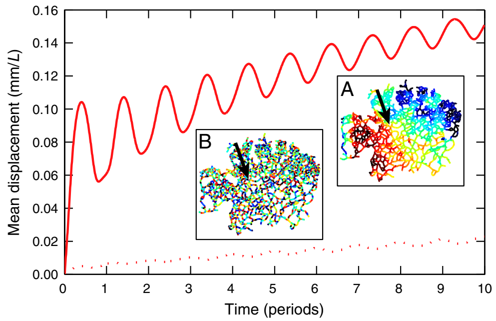
Alim K, et al., Brenner MP, Pringle A. *Proc. Natl Acad. Sci. USA* 110, 13306-13311 (2013)

Optimal transport in a random *Physarum*

- **Phase patterns in plasmodia:**
- At any single point in the network, the phase increases linearly over time
- The spatial phase gradient between adjacent points along a tube stays constant.
- **The spatial phase gradient is linear across organisms**
- **The maximal phase gradient equals a cycle 0-2π** irrespective of organism size.



- Networks optimized for minimal local phase difference, given constraint of mass conservation, maximize particle transport.
- **The movement of signals is optimized when the wavelength of the peristaltic wave is of the order of the size of the network.**

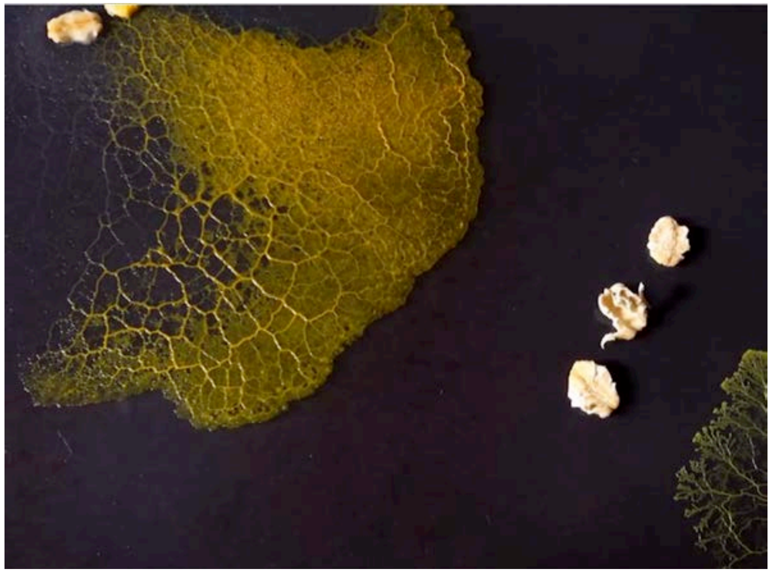


Numerically calculated mean displacement of tracer particles within the large real *P. polycephalum* network architecture with optimised and random phase patterns.

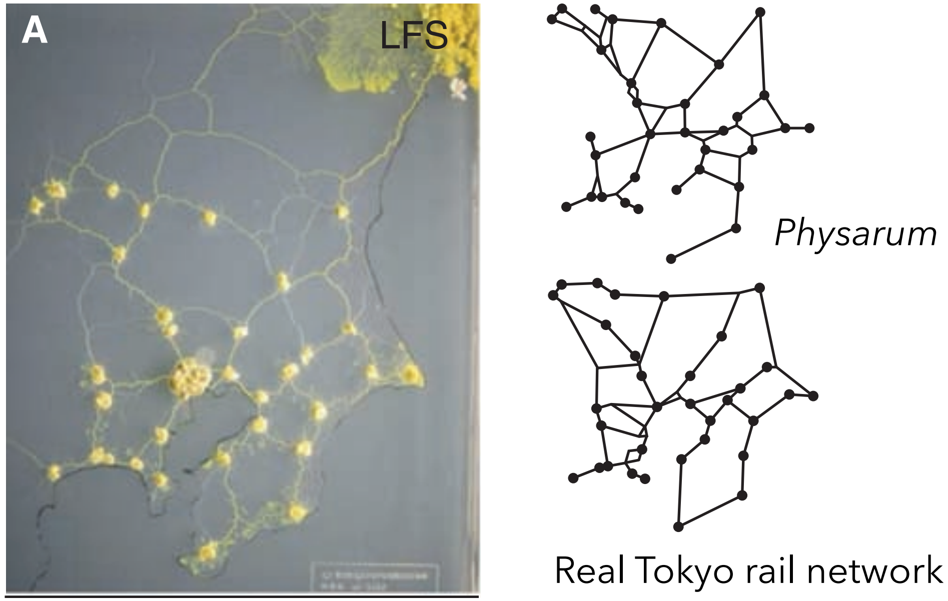
Alim K, et al., Brenner MP, Pringle A. *Proc. Natl Acad. Sci. USA* 110, 13306-13311 (2013)

How does *Physarum* tunes its architecture in response to food signals?

- Food increases the contraction frequency
- Repellants decrease the contraction frequency
- Contraction affects network architecture
- **What is the underlying mechanism?**



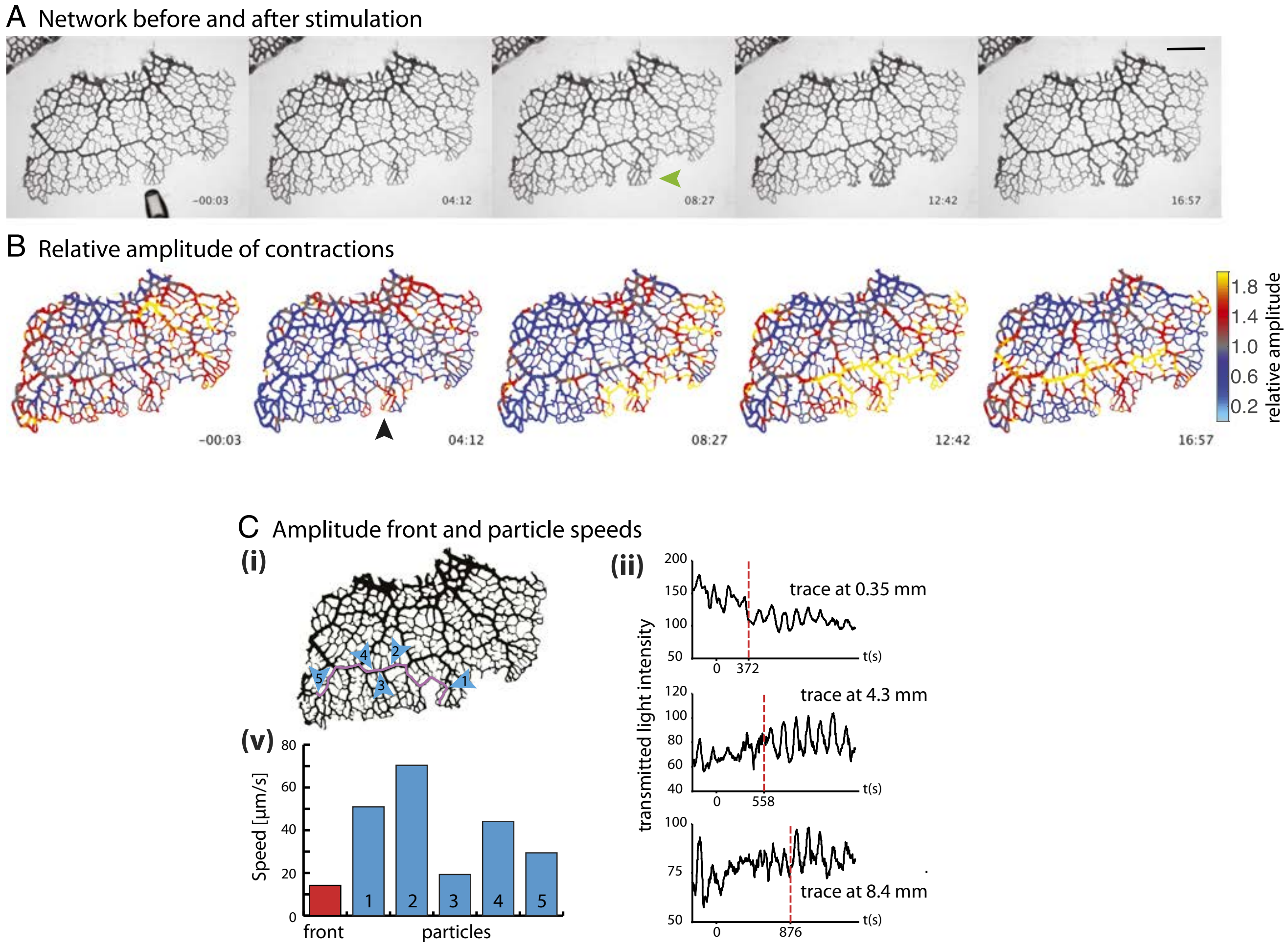
- ***Physarum* can compute the shortest path connecting food sources**
- Emergent property of self-organised network
- **What are the feedback self-tuning mechanisms?**



Shape adaptation in response to environment

- Local stimulation is followed by a wave of contraction in the network
- The speed of contraction wave ($13\mu m/s$) is 2-3 times lower than the maximum flow speed.
- In same order as transport velocity within the cytoplasm

- Suggests a mechanism coupling signal inducing contraction and flow

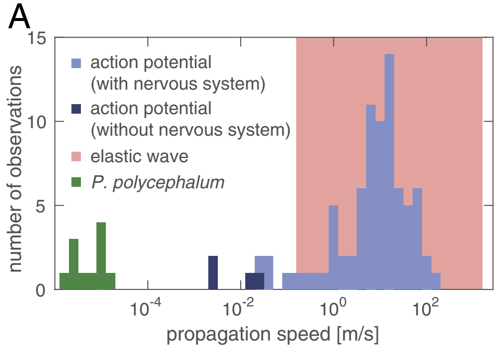


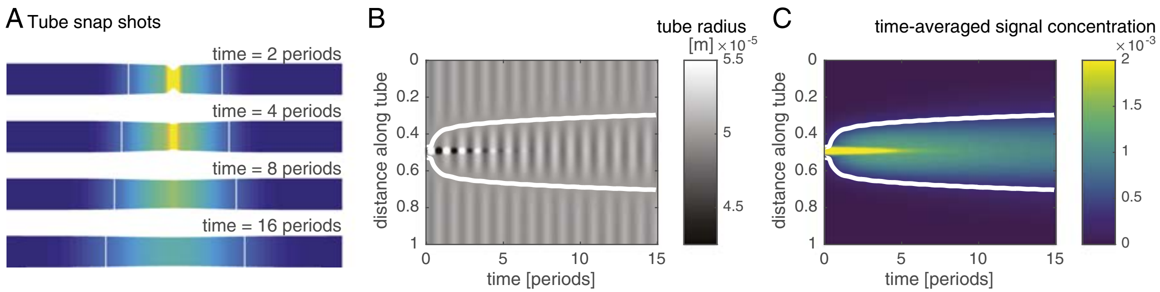
Shape adaptation in response to environment

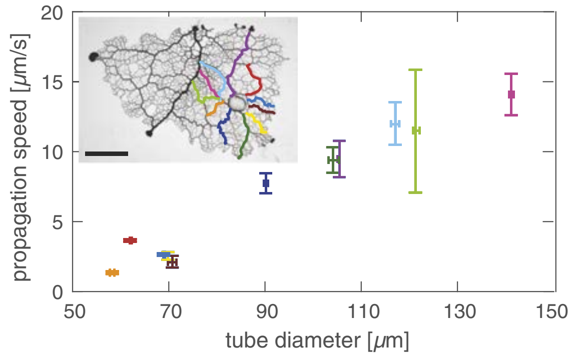
- **A chemical signal advected with the flow is a likely mechanism for coupling contractility and cytoplasmic flow**

- **Model:**
  - Principle: basic feedback mechanism: An initial stimulus triggers release of a signaling molecule and the molecule changes local wall contractions, increasing local fluid flow. Greater flow increases the dispersion of the signaling molecule away from its source, and the molecule continues to trigger wall contractions downstream.
  - **The dynamics give rise to a self-propagating front of increased contraction amplitude** (Taylor dispersion)

  - **Predictions:**
    1) similar kinematics of contractility wave front and signal propagation;
    2) the propagation speed increases with tube diameter, consistent with observations.





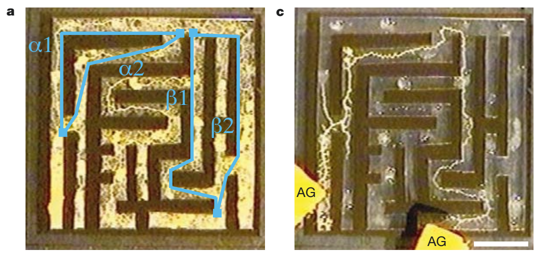


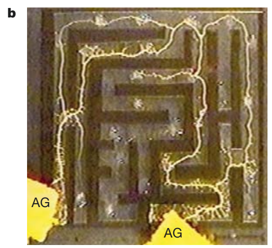
Shortest path selection by *Physarum*

- Increases in contraction amplitude will increase the flow rate in a route proportional to the average amplitude increase along the entire route.
- The region of high contraction amplitude has a fixed length scale.
- In shorter routes, this length scale is a bigger fraction of the route so the average contraction amplitude is higher than on a longer route where the contraction amplitude is « diluted ».
- Therefore, longer routes will experience a smaller increase in flow rate compared with shorter ones.
- Explains why shorter paths are selected in the growth of *Physarum*

Maze-solving by an amoeboid organism

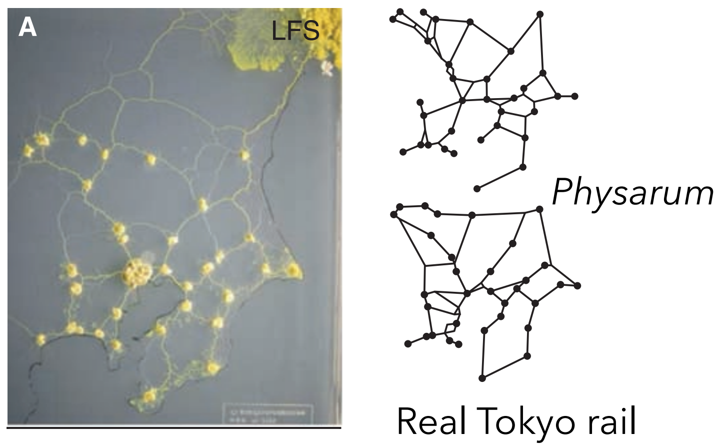
Physarum has the ability to find the minimum-length solution between two points in a labyrinth.





d

	None	β1	β2	β1, β2
None	2	0	0	0
α1	0	0	0	0
α2	0	5	6	3
α1, α2	0	0	0	3

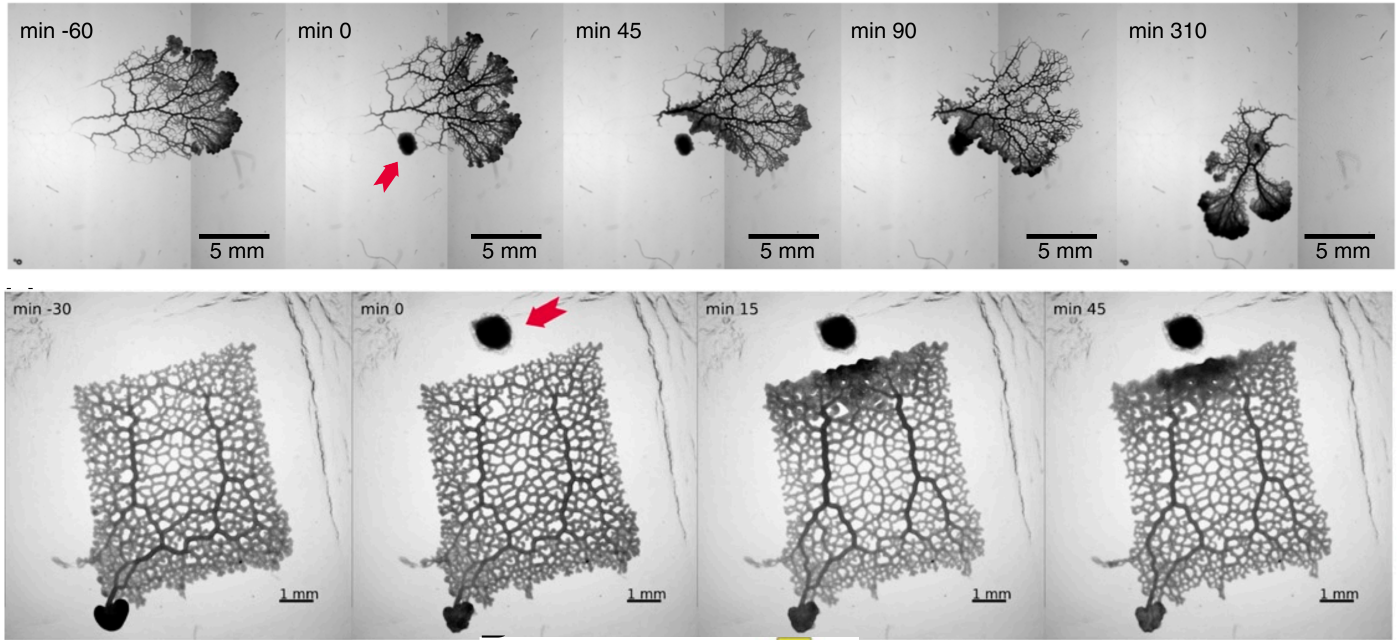


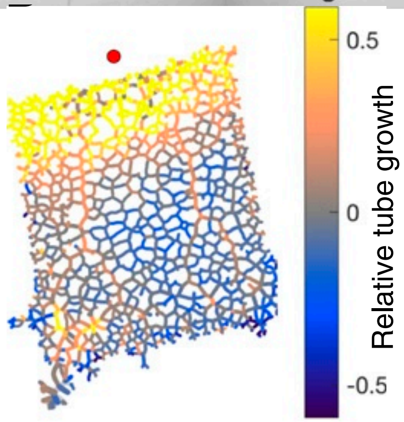
T. Nakagaki, H. Yamada, Á. Tóth, *Nature* 407, 470 (2000).

Tero A, et al. *Science* 327:439–442 (2010)

Structural memory and learning in *Physarum*

- In the presence of an external source of food, *Physarum* reorganises within 10 min the diameter of internal tubes.
- **In the vicinity of the food source, the diameter of tubes expands, while they shrink at a distance** (due to constant volume: mass redistribution).
- **Nutrient location is imprinted in the network hierarchy by thick tubes formed around the nutrient source.**
- This effect persists 10s of minutes after the food has been consumed by *Physarum*.
- **This shows a structural/geometrical memory in its organisation.**





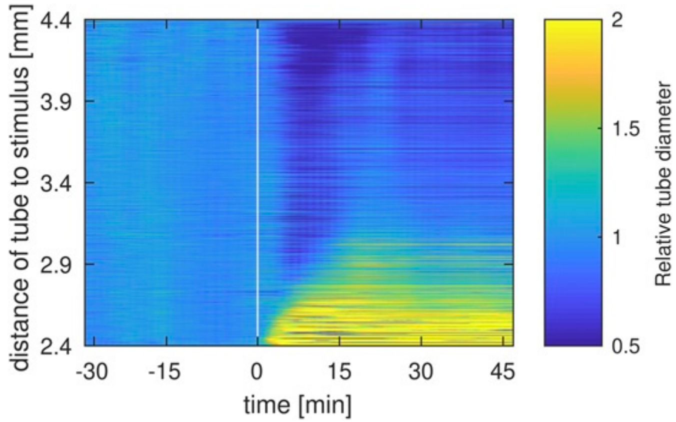
M. Kramar and K. Alim *PNAS* 118, 10 e2007815118 (2021)

Structural memory and learning in *Physarum*

- Tube dilation propagates by flow transport velocity from the food source (stimulus) at $v = 15\mu\mathrm{m/s}$

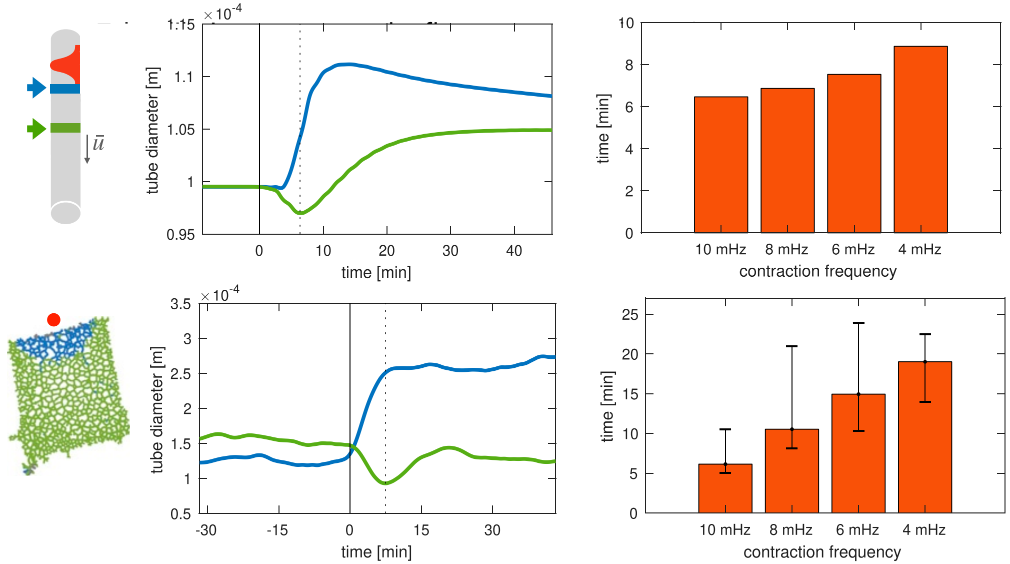
- **Hypothesis:** a tube dilation molecule triggered by the stimulus propagates by advection in the flow emerging from the peristaltic wave.

- **Model and Expts:**
  - Theoretical model of elastic tube dilation triggered by flow-transported softening agent.
  - The tube dilates in the vicinity of the source, but less so at a distance.
  - **The response time (the time from stimulus to minimum of tube diameter at a distance) increases as the frequency of contraction decreases.**



Model

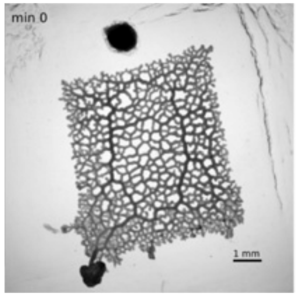
Data

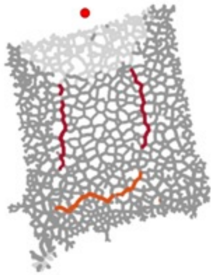


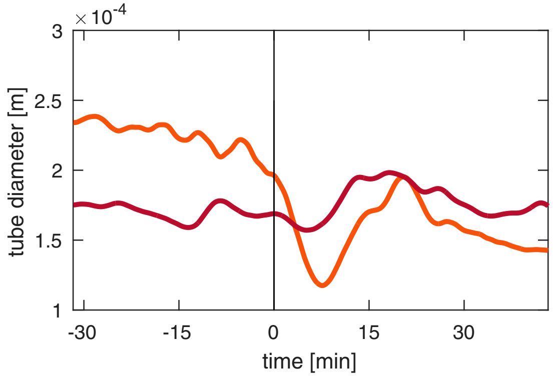
M. Kramar and K. Alim *PNAS* 118, 10 e2007815118 (2021)

Structural memory and learning in *Physarum*

- Stable internal representation (tube hierarchy) as memory
- Improved performance associated with structural memory



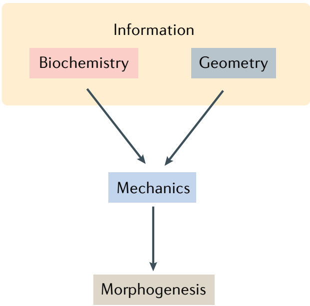




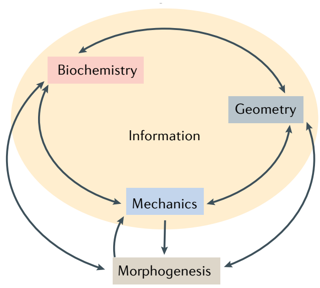
- Thick tubes starting close to the stimulus (red) hardly undergo a decrease in the diameter next to thin tubes that strongly shrink in a shrinking domain.
- But thick tubes at a distance shrink because they do not receive softening agents by flow.
- Tube diameter hierarchy does impact stimulus response.
- **Having thick tubes as memories of previous stimuli positioned close to the stimulus allows the new stimuli to spread more quickly and reorganize mass transport more efficiently.**

M. Kramar and K. Alim *PNAS* 118, 10 e2007815118 (2021)

Self-learning and self-organisation



- Programme: Initial conditions and execution of a deterministic programme
  - Inheritance of specific conditions and of algorithms in the genome
- Self-organisation: internal algorithm that characterises interaction rules
  - The algorithm is distributed in the whole cell: genome plus cell.
  - The algorithm is not static (in the genome).
  - The algorithm changes in time: it learns some parameters.



- Where does the update come from? From environment of cells.
- The environment is updated as a function of development itself

Tuning, Adaptation and Learning

- *Pre-conditionned and determined* state:
  - Heredity of genome, chemistry, structures, cellular algorithmic processes.
  - Dynamics of cells and embryos follows a rule-based sequence of steps in a set order.

- *Propensity to respond to environment and reset* state:
  - Interaction with the environment, update and tuning of internal state variables.
  - *Tuning:* internal variables are updated
  - *Adaptation:* return to initial configuration following perturbation and deviation
  - *Learning:* update with memory (of varying time scale), as internal representation of environment (training data set), to *increase* performance or *acquire* new state.

- General properties of living system, from cells to embryos and organisms. The nervous system is an advanced version of these universal properties.

Overview of past 2 years on Information

1. Transmission: Encoding, Recoding and Decoding
    - Shannon information theory: mutual information
    - Chemical, mechanical information

2. Logic of biological computation:
    - Levels of analysis: computation; algorithmic; implementation
    - Algorithmic information and complexity

3. Self-tuning and self-learning
    - Internal, low dimensional representation and memory
    - Update rules and Learning rules: learning algorithms
    - Self-organisation reflects such properties