# **What is biological information?**



### enzymes E~, E2, E3 and El', E2', E3'. Enzyme E1 is in-<u>Course 6:</u> Cellular memory and learning

versely, enzyme E~' is inhibited by metabolited by metabolited by metabolite d, pro-Thomas Lecuit chaire: Dynamiques du vivant



# 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



OLLÈGE Thomas LECUIT 2024-2025

- *Learning*: sensing and decoding *external* information with memory
- *Memory*: transient or long term storage or representation of external information ry<br>rr ra<br>C ,<br>ms<br>or<br>rr



- Sensory systems: Bacteria chemotaxis, photon detection, acoustic pressure etc
- Nervous sytem: Internal representations of past experience
- Immune system: adaptive immunity, memory B cells
- of the system.<br>  $\bigcup_{n=1}^{\infty}$   **Evolution:** internalisation via selection of external world inside cells/organisms:
	- the circadian clock network is an internal representation of external diurnal cycle,
- ~-------------<----------------~--------------------------- die,<br>Digital plots of the displacement of the displacement of a wild to a wild the set of a wild the set of a wild t<br>displacement of the displacement of the mutant, A W 405, and a W 405, and a general set of the mutant, A 12.6 words (data points) per second. Tracking began at the points indicated by the large dots. The plots are planar projections of three- dimensional paths. If the left and upper panels of each figure are folded out of the page along the dashed lines, the projections appear in 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.
- 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.







- 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)



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# 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





- 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.





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



- 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 posttranslational 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 cycles: molecular switch or allosteric transition

 $\bullet$  Signalling pathways may be in an active or inactive state.

 $125.8\pm0.2$  and  $20.8\pm0.2$  and  $20.8\pm0.2$   $\pm0.2$   $\pm0.2$ 

centration is changed. The outcome is that a ligand can serve to regulate when molecules like those shown in Figure 1.2 are active. Our task is to explore different task is to explore

- $\bullet$  This rests on protein that exist in 2 co  $\bullet$  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). tence as they switch between active and proteins. These proteins in turn  $\frac{1}{2}$  an effector and/or inducer favoured in the active state (eg. open).
	- $\bullet\,$  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.  $\begin{array}{|c|c|c|c|c|}\hline \end{array}$





### Molecular cycles: molecular switch or allosteric transition<br>— *Molecular cycles: molecular switch* or allosteric transition  $125$  Molecular cycles: mo

• Time scale of transition: micro to millisecond..

✐

- Stability of new state following allosteric transition: 2-4 orders of magnitude longer.  $\blacksquare$  Time scale of transition: micro to millisecond.. new state following allosteric transition: 2-4 orders of h
- 106 Chapter 3 Signaling at the Cell Membrane: Ion Channels  $3.6$  Rate Equation Description Description  $\mathcal{O}(\mathcal{A})$ • Ex 1: Acetylcholine receptor: a ligand gated Na+ channel. 82 Chapter 3 Signaling at the Cell Membrane: Ion Channels

✐



 $\sum_{i=1}^n$  36), these definitions mean that we can write the probability of the open that write the open the open the open the open the open that we can write the open the open the open the open the open the open the ope *popen* <sup>=</sup> *<sup>e</sup>*−βε*open <sup>e</sup>*−βε*open* <sup>+</sup> *<sup>e</sup>*−βε*closed*

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R. Phillips, The Molecular Switch: signaling and allostery. Princeton Univ. Press. 2020 *on*, (3.71)

Kinetic scheme for the simplest MWC ion  $s^{-1}$  $10^4$  $10^{-1}$  $b<sub>0.2</sub>$  $\frac{10}{10^2}$  $\frac{10}{10^4}$ 

 $10<sup>6</sup>$ 

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

![](_page_11_Picture_4.jpeg)

#### Molecular memory polarism non-stellar continuum which has been a continuum which has been a continuum which has been a continuu *<i>R I*nemory *Cambridge, Cambridge CBJ OHA, UK.*  middle. De broad de<br>De broad de *Andrew Lawrence is in the Department of*  monomers are initially unmodified. lecular memory whether the dimer  $\boldsymbol{\zeta}$

state or in the inactive (-,-) state, the substitution of a single new unmodified

#### Memory and molecular turnover music molecular turn

*from Francis Crick* 

**Neurobiology** 

*London E1 4NS, and Martin Ward is at the* 

RECENT spectacular advances in molecular NATIJRE VOL.312 8 NOVEMBER 1984 ----------NEWS AND VIEWS **MATURE VOL. 312 8 NOVEMBER 1**<br>NATURE VOL. 312 8 NOVEMBER 1 will obtain the course remain (-,-) during  $\alpha$ metabolic turnover. This mechanism is

- $\bullet\,$  How is memory stored in the brain so that its trace is  $\qquad \bullet\,$ relatively immune to protein turnover?  $\mathbf s$  so that its trace is a contact technical reason why all its components  $\alpha$  $\overline{U}$  so that its trace is  $\overline{O}$ **•** How is memory stored in the brain so that its trace is RECENT spectacular advances in molecular biology immune  $t_{\rm tot}$  used in cells of the immune system. o protein turnover?  $\hspace{0.1mm}$
- $\bullet\,$  All proteins turnover in hours or days. days. Sequenced and characterized. We also characterized a days. massive impact on certain key problems in  $\bullet\,$  All proteins turnov that there is a special *local* piece of DNA (or  $\mathop{\mathrm{er}}\nolimits$  in nours or days.
- Memory could be encoded in alterations to particular sequences of DNA: in cells (akin to immune cells) or locally at synapses. terations to particular to immune cells) or loca orations to portioular erations to particular  $\mathsf{r}_\mathsf{c}$  imposing collected or locally sequences of DNA: in cells (akin to immune cells) or locall  $\bullet$  Moreonicoould be  $\bullet$  when not y could b sequences of Divi  $\alpha$ to  $\gamma$  impose. peoded in elterations to pe  $\mathop{\mathsf{incode}}$ a in alterations to pa in calle (akin to immune ce needs (aktive international might be worth bearing in mind, since each  $\blacksquare$ cuidi models of this general type. The type of this general type. The type of this general type. The type of the type. The type of the type of the type of the type of the type. The type of type of type. The type of type of  $\Omega$  or locally
- Or RNAs: alternative promoter choice (eg. Protocadherins, 60 variable exons), or alternative splicing. RNAs tend to be short lived noice (eg. Protocadherin spilcing. Kivas tend to b very large low density regions may remain  $\bullet\,$  Or RNAs: alternative promoter choice (eg. Protocadherins thousand thousand the less control of the AGN contr spilcing. Rivas tend to be  $\mathbf{r}$  and the species. All this, together with techniques such as paralleles such as paralleles such as paralleles such as paralleles such as  $\sim$ ation in the process tell us and in the process of e promoter choice (eg. Protocadherins, which is not it also Another alternative is that each synapse or alternative splicing. RNA relatively immune from molecular turnlation and so forth.
- Memory could be encoded in very stable proteins (ex. Prions) ery stable proteins (ex.  $\;$ ry stable proteins (ex. a Momory.could be  $\bullet$  ivierriory could be and longable a could be a moto  $f$ ncoued in very stable prot $\epsilon$ during development.  $f(x)$  is mature form, to migrate from  $f(x)$

Since none of these alternatives seems since none of these anematives seems<br>especially attractive, one is more inclined to  $\frac{1}{2}$  or a seconomistic day of  $\frac{1}{2}$  $\mu$  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 pro-sooperative in suggest models that are cooperative in  $\mathbb{R}$  ratios. That is the unclearly in the soft **g** the overall state of **Memory and Memory an** the structure.

![](_page_12_Picture_10.jpeg)

will be it in the same state. That is, the same state is, that is, that is, the same state is, that is, that i

Francis Crick

- A Consider a protoin  $\bullet$  Consider a protein relative on noc aepenanig on pos abosphandation a priosprior yiauon, a  $\frac{1}{2}$ nat may be active  $(\pm \mu)$ ir ranglational modification ransiational modification  $f_{\rm con}$  dimerically  $\mu$  can unnerise.  $\bullet\,$  Consider a protein P that may be active (+)/in do nonding on noct the is very weak. shop through the workshop, or priosprior yiation, ar  $\mathcal{P}_1$ ,  $\mathcal{P}_2$  are more  $\mathcal{P}_3$  and  $\mathcal{P}_4$  on  $\mathcal{P}_5$  are may be active (+)/inactive (-) ranclational modification can dia dependent in distribution in the set of the set be reduced. The mechanism can be reduced. phosphorylation, and can dimerise. fiable site per monomer; rather than phos- $\mathbf{p}_1$  depending on post translational modification eg.
- de decument Since the directions in the set dimer is active: activates P if the other prote activates for the other prote sized monomers should be immune to the  $\rho$  Assume that an enzym produce and the entry of rtivates P if the other proto activates in the other prote molecular turnover and that these new  $\mathsf{nd}$  to be  $\mathsf{d}$  are a number of subsidiary con- $\det$  divide  $\det$   $\theta$  assume that an enzyme activates P if the other protein in

suggest models that are cooperative in (-, +) -> (+,+) and ( -) unchanged  $\mathbf{r}$  to  $\mathbf{r}$  the picture in the p  $(-, +)$   $->$   $(+, +)$  and ( ns (ex.  $\left(\frac{1}{2}, +\right) \rightarrow \left(\frac{1}{2}, +\right)$  and (-, -) unchanged

- s New menemers are in  $\bullet$  rew monomers are  $\mathfrak n$  $\tau$ **•** New monomers are inactive when produced. • New monomers are inactive when produced.
- $\bullet$  Protein turnover does the structure of the structure to cont change the state  $s$  and proposed of different method. **•** Protein turnover doesn't change the state of dimer. substitution of a single new units.  $\frac{1}{2}$  $\bullet~$  Protein turnover doesn't change the state of dimer.
- Synapse reinforcement leads to phosphorylation of F occurred to me to think of the simplest. versa for inhibition). fully for modifications to synaptic proteins will leave it in the same state. That is, the same state is, the same state is, that is, the same state is, that is, the same state is, the same  $\bullet~$  Synapse reinforcement leads to phosphorylation of P (or vice
- cunoped rainforcament Can by capital can exist in the state in in spite of protoin turnover in spite or protein turnover. p spite of protoin turnover n spite of protein turnover. • Synapse reinforcement in spite of protein turnover. with the above processes.

![](_page_12_Picture_19.jpeg)

Seyfert Type II NGC1068 has a highly

Post-translation modifications: Reversible protein modifications induced by pairs of proteins *GTP cycle, phosphorylation cycle, methylation cycle*

![](_page_13_Figure_2.jpeg)

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

![](_page_14_Figure_3.jpeg)

Cellular behaviour/state Cellular dynamics

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

![](_page_14_Picture_7.jpeg)

 $\mathsf{G}$ 

15

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

![](_page_15_Figure_3.jpeg)

![](_page_15_Picture_4.jpeg)

# 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

![](_page_16_Figure_5.jpeg)

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

![](_page_16_Picture_7.jpeg)

#### Hebbian learning - lessons from neuroscience  $\mathsf{Q}$  - lesso that that  $\mathsf{U}$ anatomy and physiology of the 1940s was irrelevant. Italia in as seems ob is a final deposition and set that the parties of the set of the s neural data, and his theory of the claimed that his theory of the claimed that his theory of the con- $\mathsf{q}$  - lesso that the  $\mathsf{u}_\mathsf{A}$ anatomy and physiology of the 1940s was irrelevant. If, as seems obvious, behaviour electrical bearning - lesso  $1111$ y consider be considered as  $1111$ representations of the S–R relationship in but was van die van di<br>Die van die va different receptors could reach the same learned recognition structure. Hull36 suggested electrical activity changed all this. Simple all this is a simple all this is a simple all this is a simple al tions consider be considered as  $\mathbf{r}$

![](_page_17_Picture_1.jpeg)

1949

![](_page_17_Picture_3.jpeg)

#### Donald E. Hebb (1904-1985) Box 2 | Development of the 'Hebb synapse' postulate: 1934 Box 2 | Development of the 'Hebb synapse' postulate: 1934

![](_page_17_Figure_5.jpeg)

phenomena must be related to neural activity,

phenomena must be related to neural activity,

living organisms; the intrinsic activity of the

![](_page_17_Figure_6.jpeg)

different receptors could recept the same learned recognition structure. Hull36 suggested that it was by "afferent neural interaction", but it was by "afferent neural interaction", but it was a strategies of the strategies did not explain how that process might work. Hebb that the second that the second that the second that the second the be solved by the application of up-to-date

on the pattern of the stimulus, and not on the stimulus, and not on the stimulus, and not on the stamulus, and specific location of the stimulated receptors, so that stimulated receptors, so that is so that in the stamps of similar patterns always gave rise to the same field. Gestalt theory could not explain how the could not explain how the could not explain how the could not recognition of the field was acquired, however, however, When this question are the Gestalt answers are the Gestalt answers are the Gestalt answers are the Gestalt answers and was that recognition took place in the mind. The rival behaviourist school of the rival behaviourist school of the rival behaviour on the other hand, could explain the learning but was vague as to how a pattern falling on different receptors could reach the same learned recognition structure. Hull36 suggested that it was by "afferent neural interaction", but it was by "afferent neural interaction", but it was a strategies did not explain how that process might work. Hebb that the thought the these problems could be solved by the application of up-to-date application of up-to-date application of up-to-date application of u neural data, and his theory is the claimed that his theory is the claimed that his theory is the claimed that h

different receptors could recept the same learned recognition structure. Hull36 suggested that it was by "afferent neural interaction", but it was by "afferent neural interaction", but it was a strategies of the strategies did not explain how that process might work. Hebb that the thought that the theoretical be solved by the application of up-to-date application of up-to-date

intention or desire, should such 'heresy' ever Hans Berger's announcement, in 1929

living organisms; the intrinsic activity of the path must be taken into account. For Hebb, account this meant that psychologists could no longer

that it was by "afferent neural interaction", but

only marginally better than the 1920s. The 1920s of the 1920s of the 1920s of the 1920s of the 1920s. Little was known about the structure and structure and structure and structure and

only marginally better than the 1920s. Little was known about the structure and structure and structure and

As **a Ph.D. student at the University of Chicago in 1934, Hebb research in a paper for the student of Chicago in A** direction of transmission of impulses. direction of transmis **figures from this paper (panel a) illustrates the Hebb synapse principle. A represents an afferent**

**As post processor in 1936, Hebbers in 1935, Hebbers in 1936, Hebbers in 1936, Hebbers** do not necessarily activate B. Arrows show **find to turn**<br>direction of transmission of inpulses. Figure 2. Representation of cel activates two others in the cord. Cell D forms a possible route A,A',D,C so that impulses in A' of impulses.

Acquisition of conditioned reflexes. Co-incidence of the pair **his anatomy class, entitled 'The interpretation of experimental data on neural action'. One of the figures from this paper (panel a) illustrates the Hebb synapse principle. A represents an afferent his anatomy class, entitled 'The interpretation of experimental data on neural action'. One of the** excitation in A and reflex activity in X reinforces the synapse whole w **ricy** in A commonses and Synapes **WHOIC**  $h_{\rm H}$  when we write  $\sigma_{\rm H}$  whose writing his book, when  $\sigma_{\rm H}$ excitation in A and reflex activity in X reinforces the synapse  $\frac{1}{2}$  whole he would have woven from it? 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 learned (auto-associated) pattern an engram » The legacy of Donald O. Hebb: more than the Hebb Synapse The legacy of Donald O. Hebb: more than the Hebb Synapse the biown and i.i., miner *intuite regional coronal composition* in  $(2000)$ , 7.1015-1017 The legacy of Donald O. Hebb: more than the Hebb Synapse re Neuroscience, (2003), 4:1013-1019 learned ( The legacy of Donald O. Hebb: more than the Hebb Synapse  $n, 4.1013 - 1019$ **Hebb modified the neurobiotaxis theory in two ways: 1) only active axons would grow towards active R.E. Brown and P.M. Milner** *Nature Neuroscience.* a the legacy of Donald O. Hebb. more man the Hebb **S** 

courtesy of Mary Ellen Hebb. courtesy of Mary Ellen Hebb. did just that the second that the second that the second terms of the second terms of the second terms of the anatomy and physiology of the 1940s was only marginally better than that of the 1920s.

Figure 2 | **Dalhousie University.** Donald O. Hebb at Dalhousie University, circa 1922. Photo

Figure 2 | **Dalhousie University.** Donald O. Hebb at Dalhousie University, circa 1922. Photo

### er if they

# fire together »

 $\overline{\text{ }}$  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 ». Let us assume that the persistence depeated in persistently take  $\sum_{n=1}^{\infty} B_n$  is increased the set was available to  $\mathbf{H}$  proved to be unreliable.  $\ll$  Let us assume that the persistenc  $\frac{1}{2}$  =  $\frac{1}{2}$ I allear repeatedly or persistently take be cells firing  $R$  is increased  $\infty$  $\blacksquare$  the cells firing B, is increased ».  $\mu$  changes that and to  $\mu$ cortex is the learning for learning  $\frac{1}{2}$ . dly or persistently takes i process or inetabolic char by sight and  $\sum_{i=1}^n$ stem nuclei. Synaptic transmission was still ever be ration, making in the psychological data that the psychological data that  $\mathbf{r}$  is a reduced by  $\mathbf{r}$  $t_{\text{sc}}$  action of psychoactive drugs, learning, l neurig con nisms much more difficult to understand than the today in the total than the top show that we know that we know the show that we have found the show that  $B$  and repe most synaptic transmission is chemical. the case. Hebb also believed that perceptual  $\frac{1}{2}$  $\mathcal{L}$  as convinced, on the basis of his 1929  $\ldots$ learning developed slowly, whereas we now  $k = \frac{1}{2}$ by sight with within a few hours of birth, and might with  $\mathbf{u}$ 

« 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 ing to turn on every office elements that do not form part 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 If the inputs to a system cause the  $100 \text{ ergy}$  incr-associated. That is, viloit will become auto-associated earned (auto-associated) pattern an eng If the inputs to a system cause the s phase-sequences. Here is a sequence of the sequence of  $\frac{1}{2}$ trongly inter-associated. That is, each  $\frac{1}{1}$  is  $\frac{1}{1}$  in  $\frac{1}{1}$ whole will become 'auto-associated'. s to a system cause the s sequences as neural representations of individual representations of images as neural representations of images  $-$ associated. That is, cach **figures from the nervous from the nervous principles from the nervous principles principles principle. A represent of the elements that do not have recognized the nervous principles in the nervous principles of the nervou** henest so measures of the active reflexion of the pattern. To put it another way, the co-incidence of the pattern bedine also asse need revision in the light of new discoveries.

 $he$  Organization of Behavior $\cdot$  a Neuronsych  $(Wiley, New York, 1949)$  $\left(1, 1, 1\right)$ **routes, such as A–C–Y, A–D and A–E. So, to explain the acquisition of conditioned reflexes,**  $H(x, t)$  and  $\theta$ **routes, such as A–C–Y, A–D and A–E. So, to explain the acquisition of conditioned reflexes, built shifted units interneuron D. O. Hebb, The Organization of Behavior; a Neuropsyce** D. O. Hebb, *The Organization of Behavior; a Neuropsychological Theory* 

![](_page_17_Picture_17.jpeg)

**Thomas LECUIT 2024-2025 as LECUIT 2024-2023 and 20 as LECUIT 2024-2025 and 20**  $10$ 

#### Hebbian learning - lessons from neuroscience synaptic neurons and thus forms a retrievable memory. As a result, cue-driven recall in neural circuits with only  $\epsilon$ non-Hebbian-Iearning - lessons trom-neuroscier, where the bianan extension to achieve a better fit with experimental learning - lessons from neuroscience  $\overline{\phantom{a}}$  receiving the achieve a better fit with experimental  $\overline{\phantom{a}}$ is unspecific by enhancing all outgoing synapses from neurons activated by a stimulus. In contrast, Hebbian plasticity potentiates selectively synapses targeting only active postsynaptic neurons and thus forms a retrievable memory. As a result, cue-driven recall in neural circuits with only

![](_page_18_Figure_1.jpeg)

nd a small recurrent attractor memory using Hebbian plasticity. Synaptic  $\mathbb{R}^n$  $B<sub>1</sub>$  The below discrimination plasticity is functionally from encoding seven sparse (W) resulting seven space  $\mathcal{L}$ 

![](_page_18_Picture_3.jpeg)

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non-Hebbian-STP leads to a spreading activation, unlike in circuits with Hebbian-STP, where  $\alpha$  retrievable memory is encoded.

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

- $\bullet$  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.

![](_page_19_Figure_4.jpeg)

![](_page_19_Figure_5.jpeg)

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

![](_page_19_Figure_7.jpeg)

# 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.

![](_page_20_Figure_8.jpeg)

![](_page_20_Picture_9.jpeg)

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

# 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

![](_page_21_Figure_5.jpeg)

![](_page_21_Figure_6.jpeg)

Wilson et al., and J. Toettcher. *Molecular Cell* 67, 757–769 (2017) orescence microscopy images of the three stages measured during the signaling H.G. Garcia and R. Phillips. *Physical Genomics - from E.coli to Elephants, PUP* 

# 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.
	- o If time is too long,, fewer pulses and transcription is lower.

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

![](_page_22_Picture_10.jpeg)

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![](_page_22_Figure_12.jpeg)

 $10^2$   $10^3$   $10^2$   $10^3$   $10^5$   $10^7$   $10^8$   $10^9$   $10^8$   $10^9$   $10^9$   $10^8$   $10^9$   $10^9$   $10^9$   $10^9$   $10^9$   $10^9$   $10^9$   $10^9$   $10^9$ 

 $10^{1}$   $10^{2}$   $10^{3}$   $10^{1}$   $10^{2}$   $10^{3}$   $10^{1}$   $10^{2}$   $10^{3}$   $10^{1}$   $10^{1}$   $10^{1}$   $10^{2}$   $10^{3}$ 

 $10^{1}$ 

# 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).

![](_page_23_Figure_6.jpeg)

![](_page_23_Picture_7.jpeg)

Thomas LECUIT 2024-2025

24 Ming, Zhu, Li. Journal of Genetics and Genomics, [doi.org/10.1016/j.jgg.2021.01.006](http://doi.org/10.1016/j.jgg.2021.01.006) (2021)  $\mathcal{L}$  is an uncervative observation, considering the well-known  $\mathcal{L}$ 

# Molecular memory in the life time of an organism

VDJ recombination in immune cells (B and T lymphocytes)

![](_page_24_Figure_2.jpeg)

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

![](_page_24_Picture_4.jpeg)

![](_page_24_Picture_5.jpeg)

mental challenge (such as virus infection), resulting in a

#### CRISPR mediated immunity against bacteriophages a iminumiy agamst bactenop tospacer Adjacent Motif (PAM), a short sequence next to the protospacer that is recognized by the adaptation  $\mathcal{L}$

- 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.

![](_page_25_Figure_5.jpeg)

array. Obviously, such targeting would targeting would targeting would targeting would targeting would targeting  $\sim$ 

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

![](_page_25_Figure_7.jpeg)

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

![](_page_26_Picture_5.jpeg)

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.

![](_page_27_Picture_4.jpeg)

### Memory of cellular state - Signalling **induced upon the Memory of cellular state**

![](_page_28_Picture_1.jpeg)

tached. Such a system would be completely independ-

#### F. Jacob and J. Monod F. Jacob and J. Monod

**EXECUTE:** General Conclusions: Teleonomic Mechanisms in Cellular **Metabolism, Growth, and Differentiation**   $\alpha$ <sup>, S</sup>G<sup>3</sup> and another regulator  $\alpha$  and  $\alpha$  and  $\alpha$  and  $\alpha$  and  $\alpha$ Metabolism, Growth, and Differentiat

**I2** 

by JACQUES MONOD AND FRANÇOIS JACOB

.<br>*Services de Biochimie Cellulaire et de Génétique Microbienne, Institut Pasteur, Paris* duces de Diochimie Cettataire et de Genetique mucrootenne, finstitut flasted

- $\bullet$  Cell differentiation in eukaryotes persists once it has been induced.
	- $\bullet$  What are the mechanisms of perpetuation of collular state? of the past eight days, we would like to express the  $\bullet\,$  What are the mechanisms of perpetuation of cellular state?

of the subject and the timing of this conference were The models involving only metabolic steady-states interest of the sessions. The sessions of the session in the session of maintained by allotteric effects are insufficient to account for differentiation, which must involve directed Island Biological Laboratory, and to Dr. Umbarger alterations in the capacity of individual cells to *syn*we show the processes. Such models would seem to ceedings of a meeting where such an abundance of obous, and thereafter more or less permanent, "memorization" by cells of a chemical event. The problem of memory itself might usefully be considered from this the solution of the same solution of the use as a result of the same state  $\alpha$ maintained by allosteric effects are insufficient to acthesize specific proteins. Such models would seem to be most adequate to account for the almost instantanememory itself might usefully be considered from this

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

![](_page_28_Picture_10.jpeg)

might function in apparently unrelated pathways.

is an inducer or a repressor of the other. Another type

erties of this circuit will show that, provided ade-

![](_page_29_Figure_1.jpeg)

temporary metabolic advantage, will permanently in-

 $\bullet\,$  Network with cross inhibitory feedback enzymes E~, E2, E3 and El', E2', E3'. Enzyme E1 is ininhibitory feedback  $\mathcal{L}_{\mathcal{A}}$  and the active pathway. It should be noted that  $\mathcal{L}_{\mathcal{A}}$  $\bullet$  inetwork with cross was discovered) to account for certain alternative control of certain alternative control of certain alternative

![](_page_29_Figure_3.jpeg)

 $\bullet$  Inducible system positive feedback circuit wide inhibition) (vid double immolder) positive feedback circuit  $(a_i, b_j)$  in the system by induction  $(a_i, b_j)$ 

![](_page_29_Picture_5.jpeg)

 $\overline{DE}$  FRANCE Thomas LECUIT 2024-2025

![](_page_29_Figure_7.jpeg)

• Network with cross inhibition be synthesized unless already present, when it will  $\bullet$  inetwork with cross inhibition  $\bullet$  Notwork with cross inhibition  $\overline{\phantom{a}}$  incredit with Cross immortion **•** Network with cross inhibition

![](_page_29_Figure_9.jpeg)

 $\bullet\,$  Network with co-activation repressive synthesized by the regulation.  $\bullet$  Network with co-activation **The regulation system co-dcuval** 

*thesize* specific proteins. Such models would seem to *« 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  $h_{\Omega V}$ *however in an arbitrary manner. »* 

count for differentiation, which must involve directed

![](_page_29_Figure_12.jpeg)

 $\bullet\,$  Network with double negative feedback, ie. positive feedback  $\bullet$  Network with double negative tive to the repressor synthesized by RG2. The action of tivates  $S_{\rm{eff}}$  sG8 and RG2 (and therefore inactivates in activates in activates in activates in activates in

Monod, J. & Jacob, F. *Cold Spring Harb. Symp. Quant. Biol.* 26, 389–401 (1961).<br>Thomas LECUIT 2024-2025 Monod, J. & Jacob, F. Cold Spring Harb. Symp. Quant. Biol. 26, 389–401 (19

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

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

#### JOHN E. LISMAN

Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology<br>Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology (Neurobiology

Department of Biology, Brandeis University, Waltham, MA <sup>02254</sup>

Communicated by William P. Jencks, January 14, 1985

ABSTRACT A mechanism is proposed for <sup>a</sup> 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.

![](_page_30_Figure_7.jpeg)

![](_page_30_Figure_8.jpeg)

![](_page_30_Picture_9.jpeg)

Downloaded from https://www.pnas.org by "INIST-CNRS CS10310, INEE & INSB" on December 13, 2024 from IP address 193.54.110.55.

#### Memory of cellular state - Bistability rallular stat*c* triggering s :I:

Figure 1

- (red), and protein B inhibits or represses A. ictable could be a state with the state with  $\sim$ • A genetic or biochemical network is bistable  $\begin{bmatrix} \text{[trigger 1]} & \rightarrow \text{A} \\ -T & -T & -T \end{bmatrix}$ when two states are possible at the same  $\hskip1cm \Box$ concentration of a stimulus.
- there could be a stable steady state with both • Two general classes of bistable networks:  $\left|\frac{\ddot{\ddot{\xi}}}{\dot{\xi}}\right|_A\left|\frac{\ddot{\xi}}{A}\right|_A$ 
	- Mutual cross-inhibition
	- Positive Feedback
- Bistability requires minimally:
	- $\mathcal{S}$ a non linear step (eg. ultrasensitivity).
	- t the network. The issue that  $\mathbf{r} = \mathbf{r} \cdot \mathbf{r}$ its off or its only if the state  $\mathbf{r}$ t the network in a bis A relative symmetry in the 2 arms of the network.
- path-dependent l  $\bullet$  Bistability requires hysteresis, namely path-dependent  $\qquad \qquad \qquad \overline{\Box}$  $me^{100}$ behaviour, such that the trajectory forms a loop.  $\qquad \qquad \rule{2.5cm}{0pt}$   $\qquad \qquad \rule{2.5cm}{0pt}$
- Hysteresis locks the system in a given state, and  $\begin{array}{cc} \mid & \mid & \mid \end{array}$ imparts memory to a transient stimulus

![](_page_31_Figure_10.jpeg)

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

Feedback Network in silico  $\blacksquare$ . The indicativation reaction is assumed to be unregulated; its rate uncertainty is rate under the unregulated; its rate uncertainty is rate uncertainty in the unregulated; its rate uncertainty is rate unregulated; • Bistability in a simple Positive Feedback Network *in silico* 

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

 $\mathcal{P}_\text{max}$  and the rate of production of more  $\mathcal{P}_\text{max}$  (1), second (1), second (1), second (1), second

K is the effector concentration for half-maximum response (EC<sub>50</sub>) for the feedback as a function of [A\*]  $T$  this differential equation was solved numerically (by using  $T$ *f* represents the strength of the feedback

As the strength of the feedback increases, the response of the results are shown in below the calculated steady-state step check responses shown as unbroken lines and the discontinuities shown as unbroken lines shown as unbroken lines shown as unbroken lines and the discontinuities shown as unbroken lines and the discontinuities shown as unbroken li evolves.

- First, <mark>Michaelis-Menten kinetics</mark> at *f=0*  $\,$
- As *f* increases, non-linear feedback increases which induces sigmoid kinetics in the response as a function of stimulus. But still curve is a smooth microstable of the strength o
- Beyond a threshold, *f*=0.07, the system is bistable and hysteresis keeps increasing (the range of [stimulus] with bistability)

![](_page_32_Figure_8.jpeg)

term ). The inaction reaction is assumed to be unregulated; its rate  $\alpha$ 

positive feedback loops. This is true in the case of complicated positive

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

the response of  $\mathcal{L}$ 

### **bistable system** Memory of cellular state - Bistability  $\mathbf{b}$

- $\bullet$  Bistability in a complex Feedback Network *in vivo* rest in intermediate states, and under what circumstances progesterone needed to induce p42 MAPK phosphorylation and Cdc2 activation differs from that needed to maintain the activities
- Oocyte maturation is induced *irreversibly* by a short exposure to Progesterone
- **•** This entails two coupled positive feedback networks and continue the couplex positive to the signal
	- Testing hysteresis: Induction by increasing [Stimulus] and maintenance by decreasing Extrimulus] and maintenance by accreasing the reducement of Progesterone of the Cestradiol RafER (Stimulus).

![](_page_33_Figure_5.jpeg)

 $\Gamma$ ing at externation.  $\Gamma$ versus maturation from three independent experiments. d, View of the signal transduction

ppus oocytes are arrested in G2 *Xenopus ooc*ytes are arrested in G2 phase. In response to steroid hormones, the oocyte is released  $\frac{1}{2}$  are compared in decrees  $\frac{1}{2}$ from G2 arrest, undergoes germinal vesicle breakdown (GVBD), completes meiosis I arrests in  $\frac{1}{2}$  phase of moiosis  $\frac{1}{2}$ metaphase of meiosis II.

one. This amounts to determining whether the concentration of

![](_page_33_Figure_8.jpeg)

![](_page_33_Figure_9.jpeg)

![](_page_33_Figure_10.jpeg)

![](_page_33_Figure_11.jpeg)

![](_page_33_Picture_12.jpeg)

Thomas LECUIT 2024-2025 **Xiong, W., and Ferrell** 

the induction period and the end of the maintenance period. We may be end of the maintenance period.  $f_{\rm 34}$  Map  $f_{\rm 6}$  Map  $f_{\rm 7}$ oestradiol. a, Time course of oestradiol-induced DRaf:ER and p42 MAPK activation, assessed by ER immunoblot analysis,  $\mathbb{E}[\mathbf{E}]$ 

# Memory of cellular state - Bistability

- $\bullet$  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

![](_page_34_Figure_6.jpeg)

![](_page_34_Picture_7.jpeg)

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

Thomas LECUIT 2024-2025

![](_page_34_Figure_10.jpeg)

 $\frac{1}{200}$  Glaughe I, Herberg M, Roeder I PLoS ONE 5(6): e11238 (2010) DE FRANCE Thomas LECUIT 2024-2025 H.G. Garcia and R. Phillips. Physical Genomics - from E.coli to Elephants derived. The derived in the developmental potential potential potential potential potential potential potential potential  $\alpha$ 

35

![](_page_34_Picture_13.jpeg)

#### Memory of cellular state - Multistability Nanog downregulation.  $\sum_{i=1}^{n}$  $\alpha$ ., 2014). Previous studies on the phenotype of Gata $\beta$ the Family signal signal pathway indirect sh Nanog downregulation.  $\sum_{i=1}^{n}$  $\alpha$ ., 2014). Previous studies on the phenotype of Gata $\beta$

The analysis of  $\mathcal{F}_{\mathcal{A}}$  mutants shows that this ligand is required for  $\mathcal{F}_{\mathcal{A}}$ 

The analysis of  $\mathcal{F}_{\mathcal{A}}$  mutants shows that this ligand is required for  $\mathcal{F}_{\mathcal{A}}$ 

#### • Multistability in development PrE differentiation. Although Fgf4 is not required to induce Gata6  $\bullet$  Multistability in development cell stage to drive the cells towards a PrE fate (Feldman et al., 1995; 1995; 1995; 1995; 1995; 1995; 1995; 19 PrE differentiation. Although Fgf4 is not required to induce Gata6  $\bullet$  Multistability in development

- $\bullet$  Transient signals induce a variety of stable cellular responses during development. ahoty of classic coharan responses aaring actors  $\mathbf{r}$  the present study, we further interactions the interactions of  $\mathbf{r}$  $\mathbf{F}_{\text{max}}$ ariety of stable cellular responses during develor  $\overline{a}$ , 2014). Thus, and  $\overline{b}$  $\mathsf{int}$ , we further interactions the interactions of  $\mathsf{int}$
- $\bullet\,$  Multistability allows genetically identical cells to be in molecularly distinct and mitotically stable cell states. The examination of Nanog mutant embryos uncovered a nondemonstrating that this factor is required for PrE specification and The examination of Nanog mutant embryos uncovered a noncell-autonomous role for Fgf4 in the maturation of the PrE demonstrating that this factor is required for PrE specification and for the inhibition of an Epi fate. Then, to investigate in more detail
- 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.** ouse: Specification of Epiblast and Primitive endoderm in the Inner Cell Mass.  $\mathsf{base} \colon \mathsf{Spec}$ itication of Epiblast and Primitive endoderm in the Inner Cell Mass.
- induces the expression of  $P$  results of  $P$  results of  $P$ ption factor MyoD heterodimerizes with E proteins to activate itself and the differentiation, including the effects of  $\mathbb{R}$  signaling. This is the effects of  $\mathbb{R}$  signaling. This is the effects of  $\mathbb{R}$  signaling. The effects of  $\mathbb{R}$  signalization,  $\mathbb{R}$  signalization,  $\mathbb{R}$  s myogenesis program, and Id family proteins heterodimerize with E proteins to disrupt this process.  $\,$  Ex 2: Myogenesis, the transcription factor MyoD heterodimerizes with E proteins to activate itself and the

![](_page_35_Figure_6.jpeg)

![](_page_35_Picture_7.jpeg)

 $E$  **FRANCE** Thomas LECUIT 2024-2025  $\mathbf{u}$  finitive  $\mathbf{u}$  allows for  $\mathbf{u}$  and  $\mathbf{u}$  induction of FGF  $\mathbf{u}$  in turn models. Within the  $\mathbf{u}$ 

I Chazaud *Development* 141, 3637-3648 (2014) Gata6+/<sup>−</sup> intercrosses produce Gata6−/<sup>−</sup> embryos at Mendelian ratios N. Shrode et al. *Developmental Cell 29*, 454–467 (2014)  $\Omega$  Chazaud, *Development* 141, 3637, 3648 (2014) Bessonnard et al. Chazaud. *Development* 141, 3637-3648 (2014)

embryos have shown that the PrE epithelium is not produced at E4.5

embryos have shown that the PrE epithelium is not produced at E4.5

# 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.

![](_page_36_Figure_4.jpeg)

• 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.

![](_page_36_Picture_6.jpeg)

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

# Memory of cellular state - Multistability

A synthetic multistable  $AP1903$ bioRxiv preprint doi: https://doi.org/10.1101/2021.02.10.430659; this version posted February 11, 2021. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission. Dox KBP-ZF-VP48-DHFR RES mCitrine-PEST ZFbs-ZFbs elf-activation **B** FKBP-ZF-AD AP1903+ TMP 10 uM Dove AD1003+ TMD 10 pM  $\overline{\sigma}$  $100$  $10<sup>1</sup>$  $10<sup>4</sup>$  $10$ AP1903 AP1903 (nM) nCitrine (a u TMP (nM) 0 10000 100 1000 10000 inactive complex  $1.0$  $frac{function}{in}$  $\begin{array}{c}\n\text{fraction} \\
\text{fraction} \\
\text{o.e.}\n\end{array}$ nCitrine+<br>
<sub>0.2</sub><br>
<sub>2</sub> Citrine+ Perturbation  $04$ Monoclonal **IRES mCitrine-PES** stable line ZFbs-ZFbs Ctrl Ctr Perturbation

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

- 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.

![](_page_37_Picture_6.jpeg)

• *Experimental system:*

# Memory of cellular state - Multistability

- Implementing bistability ad tristability:
	- o 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.

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![](_page_38_Figure_8.jpeg)

![](_page_38_Figure_9.jpeg)

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

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

![](_page_39_Picture_7.jpeg)

### Bacteria swim, propelled by flagella NATURE VOL. 239 OCTOBER 27 1972 OCTOBER 27 1972

![](_page_40_Figure_1.jpeg)

![](_page_40_Picture_2.jpeg)

# Chemical guidance of cell motility

![](_page_41_Figure_1.jpeg)

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 **Problem:** Bacteria can go up an exponential gradient, over 20mm.

For a 2um cell to d bacteriia inside the capillary was then For a 2µm cell to detect such a gradient, they would need to detect 0.0001% difference on both ends

Sensitivity to of 1 $\mu$ m x 1 $\mu$ m x 0.1 $\mu$ m. The standard deviation is  $\sqrt{60}$ . Yet the response is very accurate and fast (few ms)... ch fluctuat<mark>i</mark> Sensitivity to stochastic fluctuations: estimate of 60 molecules of attractant at 1µM on a sampling volume

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

![](_page_41_Picture_12.jpeg)

- $\bullet$  Spatial mechanism: comparison of chemoattractant concentration along cell length
- Temporal mechanism: comparison of chemoattractant at different positions and memory.

![](_page_42_Picture_3.jpeg)

![](_page_42_Picture_4.jpeg)

Molecular circuit driving chemotaxis

![](_page_43_Figure_1.jpeg)

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

# Mechanism of adaptation

e/brinciple to a centration of chemoattractant. (A) The chemoattractant chemoattractant chemoattractant chemoattractant chemoat

 $\mathbf{r}$  in the ambient concentration of chemoattractant. (A) The backerium has steady-state tumble.

The evidence/principle

![](_page_44_Figure_1.jpeg)

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

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![](_page_44_Figure_3.jpeg)

![](_page_44_Picture_4.jpeg)

45

# Mechanism of adaptation **Mechanism**

- 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. ✐ "125\_81356\_Phillips\_MolecularSwitch\_2P" — 2020/4/1 — 16:37 — page 150 — #27 ✐
- In absence of ligand, receptor is on, CheB is activated and demethylates the receptor.  $Chel$

![](_page_45_Figure_4.jpeg)

![](_page_45_Figure_5.jpeg)

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

![](_page_45_Picture_7.jpeg)

# Chemotaxis entails detection of a temporal gradient entaiis detection or a temporal gradient<br>————————————————————————————————

![](_page_46_Figure_1.jpeg)

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

![](_page_46_Picture_5.jpeg)

*Salmonella typhimurium*  analysis ignores the smallest changes (Table 1, legend). Cha

![](_page_46_Picture_7.jpeg)

in the concentration of serine (!*c <* 0). Adapted from Macnab and Koshland Jr. (1972). Thomas LECUIT 2024-2025

R. Macnab. D.E. Koshland. *PNAS*. 69:2509-2512 (1972)  $\mathbb{R}$ . Iviachao. D.E. Roshiand. Tivad. 07.25  $12(1072)$  $12(1972)$ 

# How is adaptation required for chemotaxis? "125\_81356\_Phillips\_MolecularSwitch\_2P" — 2020/4/1 — 16:37 — page 134 — #11 ✐

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

 $\bullet\,$  Methylation and demethylation take a few seconds and thus reflect receptor activity a few seconds ago (« memory »). eras are a rew seconds and way

✐

- Receptor occupancy by ligand influences the current activity state (which takes a fraction of a second). erased from their molecular substrates.
- 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.

![](_page_47_Figure_5.jpeg)

![](_page_47_Picture_6.jpeg)

#### by the smaller state steps in Fig. 2. Note that the set of the set response is not saturated. For the subset of cells used in the predicted by the impulse response; the dashed line has the How is adaptation required for chemotaxis?

- is integrated over few seconds: response to very short pulse (ms). Lasts about 4 seconds Finally, we calibrated the impulse response by subtracting the signal persists after the ligand is no longer present at the cell surface (it diffuses away within a fraction of a second). We found that a response of the second  $\mathbf r$  $\bullet$  Cell response is integrated over few seconds: response to very short pulse (ms), lasts about 4 seconds,
- inse is biphasic (2 lobes): Cells increase their CC $^{\prime}$ it and undershoot below the steady state value, and catch up. In other words, cells run smoothly for 1s experiments). (≈30µm distance), then tumble for 3s and catch up. response (the smooth curve) of Fig. 1; the points comprise a  $\bullet$  The response is biphasic (2 lobes):  $\,$  Cells increase their CCW bias, ie. they run for about 1s, then, reduce sinusoidal oscillations in receptor occupancy generated by
- in Fig. 3A is the dependence of bias on ramp rate for licates that cells perceive changes in concentratio measure assumes a large response to the negative response to the negative response to the negative response to  $\bullet$  This indicates that cells perceive changes in concentration during this time interval

![](_page_48_Figure_4.jpeg)

calibration (those exposed to a-methyl-DL-aspartate; see

• Cells compare the response in first 1s (positive  $\int_{0}^{\pi}$  smooth curve of  $\int_{0}^{\pi}$  (is constructed so that its  $\int_{0}^{\pi}$ lobe), and next 3s (negative lobe).

response threshold. The slope of the predicted dependence is

- The comparison is a consequence of the  $\alpha$  dentation  $\alpha$  esheniame adaptation mechanism
- Without adaptation, cells have no memory of recent past, and cannot read temporal gradient, experiment figure 7. The reference of ref. 14, cells with deletions in generating in a control of  $\alpha$ hence cannot do chemotaxis.

SM. Block, J. Segall and H. Berg. *Cell*,. 31, 215-226 (1982) diction (Fig. 4B). We also studied the behavior of cheRcheB J. Segall, SM. Block and HC. Berg. *PNAS*. 83:8987-8991 (1986) cells over a longer time span in a flow cell (19). Some cells (19). Some cell (19). Some cells

![](_page_48_Picture_9.jpeg)

# Learning, memory and cell habituation

![](_page_49_Picture_1.jpeg)

![](_page_49_Figure_2.jpeg)

### *Stentor coeruleus*

Vance Tartar 1911-1991

![](_page_49_Picture_5.jpeg)

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# Learning, memory and cell habituation

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### Habituation: the reduction of response to repetitive stimuli.

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

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

pc<br>el<br>pr As *Stentor* cells habituate, they learn and store a memory of previous stimulation to adapt their behaviour.

![](_page_50_Figure_5.jpeg)

Stimulus Number

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

![](_page_50_Picture_8.jpeg)

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- $\bullet$  Learning: Internalisation of the receptor is induced by past stimulations.
- (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission. • 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. **+ ++**

![](_page_51_Figure_4.jpeg)

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

![](_page_52_Picture_7.jpeg)

#### Structure and Geometry: *information* and *memory* pd (1eometry: *Intc* as Turing instabilities21 produce patterns with length fields. The emergent biochemical patterns are read mation and mem sequence of the decisions.  $r$  is a continuous respective to  $r$ a reference i

transforms a homogeneous field of cells into discrete

- Cellular structures and cell geometry guide and constrain mechanochemical processes in cells. ind cell deometry quide a As another example, Turing instabilities control palid constrain mechanoche
- .<br>It • Implications:

stress. This is a dimensionless

ine etc) as a **structural and geome** structures (organelles, membranes, centrioles, ric m Length scale Length scale egg shape etc) as a **structural and geometric memory.** Distance *x* • Inheritance of cellular structures (organelles, membranes, centrioles,

interactions22 (BOX 2). Excitable systems manifest charac-

**Biochemistry Mechanics** • Stable memory, which may be reset by cellular signals.

![](_page_53_Figure_5.jpeg)

![](_page_53_Picture_6.jpeg)

# Cytoskeletal structures are dynamic and adaptive, yet manifest stability

![](_page_54_Picture_2.jpeg)

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

### Harald Herrmann (University of Heidelberg, Germany)

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

COLLÈGE **DE FRANCE** 

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

![](_page_54_Figure_10.jpeg)

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

![](_page_55_Figure_1.jpeg)

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Thomas LECUIT 2024-2025 C. Kucera et al, M. Théry and L. Blanchoin. *PNAS*, 119(31):e2209522119 (2022)  $\alpha$  and  $\alpha$ . Dianchom,  $\Gamma N A S$ ,  $\Gamma V (31)$ : $\epsilon$ 2209322119 (it  $\mathbf{r}$  $\mathcal{L}$  $\overline{11}$  minitial  $\overline{11}$  could be seen at the initial stage of the ini d L. Bianchoin. PNAS,  $119(31):e2209522119$  (2022)  $22.99999$  $\mathcal{C}$  depletes actin filaments from the volume of  $\sim$   $\sim$  $\overline{0}$   $\overline{1}$   $\overline{2}$   $\overline{1}$   $\overline{2}$   $\overline{1}$   $\overline{2}$   $\overline{2}$   $\overline{1}$   $\overline{2}$   $\overline{$ ra et al, M. Théry and L. Blancho 19(31):e2209522119 ( L. Blanchoin. PNAS, 119(31):e2209522119 (2022)

G

0 10 20

0

gliding

#### Structural memory coverslip

#### Co-assembly of MT and actin networks show reciprocal influences .<br>Fl 0" 110" 5 µm F-actin

- Co-assembly of MT and actin filament networks lead to the coordered 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).

![](_page_56_Figure_5.jpeg)

![](_page_56_Picture_6.jpeg)

O. Kucera et al, M. Théry and L. Blanchoin. PNAS, 119(31):e2209522119 (2022)  $\overline{67}$ ry and L. Blanchoin.  $PNAS$  119(31):e2209522119  $T_{\text{M}}$  and E. Dianents in Films,  $11/51/51/62207522117$ 

# 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.

![](_page_57_Figure_7.jpeg)

![](_page_57_Picture_8.jpeg)

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 $\frac{1}{2}$  Thomas ECHIT 2024-2025 (Corresponding polar histograms of gelson of generated M Théry and I Blanchoin. PMAS 1100 i E<br>Consumer and L. Blanchoin. PNAS, 119(31):e2209522119 (2022)<br>- Consumer and L. Blanchoin. PNAS, 119(31):e2209522119 (2022)  $\mathcal{O}$ . Coloration and  $\mathcal{O}$  Colored orientation and  $\mathcal{O}$  and  $\mathcal{O}$  and  $\mathcal{O}$ . First example polymerization and  $\mathcal{O}$  are  $\math$ 

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

![](_page_58_Figure_2.jpeg)

![](_page_58_Picture_3.jpeg)

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

# **Developmental Cell**

**ll**

structural memory of filament alignment during

Development Structural memory

**Developmental Cel** 0 sec 40 sec 100 sec 160 sec

### cytokinesis Structural memory in actin filament network assembly: cytokinesis

(B) Measurements of equation  $\mathcal{A}$  and myosin II (dark gray) over time during cytokinesis. Color overlays indi the three phases of cytokinesis: phase I (green), phase II (red), and phase II (blue). Top schematic indicate SEM (n  $=$ 

(C) Kymographs showing axial flows for the embryo in (A). Top schematic: regions used to make axial and equatorial and equatorial and equations used to make axial and equations used to make axial and equations used to mak

used for measurements of probe densities (box), and equatorial width (double headed black arrow).

![](_page_59_Figure_4.jpeg)

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- 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).

![](_page_60_Picture_9.jpeg)

### **COURS**

De 10hà 11h30 Amphithéâtre Guillaume Budé

![](_page_61_Picture_2.jpeg)

Thomas LECUIT, chaire Dynamiques du vivant

Qu'est-ce que l'information biologique ?

COURS : 12 novembre > 17 décembre 2024

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)

![](_page_61_Picture_28.jpeg)

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