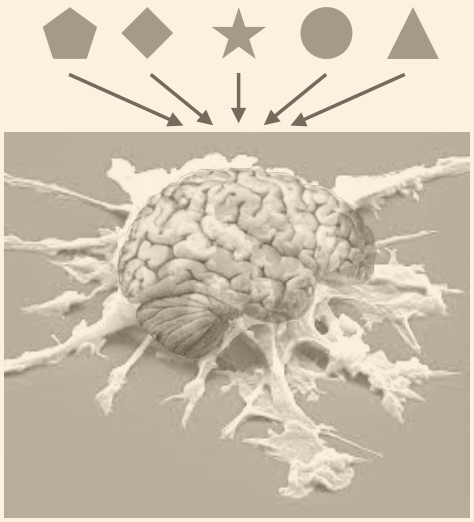
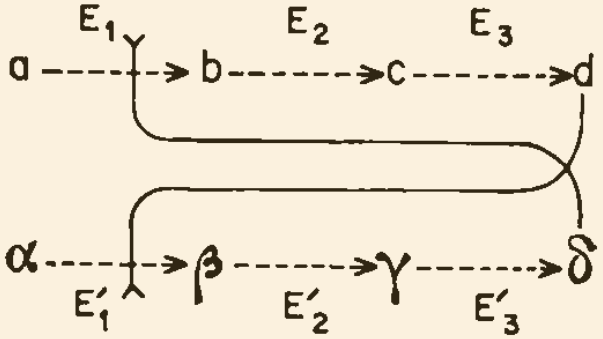
What is biological information?





Course 6: Cellular memory and learning

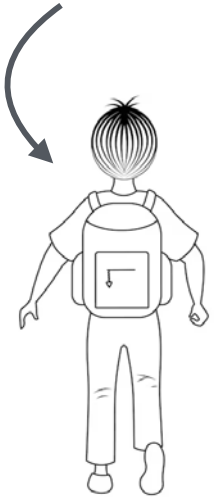
Thomas Lecuit

chaire: Dynamiques du vivant

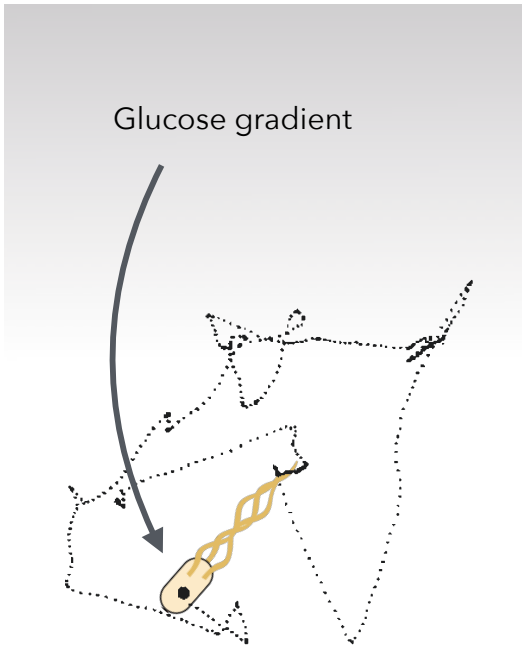
COLLÈGE DE FRANCE
1530

Learning and Memory

- *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*: sensing and decoding *external* information with memory
- *Memory*: transient or long term storage or representation of external information

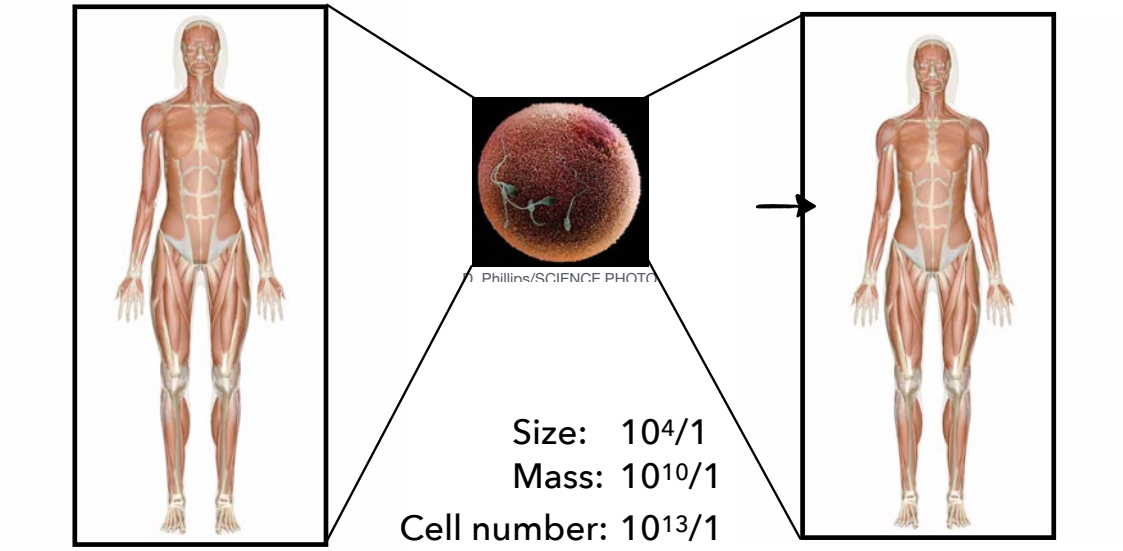


- **Sensory systems:** Bacteria chemotaxis, photon detection, acoustic pressure etc
- **Nervous sytem:** Internal representations of past experience
- **Immune system:** adaptive immunity, memory B cells

- **Evolution:** internalisation 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 .

Does increased complexity require new information?

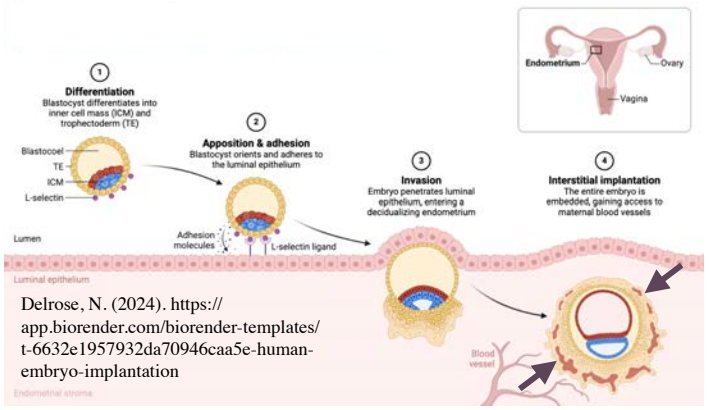
- **The complexity of an adult is seemingly compressed/represented** in a single cell
- Consider information as the set of instructions required for this process
- *Questions*:
  - does the egg contain all the information needed to rebuild a new organism?
  - does the increasing complexity during development require new information?



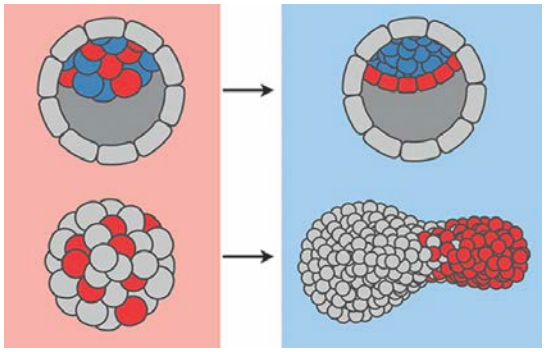
Does increased complexity require new information?

- **The information inside an embryo is usually closed,** though in mammals, via implantation, the embryo receives information from the uterus.

- **At the cellular scale information flows in various channels and is constantly decoded and recoded** (eg. positional information, signalling information, assessed via mutual information).
- **As a result, cells change state: chemical state, mechanical state, geometry.**
- Cells are wired to decode and recode information in a noisy environment, and amplify small differences/fluctuations in the environment of stem cell aggregates in vivo or in vitro.



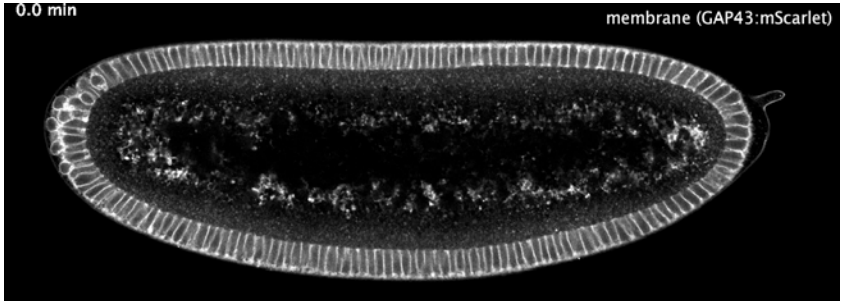
Delrose, N. (2024). https://app.biorender.com/biorender-templates/t-6632e1957932da70946caa5e-human-embryo-implantation



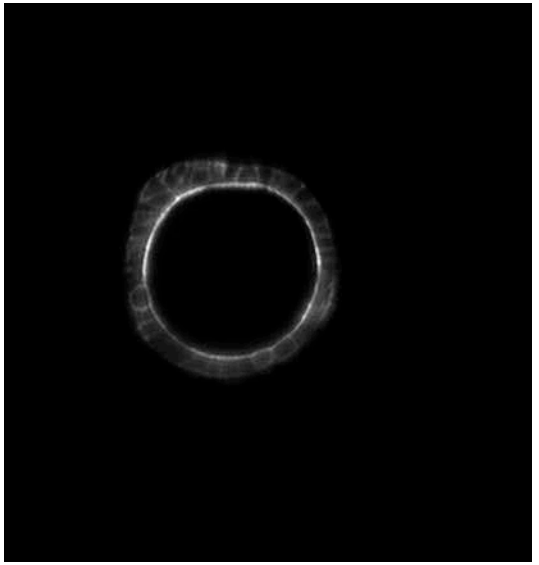
- Although the genome doesn't change, cells express new states that constitute a new set of information to be decoded within the cell and by neighbouring cells.
- As a result, a cell receives *new* information (albeit not strictly Shannon information) during development.

Learning information during development

- During development, cells learn from their neighbours, and keep a memory of these training signals.
- Fundamental property of living systems: ***Learnability***



Gehrels EW, Chakrabortty B, et al. *PNAS*. 120(6):e2214205120 (2023)



Q. Yang et al, E. Hannezo and P. Liberali, *Nature Cell Biol*. 23, 733-744 (2021)

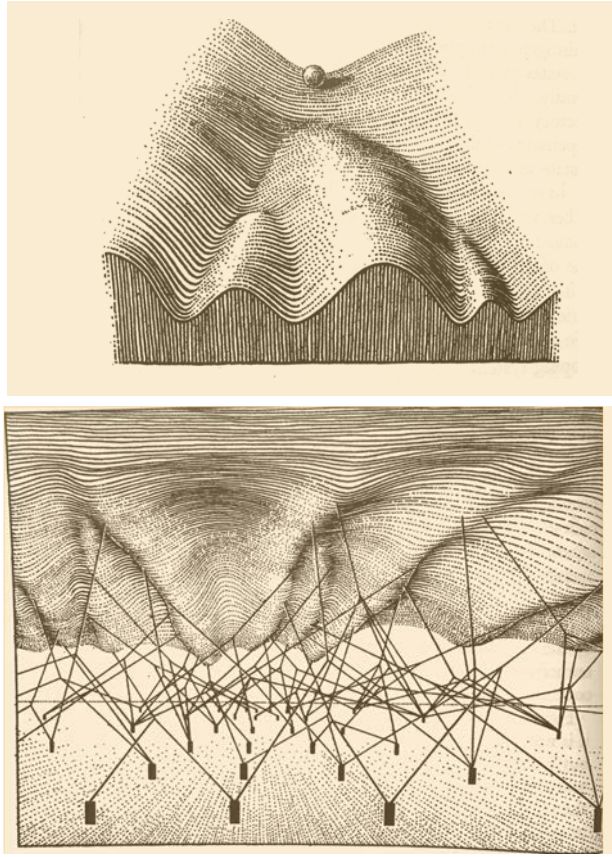
A dynamic multidimensional *information landscape*

- Encoding of diverse and specific cellular responses by chemical, mechanical and geometrical information.
  - This information controls: **cellular states** (stem, differentiation etc), **cellular shapes and dynamics,** and **cellular physiology** (behaviour).

- Cells receive and decode information, they also encode and release information to neighbouring cells.

- Cells thereby follow complex dynamics in the high dimensional space of information they encode collectively and decode individually.
- Thereby they contribute to the **building of a high dimensional space of information that will influence other cells.**

- View Waddington landscape as a multidimensional encoding of information that affects cell behaviours

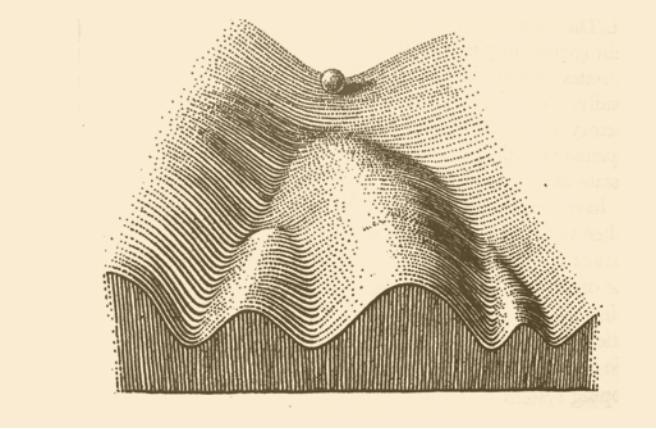


An dynamic multidimensional information landscape

- **The information landscape is not static but dynamic.** Cells are active agents that modify the landscape and their response to the landscape.

- Cells can modify their response to a given landscape (the cell is not passively following a landscape, but actively changing its course). The potential that forms the landscape is tuned by cells as they encode and decode information.

- How to encode the future of a cell (eg. Its path towards a particular fate, position and function)?
  - Initial conditions and systems properties
  - External cues along the path to orient the cells along the correct paths (continued guidance)
  - **Alternative strategy: Learning cell trajectories. Cells are exposed to transient cues in time and space and can memorise such signals.**
  - **Memory can be viewed as a relatively stable or irreversible change in landscape following a transient signal.**



Plan

- Molecular learning and memory
- Signalling learning and memory
- Cellular learning and memory
- Structural learning and memory

Molecular memories

- Genome: permanent memory on the time scale of an organism. So there is a need for mechanisms to tune this memory, to escape from the « permanent » memory of the genome: gene regulation, and post-translational modifications are mechanisms to impart tunable memory states in chemical networks and cells.

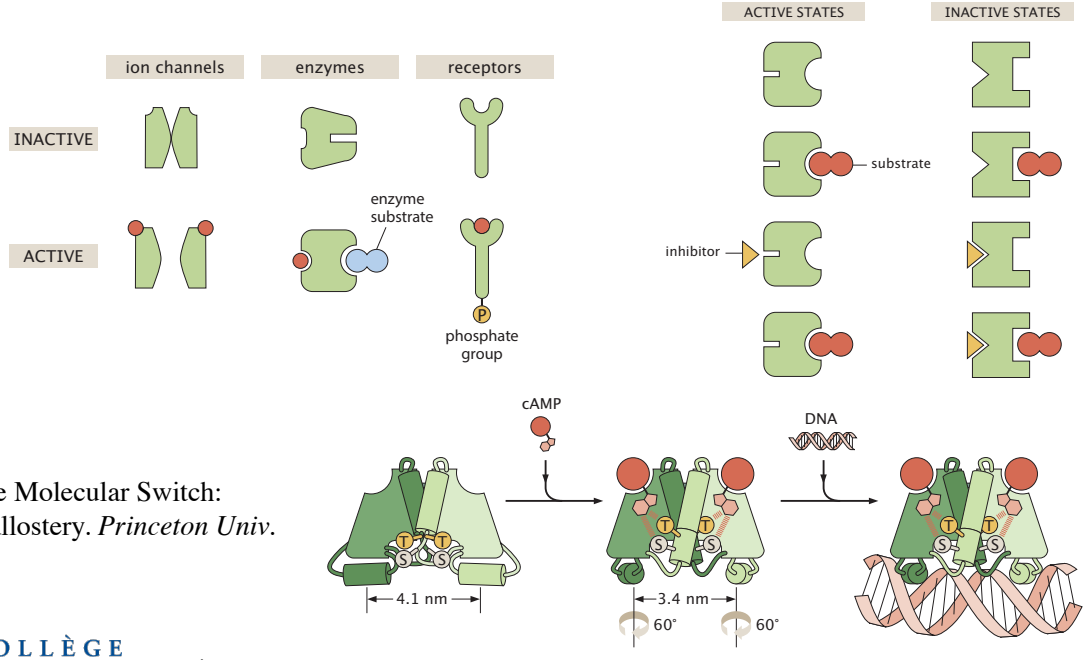
- Molecular signals stimulate a response.
  Question: how to maintain a response after disappearance of the input signal?
  how to keep the memory of input signal?
  How to tune the time scale of this memory?

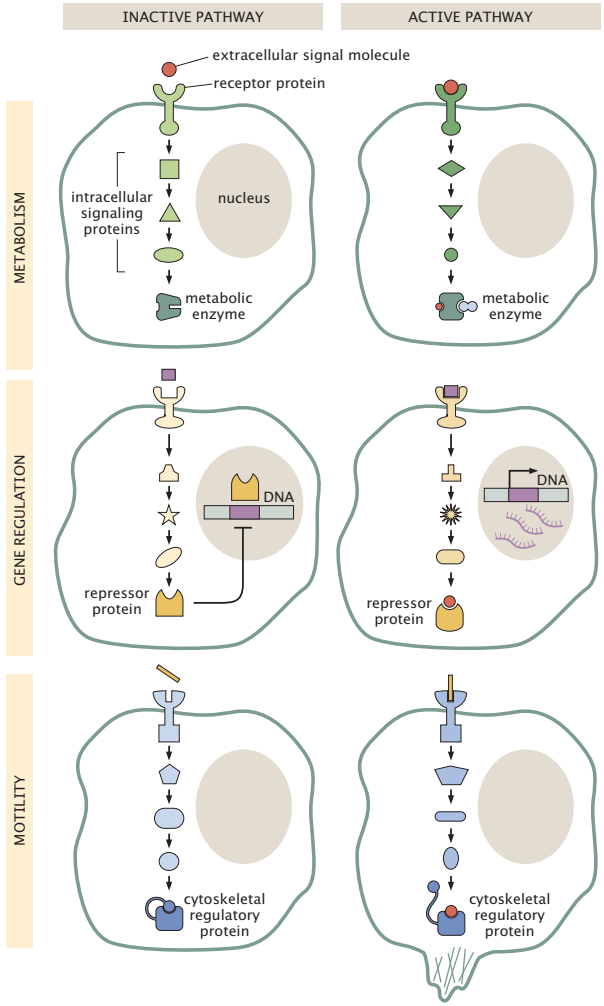
  - At single molecular scale: allosteric transition, post translation modifications.
  - Molecular complexes
  - Molecular networks and signalling.

Molecular memory

Molecular cycles: molecular switch or allosteric transition

- Signalling pathways may be in an active or inactive state.
- This rests on protein that exist in 2 conformations, an active or inactive.
- Binding of an effector and/or inducer favoured in the active state (eg. open).
- Enzyme: The binding affinities for both inhibitor and substrate are different in the two states, with the binding of the inhibitor favoured in the inactive state.



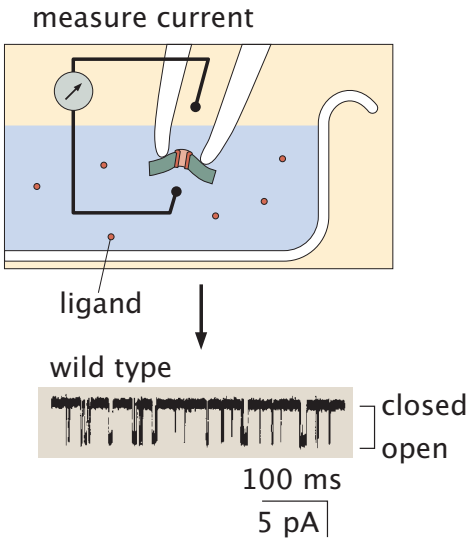


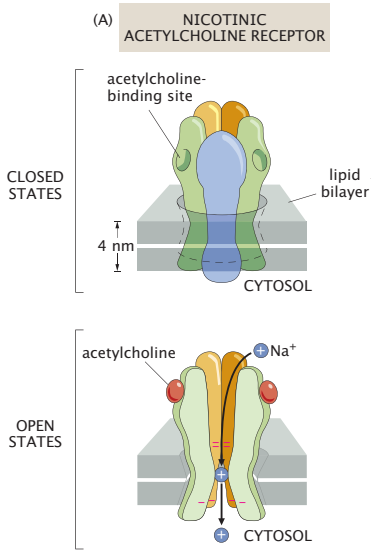
R. Phillips, The Molecular Switch: signaling and allostery. *Princeton Univ. Press*. 2020

Molecular memory

Molecular cycles: molecular switch or allosteric transition

- Time scale of transition: micro to millisecond..
- Stability of new state following allosteric transition: 2-4 orders of magnitude longer.
- Ex 1: Acetylcholine receptor: a ligand gated Na^+ channel.





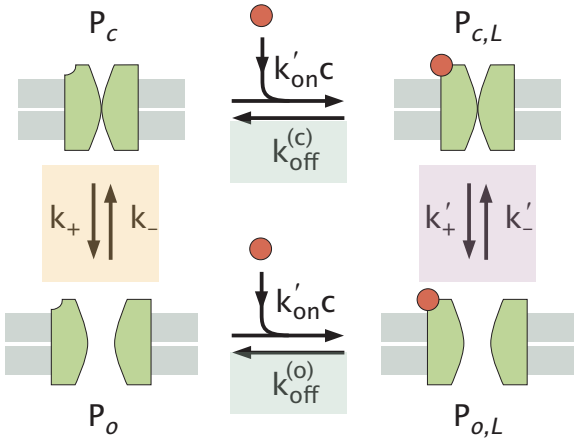


Table 3.1 Model rate constants used in examining the dynamics of the single-site MWC ion channel.

Rate constant	s^{-1}
k_{on}	10^4
$k_{off}^{(o)}$	10^{-1}
$k_{off}^{(c)}$	10^5
k_+	10^2
k_-	10^4
k'_+	10^6
k'_-	10^2

R. Phillips, The Molecular Switch: signaling and allostery. *Princeton Univ. Press*. 2020

Molecular memory

Post-translation modifications: Reversible covalent protein modifications
GTP cycle, phosphorylation cycle, methylation cycle etc

*« **Post-translational modification (PTM) is nature's escape from genetic imprisonment.** Gene sequences change on an evolutionary time scale but not on one appropriate for organismal development, adult physiology and the continual battle against disease and disintegration. »*

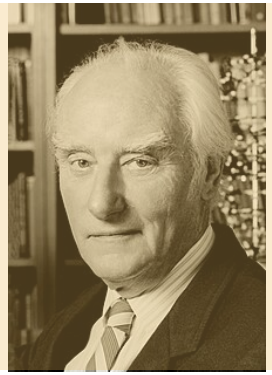
Jeremy Gunawardena

Molecular memory

Memory and molecular turnover

from Francis Crick

NATURE VOL. 312 8 NOVEMBER 1984



Francis Crick

- How is memory stored in the brain so that its trace is relatively immune to protein turnover?
- All proteins turnover in hours or days.
- Memory could be encoded in alterations to particular sequences of DNA: in cells (akin to immune cells) or locally at synapses.
- Or RNAs: alternative promoter choice (eg. Protocadherins, 60 variable exons), or alternative splicing. RNAs tend to be short lived
- Memory could be encoded in very stable proteins (ex. Prions)

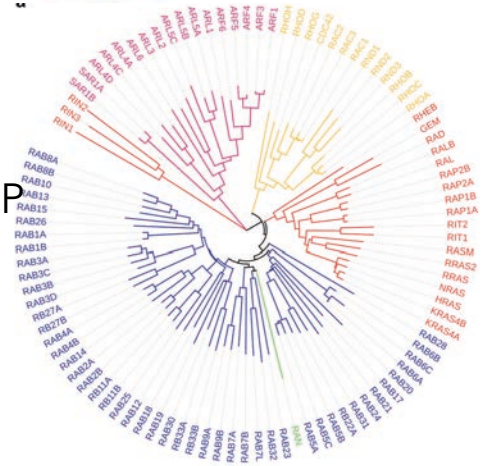
Since none of these alternatives seems especially attractive, one is more inclined to suggest models that are cooperative in nature. That is, the molecules in the synapse interact in such a way that they can be replaced with new material, one at a time, without altering the overall state of the structure.

- **Consider a protein P that may be active (+)/inactive (-) depending on post translational modification eg. phosphorylation, and can dimerise.**
- Assume that an enzyme activates P if the other protein in dimer is active:
  (-, +) –> (+,+) and (-, -) unchanged
- New monomers are inactive when produced.
- Protein turnover doesn't change the state of dimer.
- Synapse reinforcement leads to phosphorylation of P (or vice versa for inhibition).
- Synapse reinforcement in spite of protein turnover.

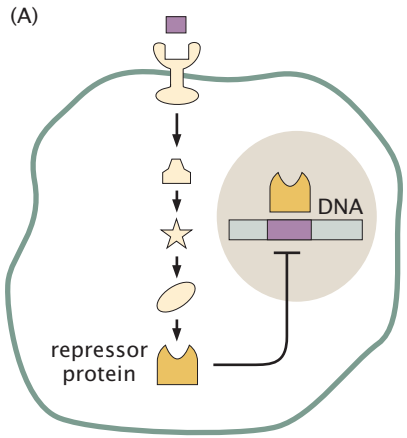
Molecular memory

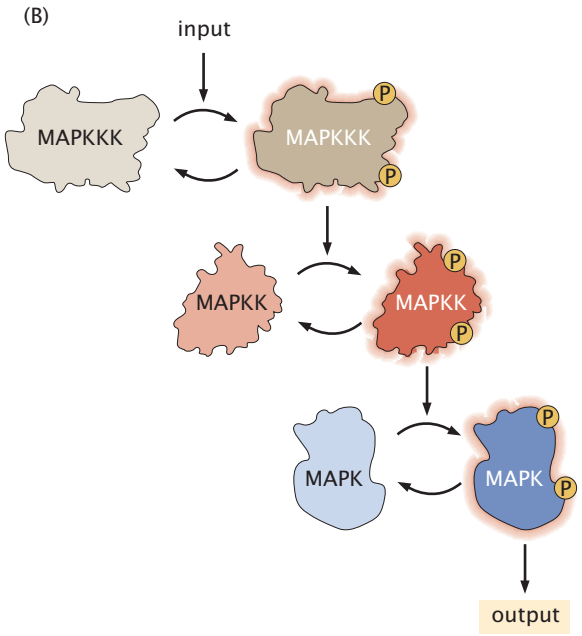
Post-translation modifications: Reversible protein modifications induced by pairs of proteins

GTP cycle, phosphorylation cycle, methylation cycle



Small GTPase: GEF/GAP





Phosphorylation cascade: Kinase/Phosphatase

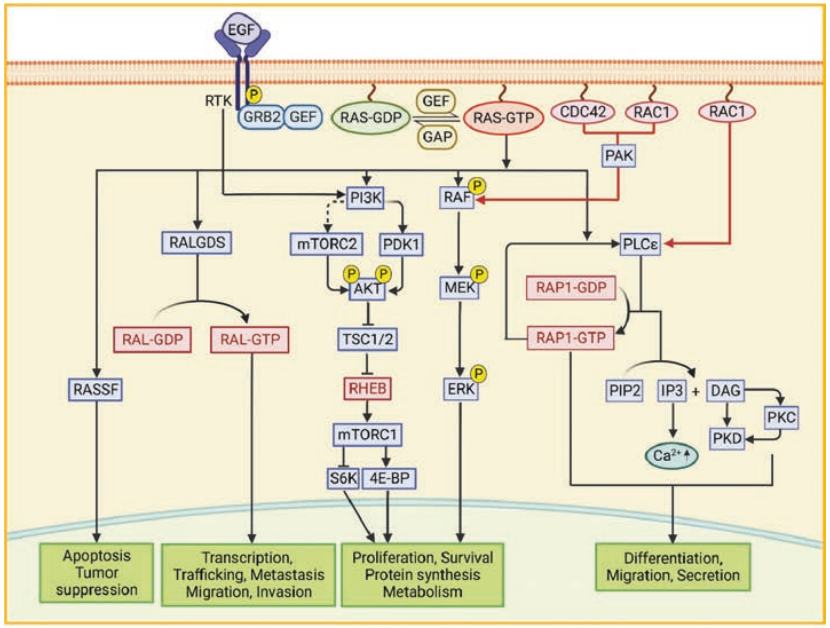
Yin et al. *Signal Transduction and Targeted Therapy* (2023)8:212

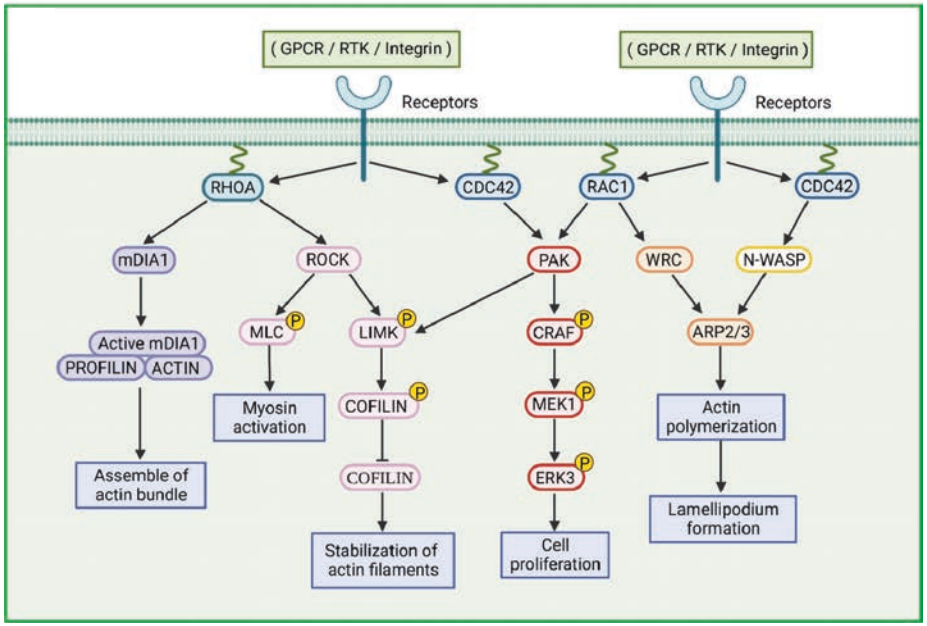
H.G. Garcia and R. Phillips. *Physical Genomics - from E.coli to Elephants, PUP*

Molecular memory

Post-translation modifications: GTP cycle, phosphorylation, methylation

Transient stimuli yield transient or more sustained response dynamics.
This is based on the coupling of reversible protein modifications organised in cycles
The reversible state allows rapid tuning of *molecular memory* to external signals





Cellular behaviour/state

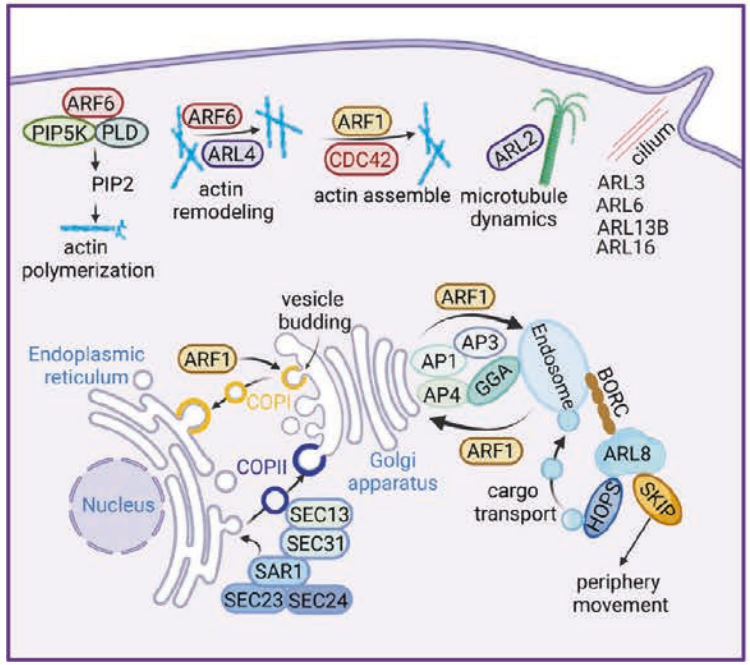
Cellular dynamics

Yin et al. *Signal Transduction and Targeted Therapy* (2023)8:212

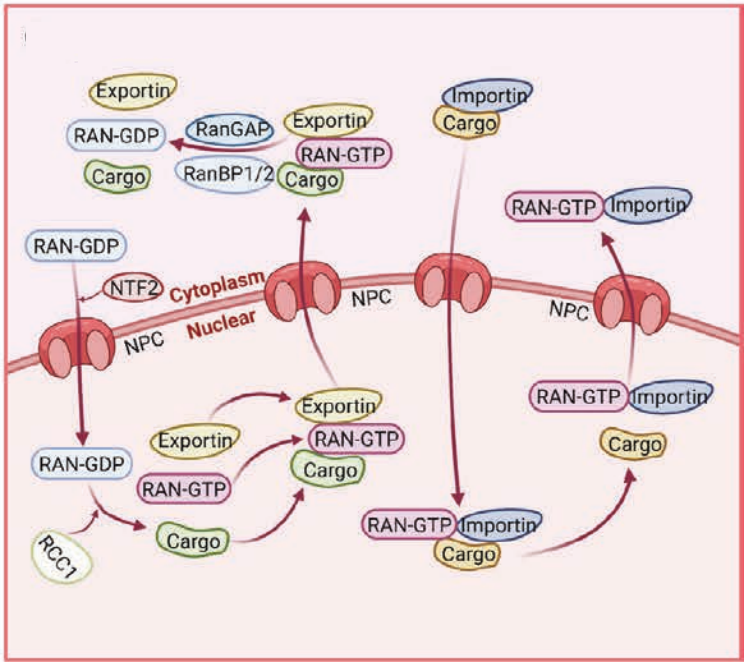
Molecular memory

Post-translation modifications: GTP cycle, phosphorylation, methylation

Transient stimuli yield transient or more sustained response dynamics.
This is based on the coupling of reversible protein modifications organised in cycles
The reversible state allows rapid tuning of *molecular memory* to external signals



Vesicular trafficking



Nuclear import/export

Yin et al. *Signal Transduction and Targeted Therapy* (2023)8:212

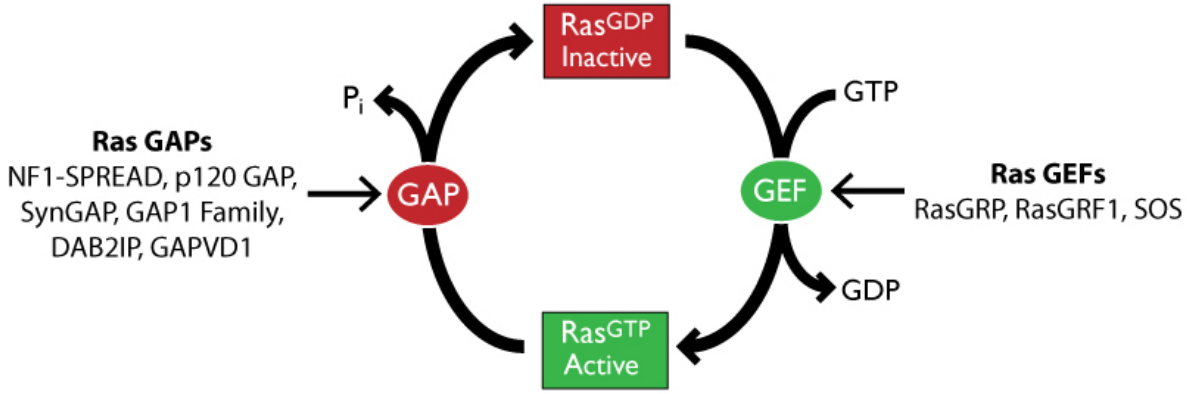
Molecular memory

Post-translation modifications: GTP cycle, phosphorylation, methylation

The life time of the GTP state depends on regulatory molecules that inhibit the GTP hydrolysis by GAP

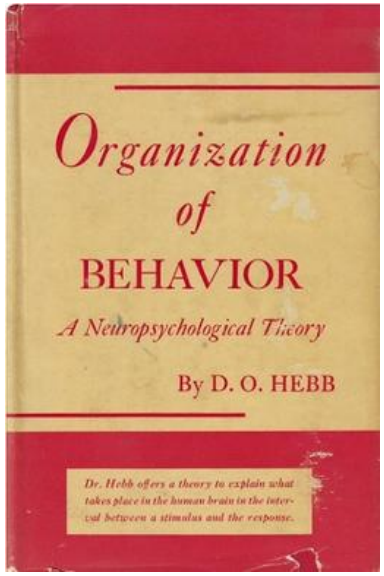
Tuning chemical state memory with proteins that kinetically enhance GTP hydrolysis (GAP): memory is reduced by GAPs.

For Ras, the intrinsic GTP hydrolysis time scale is approximately 30 minutes. However, this is significantly reduced by GTPase-activating proteins (GAPs), with a hydrolysis timescale at about 50 milliseconds

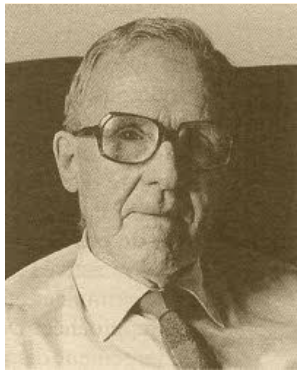


https://www.cytoskeleton.com/ras-cancer-therapeutic-targets

Hebbian learning - lessons from neuroscience



1949



Donald E. Hebb (1904-1985)

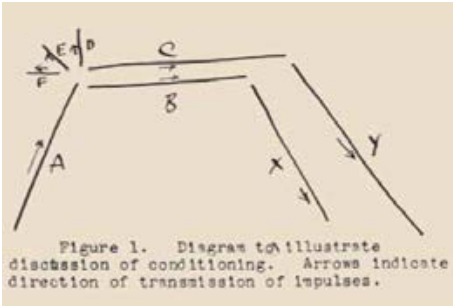


Figure 1. Diagram to illustrate discussion of conditioning. Arrows indicate direction of transmission of impulses.

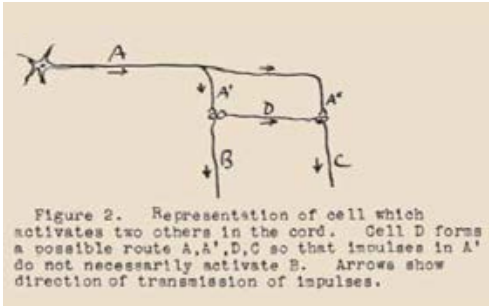


Figure 2. Representation of cell which activates two others in the cord. Cell D forms a possible route A,A',D,C so that impulses in A' do not necessarily activate B. Arrows show direction of transmission of impulses.

Acquisition of conditioned reflexes. Co-incidence of excitation in A and reflex activity in X reinforces the synapse

R.E. Brown and P.M. Milner *Nature Neuroscience*, (2003), 4:1013-1019
The legacy of Donald O. Hebb: more than the Hebb Synapse

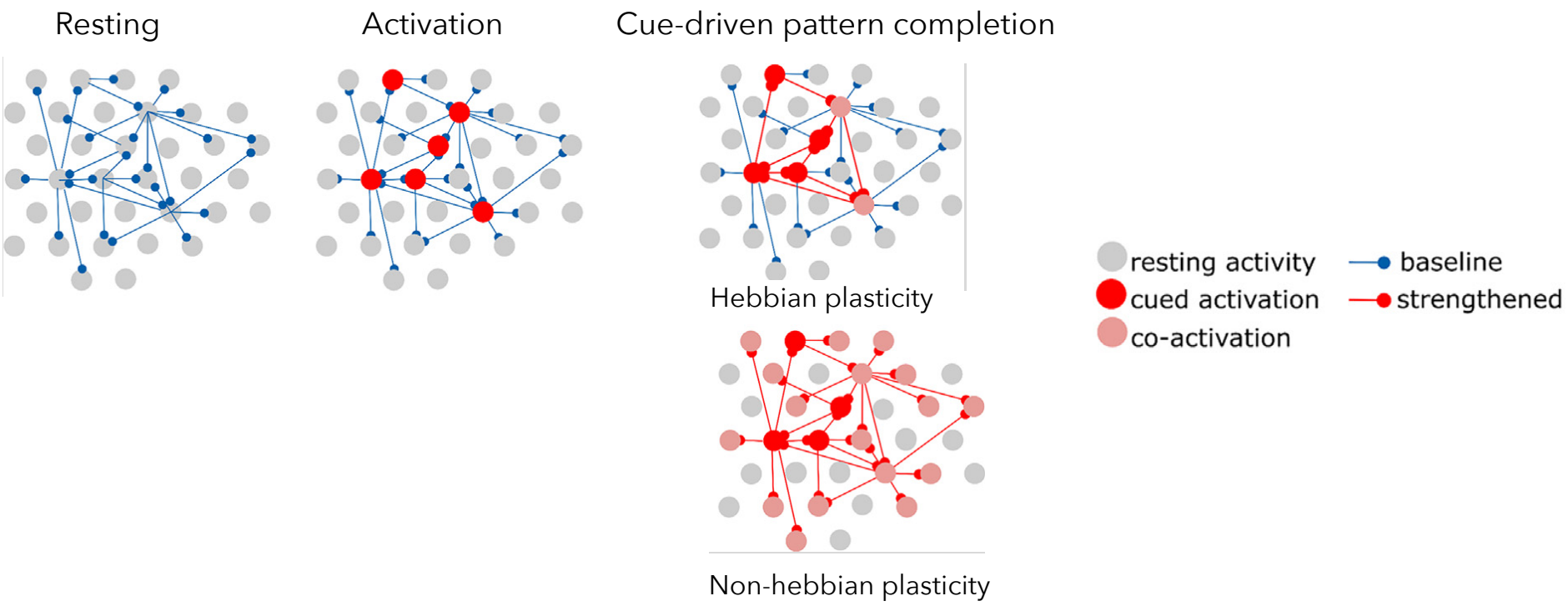
« Neurons wire together if they fire together »

« 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)

Hebbian learning - lessons from neuroscience

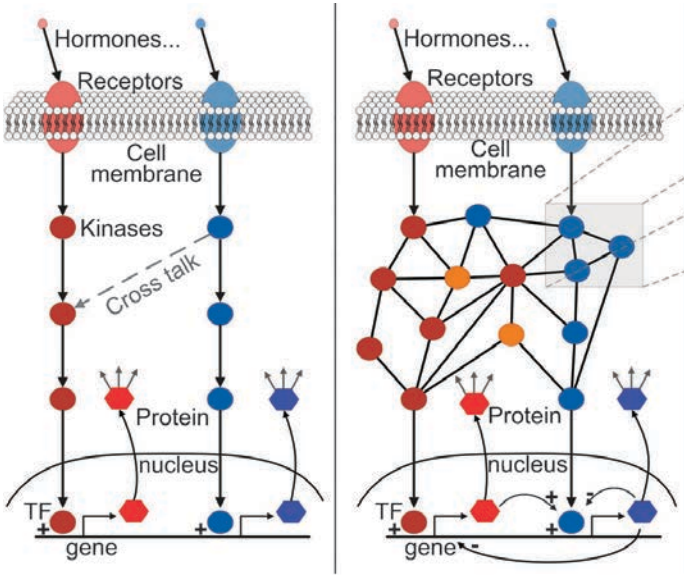


Lansner et al. *Current Opinion in Neurobiology* (2023), 83:102809

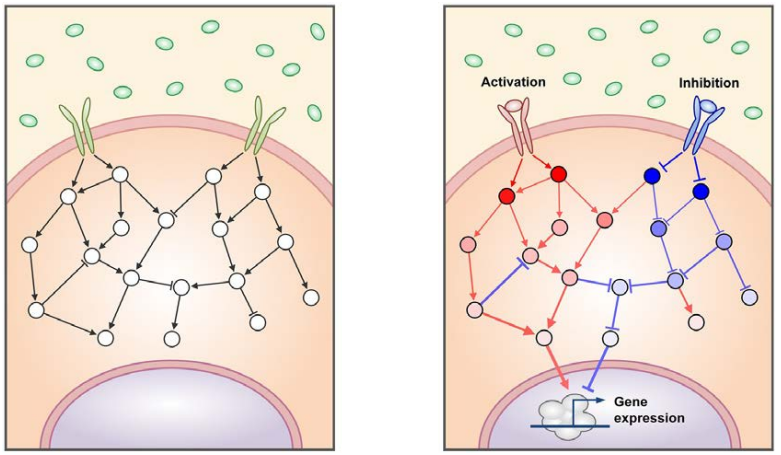
Hebbian rule in signalling networks

- Signalling networks a composed of many proteins that are shared among different pathways
- Promiscuous binding among different pathways.

- **Similar principles of cue-driven activation of molecules in a signalling network.**



Cloutier Wang. *Integr. Biol.*, 3, 724–732 (2011)



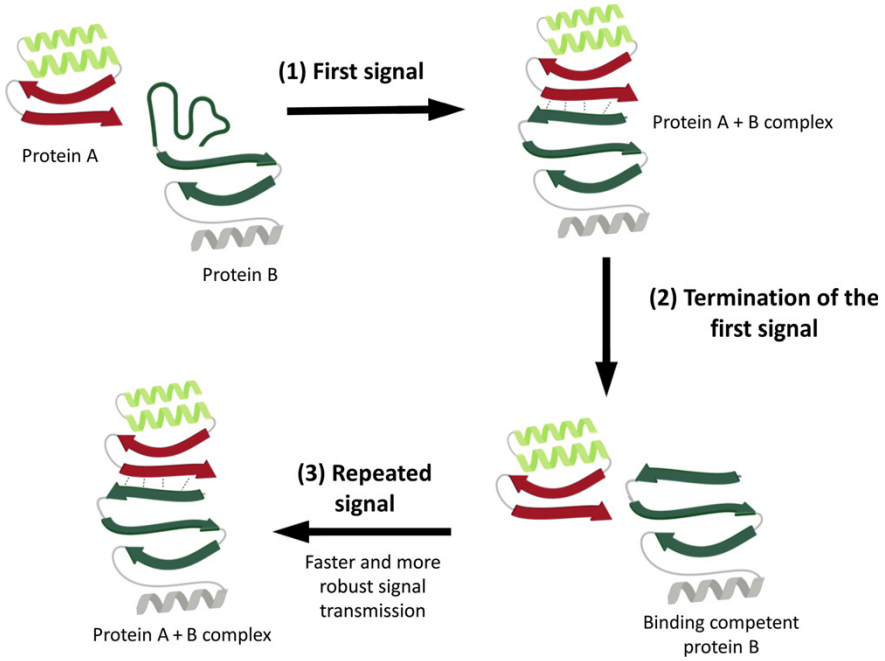
D. Lee & K-H. Cho. *Scientific Reports* | 8:5262 (2018)

Hebbian rule in signalling networks

Conformational memory

- Proteins transiently keep their binding competent state after dissociation.
- Signalling induced reinforcement of protein/protein interactions

- (1) A first signal induces the association of neighboring proteins A and B, which induces a binding-competent conformation of protein B (e.g., via folding of an IDR of protein B)
- (2) After the first signal's termination, proteins A and B dissociate. However, **within a time window, protein B keeps its binding-competent conformation as a conformational memory.**
- (3) Upon repetition of the first signal, the second signal finds protein B still in a binding-competent state, which causes a faster and more robust signal transmission.
- **The signal-induced conformational memory of protein B increases the binding affinity between protein A and protein B.**



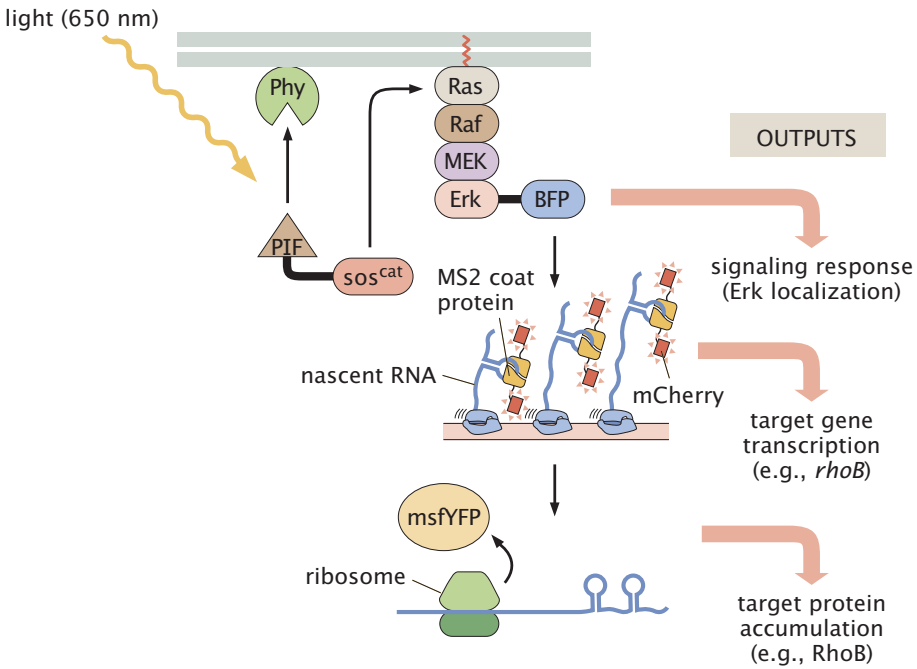
Csermely et al , and P. Tompa. *Trends in Biochemical Sciences*, (2020), 45: 284-294

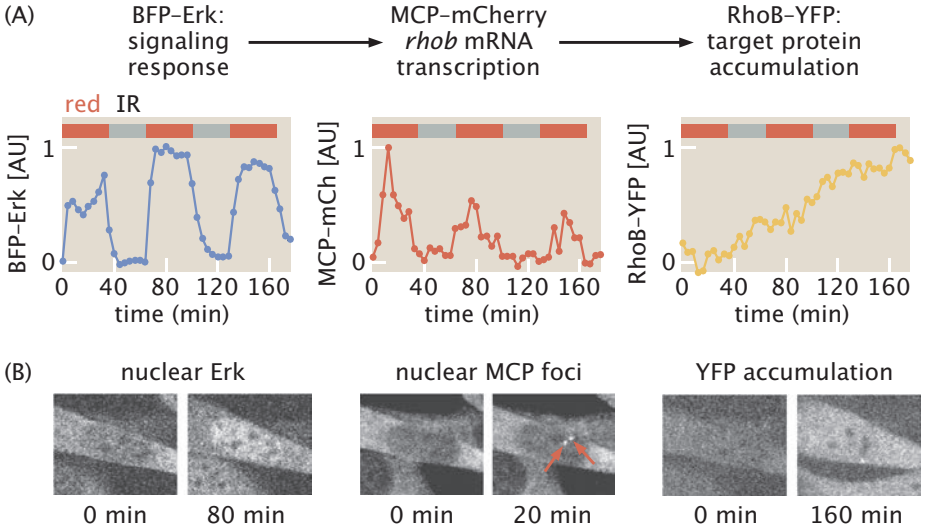
Molecular memory

How protein stability affects signalling

- If proteins turnover rapidly, there is no memory of their past expression.
- **Protein decay rate vs rate of negative feedback:** dictates the response behaviour of a signalling pathway.

An optogenetic system to study quantitatively output responses to light input/Ras activation





Wilson et al., and J. Toettcher. *Molecular Cell* 67, 757–769 (2017)

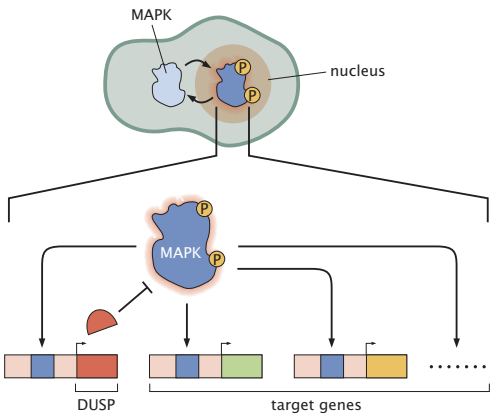
H.G. Garcia and R. Phillips. *Physical Genomics - from E.coli to Elephants, PUP*

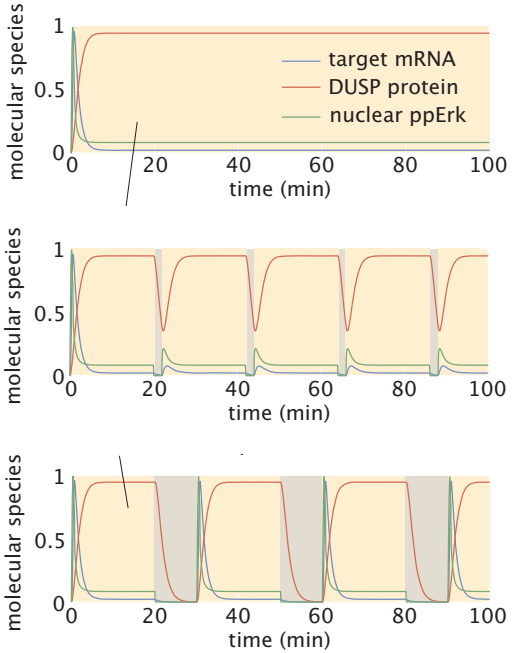
Molecular memory

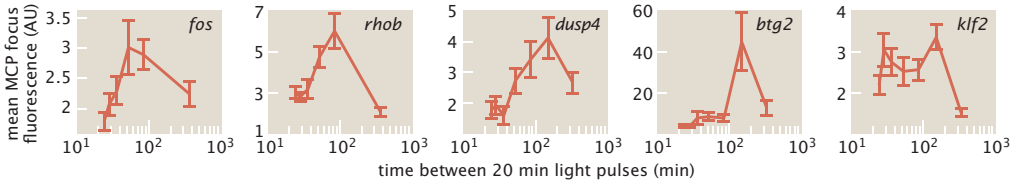
How protein stability affects signalling

- **The Dual Specificity Phosphatase DUSP is a target of ERK and exerts a negative feedback on ERK**
- This negative feedback causes a transient transcriptional activation of target genes.
- If pulses of light at different time intervals are induced, different transcriptional outputs are observed as a function of the time interval between pulses.

- **Key feature: degradation time vs time scale of negative feedback.**
  - If time delay is too short, then DUSP remains sufficiently high to maintain the negative FB and reduce target gene activation.
  - At intermediate values, loss of DUSP « memory » due to degradation allows new pulse of target gene transcription.
  - If time is too long, , fewer pulses and transcription is lower.





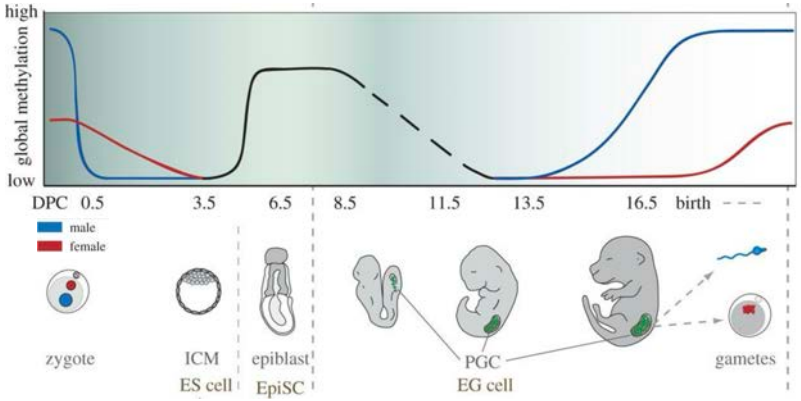


Wilson et al., and J. Toettcher. *Molecular Cell* 67, 757–769 (2017)

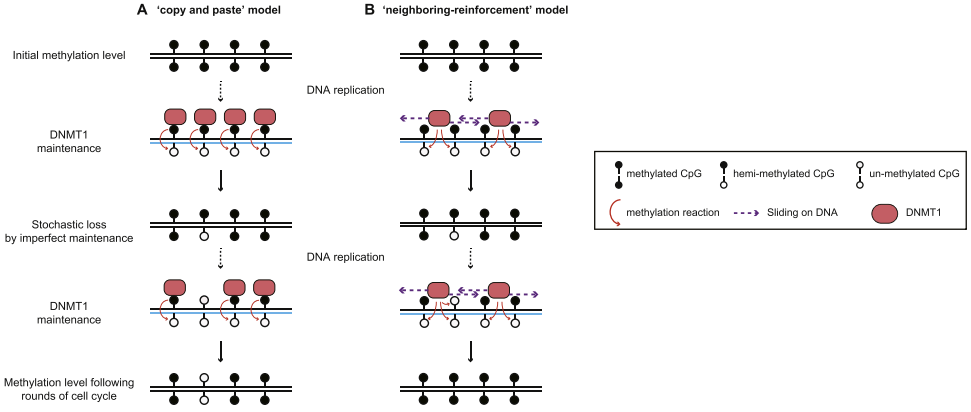
Molecular memory in the life time of an organism

DNA methylation and genomic imprinting

- DNA methylation occurs at C and A
- DNA methylation is associated with repression of transcription
- DNA methylation pattern is erased at the onset of a new generation and reestablished during development. DNA methylation is important for cell differentiation.
- **Inheritance of DNA methylation through cell division**, ie DNA replication. Hemimethylated sites are recognised and lead to methylation of unmethylated strand (following DNA replication).



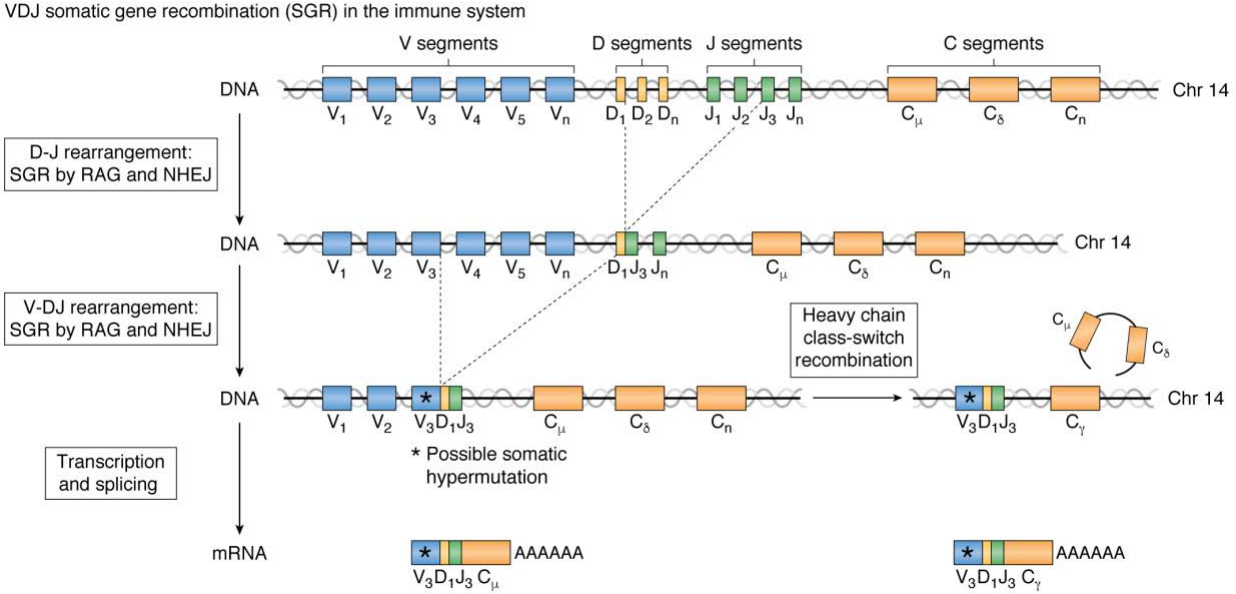
Seisenberger S, et al. *Phil Trans R Soc B* 368: 20110330 (2013)



Ming, Zhu, Li. *Journal of Genetics and Genomics*, doi.org/10.1016/j.jgg.2021.01.006 (2021)

Molecular memory in the life time of an organism

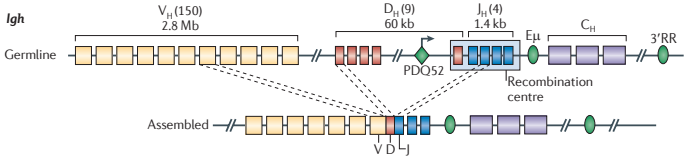
VDJ recombination in immune cells (B and T lymphocytes)



Germline DNA

Rearranged somatic DNA

Rearranged somatic DNA



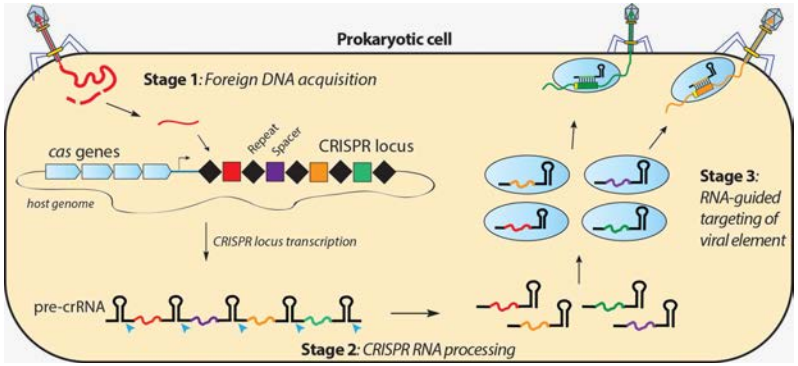
G. Kaeser and J. Chun. *Journal of Biological Chemistry* 295(36):jbc.REV120.009192

https://www.biorender.com/template/vdj-recombination

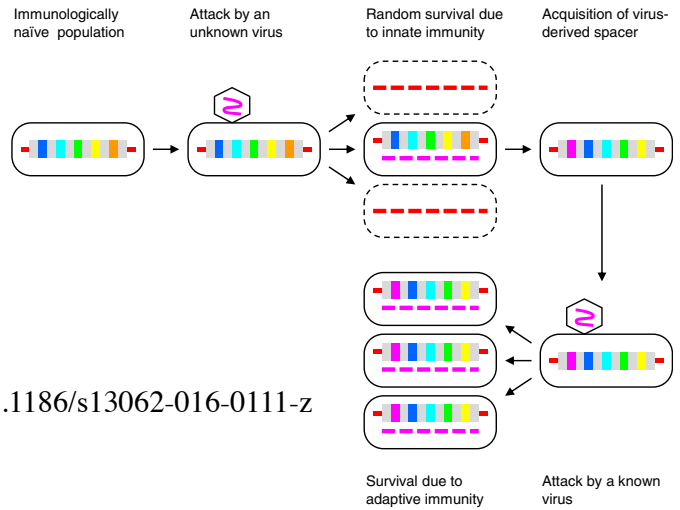
Molecular memory in the life time of an organism

CRISPR mediated immunity against bacteriophages

- Insertion of pieces of foreign DNA, such as a viral or plasmid genome, specifically into the CRISPR array.
- Utilization of the processed CRISPR transcript (crRNA) as guides for inactivation of the cognate target.
- Acquired, heritable, highly specific and efficient protection against the cognate (parasitic) element.



Doudna lab



Koonin and Wolf *Biology Direct* (2016) 11:9 DOI 10.1186/s13062-016-0111-z

Plan

- Molecular learning and memory
- Signalling learning and memory
- Cellular learning and memory
- Structural learning and memory

Signalling Learning and Memory

Transient signal (eg. from environment/neighbouring cells) leads to a sustained response and change in behaviour.
Allows the cell to retain information about transient signals long after being exposed to them.

- **What would be a cell/organism without cellular memory?**

Signals would have to be retained for as long as a response is needed.
Cells would have to remain physically near the inducing/inhibitory cues.
Complexity and cost would be intractable.

Memory of cellular state - Signalling

F. Jacob and J. Monod

General Conclusions: Teleonomic Mechanisms in Cellular Metabolism, Growth, and Differentiation

by Jacques Monod and François Jacob

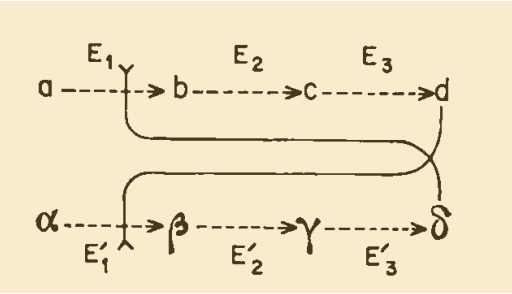
Services de Biochimie Cellulaire et de Génétique Microbienne, Institut Pasteur, Paris

- Cell differentiation in eukaryotes persists once it has been induced.
- What are the mechanisms of perpetuation of cellular state?

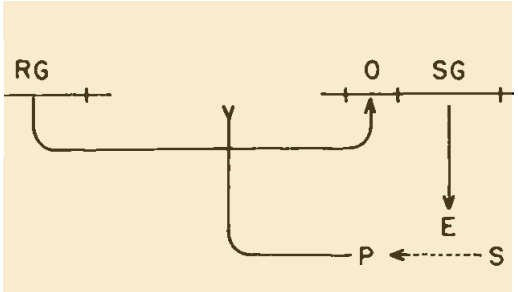
The models involving only metabolic steady-states maintained by allosteric effects are insufficient to account for differentiation, which must involve directed alterations in the capacity of individual cells to *synthesize* specific proteins. Such models would seem to be most adequate to account for the almost instantaneous, and thereafter more or less permanent, "memorization" by cells of a chemical event. The problem of memory itself might usefully be considered from this point of view.

Monod, J. & Jacob, F. *Cold Spring Harb. Symp. Quant. Biol.* 26, 389–401 (1961).

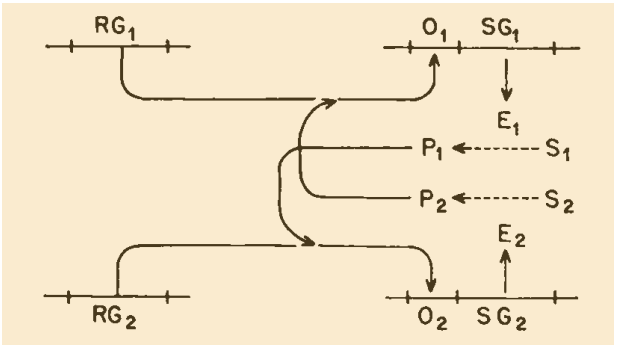
Memory of cellular state - Signalling



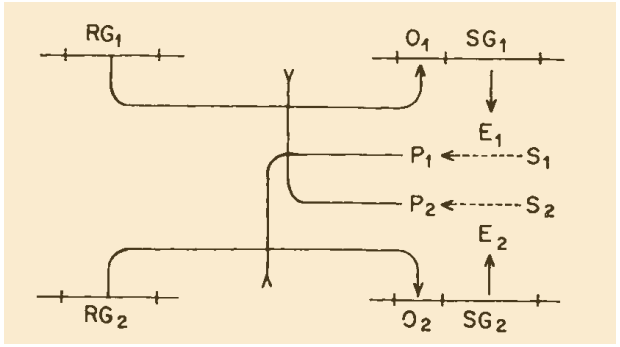
- Network with cross inhibitory feedback



- Inducible system positive feedback circuit (via double inhibition)

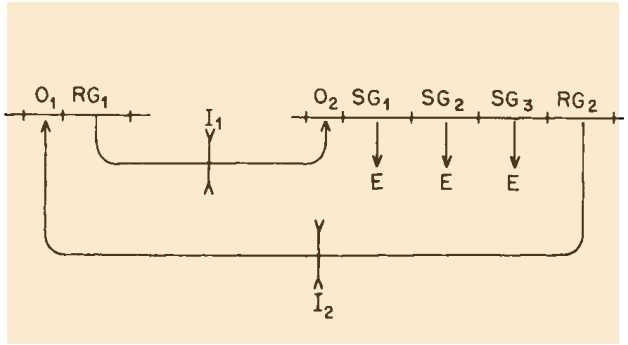


- Network with cross inhibition



- Network with co-activation

« Let us study a certain number of theoretical model systems in which we shall use only the controlling elements known to exist in bacteria, interconnected however in an arbitrary manner. »



- Network with double negative feedback, ie. positive feedback

Monod, J. & Jacob, F. *Cold Spring Harb. Symp. Quant. Biol.* 26, 389–401 (1961).

Memory of cellular state - Signalling

A mechanism for memory storage insensitive to molecular turnover: A bistable autophosphorylating kinase

(long-term memory/nervous system/protein phosphorylation)

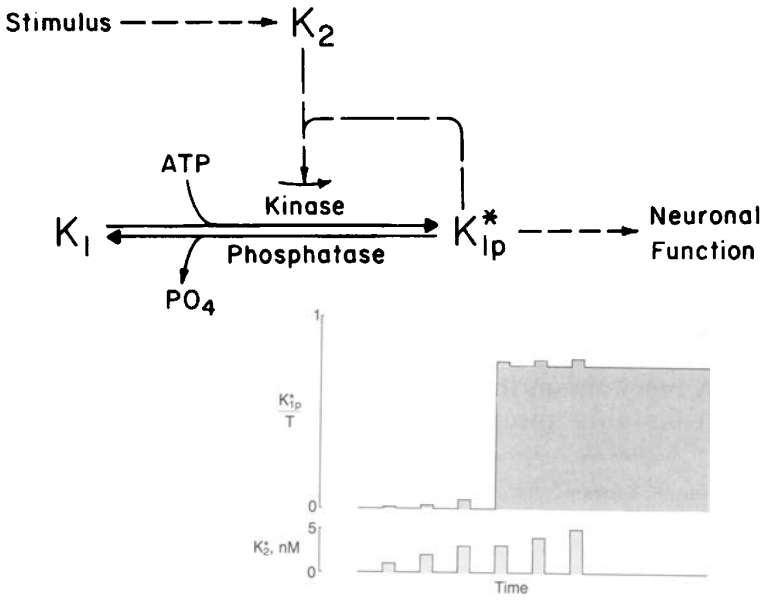
JOHN E. LISMAN

Department of Biology, Brandeis University, Waltham, MA 02254

Communicated by William P. Jencks, January 14, 1985

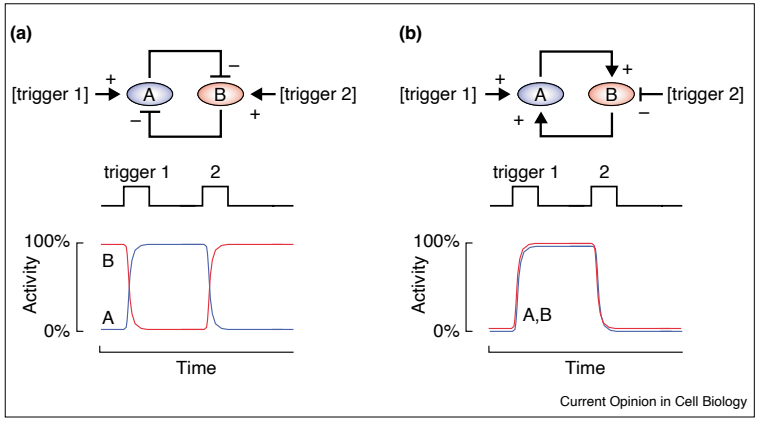
Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 3055–3057, May 1985
Neurobiology

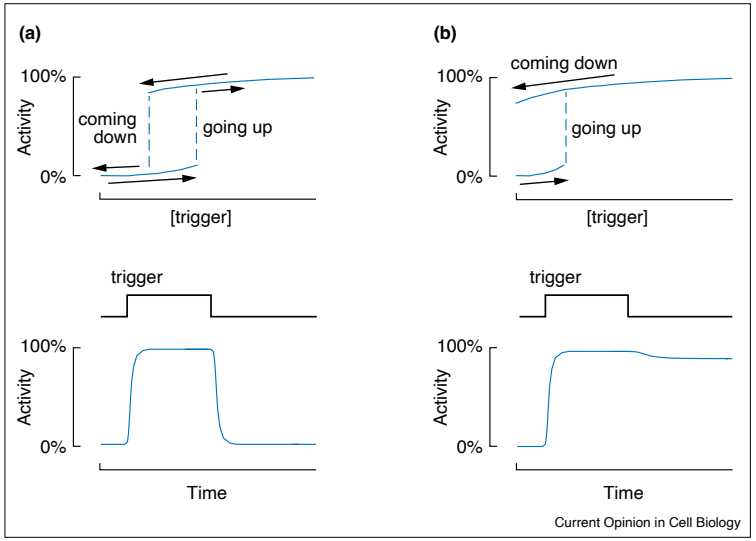
ABSTRACT A mechanism is proposed for a molecular switch that can store information indefinitely, despite the complete turnover of the molecules that make up the switch. The design of the switch is based on known types of biochemical reactions. Central to the mechanism is a kinase that is activated by phosphorylation and capable of intermolecular autophosphorylation. It is shown that such a kinase and an associated phosphatase form a bistable chemical switch that can be turned on by an external stimulus and that is not reset by protein turnover.



Memory of cellular state - Bistability

- A genetic or biochemical **network is bistable when two states are possible at the same concentration of a stimulus.**
- Two general classes of bistable networks:
  - **Mutual cross-inhibition**
  - **Positive Feedback**
- Bistability requires minimally:
  - **a non linear step (eg. ultrasensitivity).**
  - **A relative symmetry in the 2 arms of the network.**
- Bistability requires hysteresis, namely path-dependent behaviour, such that the trajectory forms a loop.
- **Hysteresis locks the system in a given state, and imparts memory to a transient stimulus**





J.E. Ferrell. *Current Opinion in Chemical Biology*, 6:140–148 (2002)

Memory of cellular state - Bistability

- Bistability in a simple Positive Feedback Network *in silico*

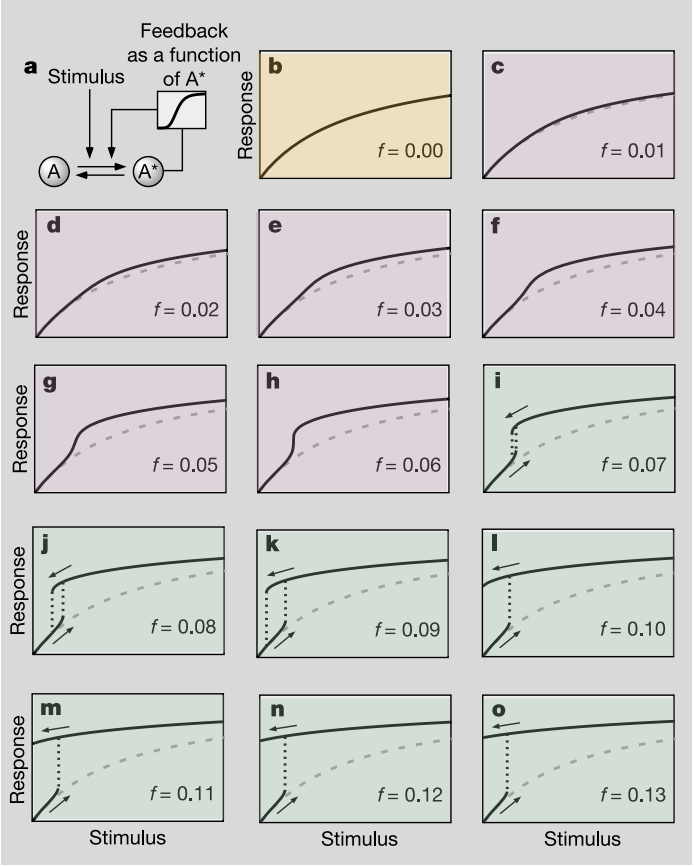
$$\frac{d[A^*]}{dt} = \{\text{stimulus} \times ([A_{tot}] - [A^*])\} + f\frac{[A^*]^n}{K^n + [A^*]^n} - k_{inact}[A^*]$$

K is the effector concentration for half-maximum response (EC_{50}) for the feedback as a function of [A*]

***f* represents the strength of the feedback**

As the strength of the feedback increases, the response evolves.

- First, Michaelis-Menten kinetics at *f=0*
- As *f* increases, non-linear feedback increases which induces sigmoid kinetics in the response as a function of stimulus. But still monostable
- Beyond a threshold, *f*=0.07, the system is bistable and hysteresis keeps increasing (the range of [stimulus] with bistability)



k_{inact} = 0.01

stimulus = 0–1

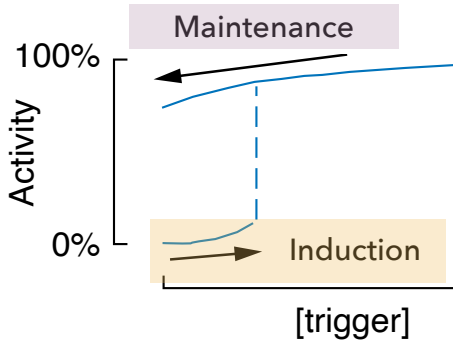
n=5, K=1

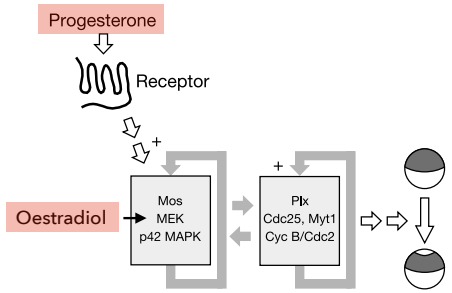
Xiong, W., and Ferrell, J.E., Jr. (2003). *Nature* 426, 460–465

Memory of cellular state - Bistability

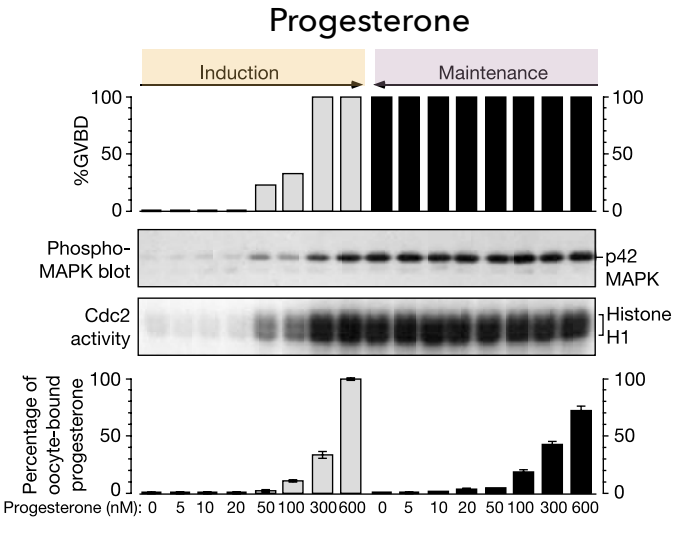
• Bistability in a complex Feedback Network *in vivo*

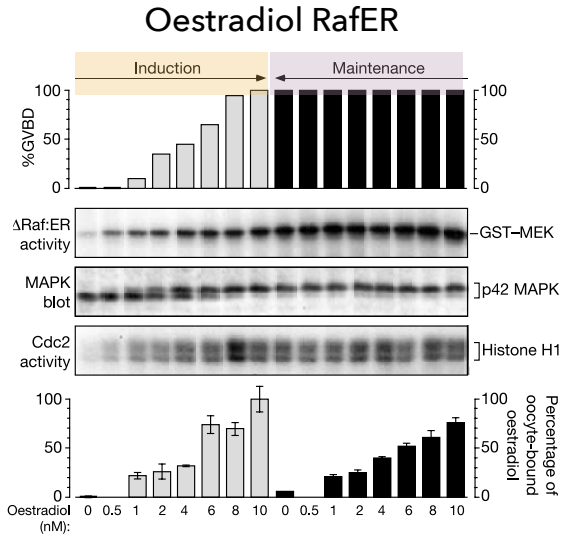
- Oocyte maturation is induced *irreversibly* by a short exposure to Progesterone
- This entails **two coupled positive feedback networks**
- **Testing hysteresis:** Induction by increasing [Stimulus] and maintenance by decreasing [Stimulus].





Xenopus oocytes are arrested in G2 phase. In response to steroid hormones, the oocyte is released from G2 arrest, undergoes germinal vesicle breakdown (GVBD), completes meiosis I arrests in metaphase of meiosis II.

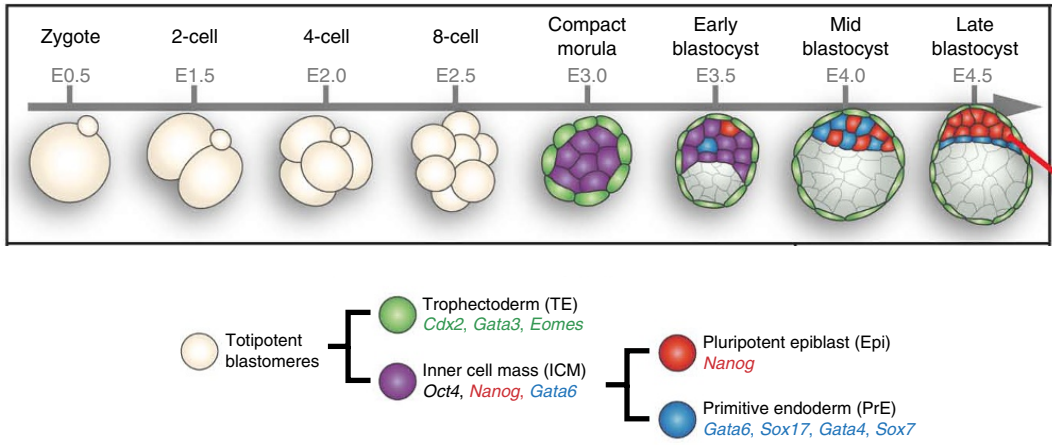




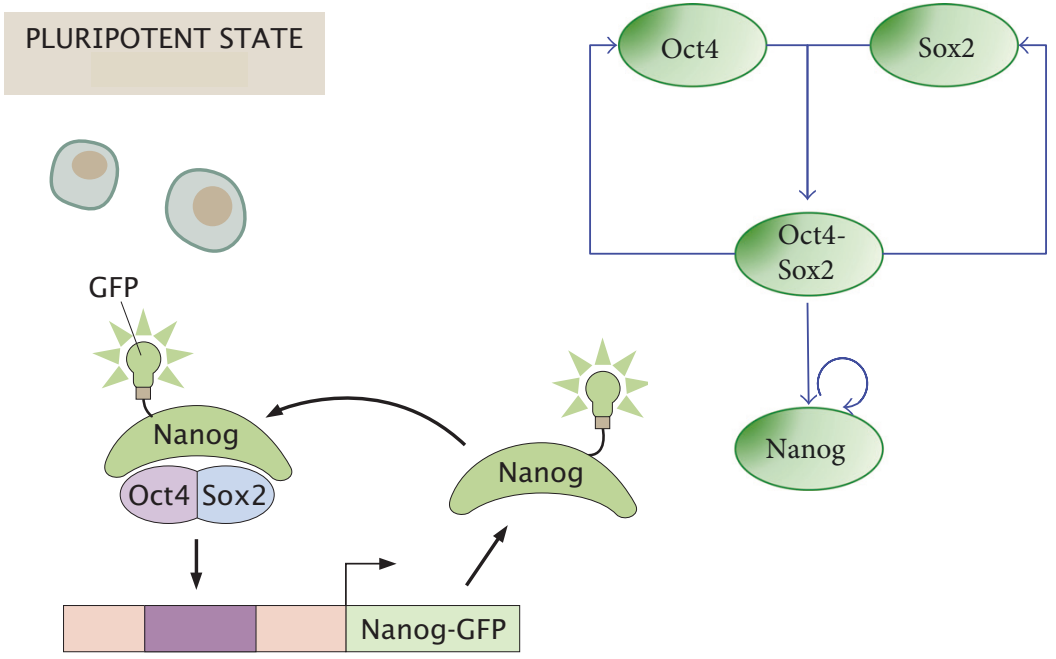
Xiong, W., and Ferrell, J.E., Jr. (2003). *Nature* 426, 460–465.

Memory of cellular state - Bistability

- **Maintenance of the pluripotent cell state in early mouse embryos with a positive feedback loop:**
- In totipotent blastomeres, the TFs Sox2, Oct4 and Nanog are expressed.
- **Positive feedbacks maintain expression of totipotency genes.**
  - Nanog activates its own expression by forming a complex with Oct4 and Sox2
  - Oct4 and Sox2 also form coupled positive feedback loops



A. Czechanski et al. *Nature Protocols* 9:559 (2014)



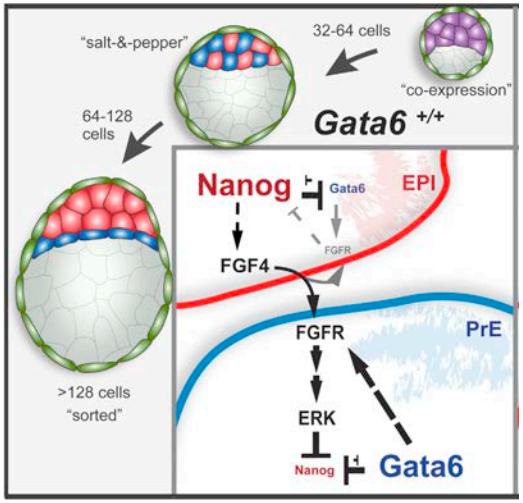
Glauche I, Herberg M, Roeder I PLoS ONE 5(6): e11238 (2010)

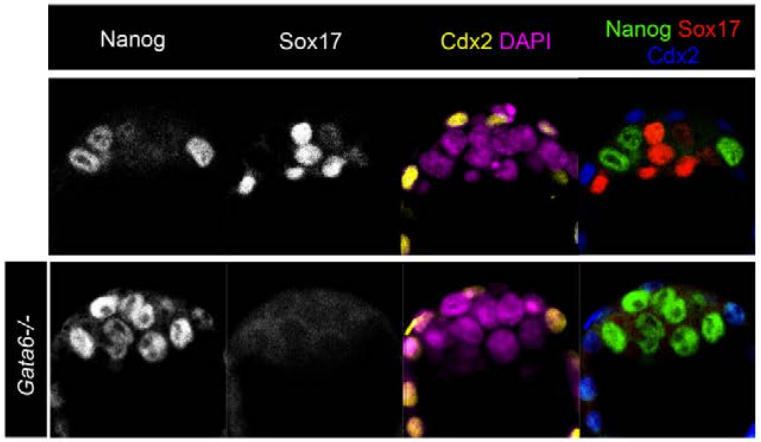
H.G. Garcia and R. Phillips. *Physical Genomics - from E.coli to Elephants*

Memory of cellular state - Multistability

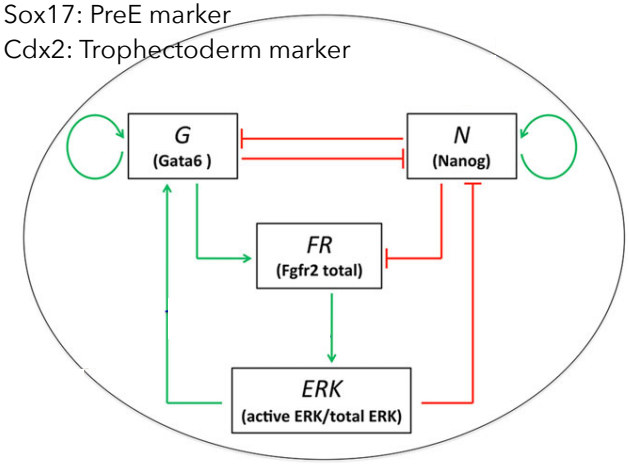
• Multistability in development

- Transient signals induce a variety of stable cellular responses during development.
- Multistability allows genetically identical cells to be in molecularly distinct and mitotically stable cell states.
  - Ex 1: Embryogenesis in the mouse: Specification of Epiblast and Primitive endoderm in the Inner Cell Mass. Tristability with pluripotency state, (GATA6+Nanog), Epi (Nanog) and PrE (GATA6). **Coupled cross inhibition.**
  - Ex 2: Myogenesis, the transcription factor MyoD heterodimerizes with E proteins to activate itself and the myogenesis program, and Id family proteins heterodimerize with E proteins to disrupt this process.





Sox17: PreE marker
Cdx2: Trophectoderm marker

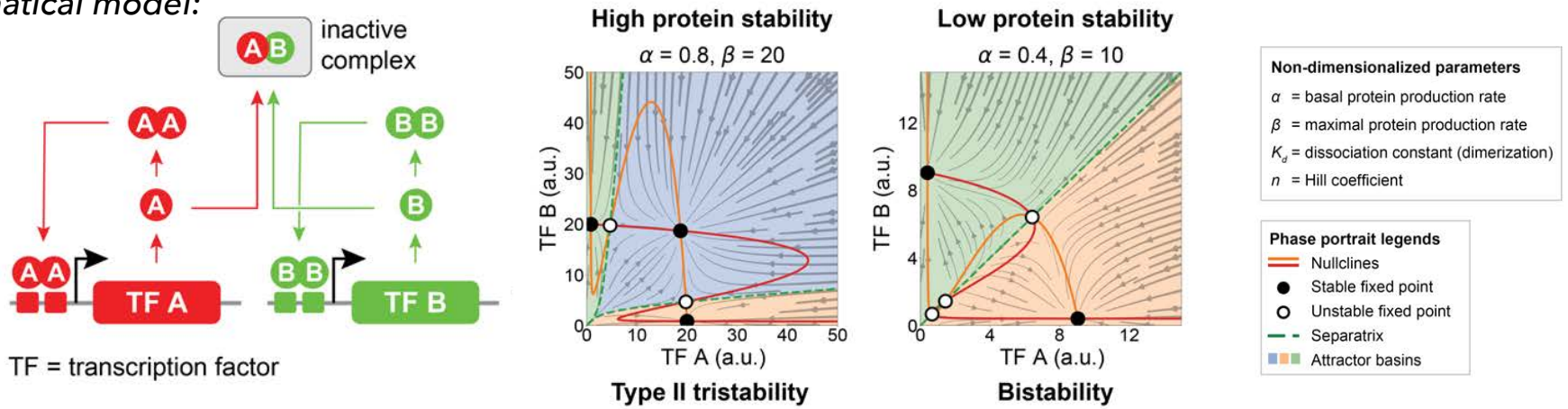


Bessonnard et al. Chazaud. *Development* 141, 3637-3648 (2014)
N. Shrode et al. *Developmental Cell 29*, 454–467 (2014)

Memory of cellular state - Multistability

A synthetic multistable system

- *Principle:* TF homodimerization causes non-linear positive autoregulation. Heterodimerization mutually inhibits each other's transcriptional activity because the heterodimer does not bind DNA.
- Tristability requires sufficient protein stability.
- *Mathematical model:*



- Type II tristability (ie. 3 states expressing either A, B, or both), is analogous to multilineage priming in uncommitted progenitor cells. Double positive state plays the role of a multipotent progenitor.

R. Zhu et al, J. Garcia-Ojalvo and M. Elowitz. *Science*, 375(6578):eabg9765 (2022)

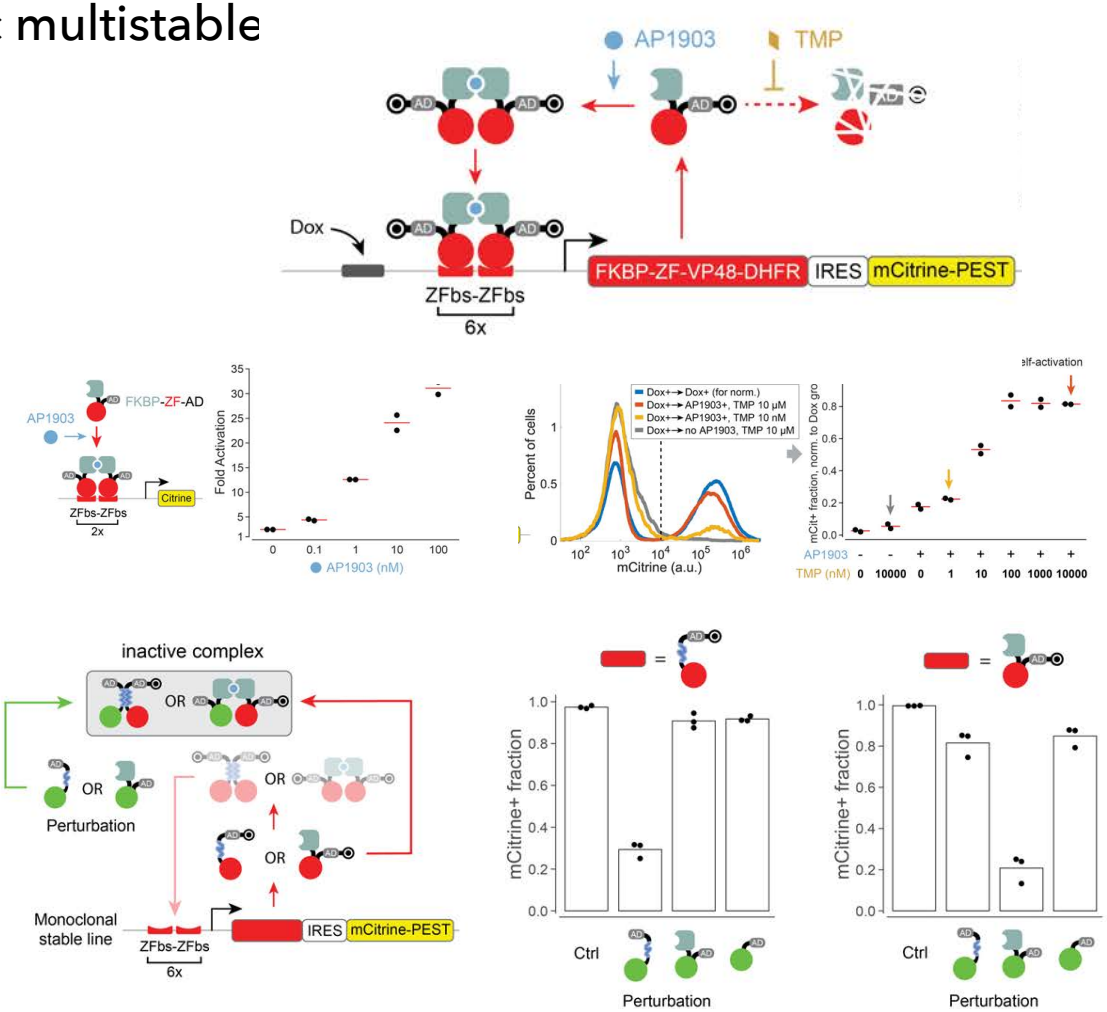
Memory of cellular state - Multistability

A synthetic multistable

- *Experimental system:*

- Transcription factor self-activation can be controlled by induced dimerisation (AP1903) and protein stabilisation (TMP).
  - Induction by DOX followed by stable expression via positive feedback. **Without homodimerization, transcriptional activation is not maintained: no memory.**

- Self-activation is inhibited by competing transcription factors that heterodimerize with self-activating TF.

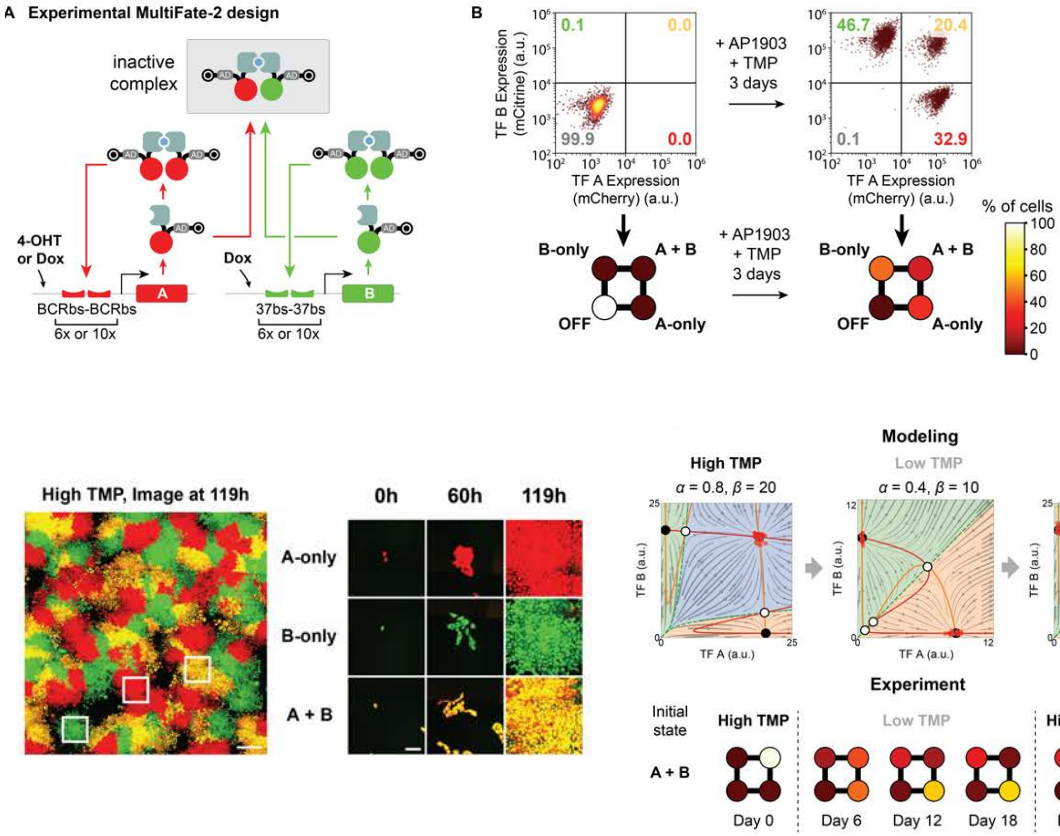


R. Zhu et al, J. Garcia-Ojalvo and M. Elowitz. *Science*, 375(6578):eabg9765 (2022)

Memory of cellular state - Multistability

- **Implementing bistability ad tristability:**
  - Induction by DOX (38h) followed by culture over 18 days.
  - Stable states over days of culture.
- Activation of dimerisation and protein stabilisation lead to 3 states (A, B or A+B).

- Imaging after few days reveals the 3 populations of cells in adjacent clonal domains.
- Reducing protein stability destabilised selectively the A+B state leading to bistability.
- ***Hysteresis*: reintroducing protein stabilisation (high TMP) did not revert to tristability.**



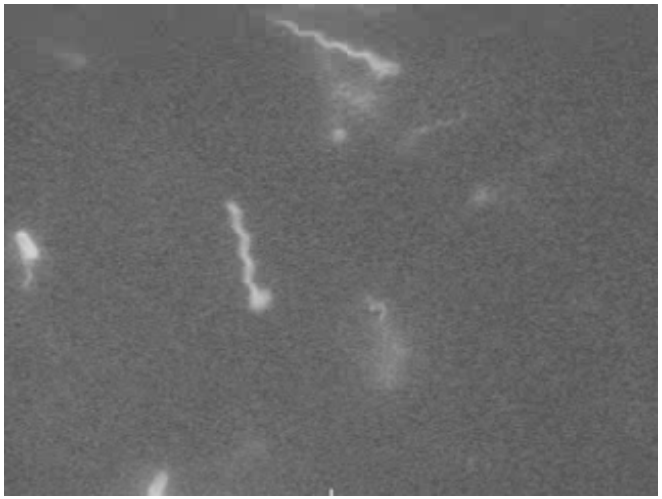
R. Zhu et al, J. Garcia-Ojalvo and M. Elowitz. *Science*, 375(6578):eabg9765 (2022)

Plan

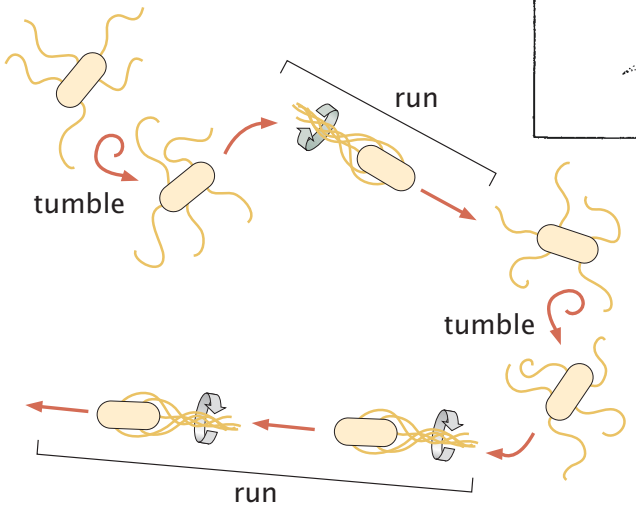
- Molecular memory
- Signalling memory
- Cellular memory:
  - Case study 1: chemotaxis in *E. coli*
  - Case study 2: cell habituation in *Stentor*
- Structural memory

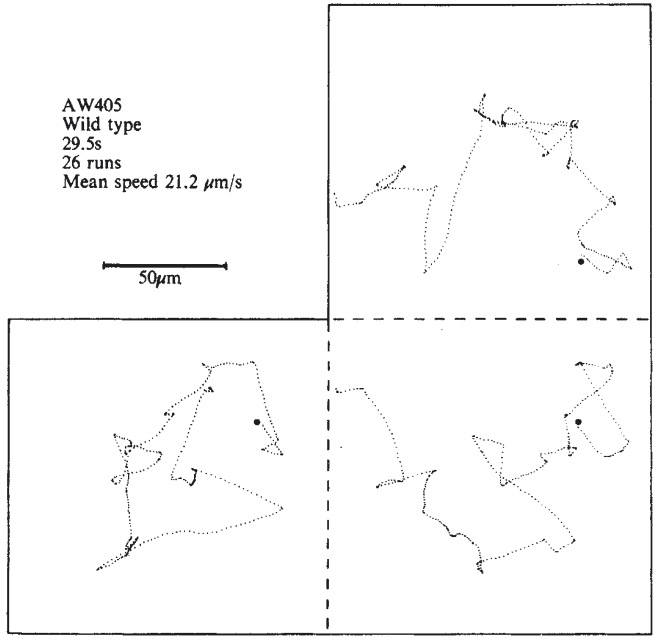
Bacteria swim, propelled by flagella

- 6 flagella bundle when they rotate counterclockwise (CCW)
- Bundles rotate and propel *E. coli* along runs
- Runs (1s long) are followed by tumbles due to CW rotation of flagella which are no longer bundled



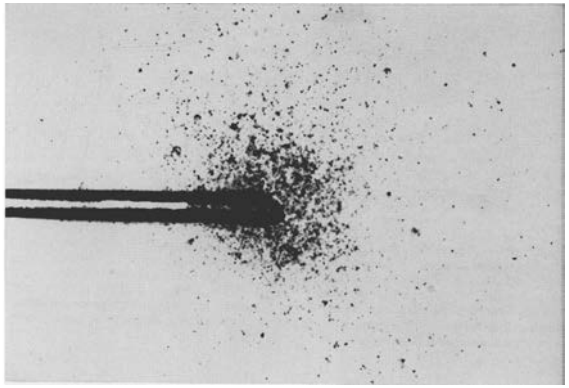
Howard Berg http://www.rowland.harvard.edu/labs/bacteria/movies/ecoli.php





Howard Berg and Douglas Brown. *Nature* 239, 500-504 (1972)

Chemical guidance of cell motility



E. coli attracted by 2mM Aspartate in capillary
Bacteria enter the capillary during 1h

Key features of chemotaxis:

- Specificity
- Cell surface sensing (receptors)
- Sensitivity to ratio (gradient) but *not difference* in concentration of attractant

- **How can cells respond to a chemoattractant gradient?**

Problem: Bacteria can go up an exponential gradient, over 20mm.
For a 2µm cell to detect such a gradient, they would need to detect 0.0001% difference on both ends

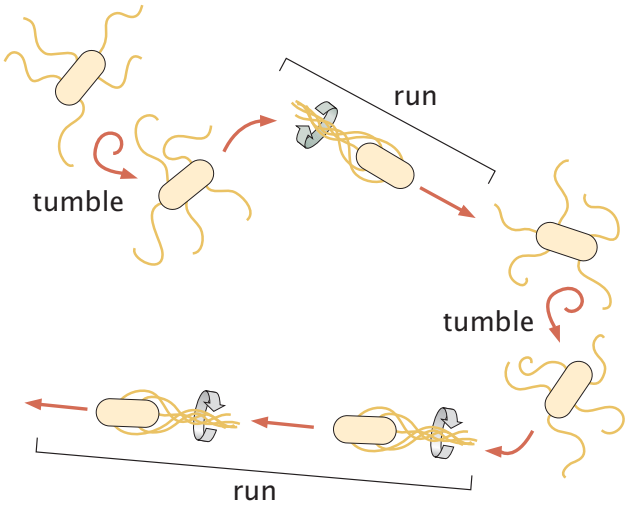
Sensitivity to stochastic fluctuations: estimate of 60 molecules of attractant at 1µM on a sampling volume of 1µm x 1µm x 0.1µm . The standard deviation is √60. Yet the response is very accurate and fast (few ms)…

R. Macnab. D.E. Koshland. *PNAS*. 69:2509-2512 (1972)
J. Adler, *Science* 166, 1588 (1969).

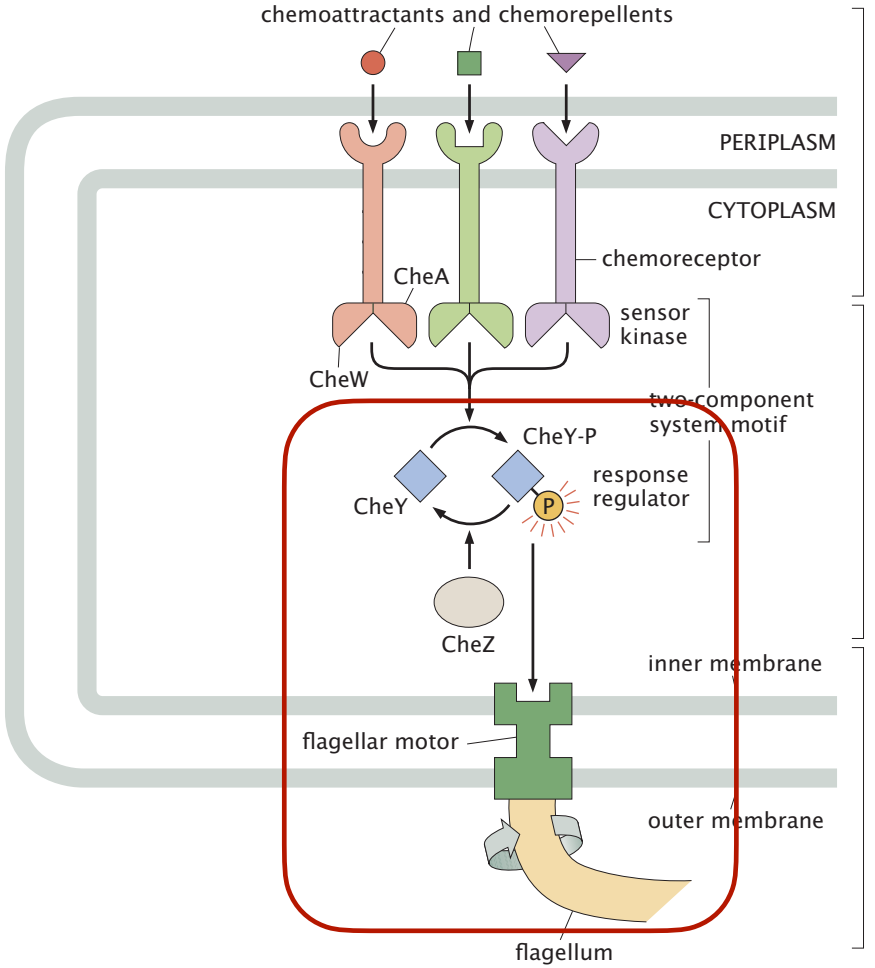
Two general classes of Mechanisms

- Spatial mechanism: comparison of chemoattractant concentration along cell length

- Temporal mechanism: comparison of chemoattractant at different positions and memory.



Molecular circuit driving chemotaxis



INPUT

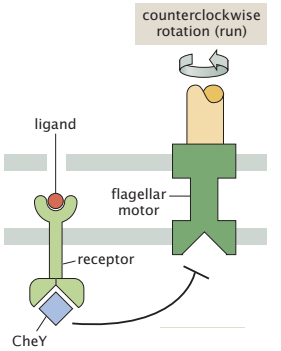
sensor module

transduction module

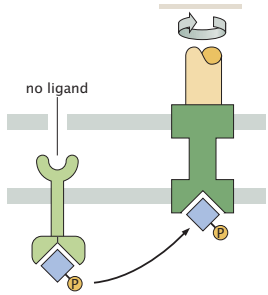
actuator module

OUTPUT

INPUT	Ligand: bound Receptor OFF
OUTPUT	Motor CCW Run



INPUT	Ligand: no Receptor ON
OUTPUT	Motor CW Tumble



R. Phillips, The Molecular Switch: signalling and allostery. *Princeton Univ. Press*. 2020

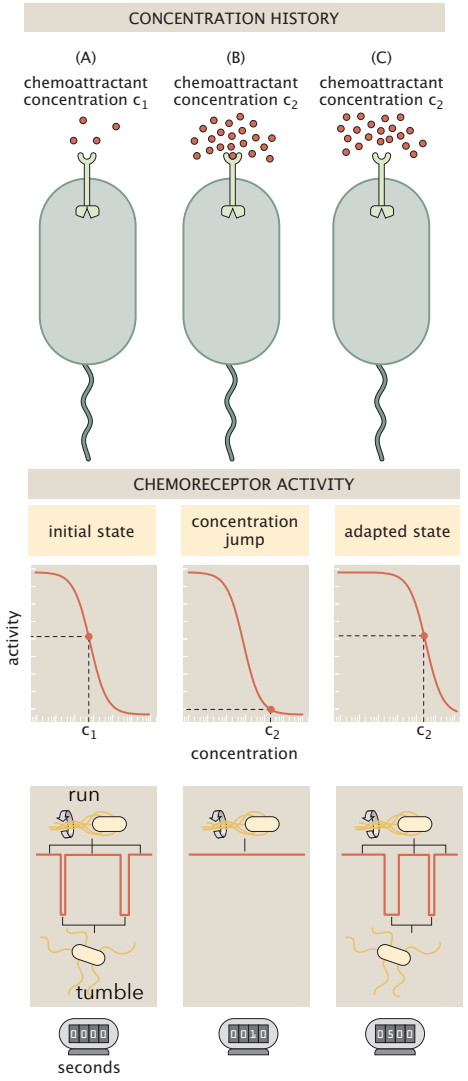
Mechanism of adaptation

The evidence/principle

- (A)-(B) Cells respond to an increased concentration of attractant (c2) by lowering activity

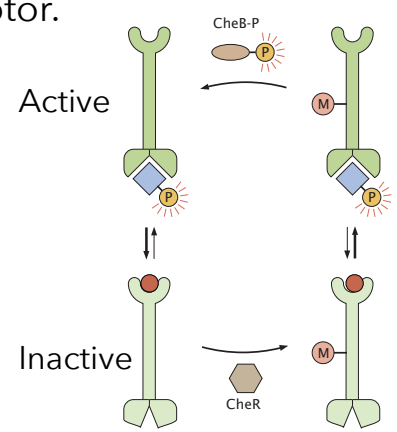
(reduced FRET reflects reduced CheY-P concentration)

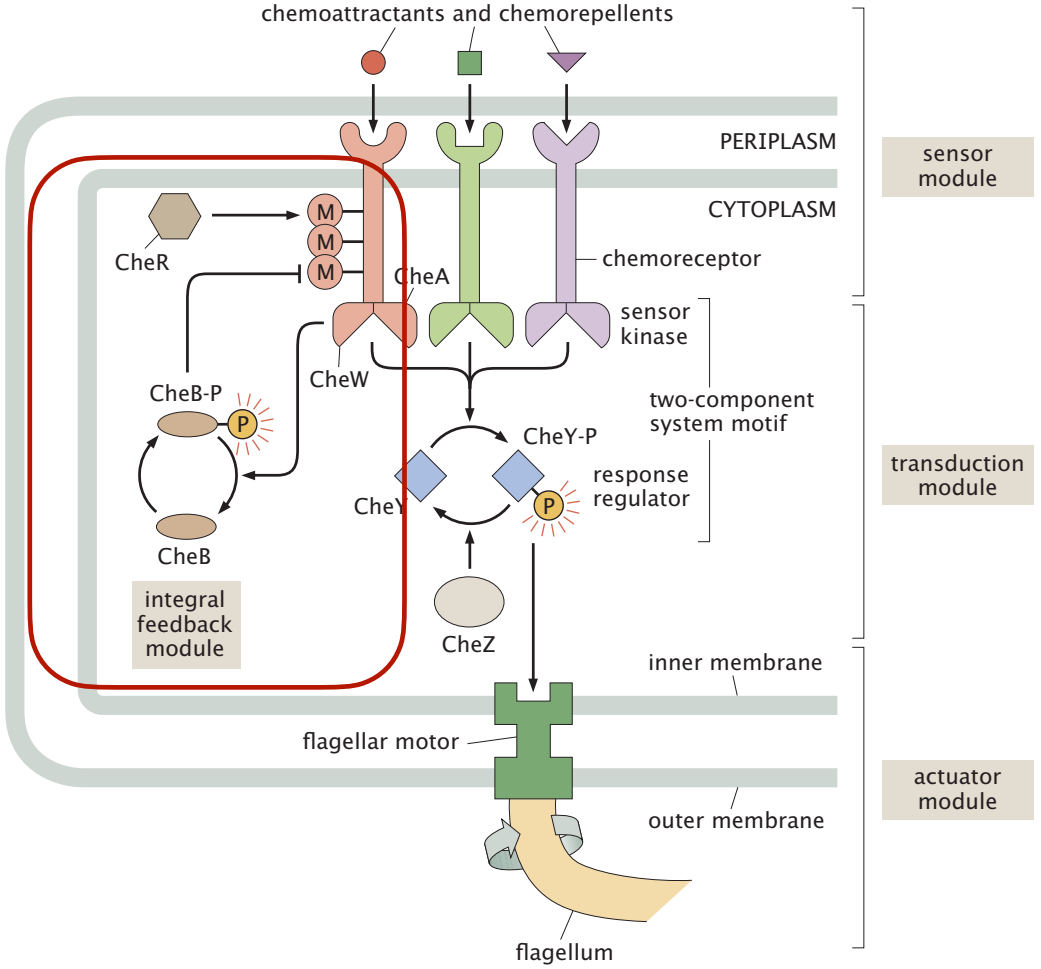
- (B)-(C) Then cells restore/reset their activity: they adapt to the new stable concentration c2



Mechanism of adaptation

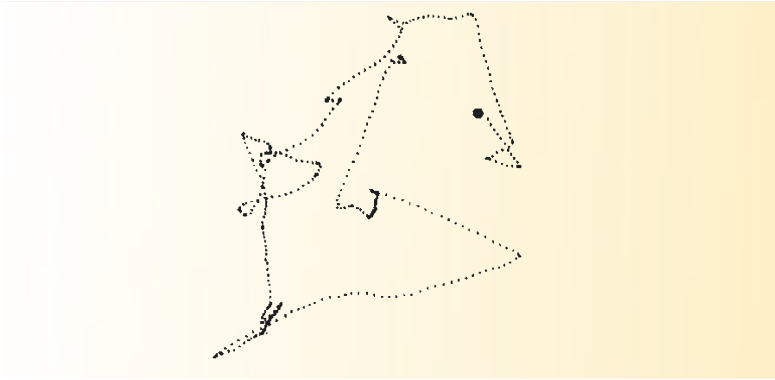
- Adaptation requires reversible methylation of the chemoreceptors by the methylate CheR and the demethylase CheB.
- In presence of ligand, receptor inactive and CheR methylates the receptor. This pushes the receptor towards the active state and the cell is reset/adapted.
- In absence of ligand, receptor is on, CheB is activated and demethylates the receptor.



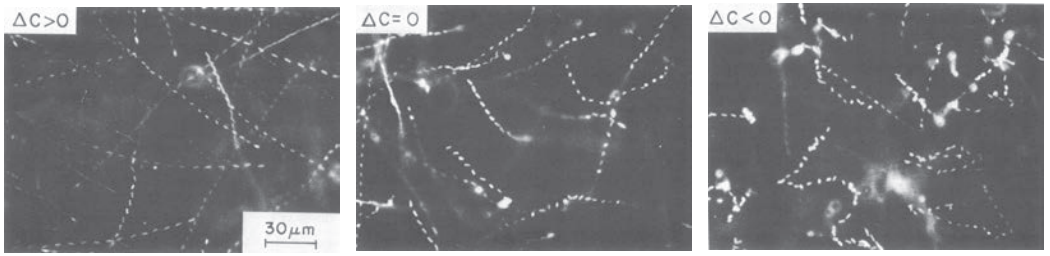


R. Phillips, The Molecular Switch: signalling and allostery. *Princeton Univ. Press*. 2020

Chemotaxis entails detection of a temporal gradient



- Bacteria detect a temporal change in concentration of chemoattractant
- As they navigate in space, they detect in time different concentrations
- This requires comparison of 2 measurements and memory



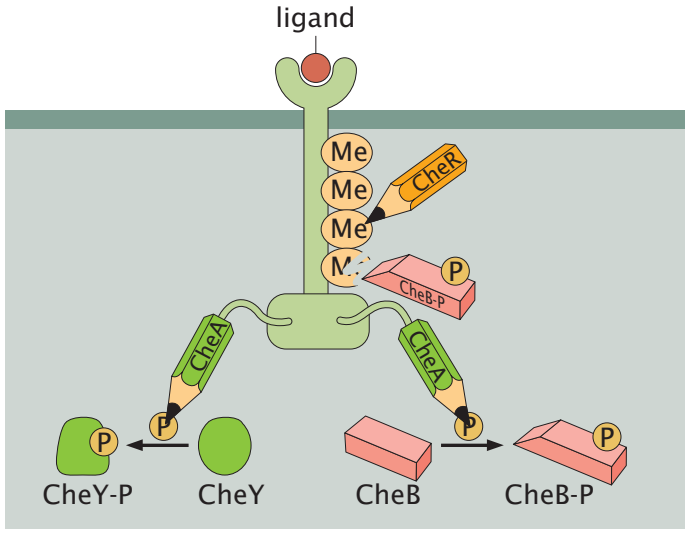
Salmonella typhimurium

R. Macnab. D.E. Koshland. *PNAS*. 69:2509-2512 (1972)

How is adaptation required for chemotaxis?

- Cells have a built-in short term memory to compare present and recent past and thereby read the concentration gradient

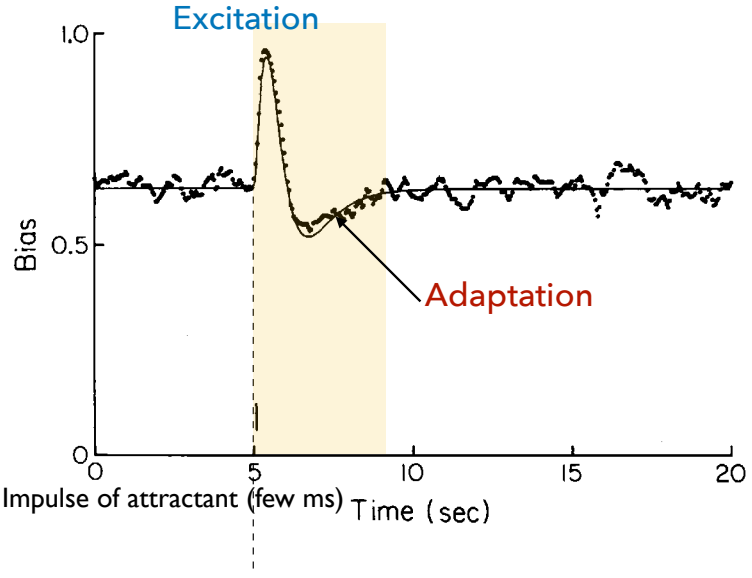
- **Methylation and demethylation take a few seconds and thus reflect receptor activity a few seconds ago (« memory »).**
- Receptor occupancy by ligand influences **the current activity state (which takes a fraction of a second).**
- By comparing the activity state of the cell (CheA) and methylation, the cell can compute how signal evolved in a few seconds, whether it increased, or decreased.



Fast (<<1s) Longer (2-3 s)

How is adaptation required for chemotaxis?

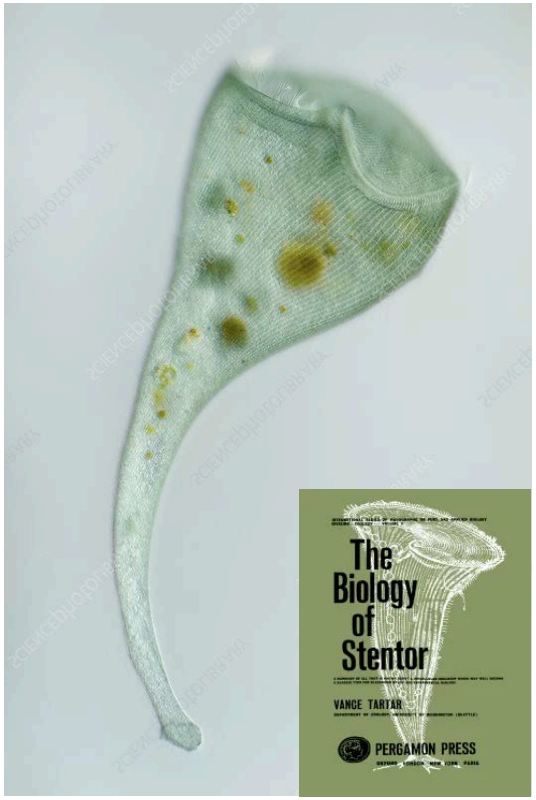
- **Cell response is integrated** over few seconds: response to very short pulse (ms), lasts about 4 seconds, the signal persists after the ligand is no longer present at the cell surface (it diffuses away within a fraction of a second).
- **The response is biphasic (2 lobes):** Cells increase their CCW bias, ie. they run for about 1s, then, reduce it and undershoot below the steady state value, and catch up. In other words, cells run smoothly for 1s (≈30µm distance), then tumble for 3s and catch up.
- **This indicates that cells perceive changes in concentration during this time interval**



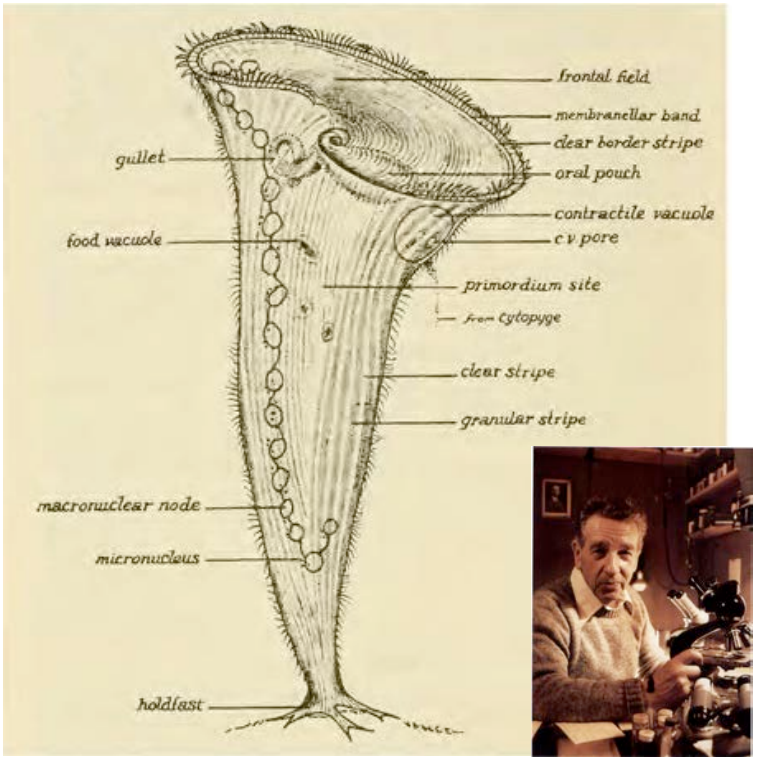
- Cells compare the response in first 1s (positive lobe), and next 3s (negative lobe).
- The comparison is a consequence of the adaptation mechanism
- Without adaptation, cells have no memory of recent past, and cannot read temporal gradient, hence cannot do chemotaxis.

SM. Block, J. Segall and H. Berg. *Cell*,. 31, 215-226 (1982)
J. Segall, SM. Block and HC. Berg. *PNAS*. 83:8987-8991 (1986)

Learning, memory and cell habituation



Stentor coeruleus



Vance Tartar 1911-1991

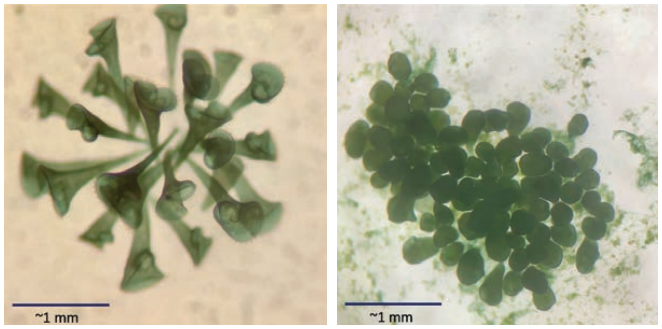
Learning, memory and cell habituation

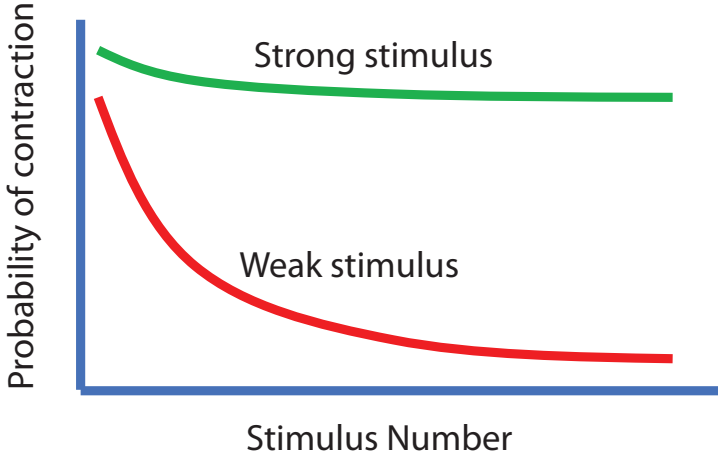
Habituation: the reduction of response to repetitive stimuli.

The ciliate *Stentor* contracts in response to mechanical stimulation. This response attenuates with repeated stimulation.

Defensive responses affect feeding, such that organisms should only respond defensively if the stimulus is really a threat.

As *Stentor* cells habituate, they learn and store a memory of previous stimulation to adapt their behaviour.

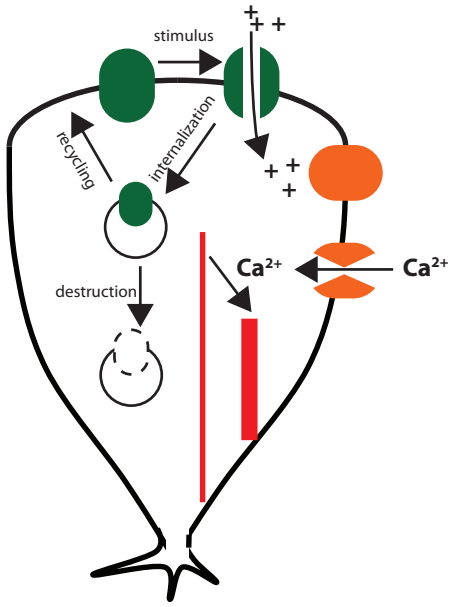


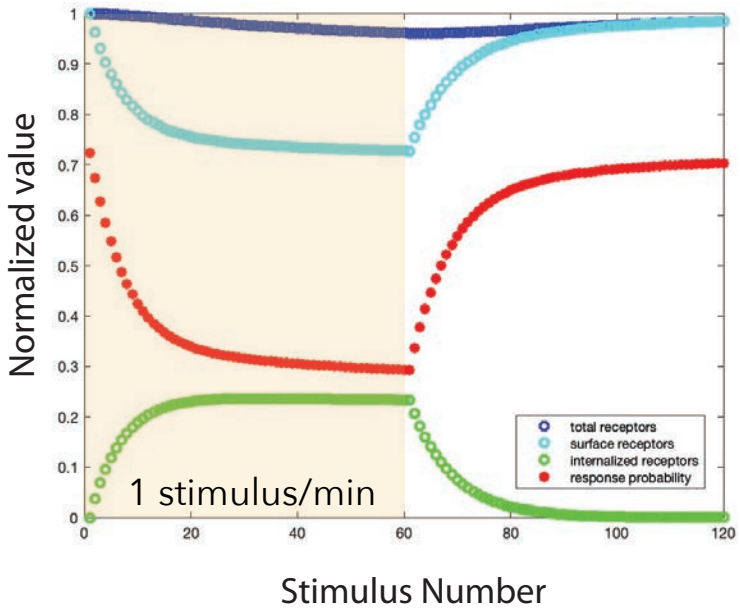


Deepa H Rajan and Wallace F. Marshall. *bioRxiv* https://doi.org/10.1101/2024.11.05.622147 (2024)

Learning, memory and cell habituation

- Learning: Internalisation of the receptor is induced by past stimulations.
- Memory: the internal pool desensitises cells and forms an internal representation/memory of past experience.
- Cells can be induced to forget by recycling the receptor at the cell surface.





Deepa H Rajan and Wallace F. Marshall. Biorxiv https://doi.org/10.1101/2024.11.05.622147 (2024)

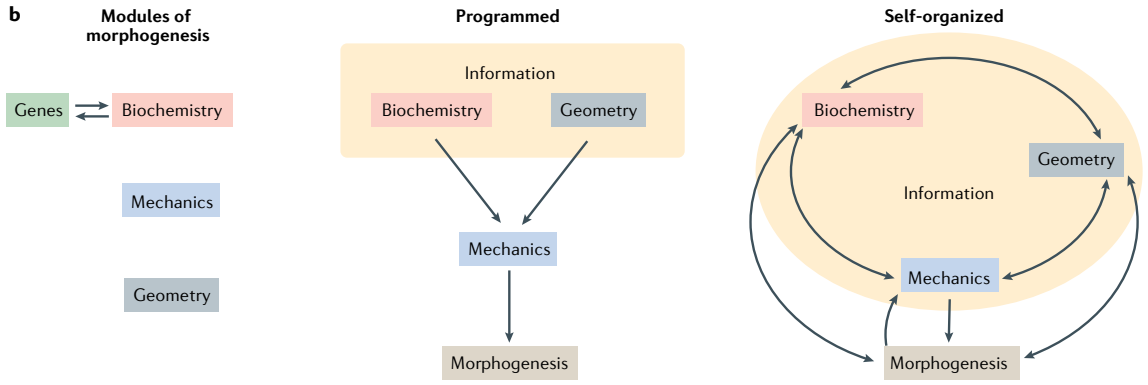
Scales of memory and learning

- Molecular memory
- Signalling memory
- Cellular memory:
  - Case study 1: chemotaxis in *E. coli*
  - Case study 2: cell habituation in *Stentor*
- Structural memory

Structure and Geometry: *information* and *memory*

- Cellular structures and cell geometry guide and constrain mechanochemical processes in cells.

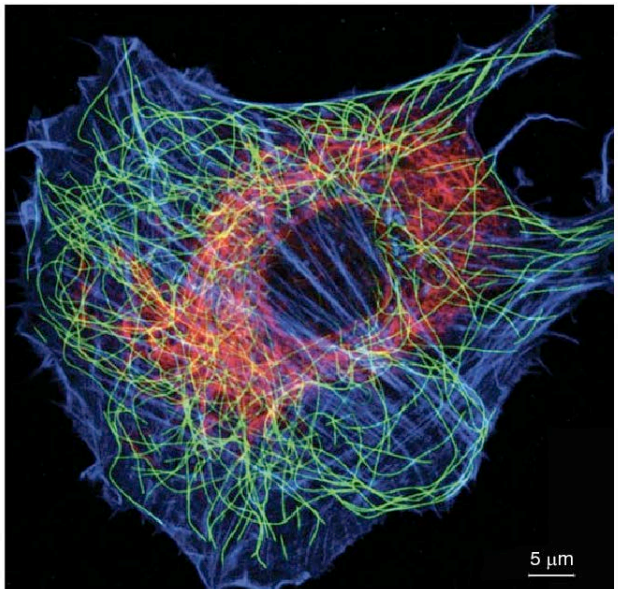
- **Implications:**
- Inheritance of cellular structures (organelles, membranes, centrioles, egg shape etc) as a **structural and geometric memory.**
- Stable memory, which may be reset by cellular signals.



Collinet C. & Lecuit T. *Nature Rev. Mol. Cell Biol.*, 2021

Structural memory

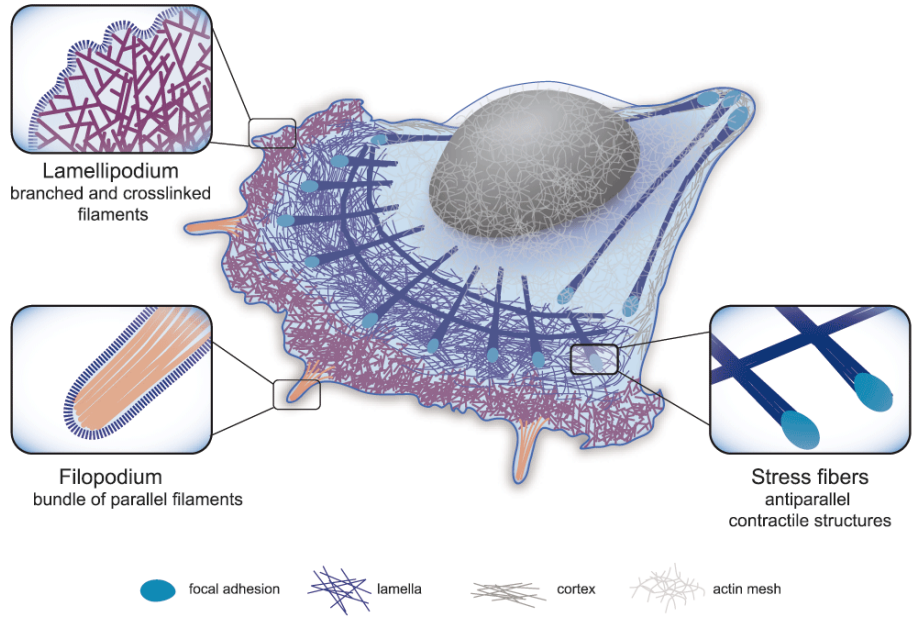
Cytoskeletal structures are dynamic and adaptive, yet manifest stability



Microtubules (green) : t~few minutes
Actin filaments (blue): t~ 10-100s.
Intermediate filaments (red): t >10 min

Harald Herrmann (University of Heidelberg, Germany)

- Turnover on different and tunable timescales.
- A brief signal may elicit a lasting structural reorganisation.



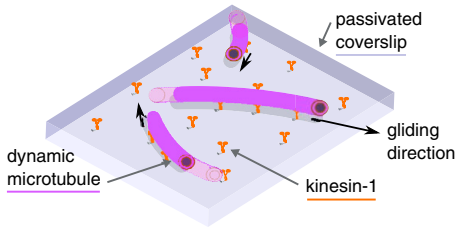
Pollard, T.D., Goldman, R.D. Cold Spring Harbor perspectives in biology 10.7 (2018).

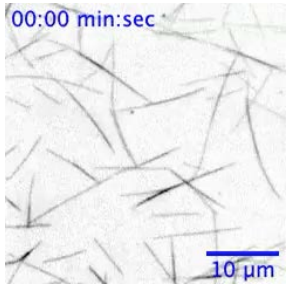
Letort G, Ennomani H, Gressin L *et al.*
https://doi.org/10.12688/f1000research.6374.1

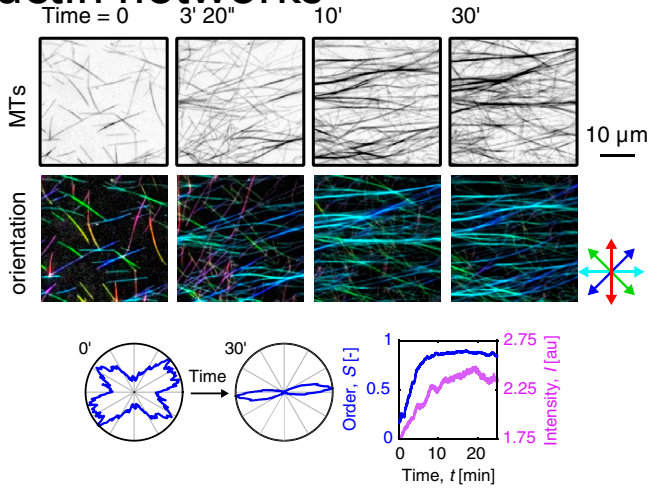
Structural memory

In vitro self-organisation of microtubules and actin networks

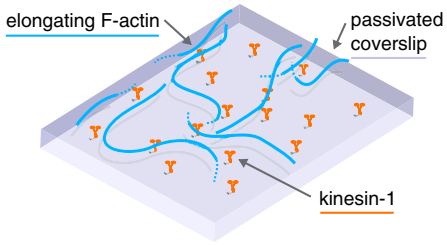
- **MT network form ordered, self-renewing networks.**
- MTs grow from seeds on glass coated with kinesis 1, with ATP and GTP, crowding agent.

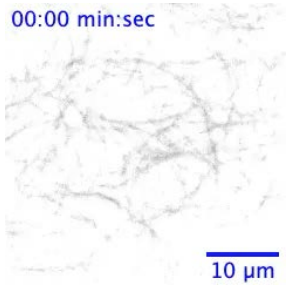


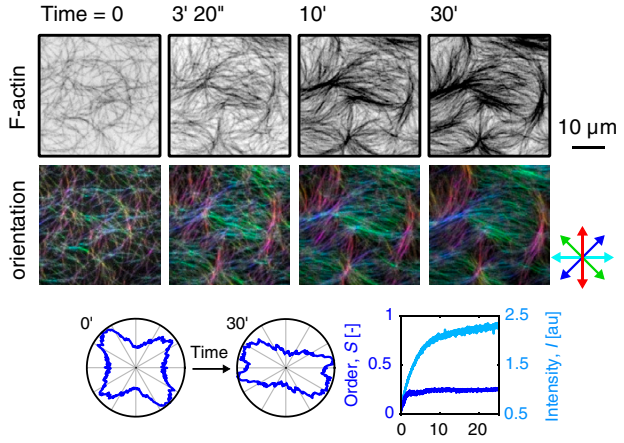




- **Actin filaments form semi disordered and stable networks.**
- Filaments are stable and don't turnover.





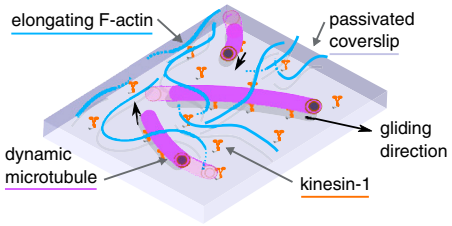


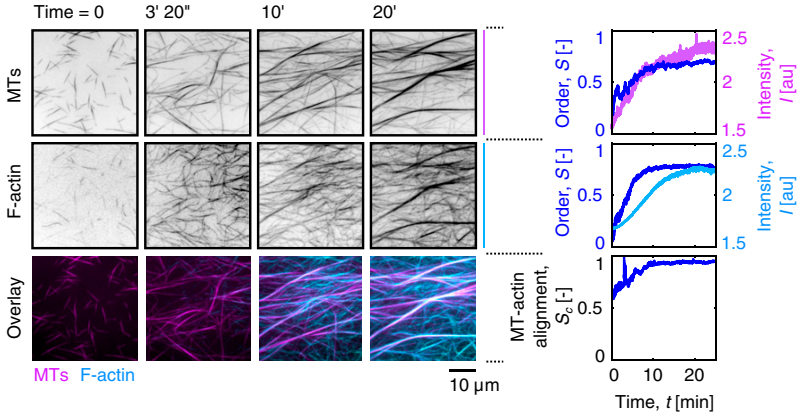
O. Kucera et al, M. Théry and L. Blanchoin. *PNAS*, 119(31):e2209522119 (2022)

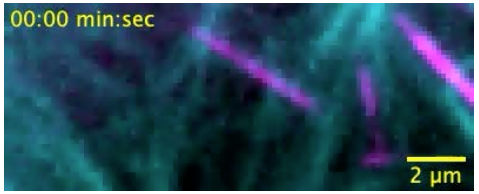
Structural memory

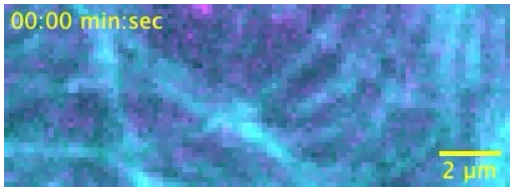
Co-assembly of MT and actin networks show reciprocal influences

- Co-assembly of MT and actin filament networks lead to the co-ordered organisation of both networks.
- Actin filaments can be deformed by growing MTs (left)
- Conversely, MTs growth may be guided by pre-existing actin filaments (right).







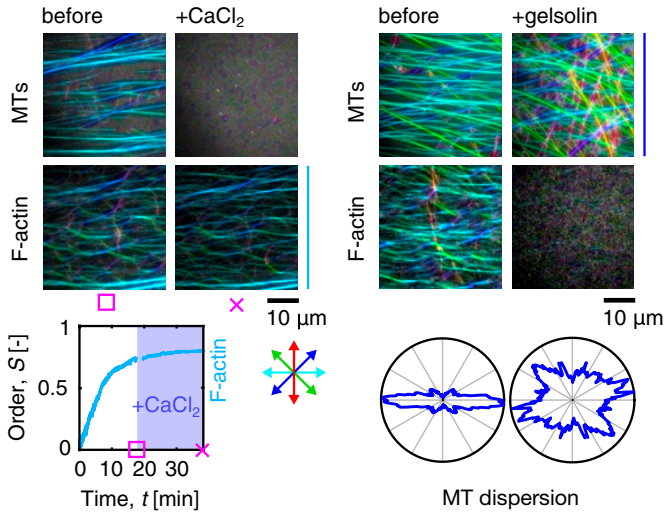


O. Kucera et al, M. Théry and L. Blanchoin. *PNAS*, 119(31):e2209522119 (2022)

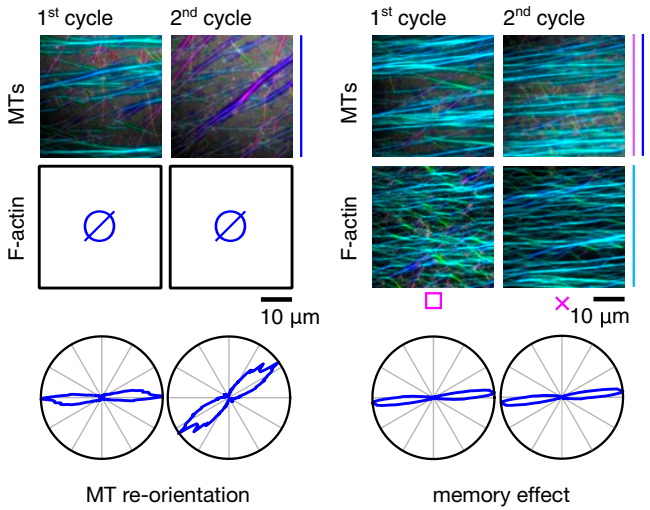
Structural memory

Stable actin filaments impart structural memory for microtubule growth

- Depolymerisation of MTs following co-assembly does not perturb F-actin organisation.
- However, actin disassembly causes MTs network to loose nematic order.



- **Sequential re-assembly of MTs after depolymerisation.**
- In absence of actin, re-assemby is in new direction.
- In presence of actin, re-assembly follows the orientation of actin network.

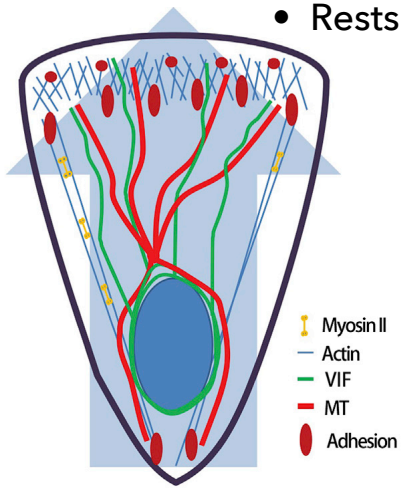


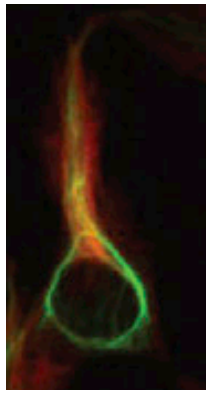
O. Kucera et al, M. Théry and L. Blanchoin. *PNAS*, 119(31):e2209522119 (2022)

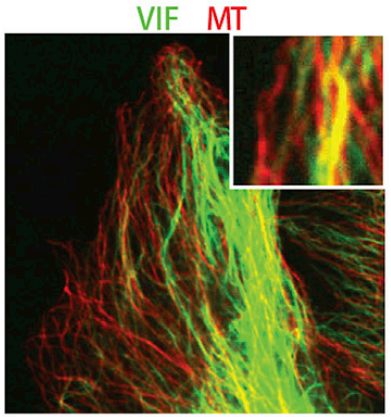
Structural memory

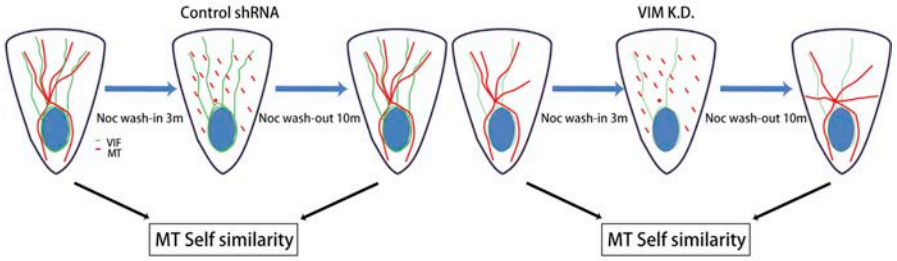
Intermediate filaments template MT growth and drive persistent cell polarity during motility

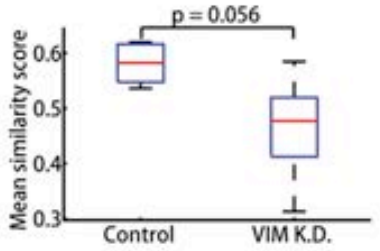
- Rests on lower turnover rate of intermediate filaments which forms a stable template

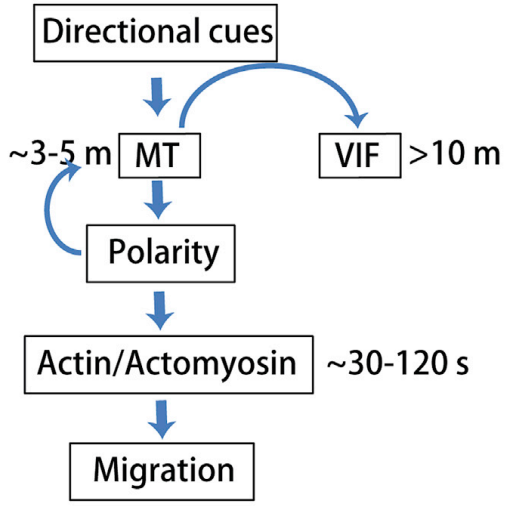










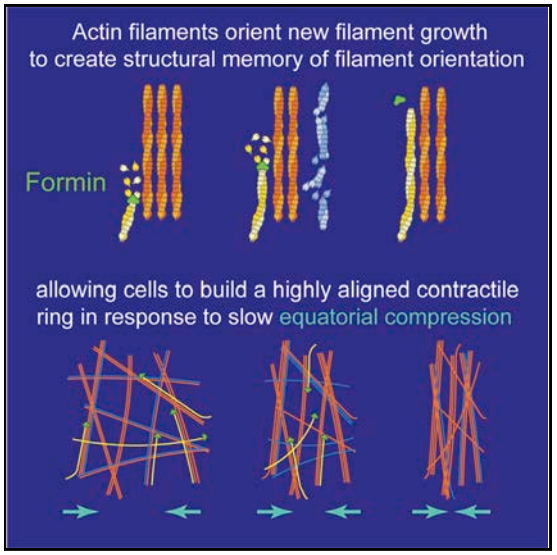


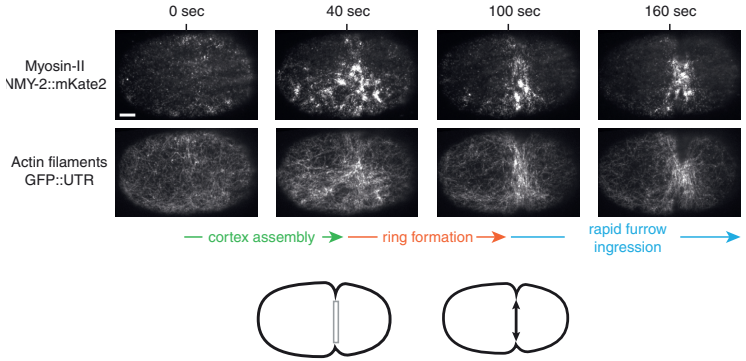
Gan et al., and G. Danuser. *Cell Systems* 3, 252–263 (2016)

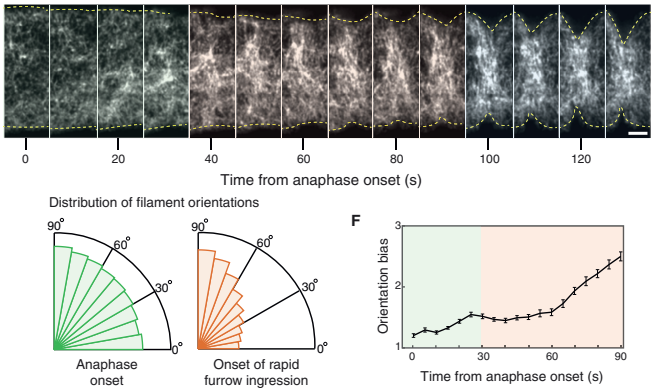
Structural memory

Structural memory in actin filament network assembly: cytokinesis

- Actin filament lifetimes are very short (<10 s) during cytokinesis in *C. elegans*
- Formin-assembled Actin filaments use existing filaments to orient their growth.
- **Filament-guided filament assembly increases the effective lifetime of filament orientation and thereby encodes structural memory of filament orientation.**
- **Structural memory allows compressive flows to build highly aligned filament arrays**







Y. Li & E. Munro, *Developmental Cell* 56, 2486–2500 (2021)

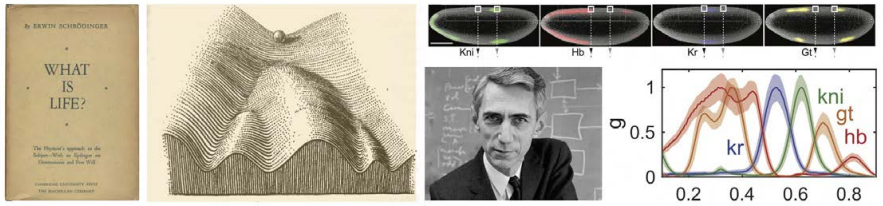
Conclusions and Perspectives

- Cells have evolved to learn and store chemical, structural information as memory.
- The time scale can be tuned (enhanced or reduced) and convey adaptive responses

Evolved learnability in biological systems? Why?

- Arriving at correct end point because initial conditions constrain and guide evolution
- In self-organised system there is no clear initial cue that constrains so reproducibility lies in properties of self-organised dynamics. Such properties are encoded in the system.
- Alternatively, such directionality may be learned in the life time of a biological system.
- Prescription (received information at onset), versus Learning.

Learnability is a key property of biological matter across scales.
Evolution produced learnable materials (chemical, mechanical and geometrical learnability).



Thomas LECUIT, chaire Dynamiques du vivant

Qu'est-ce que l'information biologique ?

COURS : 12 novembre > 17 décembre 2024

COURS

De 10h à 11h30
Amphithéâtre Guillaume Budé

Mardi 12 novembre 2024
Introduction :
quelles représentations pour le génome ?

Mardi 19 novembre 2024
Codes biologiques

Mardi 26 novembre 2024
Encodage, décodage
et représentations de *l'espace*

Mardi 3 décembre 2024
Encodage, décodage
et représentations du *temps*

Mardi 10 décembre 2024
Information structurelle et géométrique

Mardi 17 décembre 2024
Mémoires et apprentissages

COLLOQUE

De 9h à 18h
Amphithéâtre Maurice Halbwachs

Vendredi 16 mai 2025
Information Processing in Biological Systems

Les cours et colloques
sont gratuits, en accès libre,
sans inscription préalable.

- Yaron Antebi (Weizmann Institute)
- David Brueckner (Biozentrum Basel)
- Amy Gladfelter (Duke Univ)
- Thomas Gregor (Institut Pasteur, Paris)
- Steve Quake (Stanford, CZI)
- Lisa Manning (Univ. Syracuse)
- Madan Rao (NCBS, Bangalore)
- Manuel Thery (Institut Saint Louis, Paris)
- Aleksandra Walczak (ENS, Paris)
- Claire Wyart (ICM, Paris)