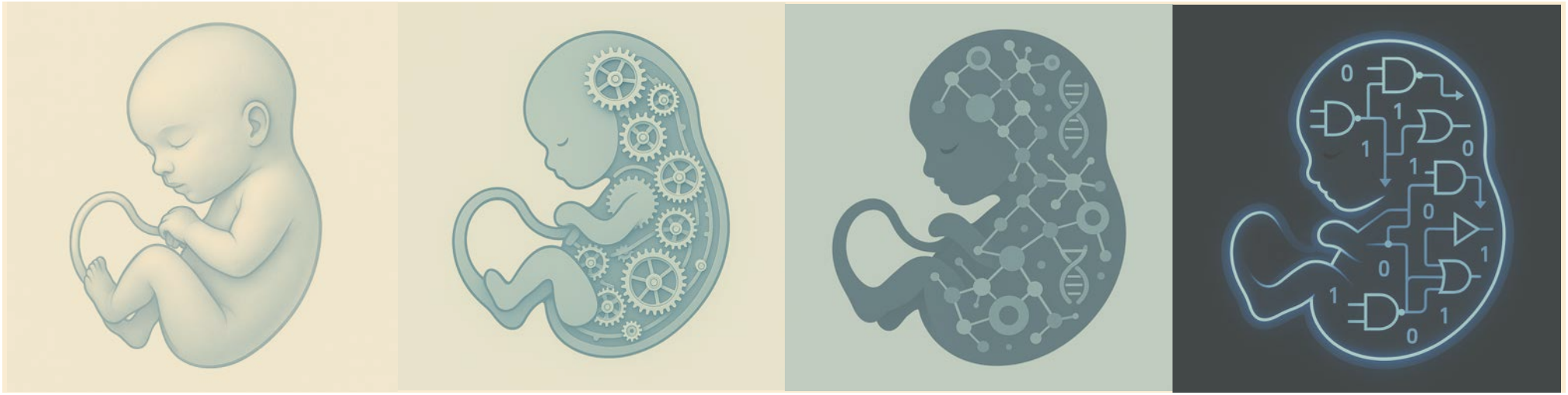
# What is biological information? (II)



## Course 4: Dynamics of information processing
## Geometric approach to cell decisions

Thomas Lecuit

chaire: Dynamiques du vivant

COLLÈGE DE FRANCE
1530

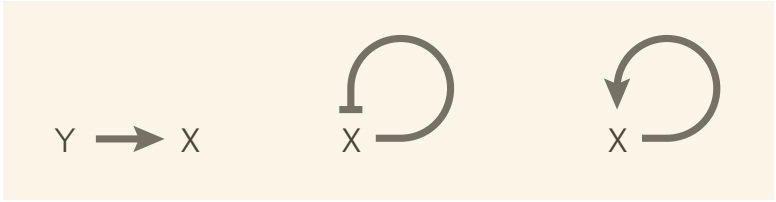
# Summary of previous course

## Course 3: A logic view of information processing: Network motifs

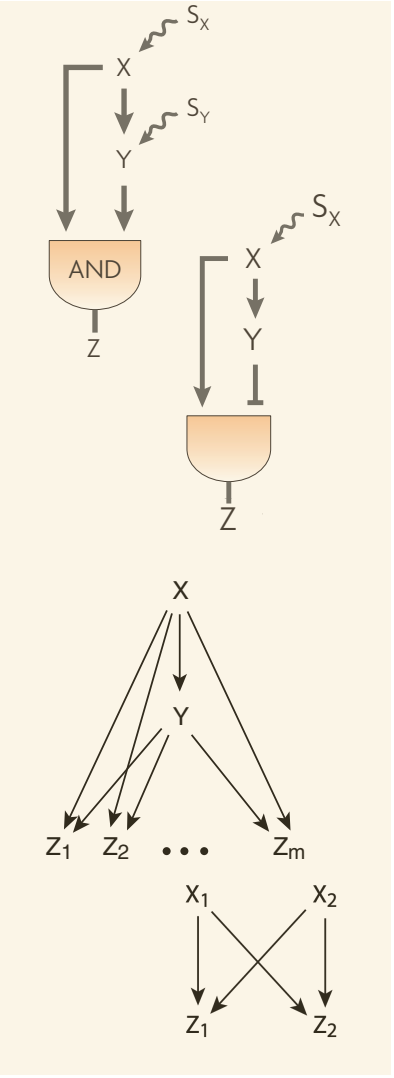
- Logic of information flow and information processing
- Abstraction to characterise the logic: algorithmic level of analysis

- Conservation of the logic more fundamental than that of genes
- Evolution by tinkering is constrained by the logic of functional systems

# Summary of previous course




- Deciphering the logic of biochemical and gene networks is possible
- The existence of network motifs reflects evolutionary constraints on the search for algorithms that fulfil a computational task.
- Examples of computational modules:
  - *Response accelerator*: NAR
  - *Persistence detector*: C-FFL
  - *Noise filtering* and *Response delay*: PAR
  - *Pulse generator* and *Temporal waves*: I-FFL and interlocked FFLs
  - *Robustness*: NAR
  - Some algorithms combine tasks: ie. PAR increases sensitivity but not noise.

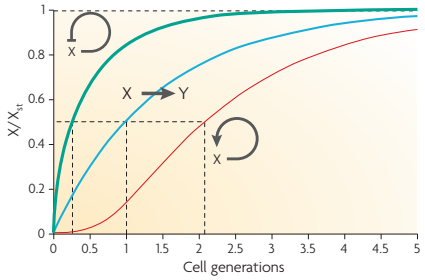


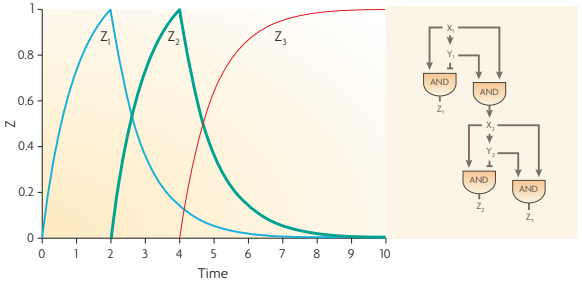
# Dynamics of information processing

- Framework to understand and predict the *emergence of cell states* (e.g. bistability)

- We need a framework to *understand the transition between states*: *Dynamics*

- Network motifs already provide an approach to deciphering the logic of dynamical responses (e.g. response acceleration or slow down, pulse waves).



# Time and dynamics in living systems

## *Time* is an *inherent property* of the living

JB de Lamarck
(1744-1829)

Dynamics

Transformism

PHILOSOPHIE

ZOOLOGIQUE.

SECONDE PARTIE.

*Considérations sur les Causes physiques de la Vie, les conditions qu'elle exige pour exister, la force excitatrice de ses mouvemens, les facultés qu'elle donne aux corps qui la possèdent, et les résultats de son existence dans ces corps.*

1809

*Caractères des Corps inorganiques mis en parallèle avec ceux des Corps vivans.*

Tout corps, au contraire, qui possède la vie, se trouve continuellement, ou temporairement, animé par une *force particulière* qui excite sans cesse des mouvemens dans ses parties intérieures, qui produit, sans interruption, des changemens d'état dans ces parties, mais qui y donne lieu à des réparations, des renouvellemens, des développemens, et à quantité de phénomènes qui sont exclusivement propres aux corps vivans; en sorte que, chez lui, les mouvemens excités dans ses parties intérieures altèrent et détruisent, mais réparent et renouvellent, ce qui étend la durée de l'existence de l'individu, tant que l'équilibre entre ces deux effets opposés, et qui ont chacun leur cause, n'est pas trop fortement détruit;

HISTOIRE NATURELLE

DES

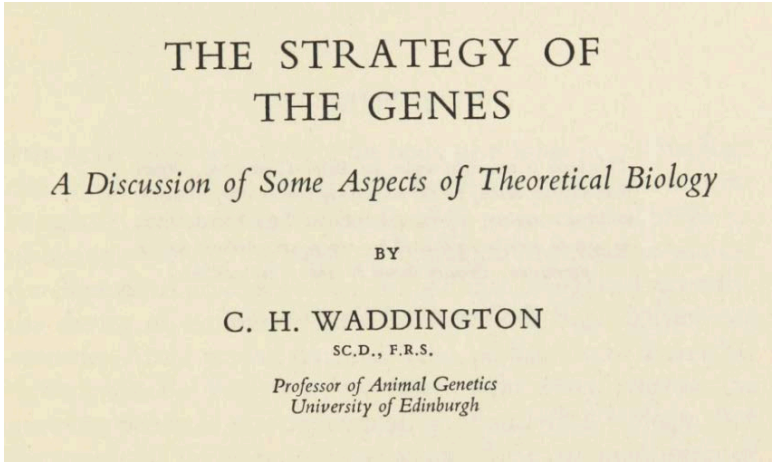
ANIMAUX SANS VERTÈBRES.

7.° La nature, dans toutes ses opérations, ne pouvant procéder que graduellement, n'a pu produire tous les animaux à-la-fois : elle n'a d'abord formé que les plus simples; et passant de ceux-ci jusques aux plus composés, elle a établi successivement en eux différens systèmes d'organes particuliers, les a multipliés, en a augmenté de plus en plus l'énergie, et, les cumulant dans les plus parfaits, elle a fait exister tous les animaux connus avec l'organisation et les facultés que nous leur observons. Or, elle n'a rien fait absolument, ou elle a fait ainsi.

1815

# Time and dynamics in living systems

## Time is not an external variable but inherent to living systems



THE STRATEGY OF
THE GENES

*A Discussion of Some Aspects of Theoretical Biology*

BY

C. H. WADDINGTON

SC.D., F.R.S.

*Professor of Animal Genetics*
*University of Edinburgh*

1957

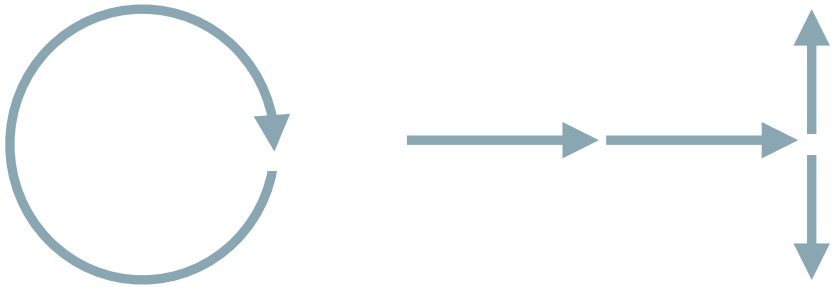
There is one category of points of view which, in my opinion, is particularly characteristic of biological entities. Perhaps the main respect in which the biological picture is more complex than the physical one, is the way in which time is involved in it. In the Newtonian system, time was one of the elements in the physical world, quite separate from any of the others; a material body of a given mass just existed, unchanging and, indeed, quite indifferent to the passage of time. But time and change is part of the essence of life. Not only so; to provide anything like an adequate picture of a living thing, one has to consider it as affected by at least three different types of temporal change, all going on simultaneously and continuously.

These three time-elements in the biological picture differ in scale. On the largest scale is evolution; any living thing must be thought of as the product of a long line of ancestors and itself the potential ancestor of a line of descendants. On the medium scale, an animal or plant must be thought of as something which has a life history. It is not enough to see that horse pulling a cart past the window as the good working horse it is today; the picture must also include the minute fertilised egg, the embryo in its mother's womb, and the broken-down old nag it will eventually become. Finally, on the shortest time-scale, a living thing keeps itself going only by a rapid turnover of energy or chemical change; it takes in and digests food, it breathes, and so on.

# Time and dynamics in living systems

- Rich dynamics but not chaotic (not sensitive to initial conditions and noise)

- *Cycles and oscillations* (see courses in nov-dec 2018)
- *Irreversibility (symmetry breaking)* and *discrete processes*: decisions and checkpoints



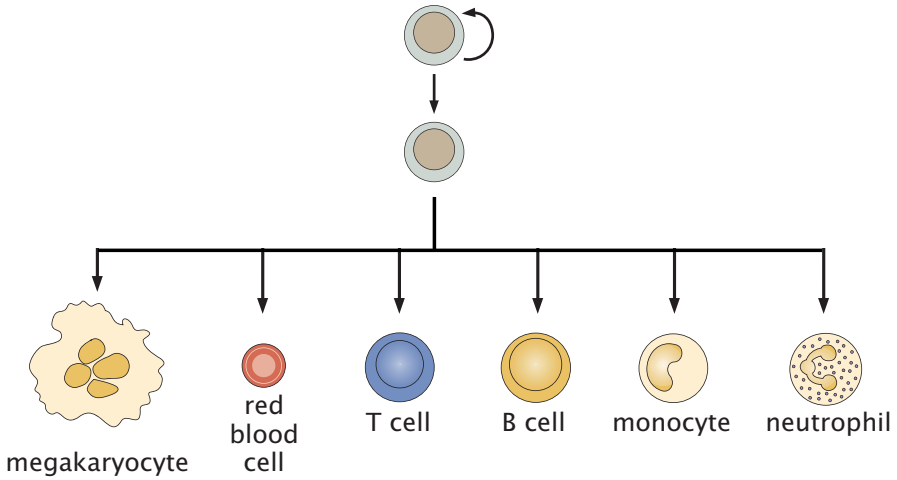
**2. Broken Symmetry and Complexity**

The first important point to note is that the micro- and macro-structures of the plants and animals which make up biology are a consequence of a massive amount of broken symmetry (Anderson, 1972; Palmer, 1982). Broken symmetry, originally a part of phase transition lore in condensed matter physics, has been slowly making its way into the rest of physics. Even the laws of elementary particle physics, which would have been believed in 1960 to be unique, are now thought of as containing elements of broken symmetry. But in most of physics, broken symmetries are few in number.

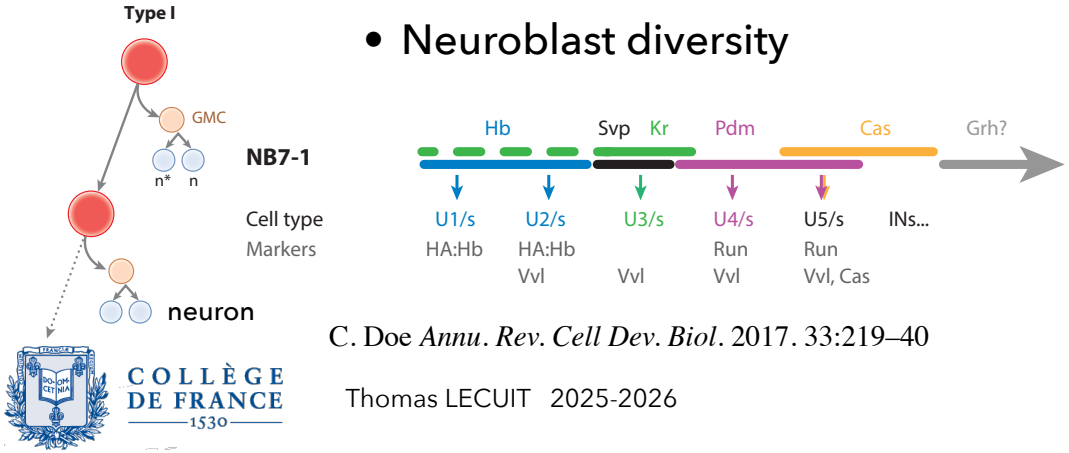
JJ. Hopfield. *Journal of Theoretical Biology* 171 (1), 53-60
Physics, computation, and why biology looks so different

# Decision making

- Hematopoietic lignage

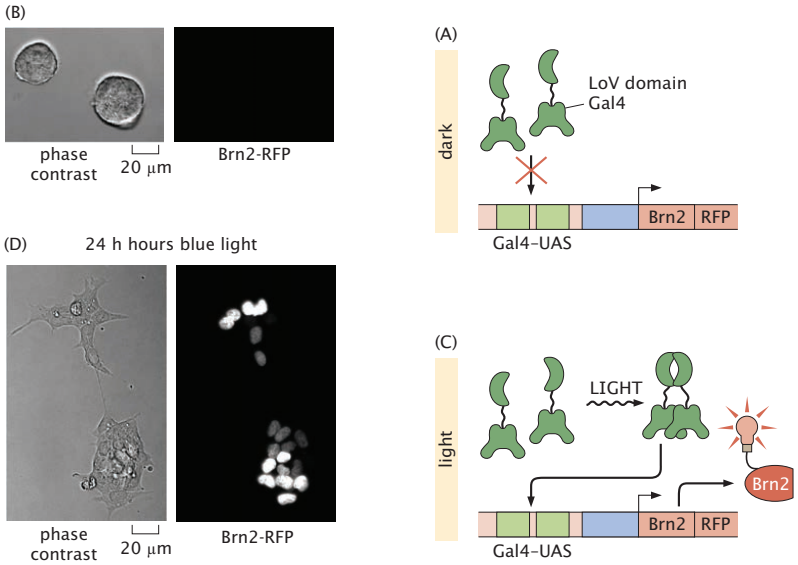



- Neuroblast diversity



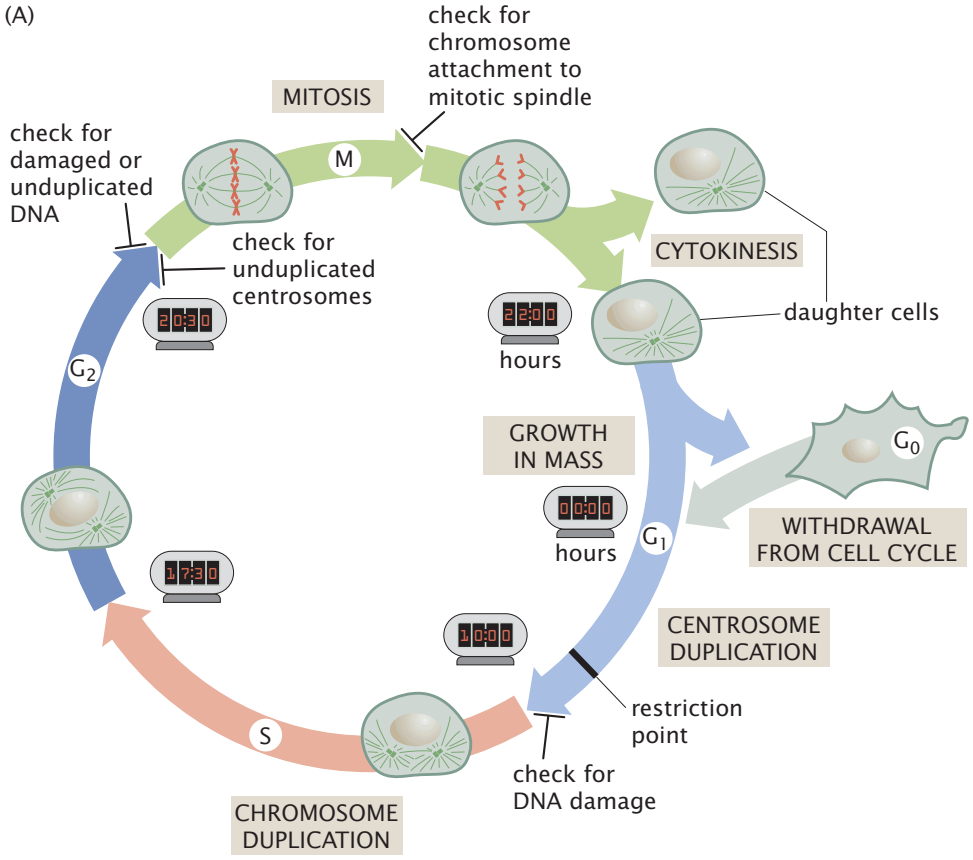

C. Doe *Annu. Rev. Cell Dev. Biol.* 2017. 33:219–40

- Genetic switch underlies cell fate

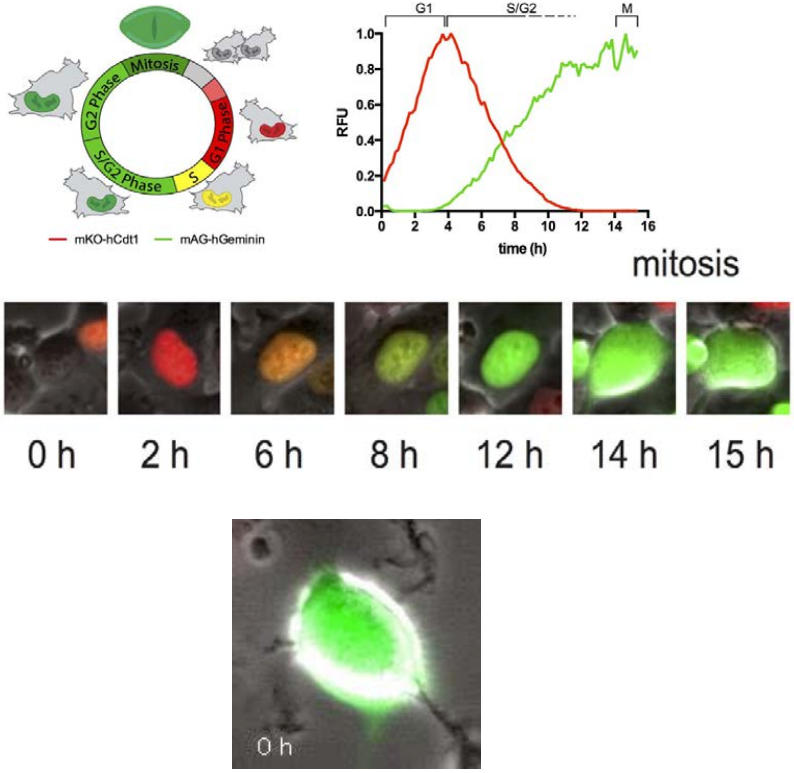



Sokolik et al., 2015, *Cell Systems* 1, 117–129
Hernan Garcia and Rob Phillips, *Physical genomics*

# Cell cycle




Period T=500-1500 min

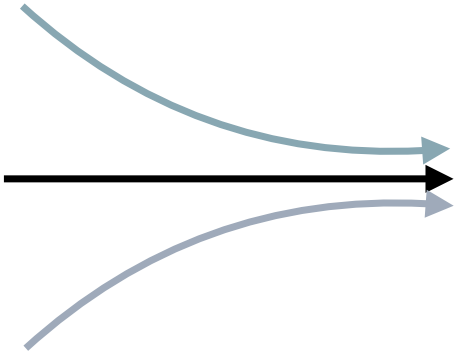


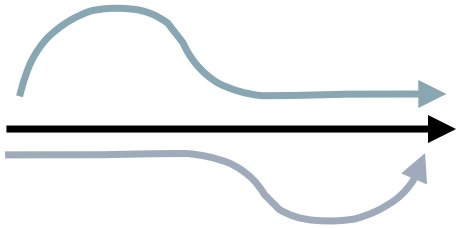

J.M. Marcus et al. *Scientific Reports* | 5:14391 | DOI: 10.1038/srep14391

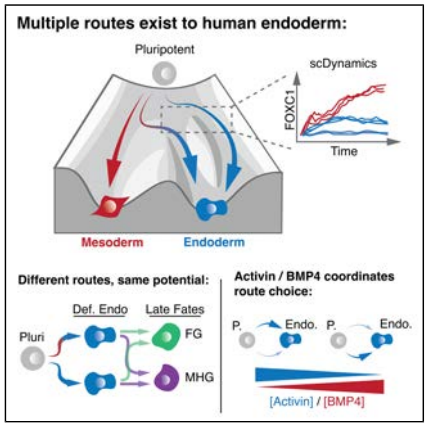
# Unusual characteristics of biological dynamics

Not really set by initial conditions:

- Convergence to end point
- Adaptation and homeostasis
- Self-organisation

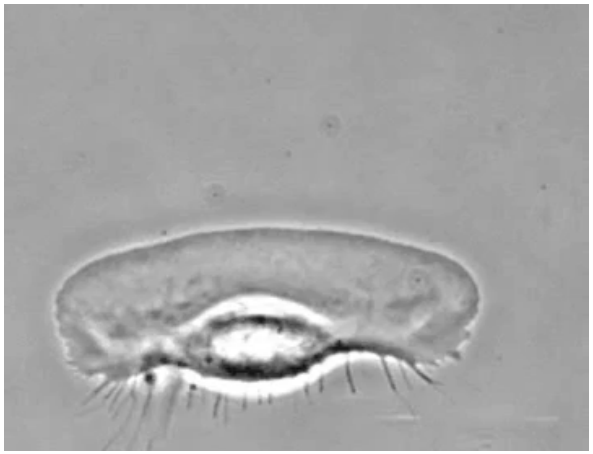


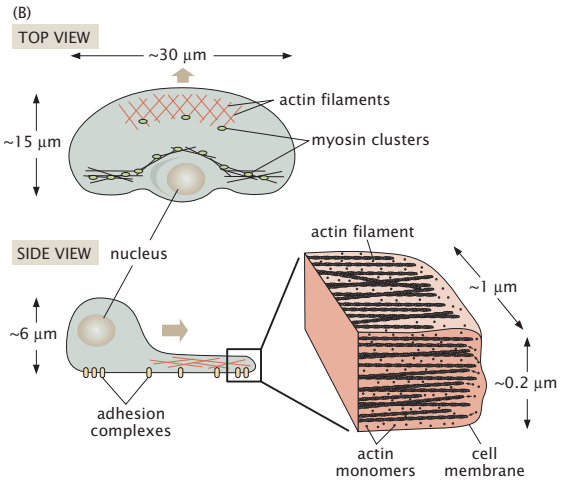


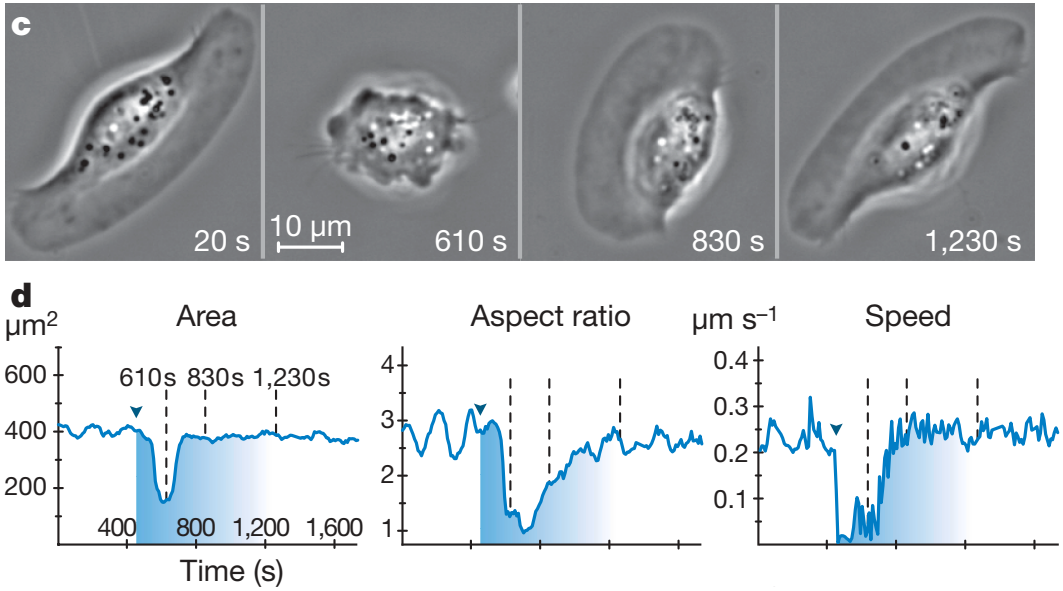



O CK. Inge et al., and S. DM. Santos. *Developmental Cell* 60, 3304–3320 (2025)

# Cellular adaptation: cell motility





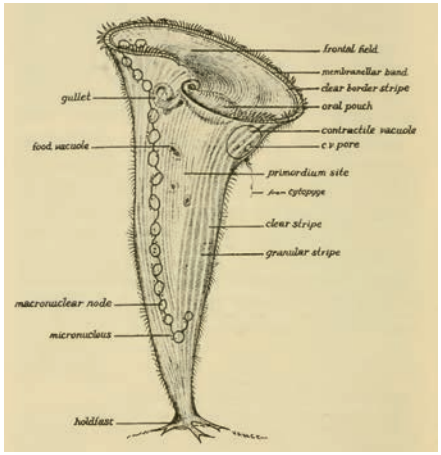

Transient DMSO treatment: lamellipodium collapse

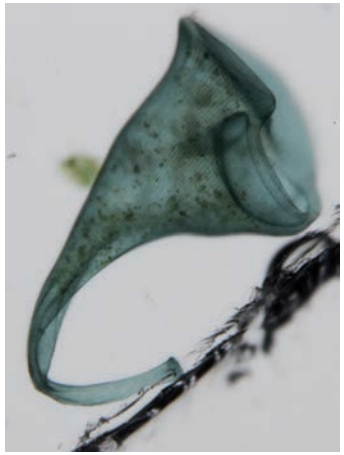
Keren K. et al, Mogilner A. and Theriot J., *Nature*, 453:475 (2008)

R. Phillips, J. Thériot, J. Kondev, H. Garcia *PBOC*

# Cellular adaptation: regeneration

Ciliate: *Stentor coeruleus*




Vance Tartar (1911-1991)  Wallace Marshall (UCSF)

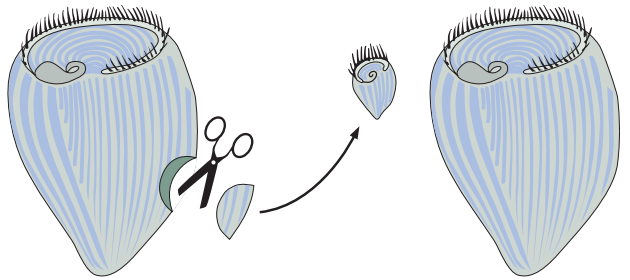
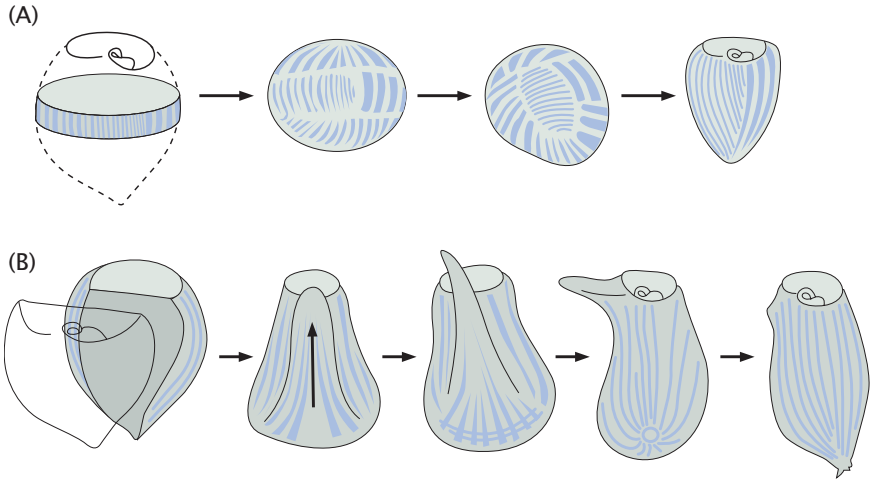
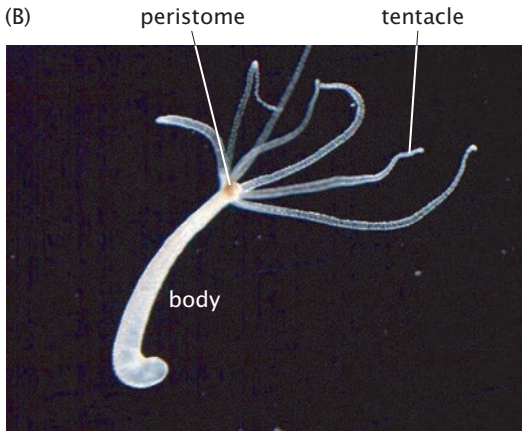


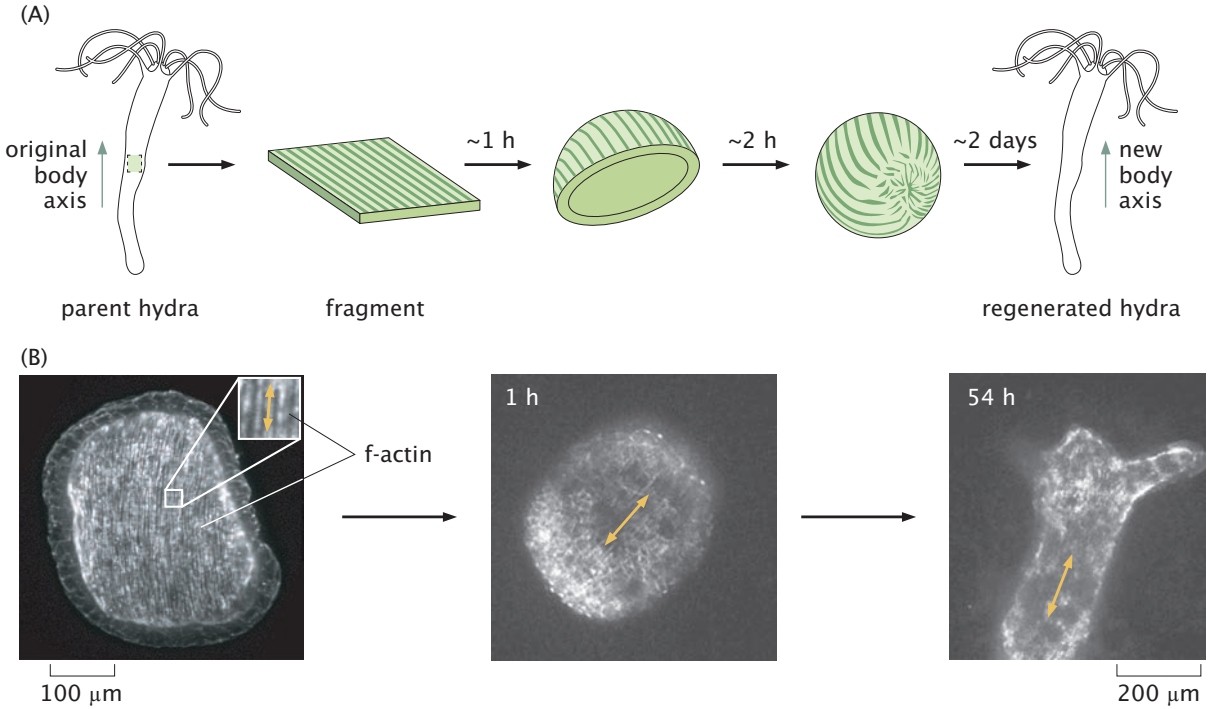
Figure 4.2: Scaling of cell shape with cell size in *Stentor*. (A) Schematic of a cutting experiment done by Tartar in which a small piece of the original *Stentor* cell is cut off and the fragment regenerates into a fully formed, but smaller cell. (B) Comparison of the sizes of *Stentor* cell and its regenerated smaller copy.



# Developmental adaptation: regeneration

Cnidarian: *Hydra*

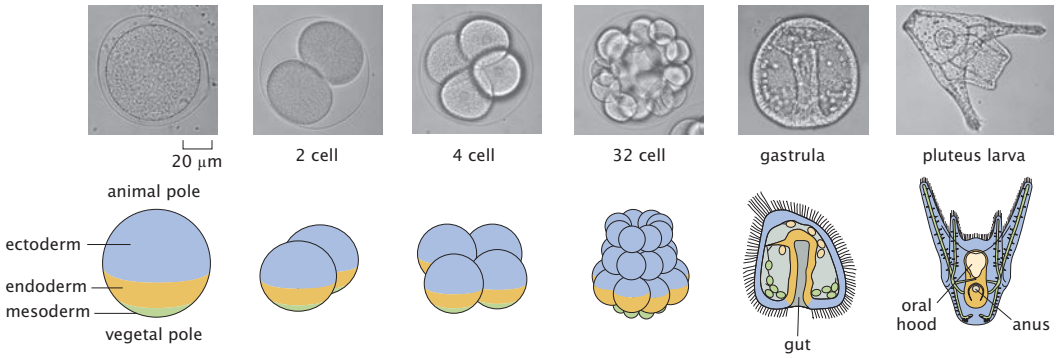


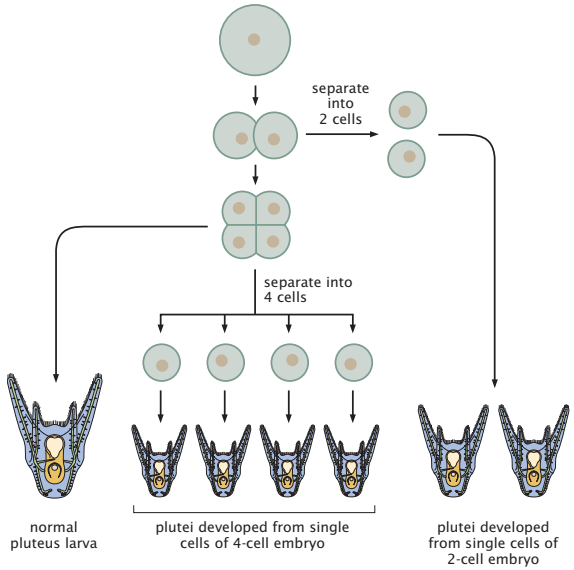



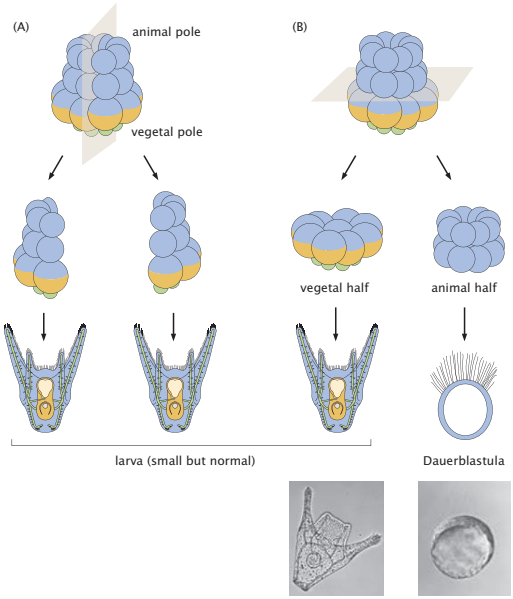

Kinneret Keren lab (Technion Israel Institute of Technology)

# Developmental adaptation: regeneration

Echinoderm: Sea urchin



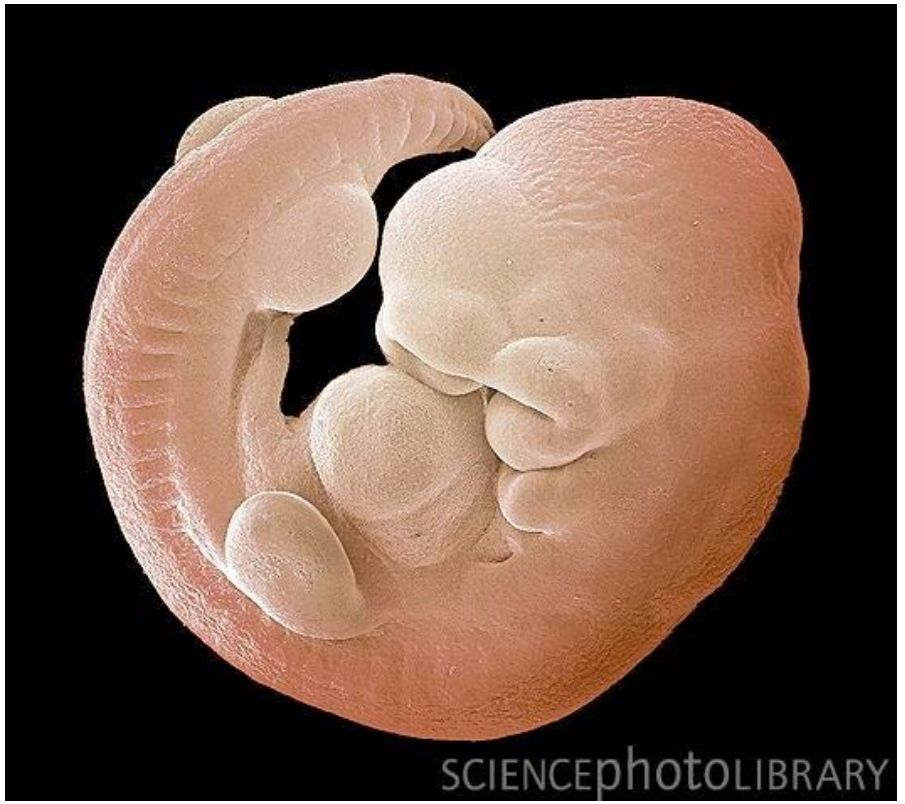



# Development as a tree of cellular decisions

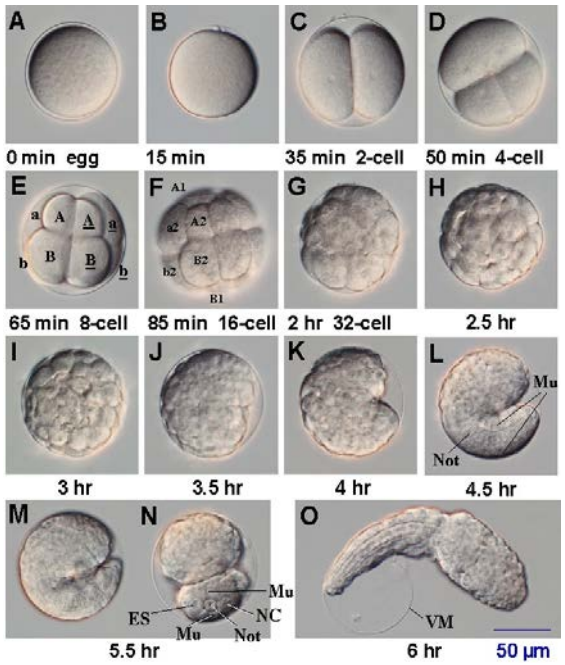


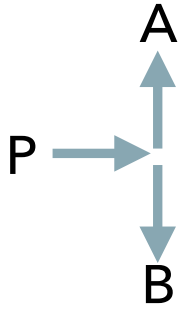
1 cell

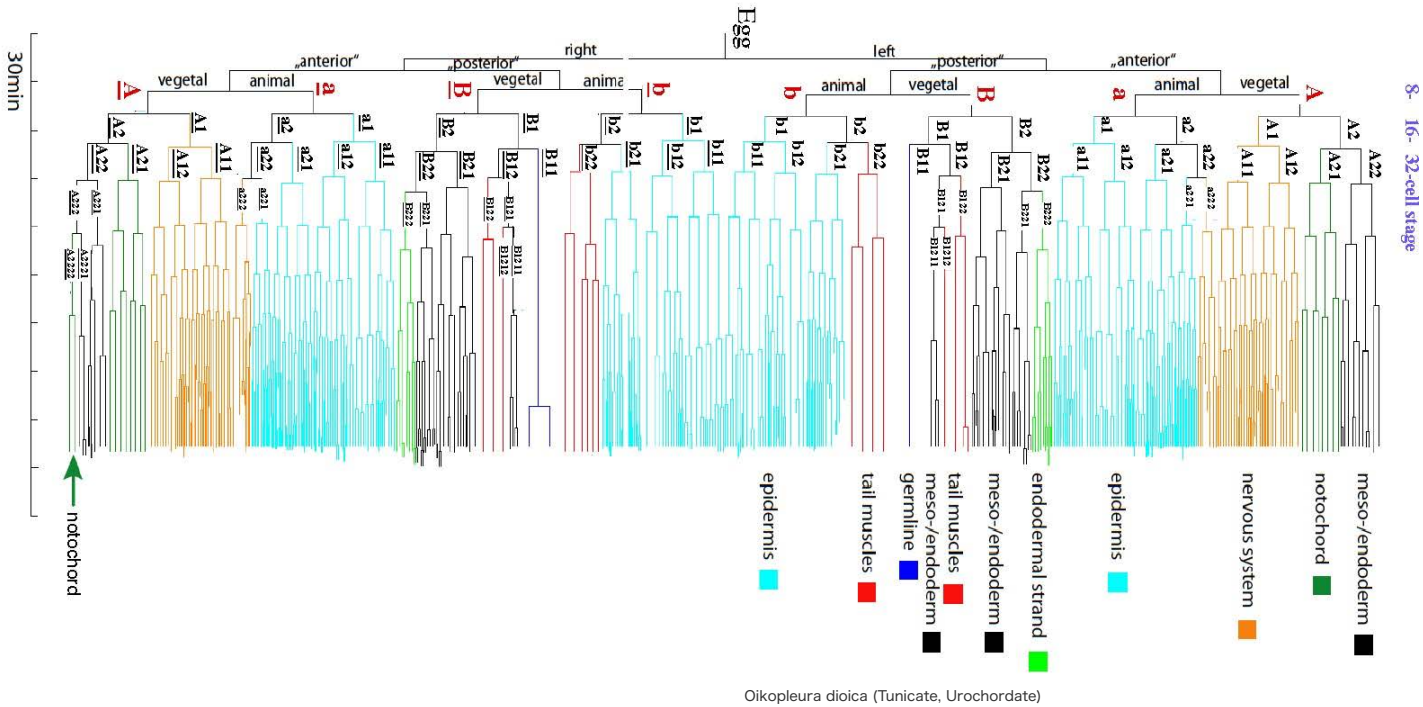



>>$10^6$ cells

# Development as a tree of cellular decisions




Oikopleura dioica (Tunicate, Urochordate)

Hiroki Nishida lab

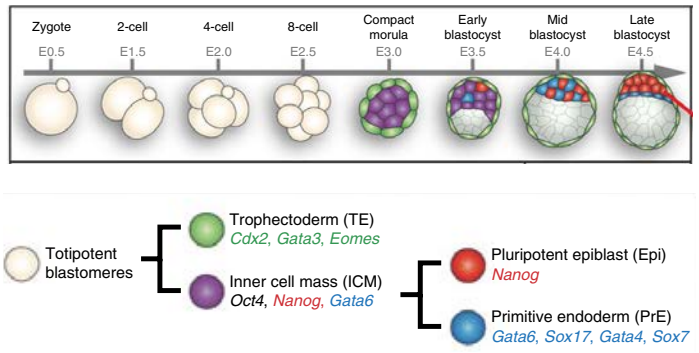
# Dynamics of cellular decisions

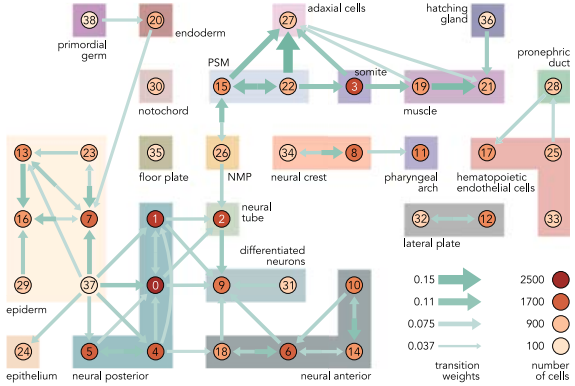
## Basic phenomenology and terminology

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

## Case studies:

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





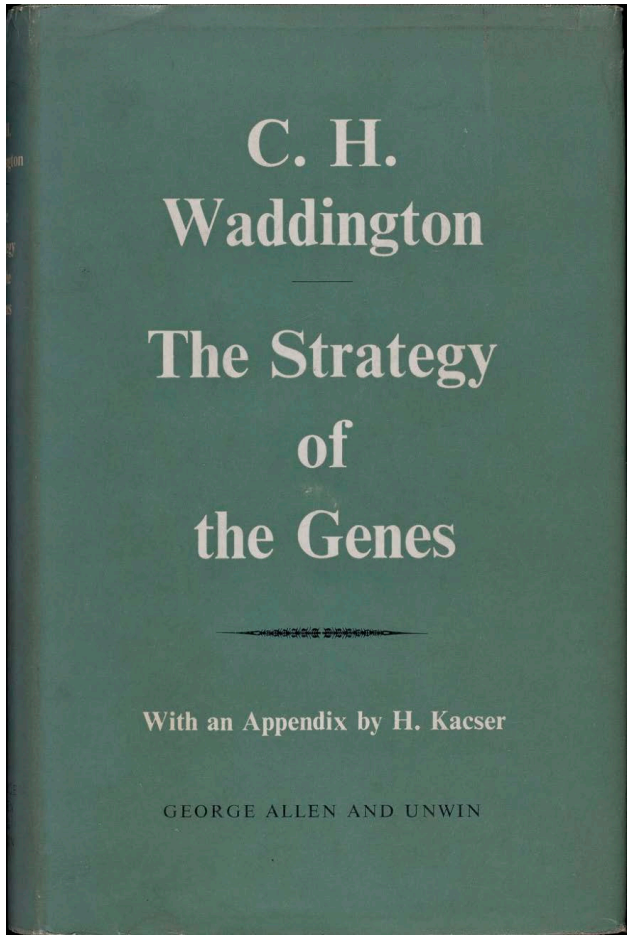

A. Czechanski et al. *Nature Protocols* 9:559 (2014)

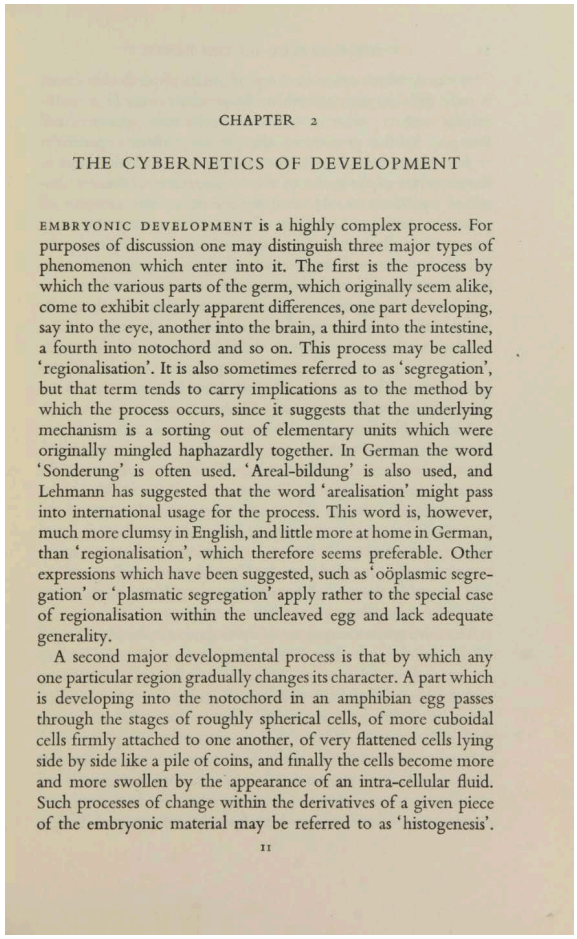
Merlin Lange et al. and Loic Royer, *Cell* 187, 6742–6759 (2024)

# Towards a geometric view of developmental dynamics and cellular decisions

C.H. Waddington
(1905-1975)

C.H. Waddington (1957). *The strategy of the genes. A discussion of some aspects of theoretical biology.*



CHAPTER 2

THE CYBERNETICS OF DEVELOPMENT

EMBRYONIC DEVELOPMENT is a highly complex process. For purposes of discussion one may distinguish three major types of phenomenon which enter into it. The first is the process by which the various parts of the germ, which originally seem alike, come to exhibit clearly apparent differences, one part developing, say into the eye, another into the brain, a third into the intestine, a fourth into notochord and so on. This process may be called 'regionalisation'. It is also sometimes referred to as 'segregation', but that term tends to carry implications as to the method by which the process occurs, since it suggests that the underlying mechanism is a sorting out of elementary units which were originally mingled haphazardly together. In German the word 'Sonderung' is often used. 'Areal-bildung' is also used, and Lehmann has suggested that the word 'arealisation' might pass into international usage for the process. This word is, however, much more clumsy in English, and little more at home in German, than 'regionalisation', which therefore seems preferable. Other expressions which have been suggested, such as 'oöplasmic segregation' or 'plasmatic segregation' apply rather to the special case of regionalisation within the uncleaved egg and lack adequate generality.

A second major developmental process is that by which any one particular region gradually changes its character. A part which is developing into the notochord in an amphibian egg passes through the stages of roughly spherical cells, of more cuboidal cells firmly attached to one another, of very flattened cells lying side by side like a pile of coins, and finally the cells become more and more swollen by the appearance of an intra-cellular fluid. Such processes of change within the derivatives of a given piece of the embryonic material may be referred to as 'histogenesis'.

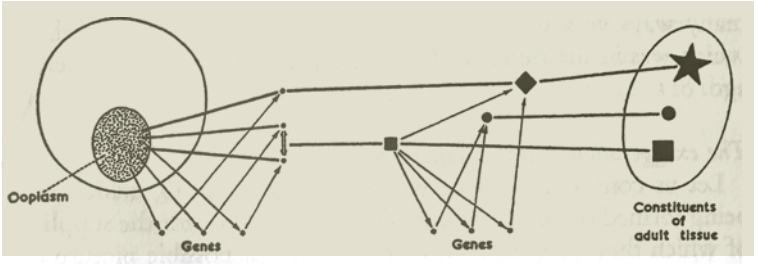
11

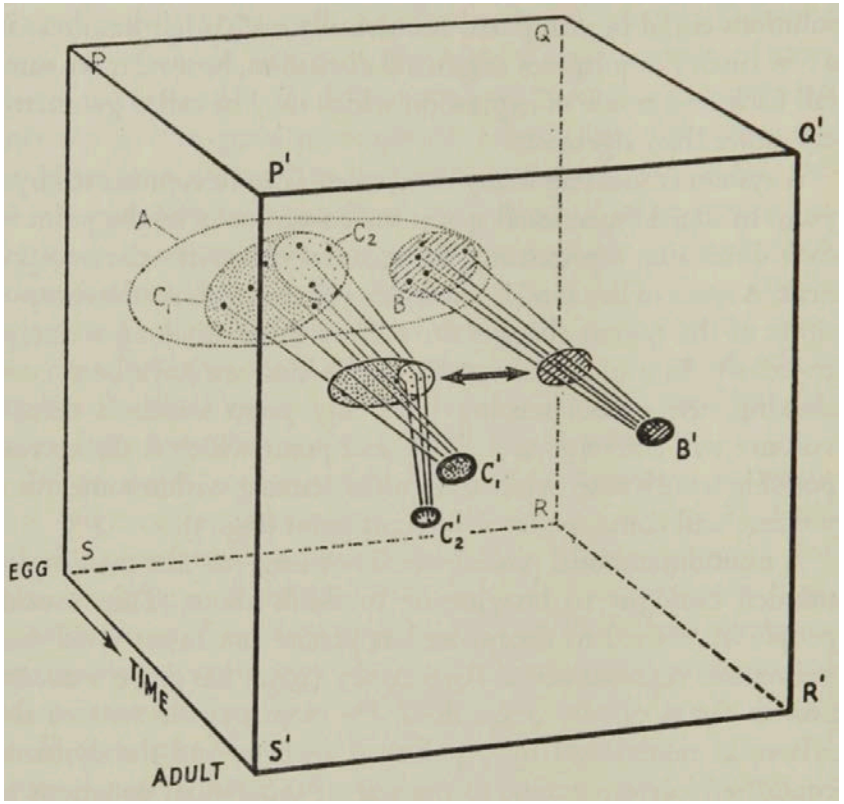
https://wellcomecollection.org/works/nzwm3z65/items

# Development as dynamics in a high dimensional space

The strategy of the genes (1957). Chap. 2. *The cybernetics of development*

- Development is complex process comprising regionalisation (patterning), histogenesis (differentiation) and morphogenesis.
- Development entails **evolution over time in a multidimensional space** that characterises its composition (genes, proteins and other components of cytoplasm).
- **A phase space best characterises development.**
- **Trajectories converge to end point**




C.H. Waddington (1957). *The strategy of the genes. A discussion of some aspects of theoretical biology.*

# Development as dynamics in a high dimensional space

- Epigenetic landscape concept
  - This system exhibits tendency towards a kind of **equilibrium centred not on state but on a direction of change** (homeorhesis, flow)
  - **A creode (« necessary path ») is a representation by a trajectory in phase space of a temporal succession of states towards which the system will relax if perturbed.**
  - **Noise** represented by irregular spherical shape of bead

Initial states (different cytoplasmic states in different parts of the egg)

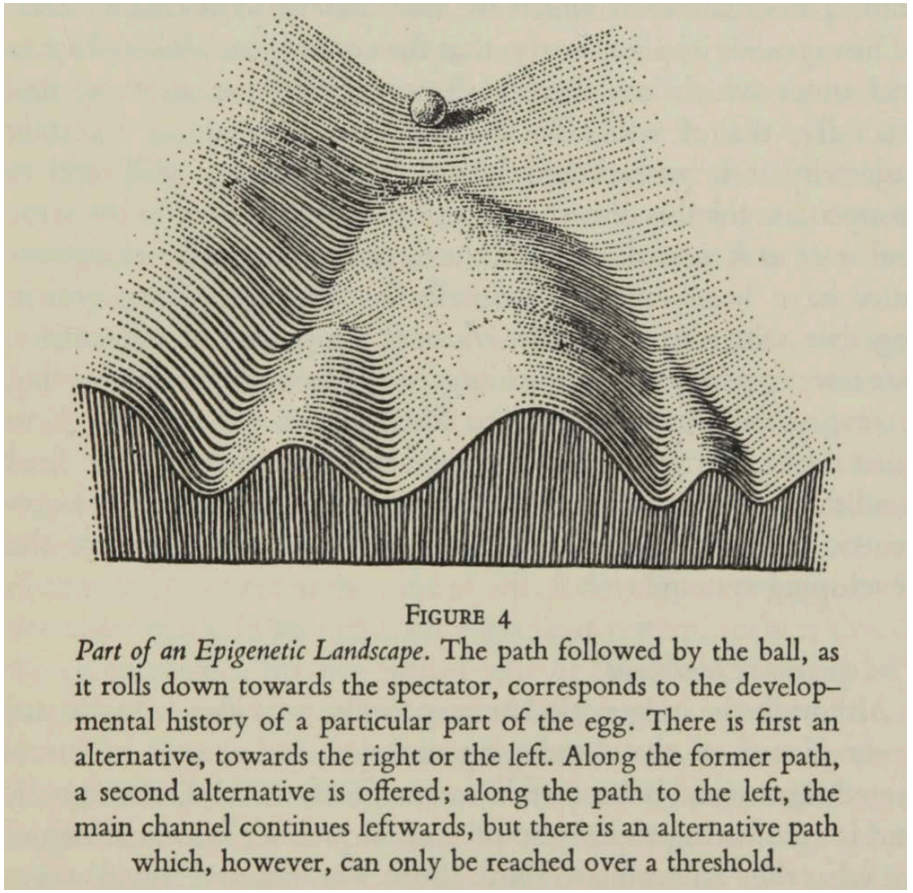


FIGURE 4

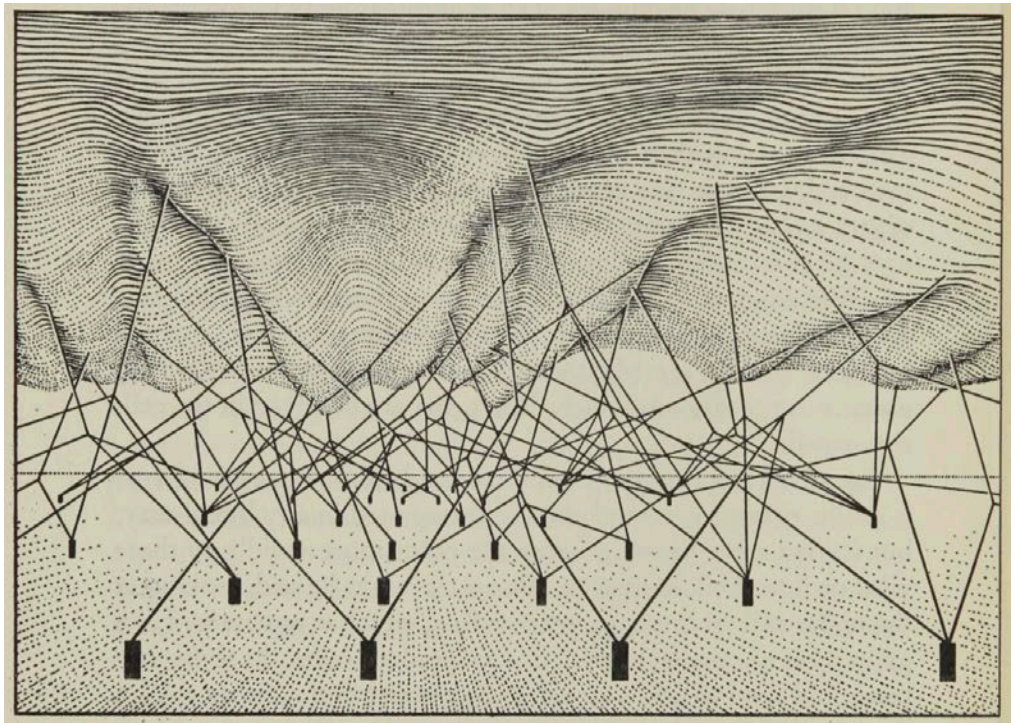
*Part of an Epigenetic Landscape*. The path followed by the ball, as it rolls down towards the spectator, corresponds to the developmental history of a particular part of the egg. There is first an alternative, towards the right or the left. Along the former path, a second alternative is offered; along the path to the left, the main channel continues leftwards, but there is an alternative path which, however, can only be reached over a threshold.

End states (eg. Eye, brain, spinal chord …)

# Development as dynamics in a high dimensional space

- Epigenetic landscape concept

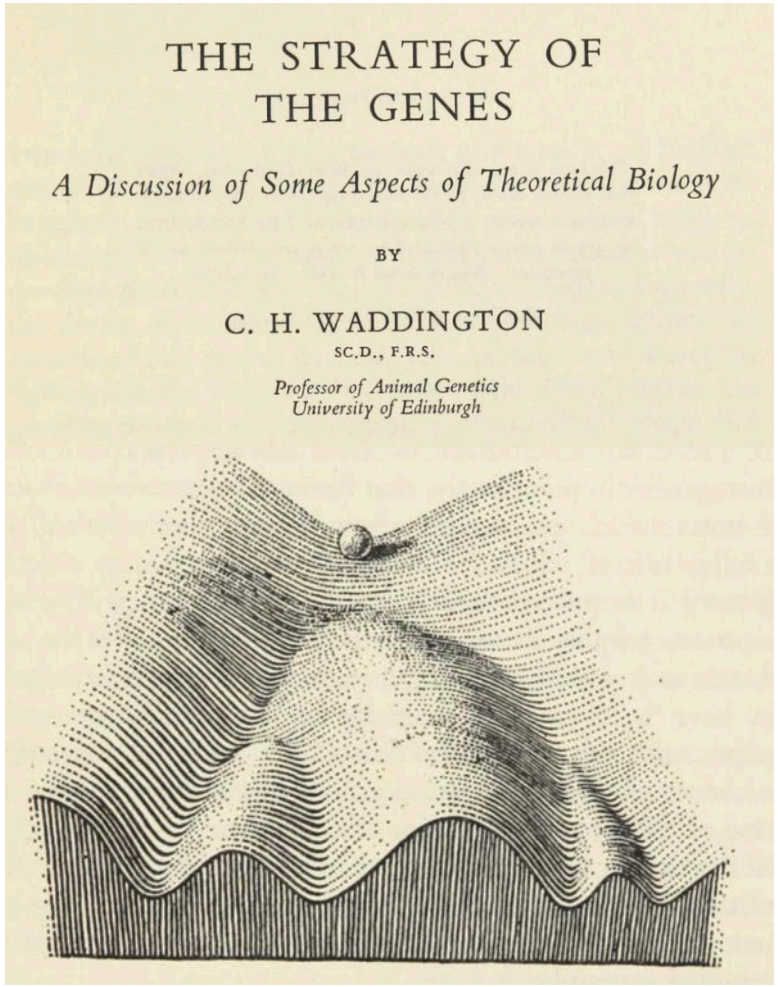
Phenotype
Low dimensional



Genotype
High dimensional

- A complex system of interactions underlies the epigenetic landscape
- Pegs represent genes and tension on guy ropes the « chemical forces » exerted by genes
- **Connection between genotype and phenotype is Non-isomorphic, non-linear, combinatorial, indirect**

# Development as dynamics in a high dimensional space


THE STRATEGY OF
THE GENES

*A Discussion of Some Aspects of Theoretical Biology*

BY

C. H. WADDINGTON

SC.D., F.R.S.

*Professor of Animal Genetics*
*University of Edinburgh*

The fundamental characteristics of the organism—its Form, to use the term which was employed in the Introduction—are time-extended properties, which can be envisaged as a set of alternative pathways of development, each to some degree, greater or lesser, a creode towards which the epigenetic processes exhibit homeorhesis. And in this way we can conceive of organic Form, not only as occupying four dimensions instead of only three, but as comprising potentialities as well as what is actually realised in any given individual. The epigenetic landscape, with its modelling of branching valleys with steep or gently rising sides, with cols and hanging valleys of more or less well defined contours, provides a rather crude but in some ways serviceable way of visualising the possible ways in which the developing system can be modified.

« Les caractéristiques fondamentales de l'organisme – sa Forme– sont des propriétés étendues dans le temps, que l'on peut envisager comme un ensemble de voies alternatives de développement, chacune étant, à des degrés divers, une chréode vers lequel les processus épigénétiques manifestent une homéorrhèsie. On peut ainsi concevoir la Forme organique non seulement comme occupant quatre dimensions plutôt que trois, mais aussi comme comprenant des potentialités en plus de ce qui est effectivement réalisé chez un individu donné. **Le paysage épigénétique, avec sa représentation de vallées ramifiées aux versants plus ou moins abrupts ou doux, avec des cols et des vallées suspendues aux contours plus ou moins bien définis, fournit un schéma assez grossier mais, à certains égards, utile pour visualiser les différentes manières dont le système en développement peut être modifié.** »

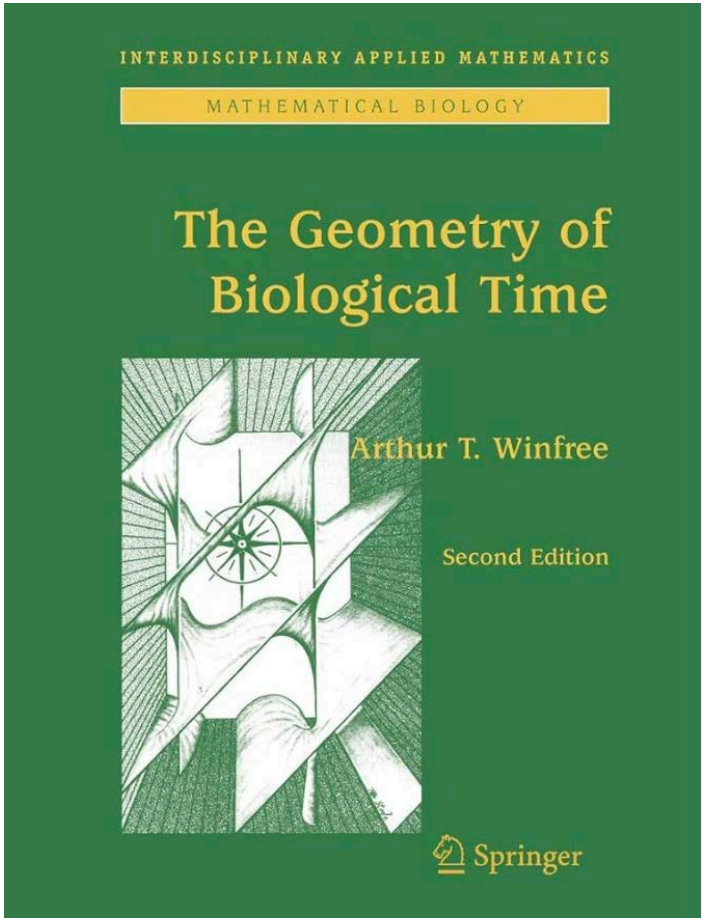
# The geometry of time

*Developmental pathways*

In the study of development we are interested not only in the final state to which the system arrives, but also in the course by which it gets there. In order to study these developmental pathways algebraically we should have to integrate the sets of equations by which the system is described. It is usually impossible to do this in any general way, although for any particular system, solutions could be computed numerically, as Turing has done in a few cases. For purposes of general discussion, however, we must fall back on a mode of expression which may be called geometrical rather than algebraic.

« Dans l'étude du développement, nous nous intéressons non seulement à l'état final auquel le système aboutit, mais aussi au chemin par lequel il y parvient. Pour étudier algébriquement ces trajectoires de développement, il nous faudrait intégrer les systèmes d'équations qui décrivent le comportement du système. Il est en général impossible de le faire de manière générale, même si, pour un système particulier, on peut toujours calculer des solutions numériquement, comme Turing l'a fait dans quelques cas.
**Pour les besoins de la discussion générale, cependant, nous devons en revenir à un mode d'expression que l'on peut qualifier de géométrique plutôt qu'algébrique.** »

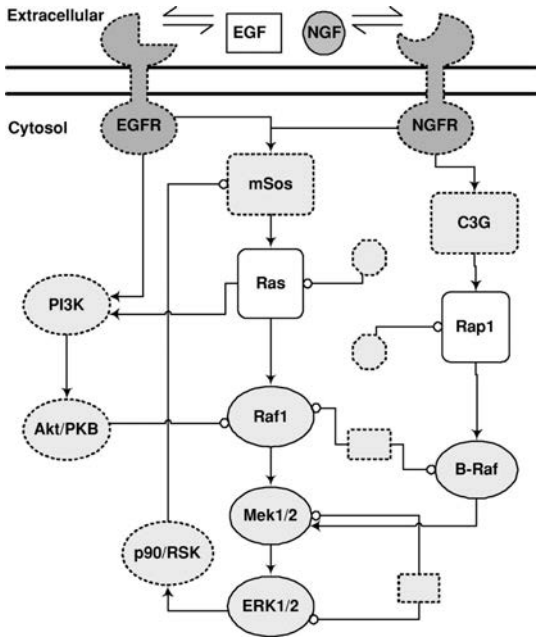
C.H. Waddington (1957). *The strategy of the genes*




A. Winfree
(1942-2002)

# Do we need ~50-parameter kinetic models?

Network for ERK1/2 activation by EGF and NGF in rat PC12 cells



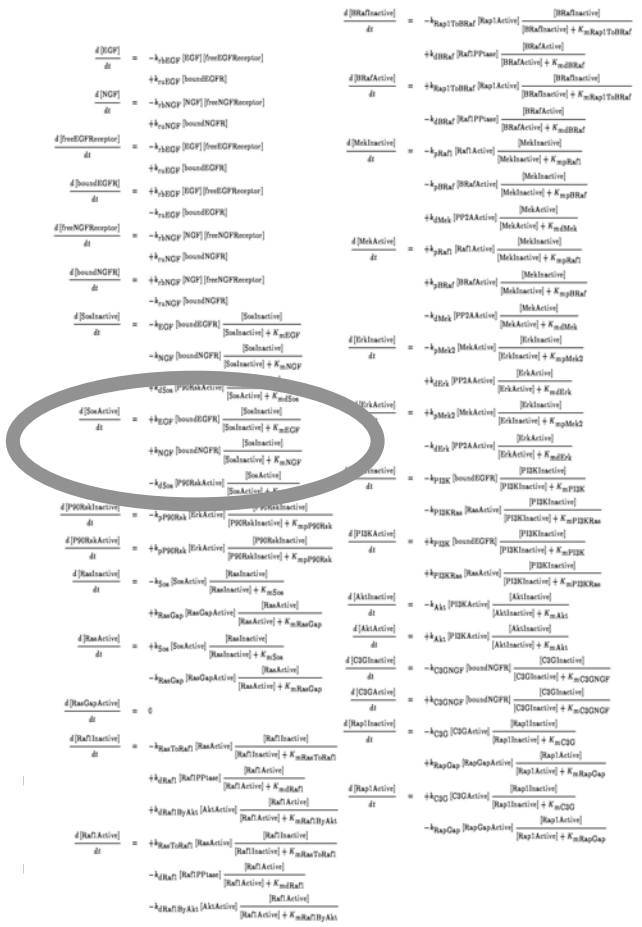

**Bad news:**

28 first order, non linear ODE
48 unknown parameters

**Good news:**

Most parameters are under-constrained (sloppy)

$$\frac{d[\text{SosActive}]}{dt} = +k_{\text{EGF}}[\text{boundEGFR}]\frac{[\text{SosInactive}]}{[\text{SosInactive}]+K_{\text{mEGF}}} + k_{\text{NGF}}[\text{boundNGFR}]\frac{[\text{SosInactive}]}{[\text{SosInactive}]+K_{\text{mNGF}}} - k_{\text{dSos}}[\text{P90RskActive}]\frac{[\text{SosActive}]}{[\text{SosActive}]+K_{\text{mdSos}}}$$



Brown and J. Sethna. *Physical Rev E* 68, 021904 2003 (2003)

# Do we need ~50-parameter kinetic models?

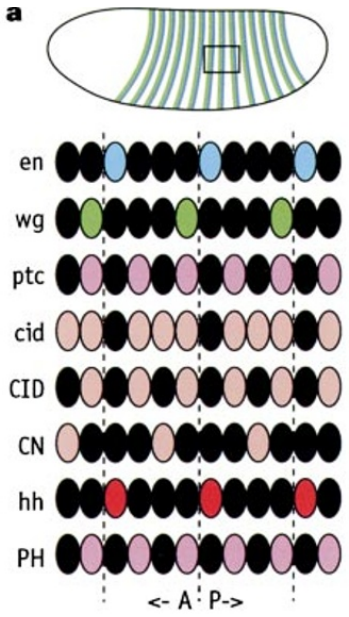
**Bad news:**

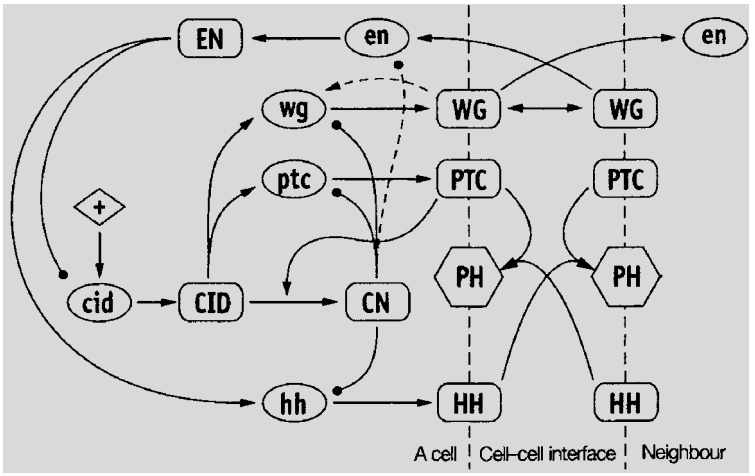
Many first order, non linear ODE
48 parameters

**Good news:**

Most parameters are under constrained (sloppy)

240,000 randomly-chosen parameter sets
1,192 solutions (1 in 200)

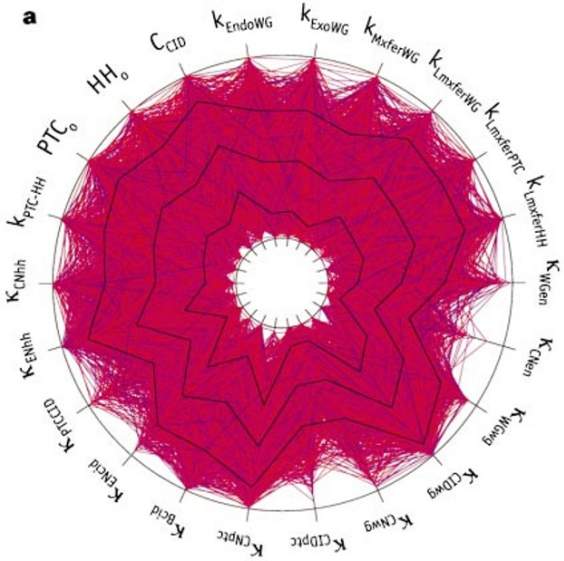



$$\frac{d[hh]_i}{dt} = T_{\max}\rho_{hh}\left[\frac{[EN]_i^{Y_{ENhh}}}{K_{ENhh}^{Y_{ENhh}} + [EN]_i^{Y_{ENhh}}}\right] - \frac{[hh]_i}{H_{hh}}$$

$$\frac{d[HH]_{i,j}}{dt} = \frac{P_{\max}\sigma_{HH}[hh]_i}{6} - \frac{[HH]_{i,j}}{H_{HH}} - k_{PTCHH}[HH]_{i,j}[PTC]_{n,j+}$$

$$\frac{d[PH]_{i,j}}{dt} = k_{PTCHH}[HH]_{n,j+3}[PTC]_{i,j} - \frac{[PH]_{i,j}}{H_{PH}}$$

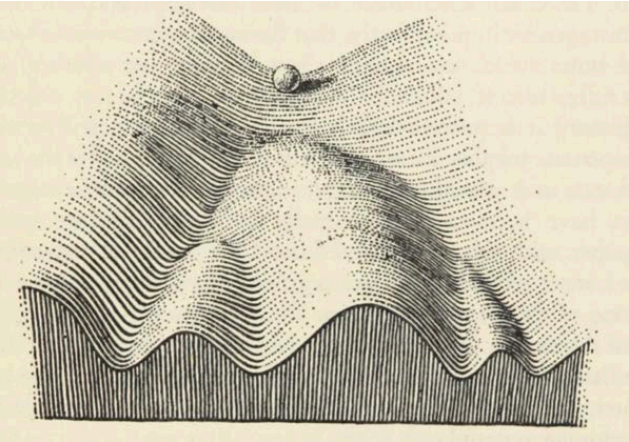




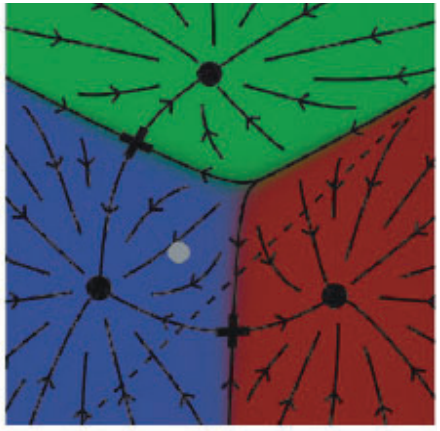

G. von Dassow et al and G. Odell, Nature 406: 188 (2000)

# Beyond gene-heavy ODE models for Development

- Need for a more intuitive approach that really captures the dynamics of signalling
- A phenomenological model that circumvents the construction of gene-heavy ODE models, with a large number of « sloppy » (under-constrained) parameters for the dynamics (eg. transcription, translation, trafficking, signalling etc).
- A parsimonious representation of how signals define fates
- Distinguishes competence, commitment (decision making) and final determination of state.



Metaphore



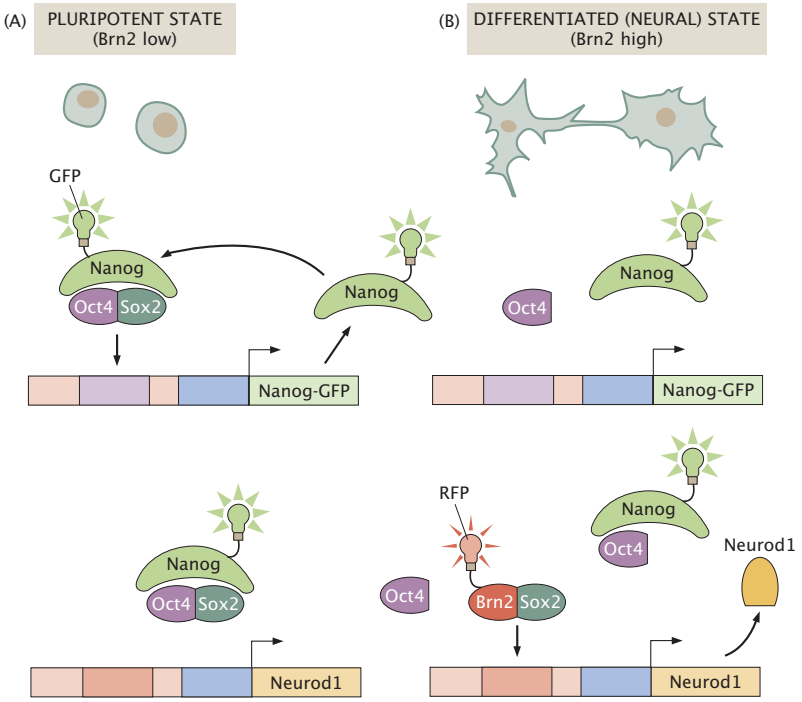
Mathematical framework

# Geometric approach to Bistability

## Positive autoregulation and Competition

Transcription factor competition forms a genetic switch in embryonic stem cells

- Nanog forms a complex with Oct4 and Sox2 to auto activate Nanog and maintain the pluripotent state.
- Brn2 competes with Nanog to bind Sox2 and induces Neurod1 transcription, and neural fate.

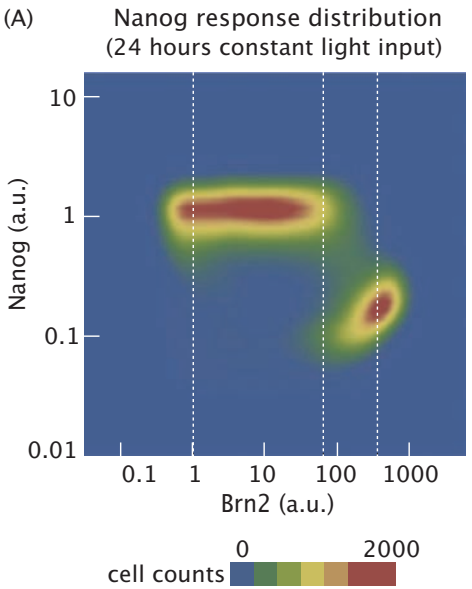


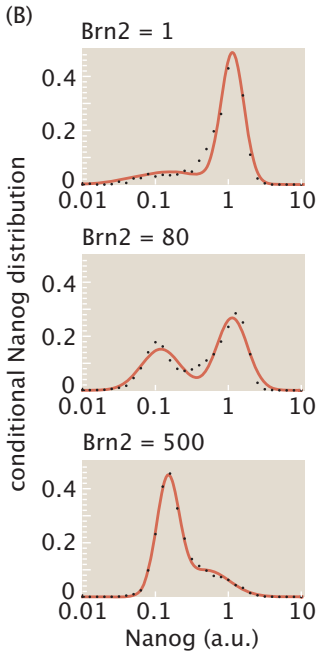

C. Sokolik et al. and M. Thomson, *Cell Systems* 1, 117–129 (2015)
Hernan G. Garcia and Rob Phillips, *Physical genomics*

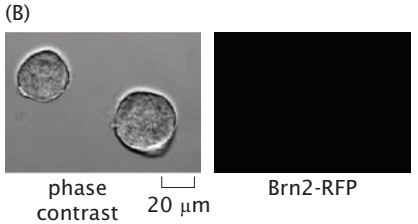
# Geometric approach to Bistability

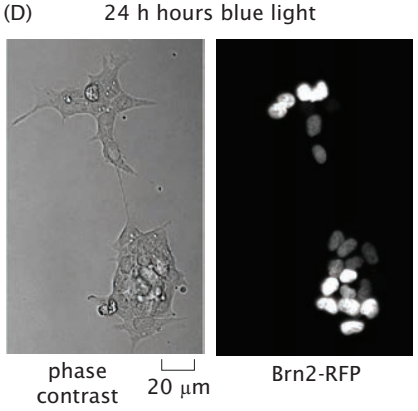
## Positive autoregulation and Competition

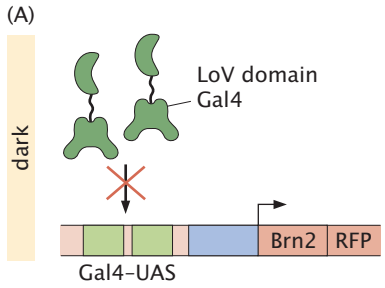
Light induced (photoactivation) expression of Brn2 represses Nanog and induces neural fate

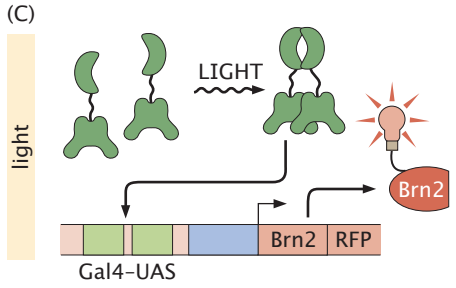





C. Sokolik et al. and M. Thomson, *Cell Systems* 1, 117–129 (2015)
Hernan G. Garcia and Rob Phillips, *Physical genomics*

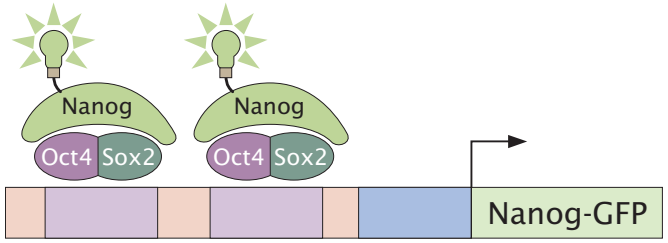
# Geometric approach to Bistability

## Positive autoregulation and Competition

- Non-linear (cooperative) activation of Nanog by the Nanog-Oct4-Sox2 (NOS) complex

Rate equation: Hill function for production and degradation

$$\frac{dN}{dt} = r\frac{\left(\frac{[N-O-S]}{K(B)}\right)^2}{1+\left(\frac{[N-O-S]}{K(B)}\right)^2} - \gamma N,$$



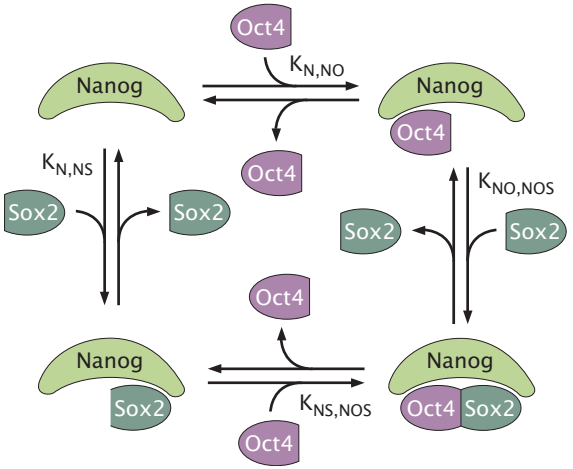

The dissociation constant depends on Brn2 (which competes with Nanog)

- Equilibrium model of NOS complex assembly:

if Sox2 and Oct4 are in excess of Nanog, then

$$[N-O-S] \approx Nc, \quad \text{with the constant} \quad c = \frac{[Oct4][Sox2]}{K_{NS,NOS}K_{N,NS}},$$

This yields: $$\frac{dN}{dt} = r\frac{\left(\frac{N}{\bar{K}(B)}\right)^2}{1+\left(\frac{N}{\bar{K}(B)}\right)^2} - \gamma N, \quad \text{where} \quad \bar{K}(B) = K(B)/c$$






C. Sokolik et al. and M. Thomson, *Cell Systems* 1, 117–129 (2015)
Hernan G. Garcia and Rob Phillips, *Physical genomics*

# Geometric approach to Bistability

## Positive autoregulation and Competition

Instead of using rate analysis and a phase portrait, we can use a geometric approach.

Principle: dynamics are derived from a « potential landscape » as follows:

$$\frac{dN}{dt} = -\frac{\partial U(B,N)}{\partial N}.$$

« Velocity » is proportional to a « force » that derives from a potential

Based on previous analysis of N rate of change:

$$-\frac{\partial U(B,N)}{\partial N} = r\frac{\left(\frac{N}{\bar{K}(B)}\right)^2}{1+\left(\frac{N}{\bar{K}(B)}\right)^2} - \gamma N. \quad \text{By integration :} \quad \int dU = -\left(\int r\frac{\left(\frac{N}{\bar{K}(B)}\right)^2}{1+\left(\frac{N}{\bar{K}(B)}\right)^2}dN - \gamma\int N dN\right).$$

We derive the Energy landscape functional form:

$$U(B,N) = r\,\bar{K}(B)\,\arctan\frac{N}{\bar{K}(B)} - rN + \frac{1}{2}\gamma N^2.$$

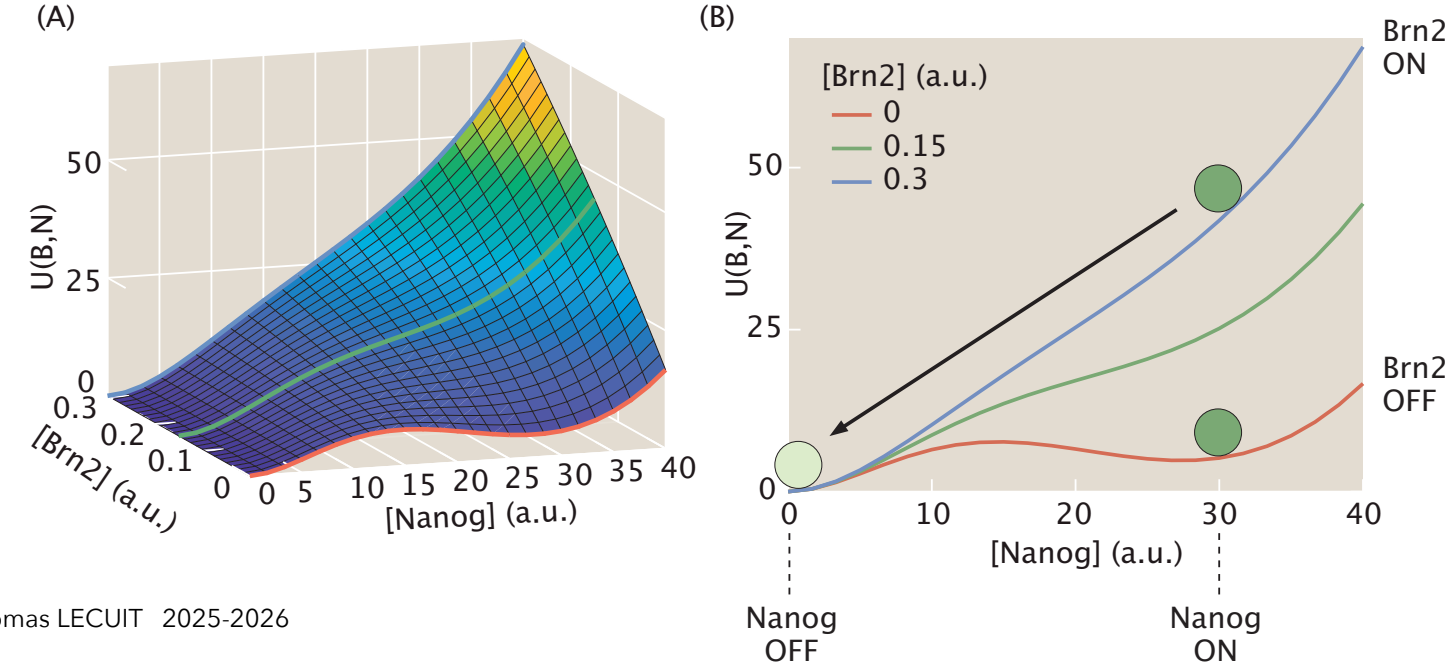
# Geometric approach to Bistability

Energy landscape functional form: this is not a fixed landscape. Its changes as a function of signals

$$U(B,N) = r\,\bar{K}(B)\,\arctan\,\frac{N}{\bar{K}(B)} - rN + \frac{1}{2}\gamma N^2.$$

Potential landscape as a function of Nanog and Brn2:

- At low Brn2 concentration, there are two minima and two fixed points (Nanog ON, Nanog OFF) and there is an unstable fixed point in between
- At higher Brn2, the high minimum disappears leaving only one state: Nanog OFF.



# Case study 1: Geometry of cell fate dynamics in *C. elegans*

A simple 2-D "fate plane" driven by two signal inputs (EGF, Notch) recapitulates the determination of 3 cell fates in *C. elegans*

## Geometry, epistasis, and developmental patterning

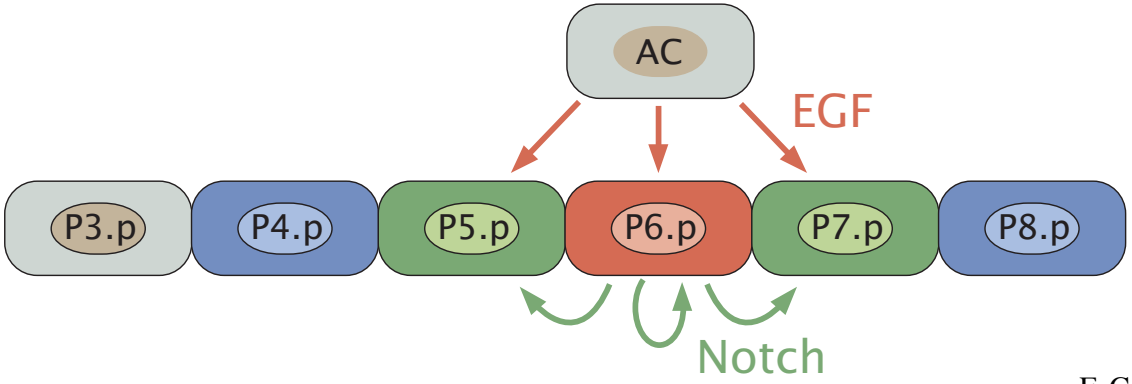
**Francis Corson and Eric Dean Siggia**[1]

Center for Studies in Physics and Biology, The Rockefeller University, New York, NY 10021

## Gene-free methodology for cell fate dynamics during development

**Francis Corson**[1]*, **Eric D Siggia**[2]*

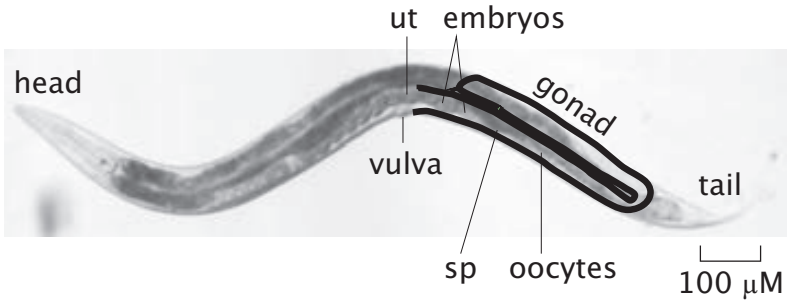
[1]Laboratoire de Physique Statistique, CNRS / Ecole Normale Supérieure, Paris, France; [2]Center for Studies in Physics and Biology, Rockefeller University, New York, United States



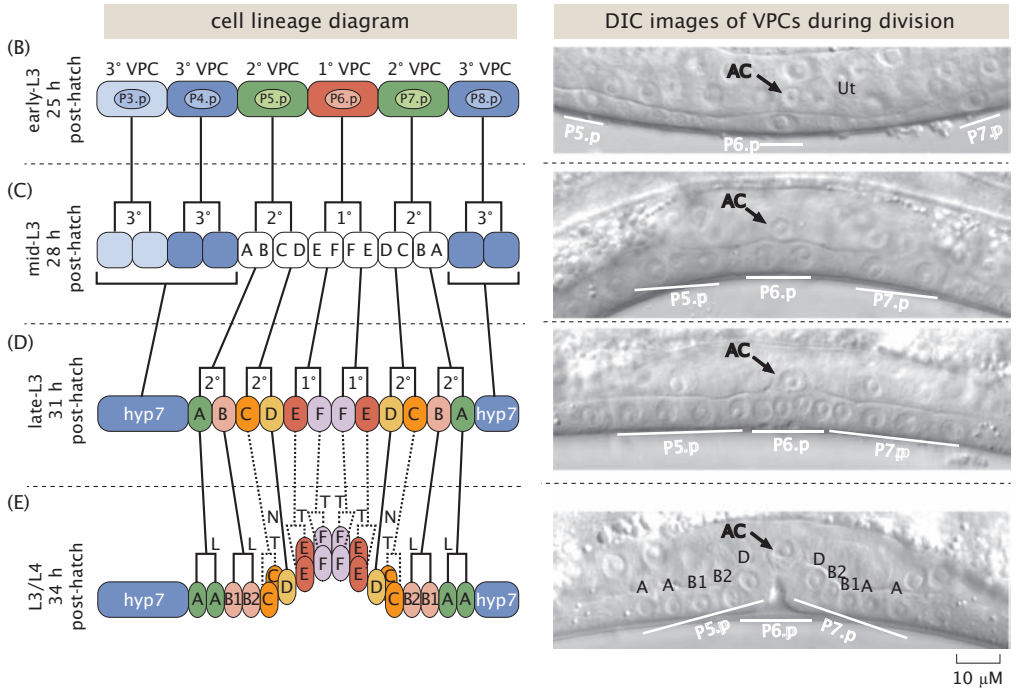

F. Corson and E. Siggia. *PNAS* 109:5568–5575 (2012)

F. Corson and E. Siggia. *eLife* 6:e30743 (2017)

# Geometry of cell fate dynamics in *C. elegans*




Vulval precursor cells (6 VPCs):
1° fate:P6.p
2° fate: P5.p and P7.p
3° fate: P4.p and P8.p, P3.p



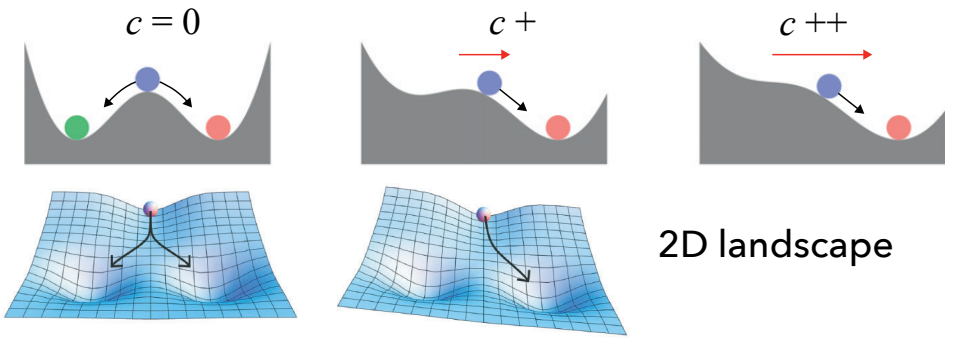
# Key features of a geometric model

- Key features:
- A phenomenological model that circumvents the construction of gene-heavy ODE models, with a large number of « sloppy » (under-constrained) parameters for the dynamics (eg. transcription, translation, trafficking, signalling etc).
- A parsimonious representation of how signals define fates
- Distinguishes competence, commitment (decision making) and final determination of state.

Bistable system: 2 wells, tilt

1D landscape: $f(x) = x^4/4 - x^2/2 + c\,x$

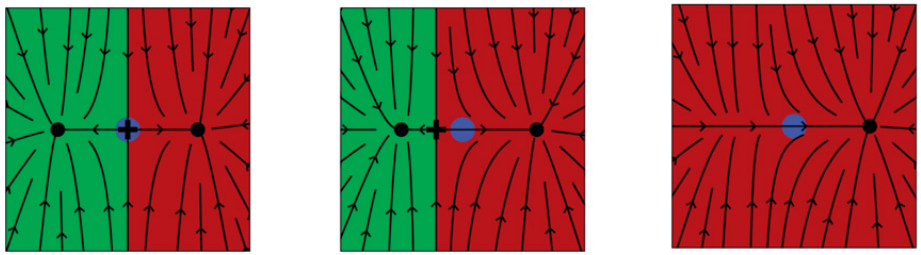
$c$ is value of a signal gradient that tilts the landscape
The signalling process C is viewed as a blackbox reduced to a single parameter $c$.




2D landscape

The landscape changes as a function of signals

Representation as flow (arrows) on a tunable 2D landscape.
Coloured domains are basin of attractions: the points that flow to the terminal states (black dots).
The saddle point (+) separates the two domains.

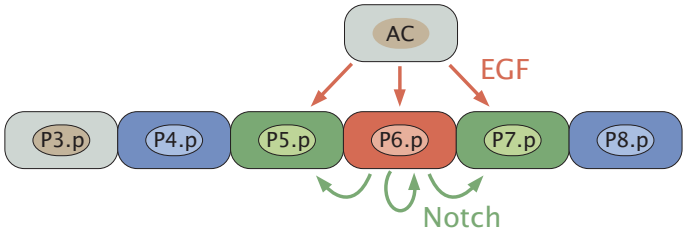




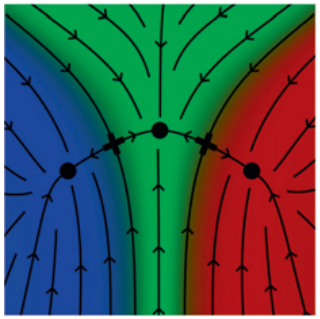
P. François and E. Siggia. *Current Opinion in Genetics & Development*, 22:627–633 (2012)

# Building a geometric model from data

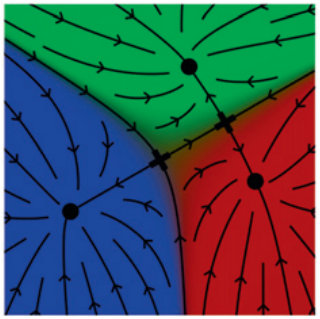
- A simple 2-D "fate plane" driven by two signal inputs (EGF, Notch)
- Three states are defined by the action of EGF and Notch signalling



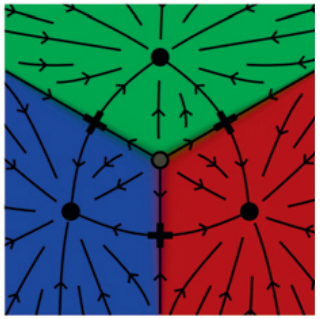

- Three possible arrangements of domains of attraction and of saddles



**Gradient model:** the basins are ordered from left to right



**2 consecutive decisions**
2 saddle points



**All transitions are possible**
Central source and 3 saddles



F. Corson and E. Siggia. *PNAS* 109:5568–5575 (2012)

# Building a geometric model from data

## Mathematical construction

- **Principle: Dynamics = Flow + Signal tilts + Noise**
  State of a cell represented as a point ***r*** in a 2-D fate plane
  Stochastic differential equation: $\frac{d\vec{r}}{dt} = \frac{1}{\tau}\left[\vec{\sigma}_1\left(\vec{f} + \vec{m}\right) - \vec{r}\right] + \vec{\eta}(t)$

- **Flow *f(r)***: characterised by the simplest polynomial vector field with 3-fold symmetry, ie. consistent with the existence of 3 states/basins of attraction (derived from cubic potential):

  $\vec{f}(\vec{r}) = 2\vec{r} + c_2[-2xy\vec{e}_x + (y^2 - x^2)\vec{e}_y]$ with $\vec{r} = x\vec{e}_x + y\vec{e}_y$

- **Signal tilt vector:** adds a constant bias to a symmetric flow
  ***m*** represents the linear contribution of vector $\vec{m}_0$ to default 3° fate and 2 signal vectors $\vec{m}_1$ and $\vec{m}_2$
  $\vec{m} = \vec{m}_0 + l_1\vec{m}_1 + l_2\vec{m}_2$ EGF dosage $l_1$: fixed exponential gradient across cells
  EGF Notch Notch dosage $l_2$: thresholded by a line in the fate plane (cells below it express ligand)
  Note: N and EGF have *independent* activities

- **Non-linear function** $\sigma_1$ ensures that dynamics is bounded (by sigmoidal function) $\vec{\sigma}_1\left(\vec{f}\right) = \tanh\|\vec{f}\|\frac{\vec{f}}{\|\vec{f}\|}$
  together with $-r/\tau$ term.

- **Noise:** Stochastic term characterised by diffusion in phase space
  $\eta_i(t)\eta_j(t') = 2D\delta_{ij}\delta(t - t')$

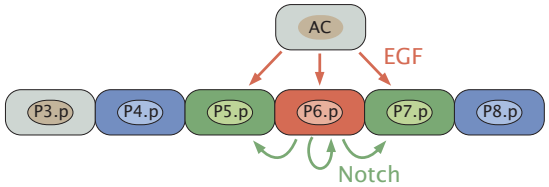


F. Corson and E. Siggia. *PNAS* 109:5568–5575 (2012)

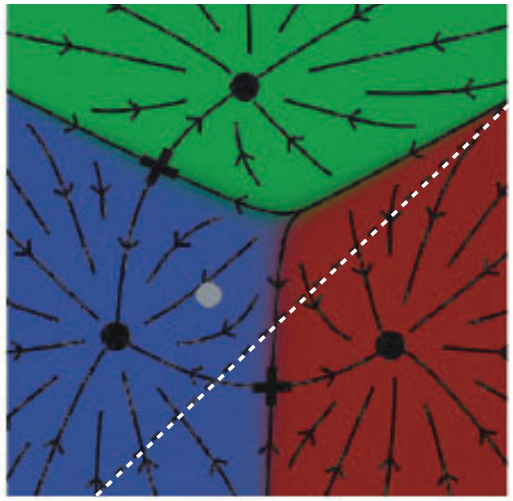
# Building a geometric model from data

- Flows in the landscape towards 3 cell fates:

$$\frac{d\vec{r}}{dt} = \frac{1}{\tau}\left[\vec{\sigma}_1\left(\vec{f} + \vec{m}\right) - \vec{r}\right] + \vec{\eta}(t)$$




Vectorial equation: **the axis do not represent gene/molecular activities.**
EGF induces 1° fate P6.p (red)
Notch induces 2° fate, P5.p and P7.p (green)
3° fate is unindexed/default (blue)



VPC indicated by grey dot.
Coloured arrows represent the strength of EGF (red) and N (green) signals.
Cells below the dashed line express Notch ligands

**A sensitized genetic background is an allele that flows near a saddle point**: noise can give rise to both adjacent fates (partial penetrance of a mutant phenotype)



F. Corson and E. Siggia. *PNAS* 109:5568–5575 (2012)

# Building a geometric model from data

- **Onset of competence (t=0+)**

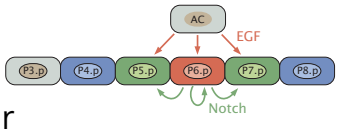
strong EGF signal (red arrow) tilts the landscape for P6.p which can only make 1°fate. The cell is above the dashed line so does not express N ligand and P7.p does not receive a signal.

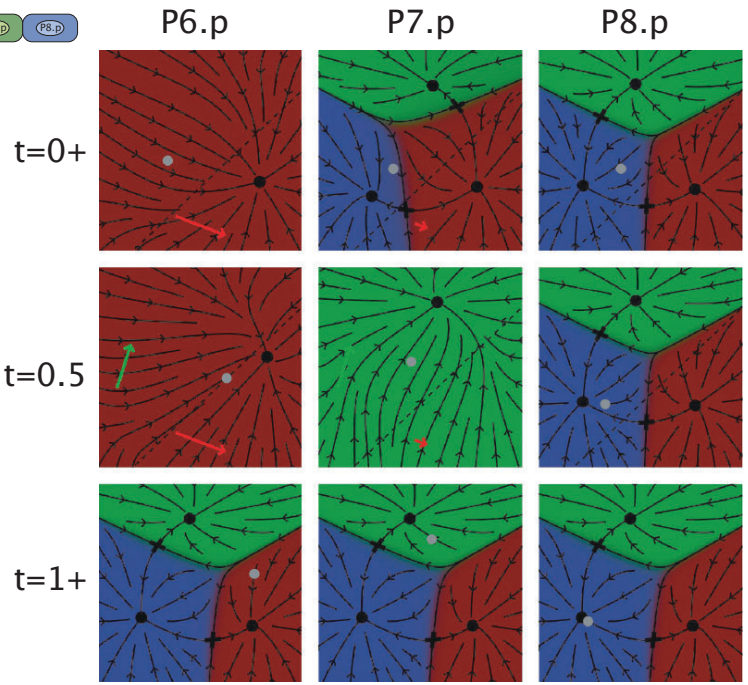
- **Mid competence (t=0.5)**

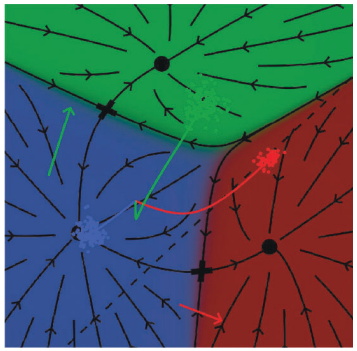
VPC reaches dashed line, expresses N ligand (green arrow)
Autocrine signalling for P6.p and paracrine for P7.p.
This tilts landscape for P7.p which can only adopt 2° fate.

- **End of competence (t=1+)**

No signalling so landscape returns to initial conditions with 3 attractor basins.
Cells are in their respective basins and reach their respective fates.



**Compact representation of cell trajectories and distribution of outcomes due to noise in a landscape without signals**

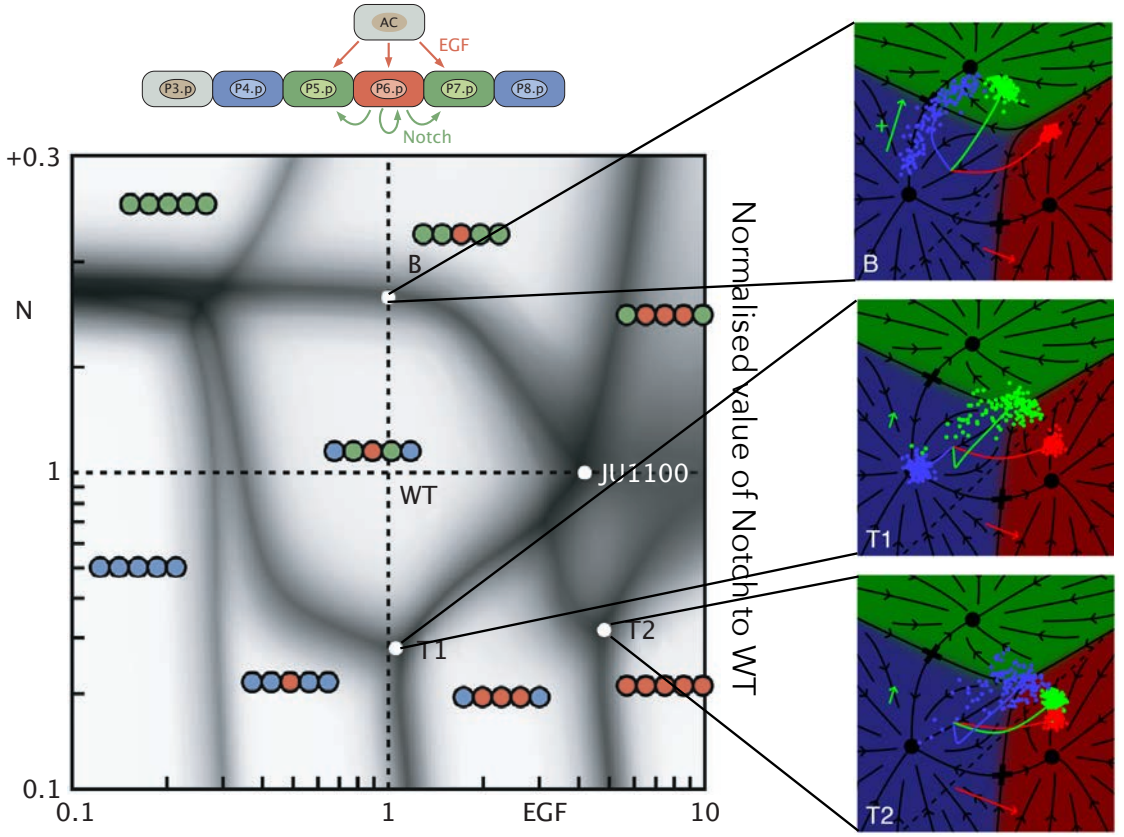
# Phase portrait of cell fate patterns

- Continuous domains with unique fates (the size of the domain is linked to robustness)
- Domains separated by fuzzy lines that reflect **partial penetrance** (phenotypic variability)
- Boundaries cross at « triple points » (e.g. $T_1$, $T_2$) where small changes in signals produce different fate patterns

- **Partial penetrance: reflected by distribution of cell fates for a given VPC across fate boundary**
- **This is used to identify saddle points**

Point B: P4/P8.p partially adopt 2° fate due to ectopic N (**+**)

Points T1/T2: P5/P7.p and P4/P8p partially adopt all fates




Normalised value of EGF to WT



F. Corson and E. Siggia. *eLife* 6:e30743 (2017)

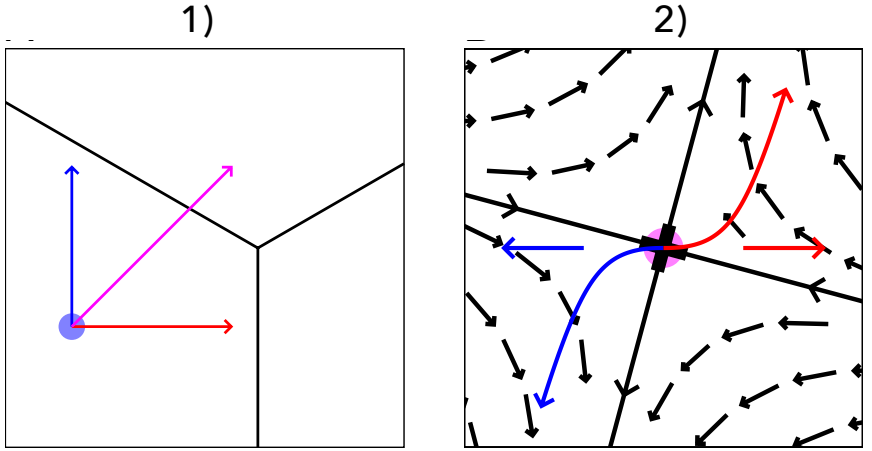
# Benefits of geometric model

- A parsimonious representation of dynamics
- No need to model with ODE and many parameters the details of dynamics
- Makes clear predictions of mutant phenotypes and gene interactions.
  - Example: epistasis

    **Non-additive interaction between alleles** of genes. The phenotype produced by mutation in gene X changes depending on mutation in gene Y.
    e.g. Sometimes two alleles in two different genes have no effect independently, but show a defective phenotype when combined (synthetic lethality).

**1) Epistasis results from continuous vector field on discrete fate map**
Additivity of vectors on landscape.
Geometric representation explains epistasis without need for explicit gene interaction (more parameters)

**2) Epistasis results from flow in vicinity of saddle.**






F. Corson and E. Siggia. *PNAS* 109:5568–5575 (2012)

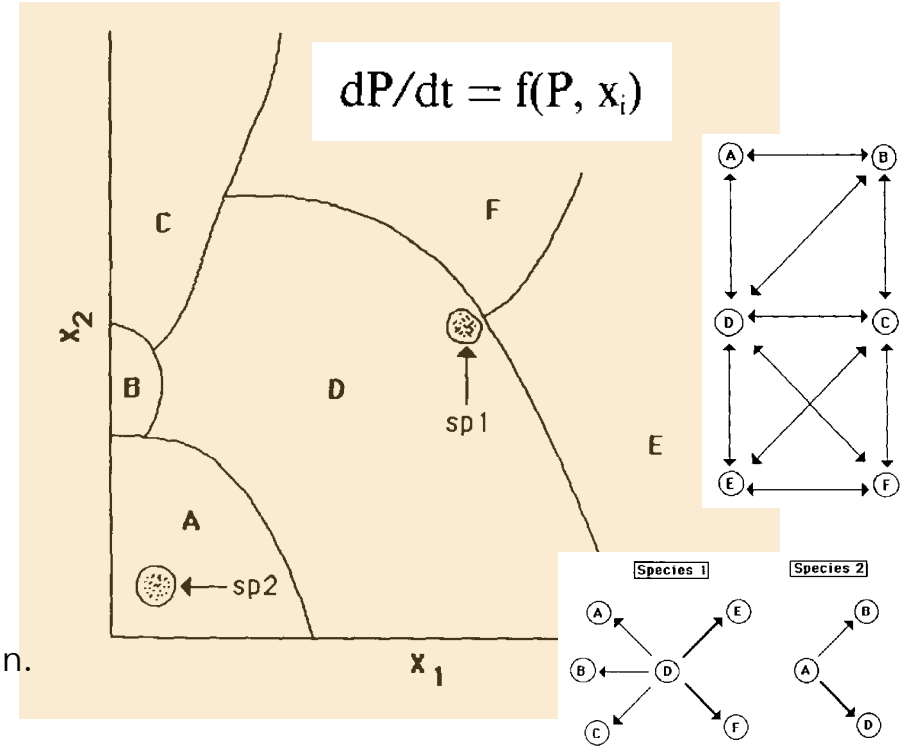
# The Genotype to Phenotype mapping

1. **Many combinations of parameter values result in the same phenotype**, that is, there is no one-to-one correlation between genotype and phenotype.

2. The **stability of a phenotype is related to the area of its domain** in parameter space (canalisation).

3. The lines correspond to critical ($x_1$, $x_2$) values. They constitute **transformational boundaries** among phenotypes.

4. The stability of a particular set of phenotypes will depend on its position in parameter space (sp1 and sp2).




**Implications:**

– **Robustness:** many genotypes give rise to same phenotype

– many genotypic changes can give rise to phenotypic transformation.

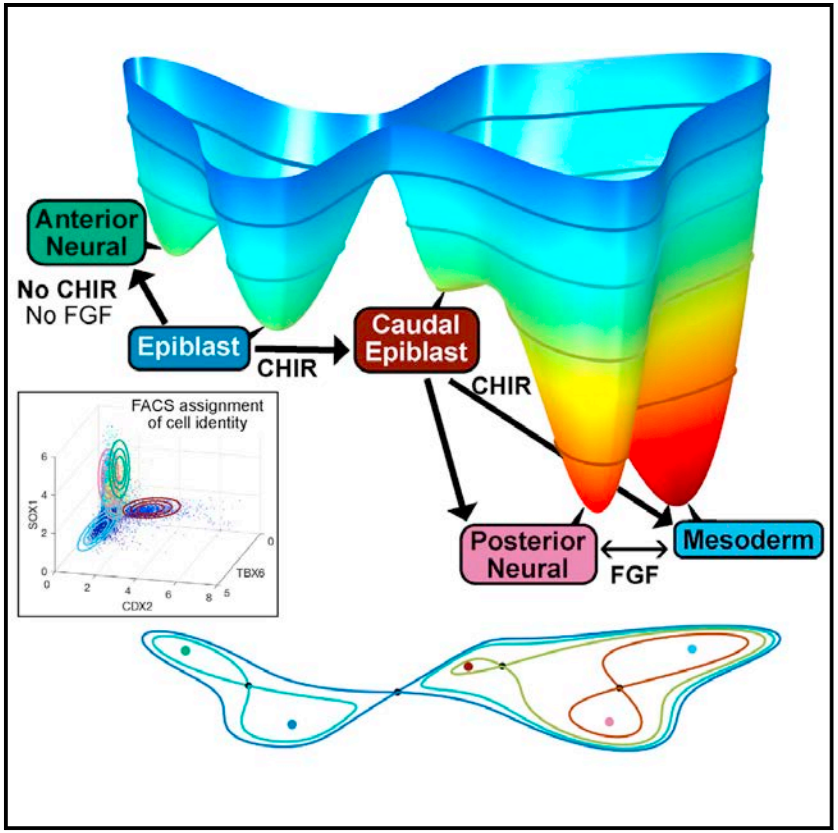
– **Evolvability:** Transformational diagram define allowed phenotypic changes, with probability set by the length of boundaries in phase space.

Pere Alberch, *From genes to phenotypes: dynamical systems and evolvability*. *Genetica* 84: 5-11 (1991)

# Case study 2: Geometric landscape of cell fate dynamics in vertebrates

## Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions

Meritxell Sáez,[1,2,5,6] Robert Blassberg,[2,6] Elena Camacho-Aguilar,[1,3,6] Eric D. Siggia,[4] David A. Rand,[1,5,*] and James Briscoe[2,7,*]





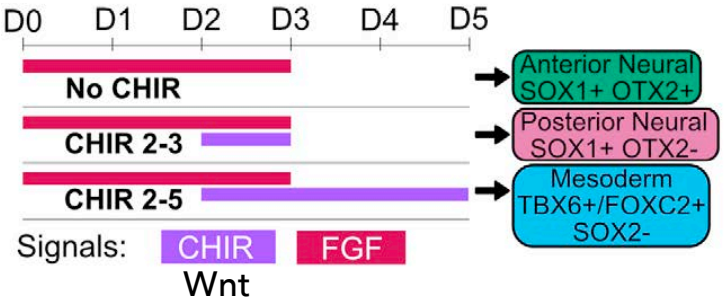

M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)

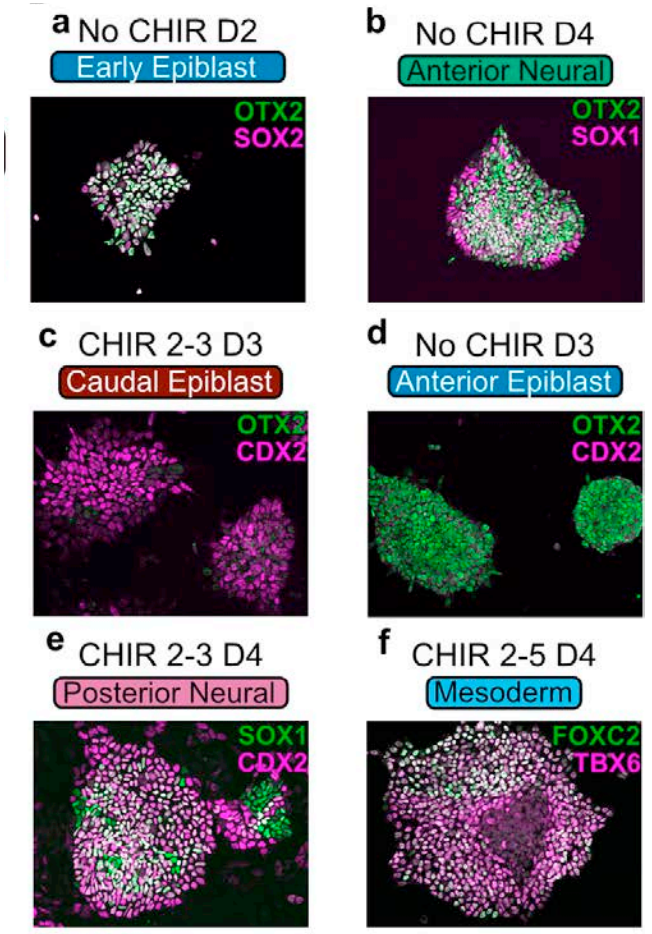
# Cell fate decisions *in vitro*

An *in vitro* system recapitulates developmental pathways
Identification of cell fates based on protein signatures

- Flow cytometry data to measure multiple protein expression in single cells accross population.
- Previous data led to the identification of a minimal set of markers to identify and distinguish between cell types.

- Time-course data at single-cell resolution in response to developmental signals
- Signalling protocols induce different cell fates





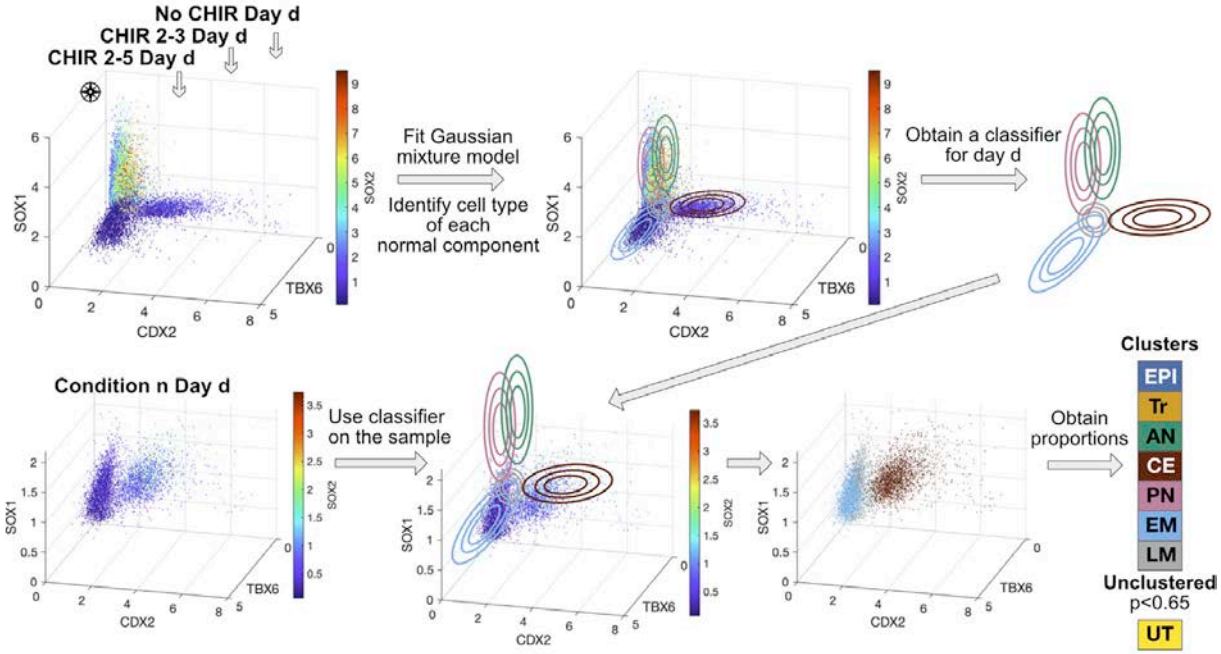

M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)

# Defining cell fates as cell clusters

## Clustering using Gaussian mixture models defines cell identities

- 6-dimensional flow-cytometry data.
- Algorithm to fit multivariate gaussian distributions to the flow-cytometry data. This defines clusters.
- **Hypothesis: these clusters correspond to an attractor on a dynamical landscape**

- A cell is assigned to a cluster if its probability for the given distributions exceeds a defined threshold.
- If it cannot be assigned to a cluster it is in transit between clusters.
- **Once clusters are defined, cells are allocated to clusters as a function of time and exposure to signals, and proportions are extracted.**



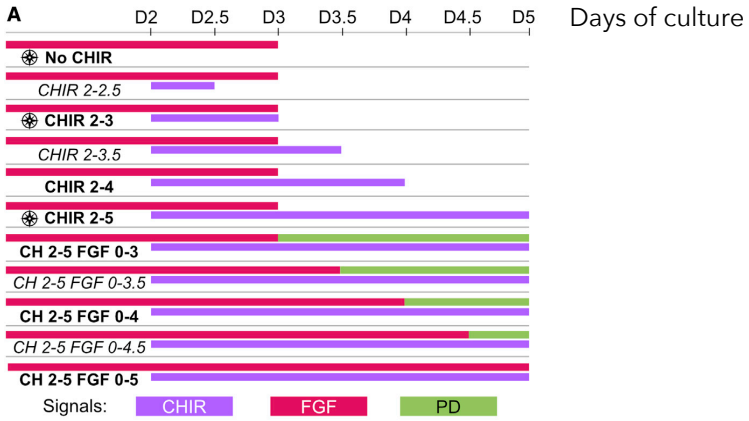

| | BRA | CDX2 | SOX1 | SOX2 | TBX6 | OTX2 | FOXC2 |
|---|---|---|---|---|---|---|---|
| EPI | | | | ++ | | + | |
| Tr | | | | + | | + | |
| AN | | | + | ++ | | + | |
| CE | (+) | + | | | | | |
| PN | | (+) | ++ | + | | | |
| EM | (+) | | | | + | | |
| LM | | | | | | | + |

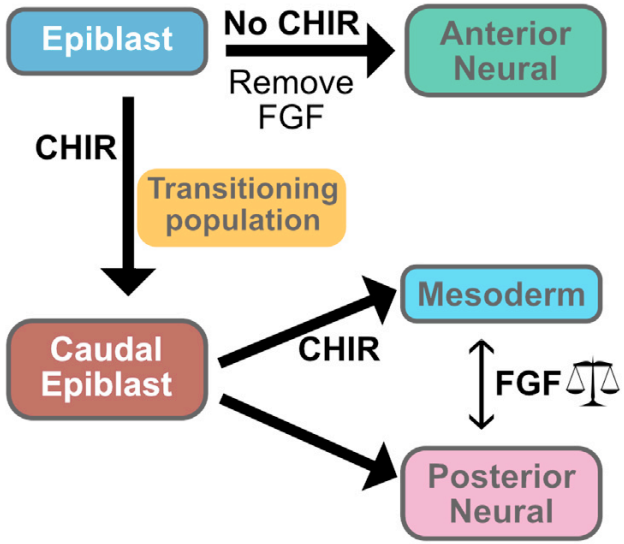
M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)

# Cell clusters as attractors in a Landscape

5 Cell types (attractors in landscape) and 1 transition state

Acquiring data sets across 11 signalling conditions
Data sets for training the model (fitting): **bold**
Data sets for testing the model: *italic*



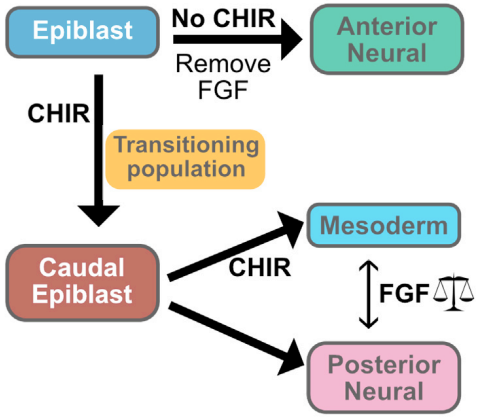






M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)

# Defining the appropriate geometrical landscapes

- Two distinct binary decision landscapes
  1. Epiblast cells become Anterior Neural (AN) upon FGF removal
     If however Wnt signalling is induced (D2), cells become Caudal Epiblast (CE)
     **This is an All or None response/decision**
  2. CE cells give rise to a mixed proportion of Mesoderm or Posterior Neural cells
     **This is a ratiometric response/decision**

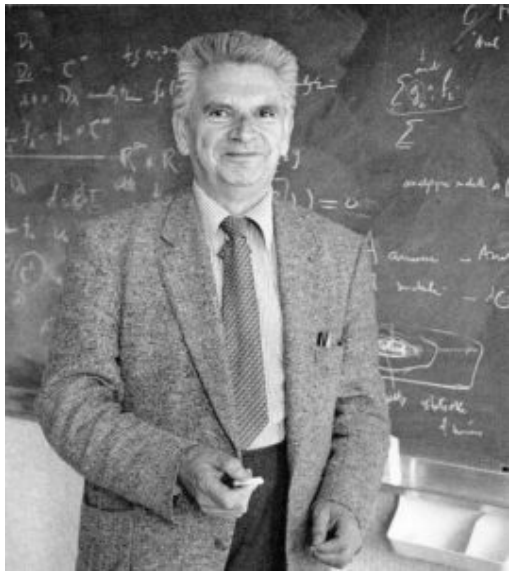



- Mathematical classification of generic 3-attractor landscapes
  - This is based on René Thom's classification of catastrophes.
  - 2D representation of dynamical system



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

# Catastrophe theory: a mathematical framework for discontinuities



René Thom
(1923-2002)

*« L'essence de la théorie des catastrophes c'est de ramener les discontinuités apparentes à la manifestation d'une évolution lente sous-jacente »*

## TOPOLOGICAL MODELS IN BIOLOGY†

R. THOM

(*Received* 28 *June* 1968)

THE PROBLEM of Morphogenesis—broadly understood as the origin and evolution of biological structures—is one of the outstanding questions in present day Biology. Many experi-

But, in most cases, when one tries to get beyond the first causative factor, the experimentalist gets lost in the seemingly infinite multiplicity of possible causes, and the bewildering variety of intermingled reactions which have to be considered. Most people—in this situation—satisfy themselves by vague appeals to differential action of genes, decoding of genic DNA ... and so on.

It should be noted, in that respect, that any morphological process involves by definition some discontinuity of the phenomenological properties of the medium

the problem is to explain the stability and the reproduction of the global spatio-temporal structure *in terms of the organization of the structure itself.*

In all these situations, a new mathematical theory, nearer to the qualitative thinking of the topologist than the quantitative estimates of classical analysis, seems particularly relevant.



Thom, R. Topological models in biology. *Topology* 8, 313–335. (1969)

# Catastrophe theory: a mathematical framework for discontinuities

Equation of dynamics:

$$dx_i/dt = X_i(x_j, \tau, t)$$ where $X_i$ is vector field

Gradient field:

$$X = -\text{grad } V,$$

Potential functions $V(x, y)$ are parametrised: $V(x,y, a, b, c, d)$

Study how fixed/equilibrium points of $V$ evolve as a function of these control parameters.

Bifurcation: appearance or disappearance of a critical point as control parameters vary (eg. disappearance of attractor by merging with saddle).

There are 7 types of catastrophes defined by the potential $V$ given up to 4 such parameters, and 2 variables.

TABLE OF ORDINARY CATASTROPHIES ON FOUR DIMENSIONAL SPACE–TIME

| | Codimension | Name | Organizing centre | Universal unfolding | Spatial interpretation |
|---|---|---|---|---|---|
| Dimension one | 0 | Simple *minimum* | $V = x^2$ | $V = x^2$ | A being<br>An object |
| | 1 | The fold<br>See Fig. 8 | $V = x^3/3$ | $V = x^3/3 + ux$ | The boundary<br>The end |
| | 2 | The cusp<br>(Riemann–Hugoniot catastrophy)<br>See Plate I, Figs. 9a, 9b, 10a, 10b | $V = x^4/4$ | $V = x^4/4 + ux^2/2 + vx$ | A pleat<br>A fault |
| | 3 | The swallow's tail<br>See Plate II, Fig. 11 | $V - x^5/5$ | $V - x^5/5 + ux^3/3 + vx^2/2 + wx$ | A split<br>A furrow |
| | 4 | The Butterfly<br>Fig. 12 | $V = x^6/6$ | $V = x^6/6 + x^4/4 + ux^3/3 + vx^2/2 + wx$ | A flake<br>A pocket<br>A scale<br>(of a fish) |
| Dimension two | 3 | The hyperbolic umbilic<br>See Plate III, Fig. 14 | $V = x^3 + y^3$ | $V = x^3 + y^3 + w\,xy - ux - vy$ | The crest<br>(of a wave)<br>The arch |
| | 3 | The elliptic umbilic<br>See Fig. 15 | $V = x^3 - 3xy^2$ | $V = x^3 - 3xy^2 + w(x^2 + y^2) - ux - vy$ | The needle<br>The spike<br>The hair |
| | 4 | The parabolic umbilic<br>See Plate IV; Fig. 16 a–e | $V = x^2y + y^4$ | $V = x^2y + y^4 + wx^2 + ty^2 - ux - vy$ | The jet<br>(of water)<br>The mushroom<br>The mouth |



Thom, R. Topological models in biology. *Topology* 8, 313–335. (1969)

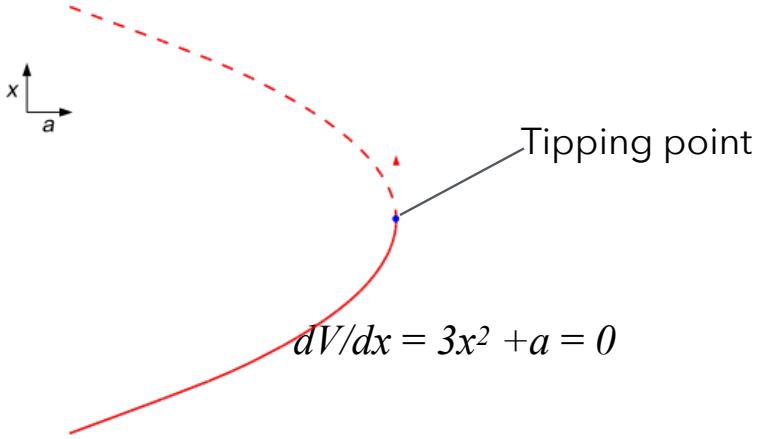
# Most common catastrophes

## Fold catastrophe: fold or saddle node bifurcation

$$V(x, a) = x^3 + ax$$

- When $a<0$, there is a stable and an unstable point.
- When $a=0$, the two points meet and annihilate.
- When $a>0$, there is no stable point.

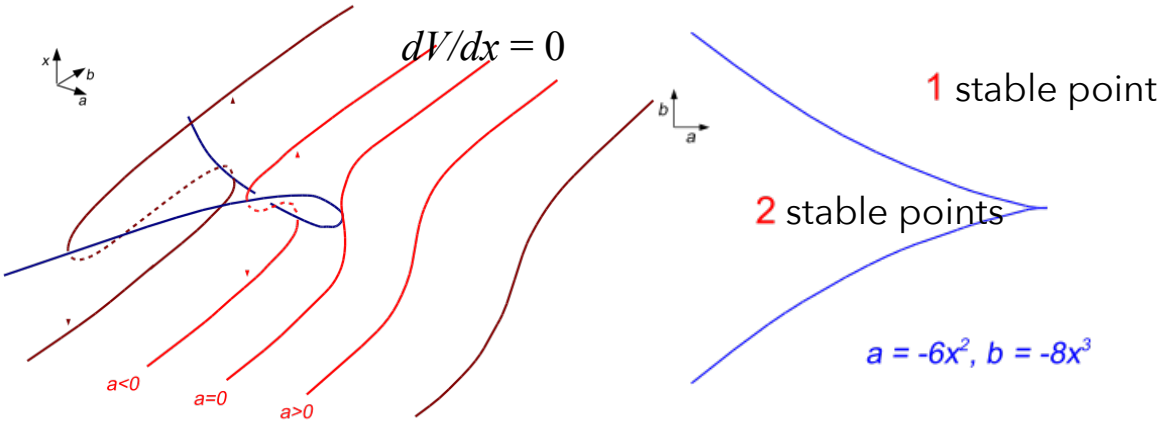
The parameter $a$ controls the system: key *information* about the system: disappearance of stable point and new behaviour emerges.




## Cusp catastrophe: cusp bifurcation

$$V(x, a, b) = x^4 + ax^2 + bx$$

- 2 parameters a and b for *V*.
- Blue bifurcation curve: points in (a, b) space where 1 stable point is lost.
- Hysteresis loop as b increases and decreases while a<0.

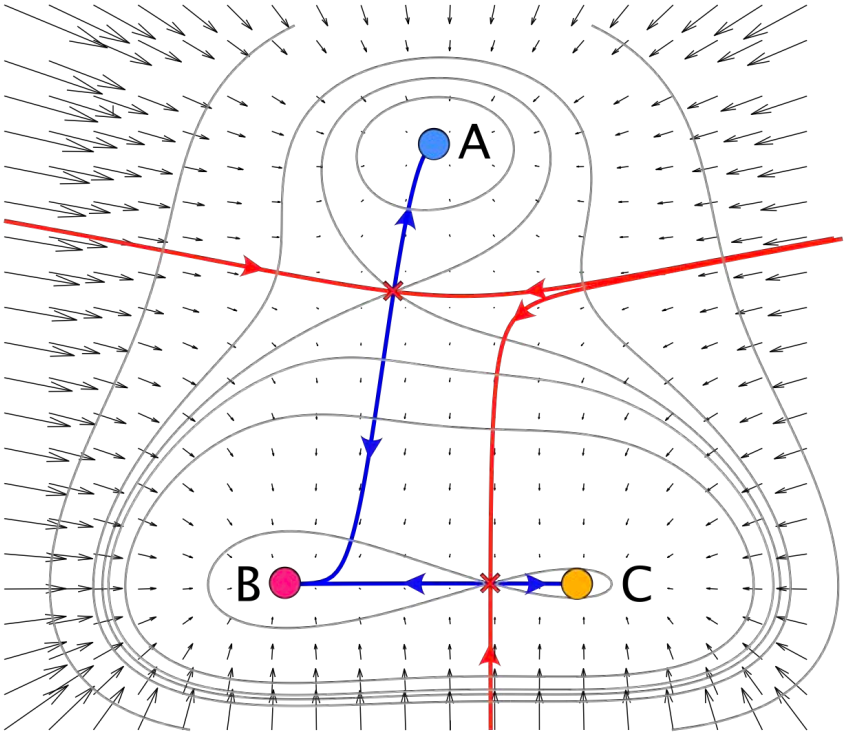


# Landscape representation

Transitions between different attractors (stable points)

Finite number of fixed points (stable and unstable)

**Manifolds represent paths between attractors and saddles**
(e.g. stable and unstable manifolds)




A B C Attractors

Saddle points

Potential lines

Stable manifolds

Unstable manifolds

Vector field

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

# Landscape for *Binary choice*

Bifurcation of EPI attractor with escape routes to 2 directions

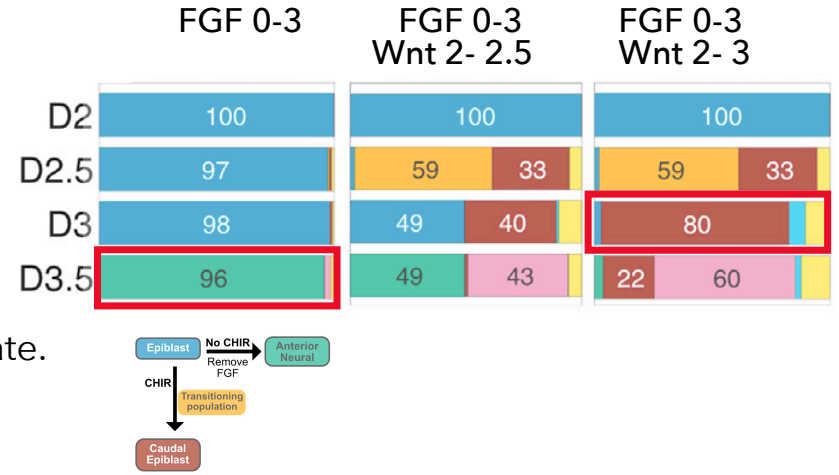
- 1st Bifurcation: (a)

In the absence of Wnt signalling, FGF withdrawal causes a loss of the EPI attractor in such a way that cells escape toward the AN attractor

- 2nd Bifurcation: (c)

But in the presence of Wnt at Day 2, cells transit at Day 3 to CE fate.

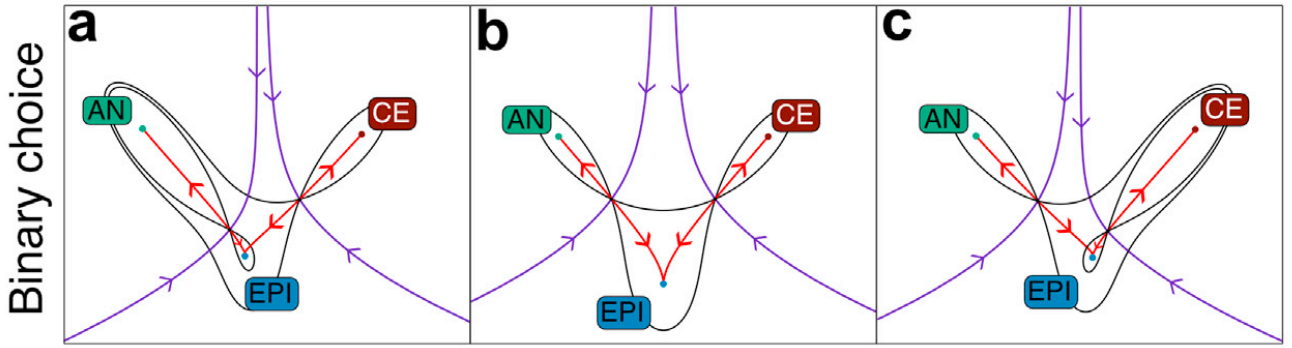
All cells transit to the same attractor: all or none decision




- Landscape for Binary choice

Only one catastrophe fits with the data:
3 attractors with 2 saddle points, 1 attractor in the middle.

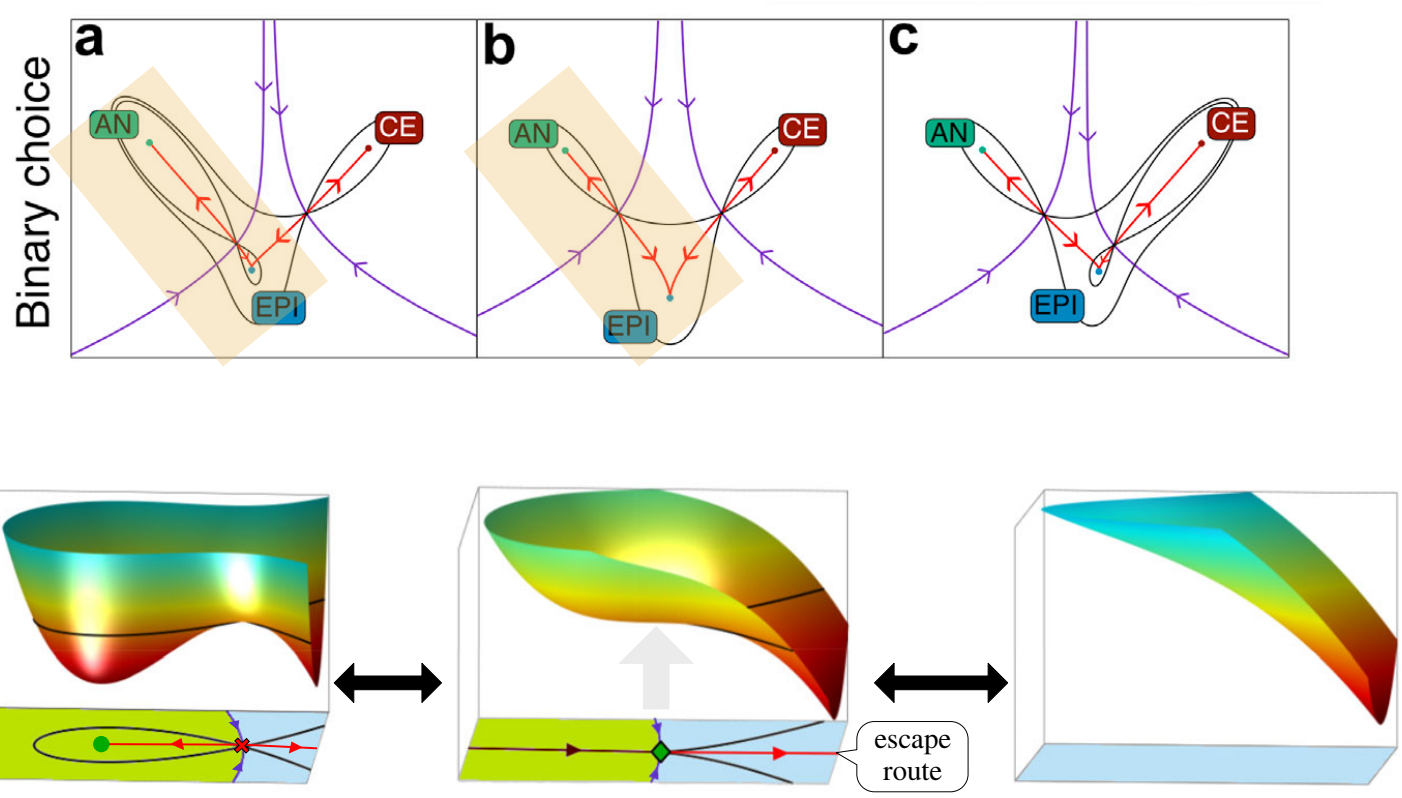
- Saddle node or fold bifurcation: Bifurcation between EPI and either of 2 saddle points.
- Peripheral attractors never connect directly






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

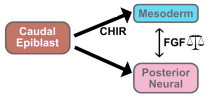
# Landscape for *Binary choice*




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

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

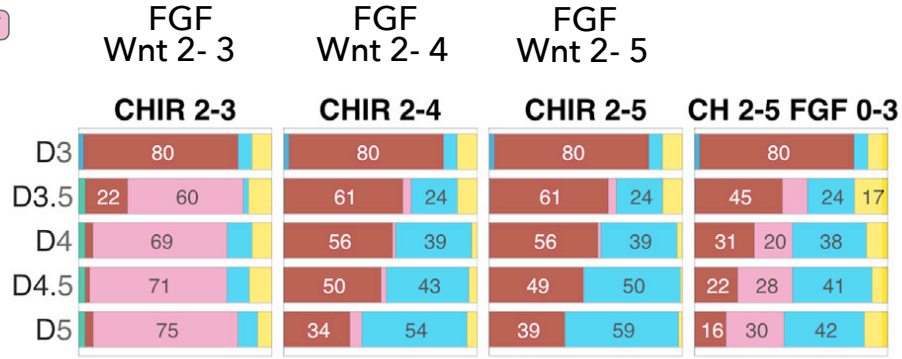
# Landscape for *Binary Flip*

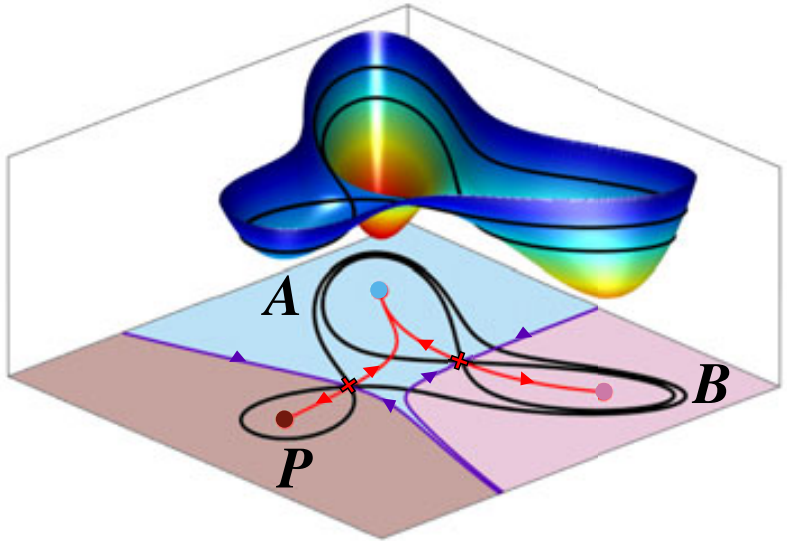



- As Wnt signalling persists cells in CE attractor transit to new attractors.
- The proportion of M or PN cells depend on the duration of Wnt signalling
  This is NOT an all or none decision.

- This suggests that these decisions are not driven by a bifurcation (disappearance of stable point), but by fluctuation driven escape from CE attractor basin.

- Landscape for Binary Flip:




M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)
Sáez M, Briscoe J, Rand DA. *Interface Focus* 12: 20220002. (2022)

# Landscape for *Binary Flip*

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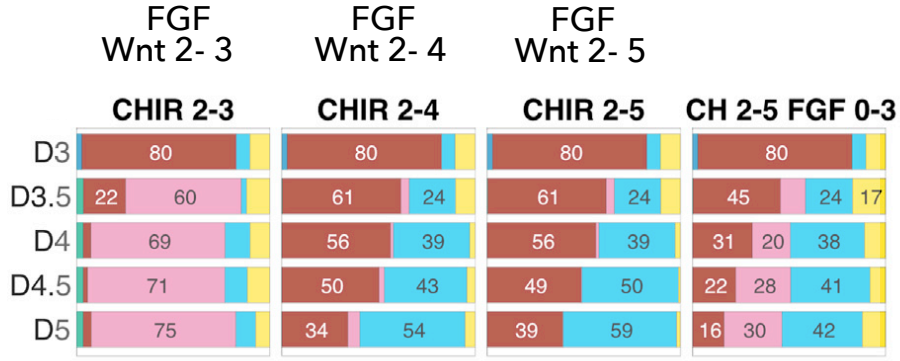
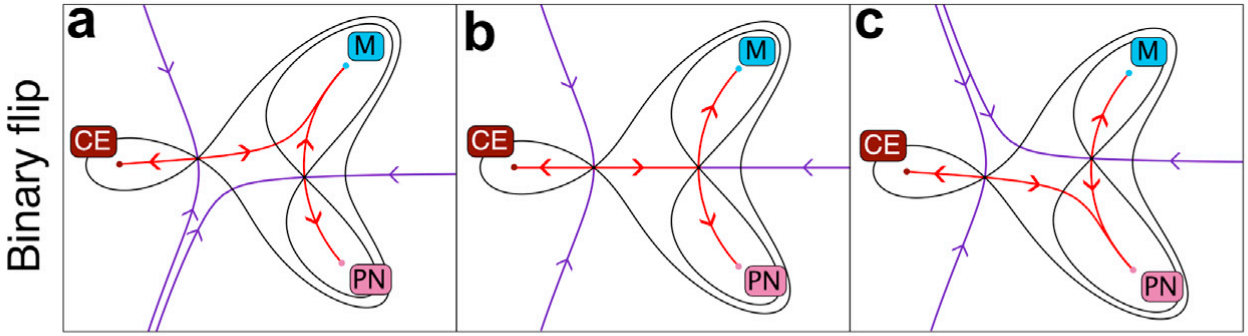


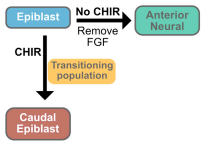

- Landscape for Binary Flip:

Flip in the escape route from saddle point.
(ie. sudden change in the unstable manifold of the saddle separating the central and peripheral attractors, as it jumps abruptly from connecting the saddle to one instead of the other.)
>Heteroclinic flip: cells tip to either of two fates.
The two peripheral attractors can connect directly



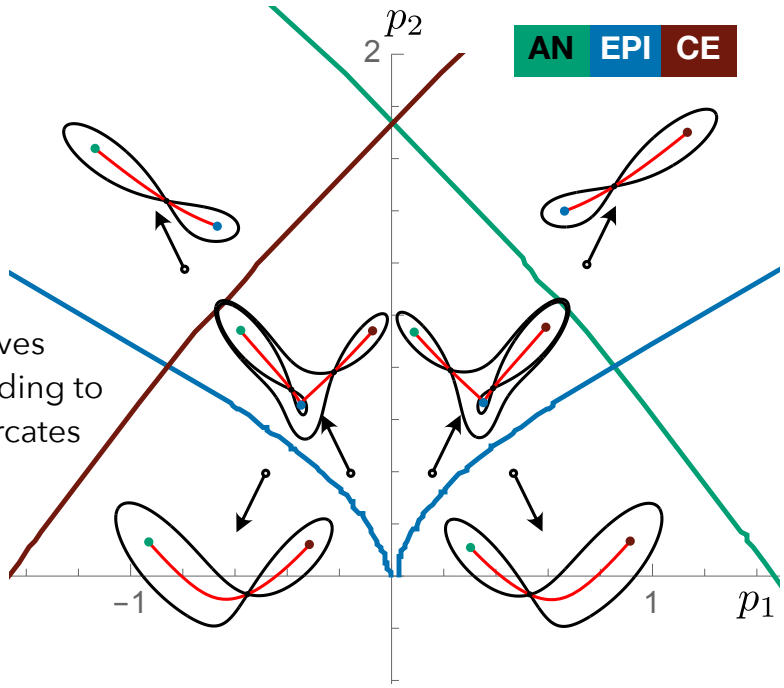

M. Sáez et al. E. Siggia, D. Rand and J. Briscoe, *Cell Systems* 12, 12–28 (2022)

# Parametrisation of the landscape




## Landscape for *Binary Choice*

Saddle-node bifurcation diagram




Fold bifurcation curves colour coded according to which attractor bifurcates

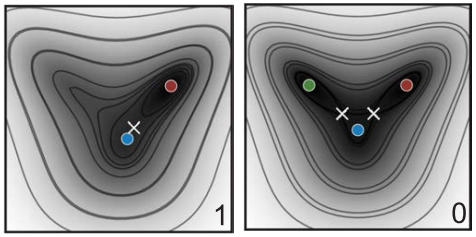
Potential function defined by a polynomial:

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

Non linear part defines the number and position of attractors

Parametrised linear part akin to a global tilt
Model the effect of signalling

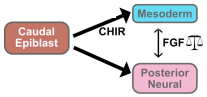
$(p_1, p_2)$ $(-1, 1)$ $(0, 0.5)$




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

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

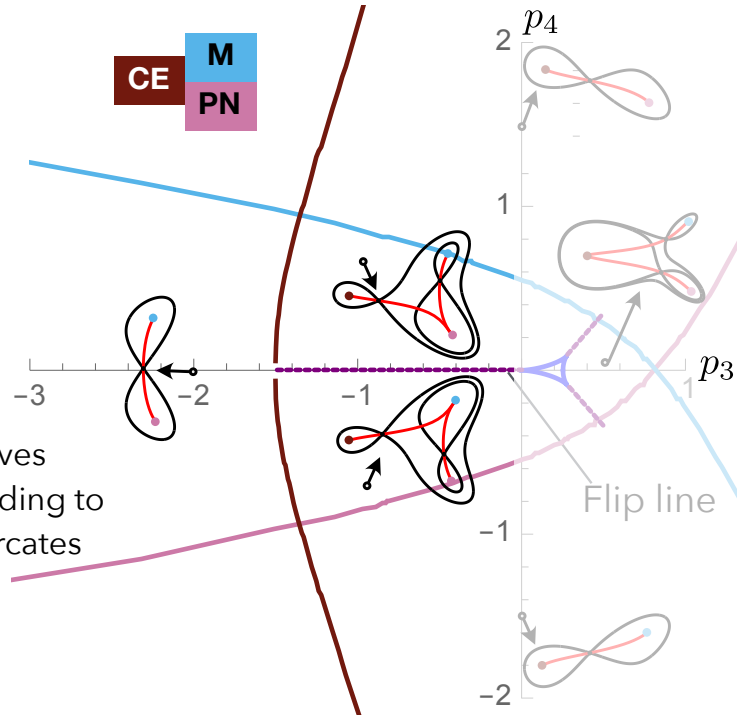
# Parametrisation of the landscape




bifurcation diagram

## Landscape for *Binary Flip*

(Heteroclinic flip)



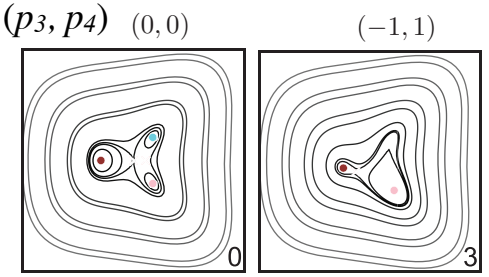

Fold bifurcation curves colour coded according to which attractor bifurcates

Potential function defined by a polynomial:

$$F_2(x, y; p) = x^4 + y^4 + x^3 - 2xy^2 - x^2 + p_3\, x + p_4\, y.$$

Non linear part defines the number and position of attractors

Parametrised linear part akin to a global tilt
Model the effect of signalling



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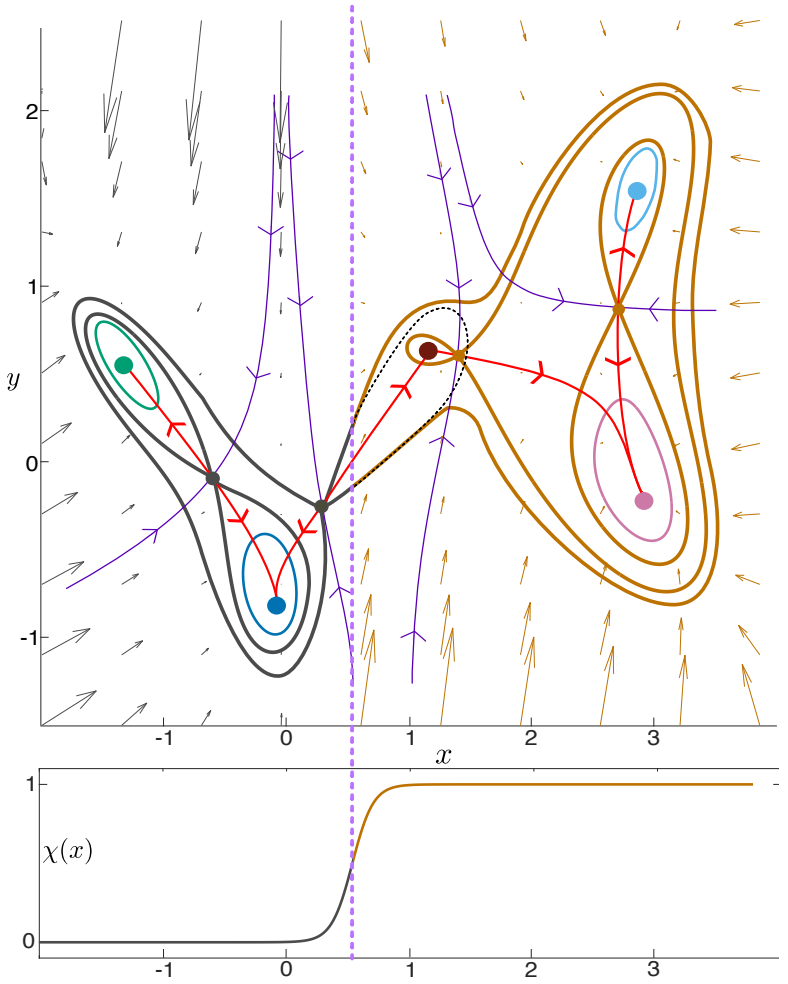
# Global landscape

Linear combination of two gradient systems
Smooth stitching/gluing of two separate systems into one

$$L(x,y,p) = -(1-\chi(x))\,p_5\,\nabla F_1(x,y;p) - \chi(x)\,p_6\,\nabla F_2(x+2,y+1;p)$$

gluing function. $\chi(x) = \frac{tanh(10(x-0.5))+1}{2}$

| Parameter | Meaning |
|---|---|
| $p_1$ | topology of first decision |
| $p_2$ | topology of first decision |
| $p_3$ | topology of second decision (CE stability) |
| $p_4$ | topology of second decision (PN/M distribution) |
| $p_5$ | velocity of first decision |
| $p_6$ | velocity of second decision |

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# Parameterisation of the model

## Linear combination of two gradient systems

$$L(x,y,p) = -(1-\chi(x))\,p_5\,\nabla F_1(x,y;p) - \chi(x)\,p_6\,\nabla F_2(x+2,y+1;p)$$

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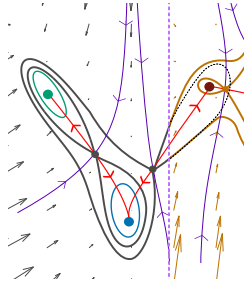
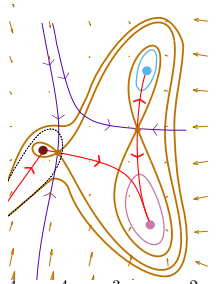


$$F_1(x,y;p) = x^4 + y^4 + y^3 - 4x^2y + y^2 - p_1\,x + p_2\,y.$$



$$F_2(x,y;p) = x^4 + y^4 + x^3 - 2xy^2 - x^2 + p_3\,x + p_4\,y$$

## Effective levels of signals: $S_1$ for Chir (Wnt) and $S_2$ for FGF

$$p(S_1,S_2) = (p_1(S_1,S_2),\ldots,p_6(S_1,S_2)) = w_0 + S_1\,w_1 + S_2\,w_2 = w_0 + (S_1\ S_2)\begin{pmatrix} w_1 \\ w_2 \end{pmatrix}$$

| Parameter | Meaning |
|---|---|
| $w_0$ | Landscape parameters with No CHIR and PD |
| $w_1$ | Effect of CHIR in the landscape |
| $w_2$ | Effect of FGF in the landscape |

| | |
|---|---|
| $\tau$ | Memory to CHIR threshold |
| $\sigma$ | Noise amplitude |

## Stochasatic differential equation model:

$$(\dot{x},\dot{y}) = L(x,y;S) + \sigma dW$$

20 parameters in total

**Parameter fitting** using 7 training datasets over 7 time points



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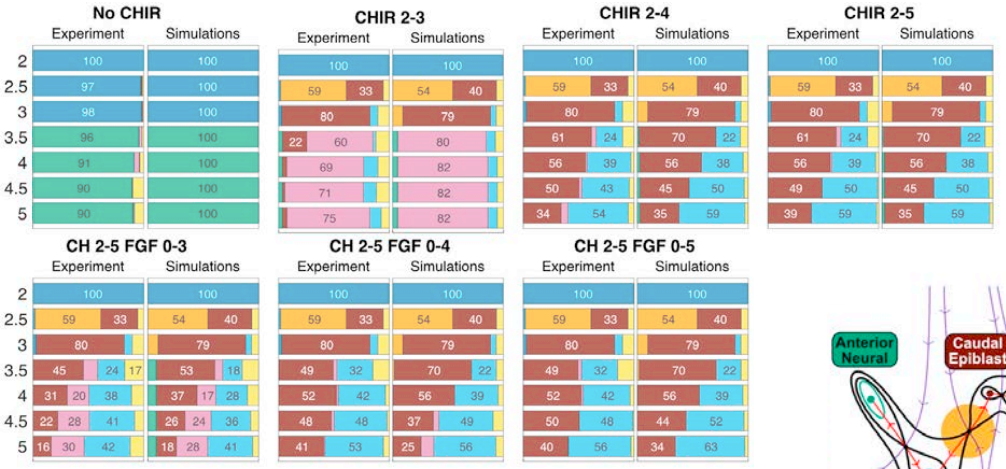
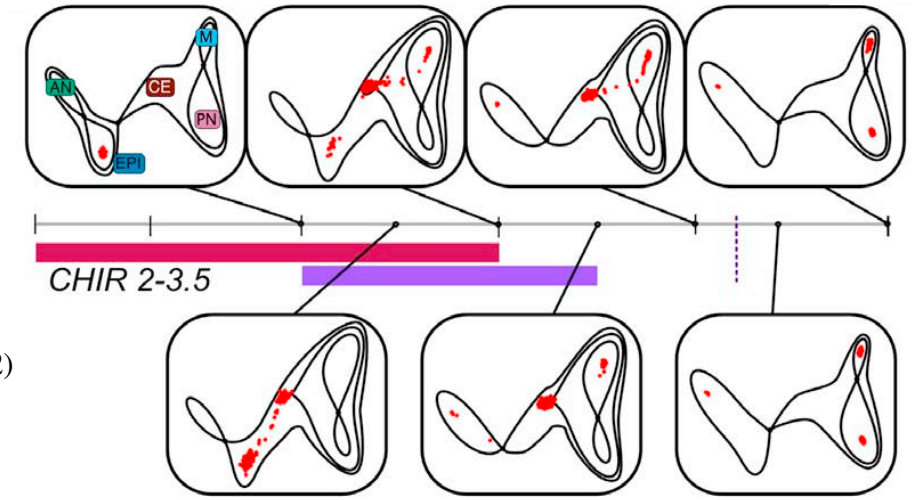
# Comparison of model simulations and data

Model based on global landscape
Simulations of cell occupancy of attractors




Red points represent the location of cells in the landscape at specific time points.
Cells are initialized in the EPI attractor.
Their location evolves as a function of dynamical system defined by the landscape, and tilt induced by the two signaling pathways (FGF and Wnt)

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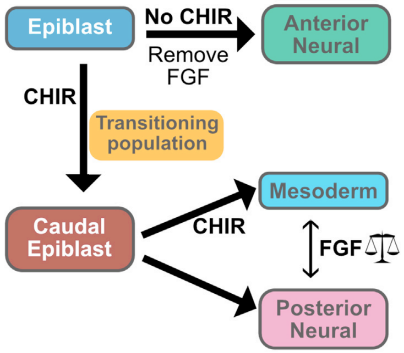
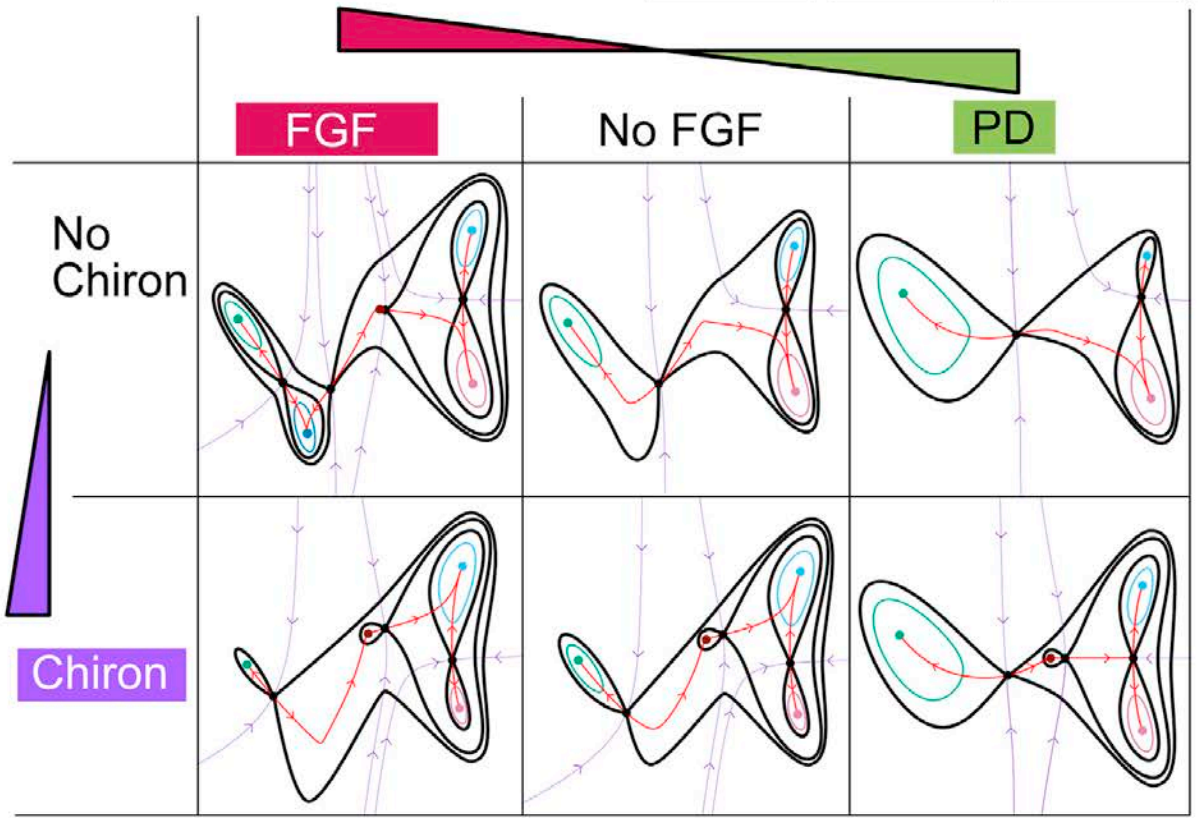
# Evolution of landscape geometry as a function of signals




Wnt signalling



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# Learning geometric models

PHYSICAL REVIEW X **15,** 031070 (2025)

**Learning Geometric Models for Developmental Dynamics**

Addison Howe* and Madhav Mani

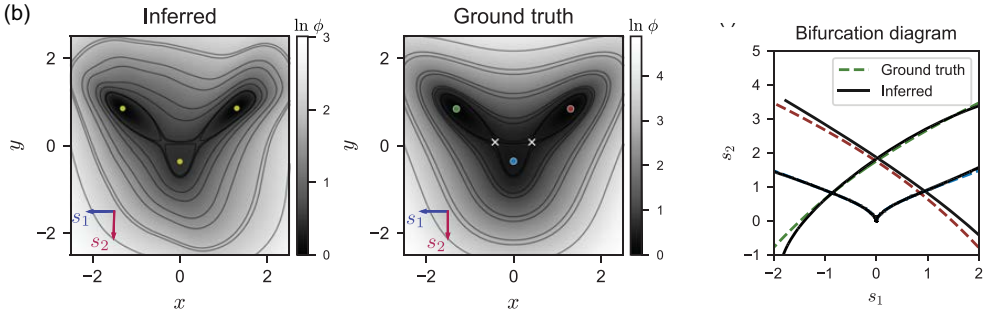
*Department of Engineering Sciences and Applied Mathematics, Northwestern University, Evanston, Illinois 60208 USA*

Synthetic model

$$\phi_1^*(x, y; \boldsymbol{\tau}(\boldsymbol{s})) = \tilde{\phi}_1^*(x, y) + \tau_1 x + \tau_2 y$$

$$\boldsymbol{\tau}(\boldsymbol{s}) = \mathbf{A}^* \boldsymbol{s} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \begin{bmatrix} s_1 \\ s_2 \end{bmatrix}$$

$$\sigma^* = 0.1$$




- In situations where the knowledge of the biology is insufficient to define the number of cell states and relationships.
- Inference of potential and effect of signals, bifurcation diagram



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

# More general framework

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

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

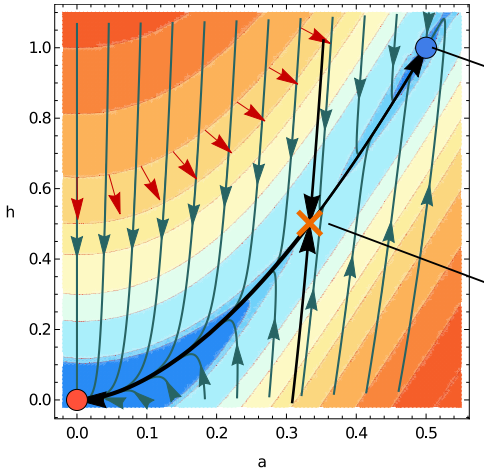
Inverse of metric tensor: Local distortion of landscape

Gradient-like dynamics

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

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

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




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

# Conclusions

- Compare logic view and dynamic view of information processing
- Geometric landscape models do not account for existence of different states
  The model predicts transition steps between states and how signals exert a force that steers cells in the landscape
- The exact dynamics and path followed by cells is not yet captured but can be.

So far, use of « flat » representations for cell states with gradient field.
Signals globally tilt the landscape and cause bifurcations.

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