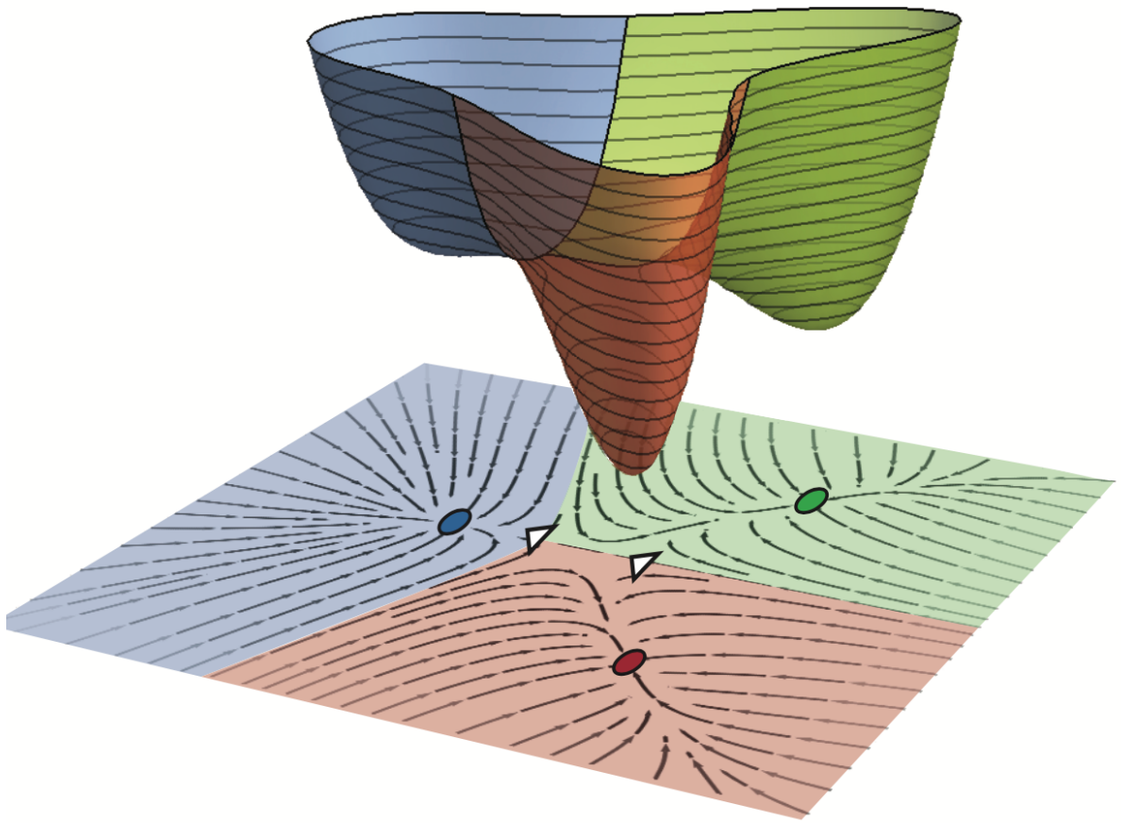
Building dynamical landscapes of cell fate transitions



Flags, Lanscapes, Signaling
IMSc Chennai
May 14th, 2024

Elena Camacho-Aguilar

Centro Andaluz de Biología del Desarrollo

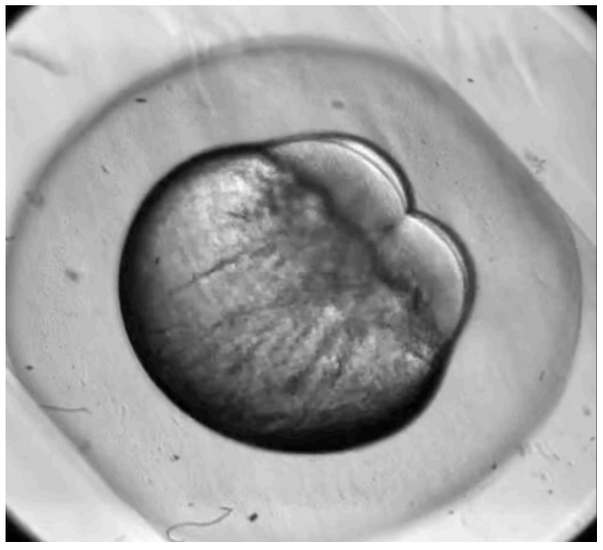
@elecamagu

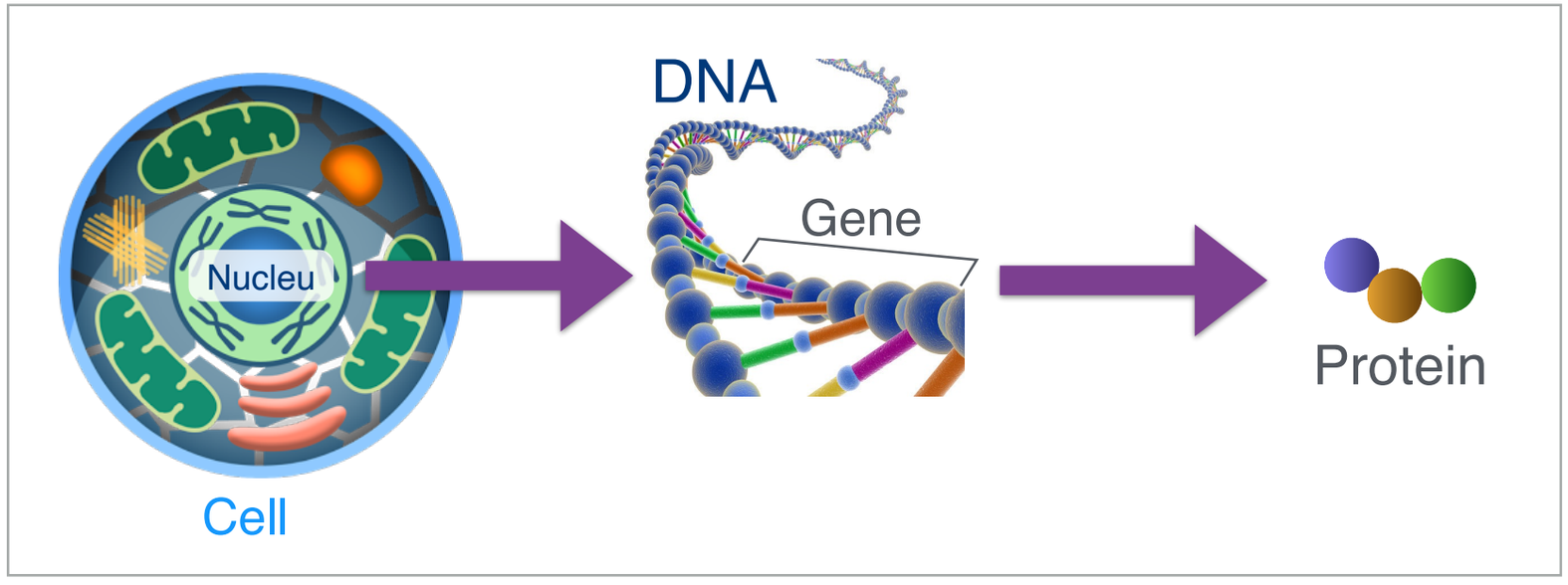
CSIC
Consejo Superior de Investigaciones Científicas

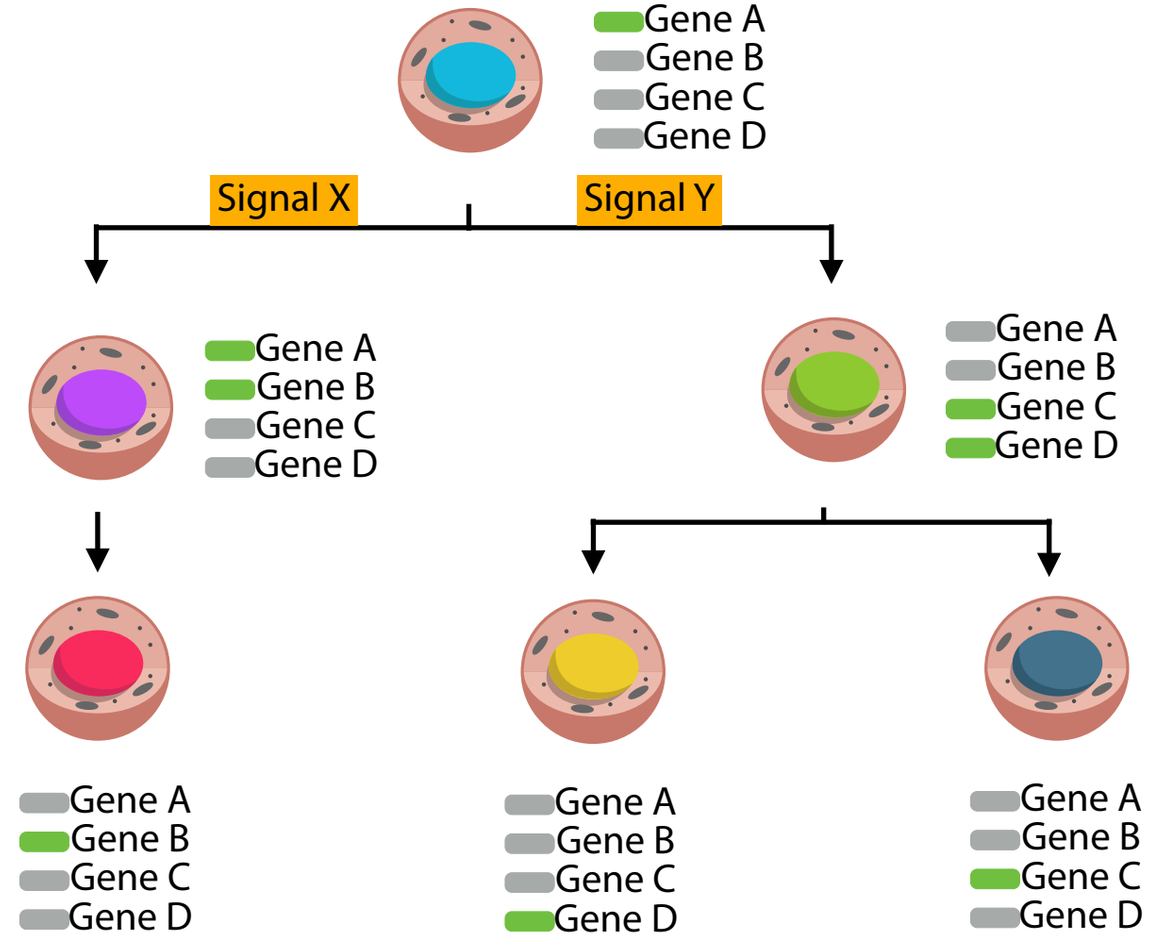
EXCELENCIA MARÍA DE MAEZTU
AGENCIA ESTATAL DE INVESTIGACIÓN

Centro Andaluz de Biología del Desarrollo

Cell state transitions are key to embryonic development and regenerative medicine

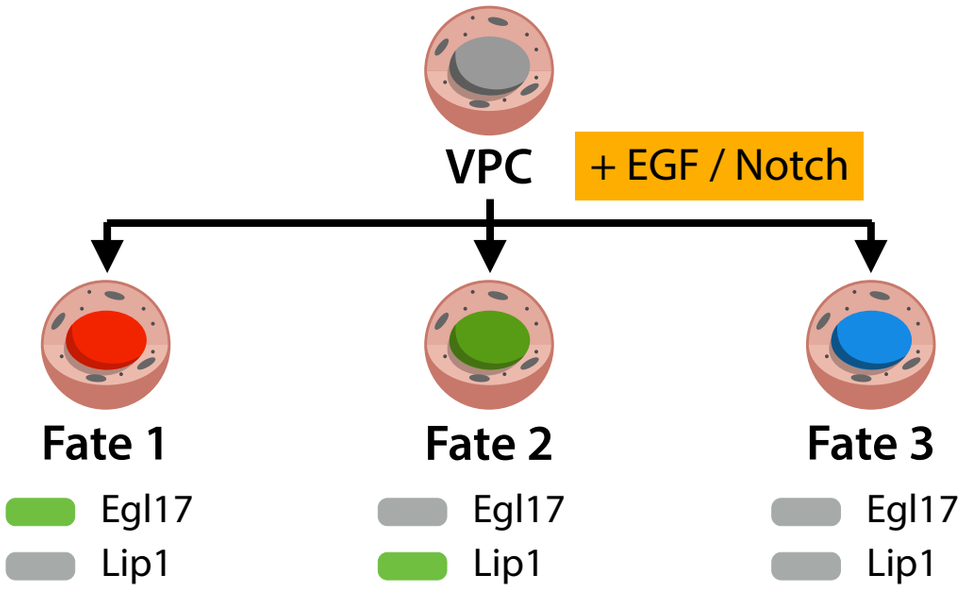




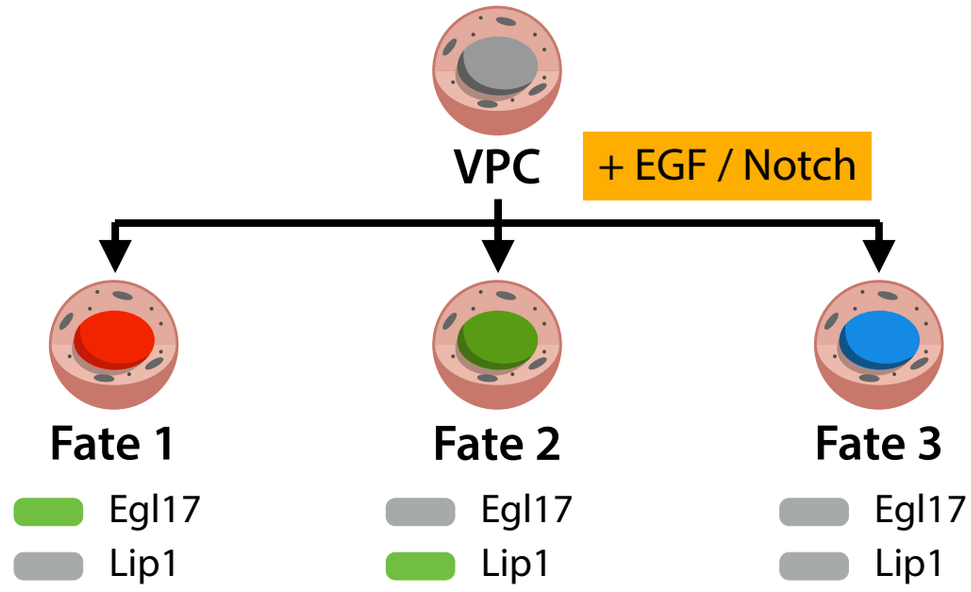


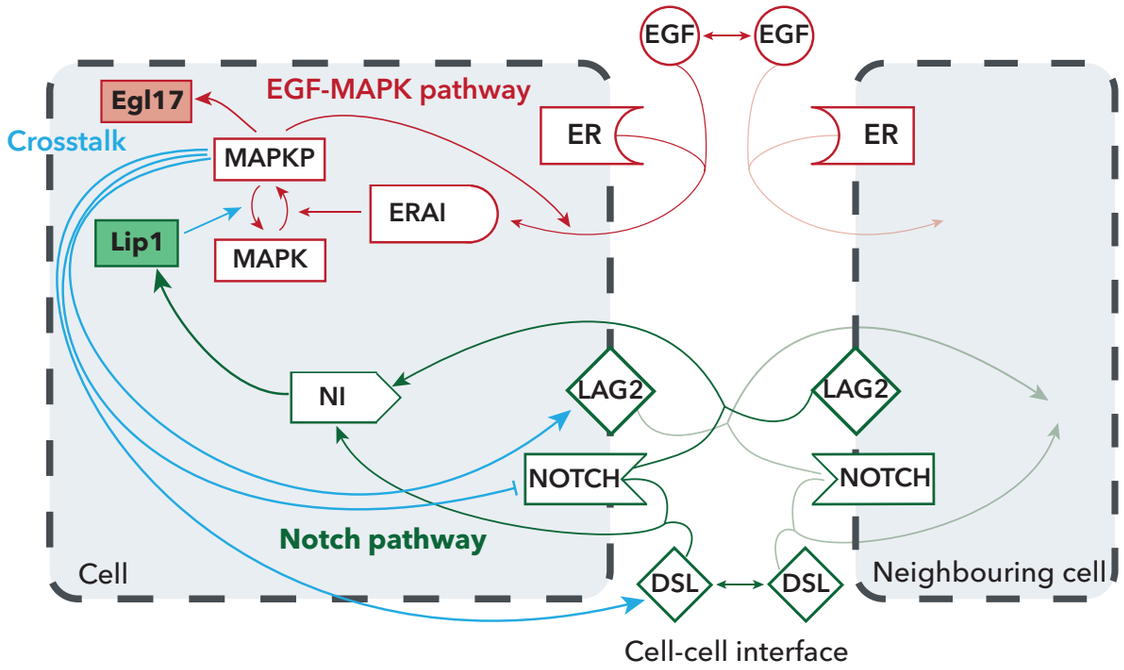
https://www.youtube.com/watch?v=ahJjLzyioWM

Gene regulatory network models (GRN) are commonly used to study cell state transitions but they are highly dimensional



Gene regulatory network models (GRN) are commonly used to study cell state transitions but they are highly dimensional





$$\frac{dER_i}{dt} = L_{ER} - ER_i EGF_i\left(\left(K_{EGFermx} - K_{EGFermn}\right)\Phi\left(MAPKP_i, \kappa_{MAPKPer}, \nu_{MAPKPer}\right) + K_{EGFermn}\right) - \frac{ER_i}{H_{ER}}$$

$$\frac{dERAI_i}{dt} = ER_i EGF_i\left(\left(K_{EGFermx} - K_{EGFermn}\right)\Phi\left(MAPKP_i, \kappa_{MAPKPer}, \nu_{MAPKPer}\right) + K_{EGFermn}\right) - \frac{ERAI_i}{H_{ER}}$$

$$MAPK_i = 1 - MAPKP_i$$

$$\frac{dMAPKP_i}{dt} = r_{ERAImapk} MAPK_i \Phi\left(ERAI_i, \kappa_{ERAImapk}, \nu_{ERAImapk}\right) - r_{LIPmapkp} MAPKP_i \Phi\left(LIP_i, \kappa_{LIPmapkp}, \nu_{LIPmapkp}\right) - \frac{MAPKP_i}{H_{MAPK}}$$

$$\frac{dNOTCH_i}{dt} = L_{NOTCH} - K_{DSLnotch} DSL_i NOTCH_i - K_{LAGnotch} NOTCH_i LAG_{adj(i)} - NOTCH_i\left[\frac{\Phi\left(MAPKP_i, \kappa_{MAPKPnotch}, \nu_{MAPKPnotch}\right)}{H_{NOTCHmn}} + \frac{1}{H_{NOTCH}}\right]$$

$$\frac{dNI}{dt} = K_{DSLnotch} DSL_i NOTCH_i + K_{LAGnotch} NOTCH_i LAG_{adj(i)} - \frac{NI_i}{H_{NOTCH}}$$

$$egf_{i\neq 4} = 0$$

$$egf_4 = 1$$

$$\frac{dEGF_i}{dt} = L_{EGF} EGF_i + 2D_{EGF}\left(EGF_{adj(i)} - EGF_i\right) - EGF_i ER_i\left(\left(K_{EGFermx} - K_{EGFermn}\right)\Phi\left(MAPKP_i, \kappa_{MAPKPer}, \nu_{MAPKPer}\right) + K_{EGFermn}\right) - \frac{EGF_i}{H_{EGF}}$$

$$\frac{dLAG_i}{dt} = L_{LAG}\Phi\left(MAPKP_i, \kappa_{MAPKPlag}, \nu_{MAPKPlag}\right) - LAG_i NOTCH_{adj(i)} - \frac{LAG_i}{H_{LAG}}$$

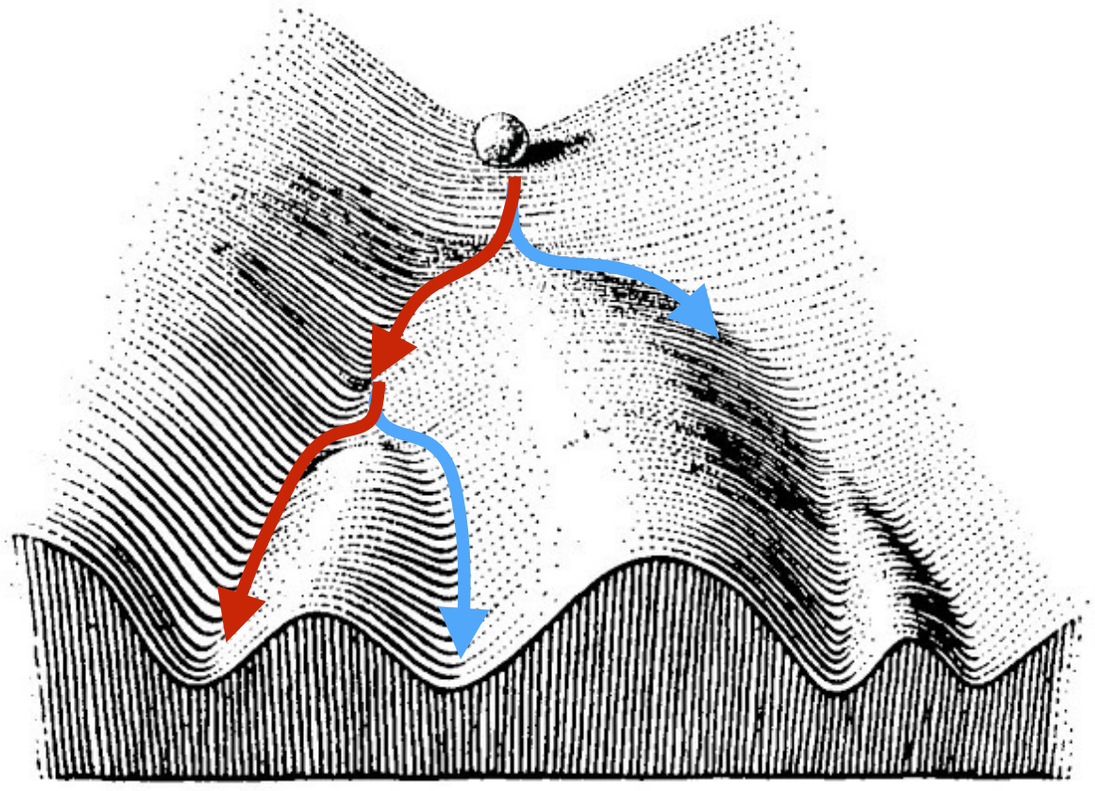
$$\frac{dDSL_i}{dt} = L_{DSL}\Phi\left(MAPKP_i, \kappa_{MAPKPdsl}, \nu_{MAPKPdsl}\right) + 2D_{DSL}\left(DSL_{adj(i)} - DSL_i\right) - K_{DSLnotch} DSL_i NOTCH_i - \frac{DSL_i}{H_{DSL}}$$

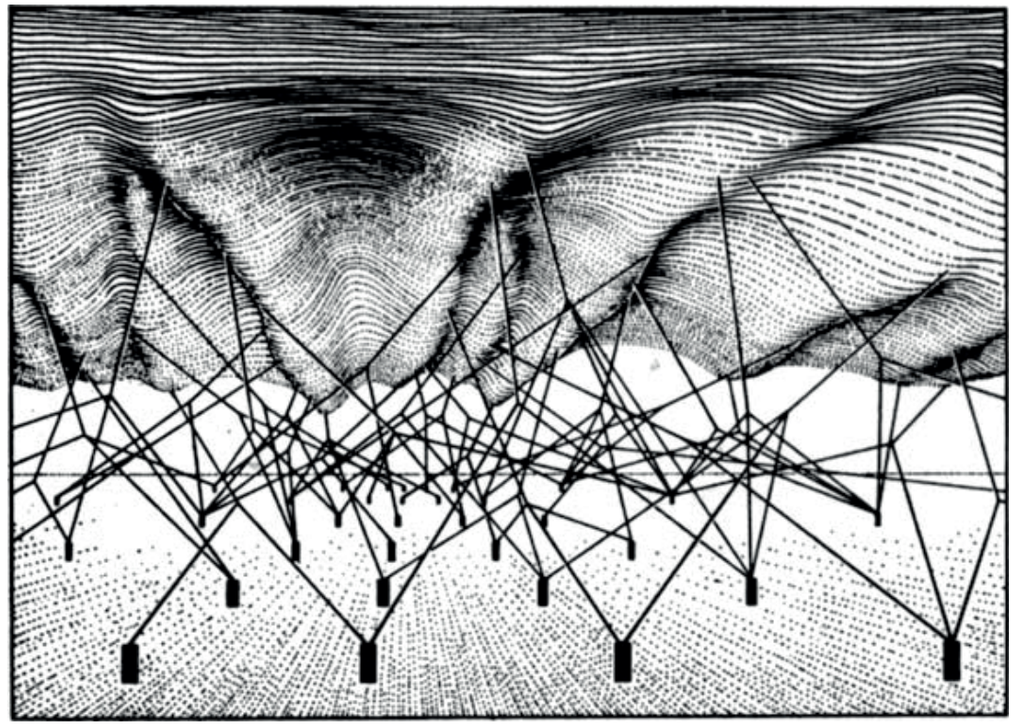
$$\frac{dEGL_i}{dt} = L_{EGL}\Phi\left(MAPKP_i, \kappa_{MAPKPegl}, \nu_{MAPKPegl}\right) - \frac{EGL_i}{H_{EGL}}$$

$$\frac{dLIP_i}{dt} = L_{LIP}\Phi\left(NI_i, \kappa_{NIlip}, \nu_{NIlip}\right) - \frac{LIP_i}{H_{LIP}}$$

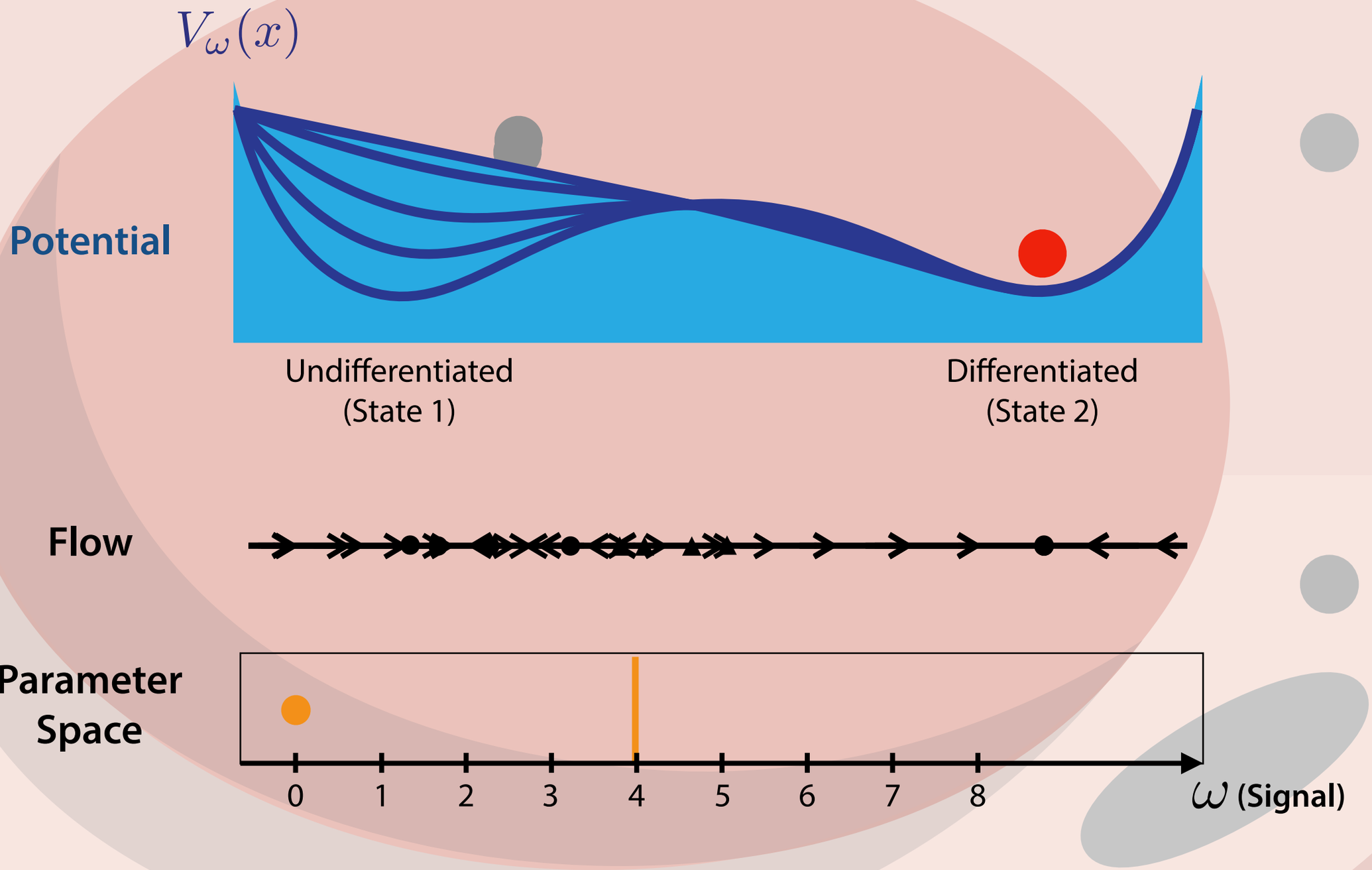
Hoyos, E. et al., 2011. Quantitative variation in autocrine signaling and pathway crosstalk in the Caenorhabditis vulval network. Current Biology, 21, pp.527–538.

Waddington's landscape: from a simple metaphor

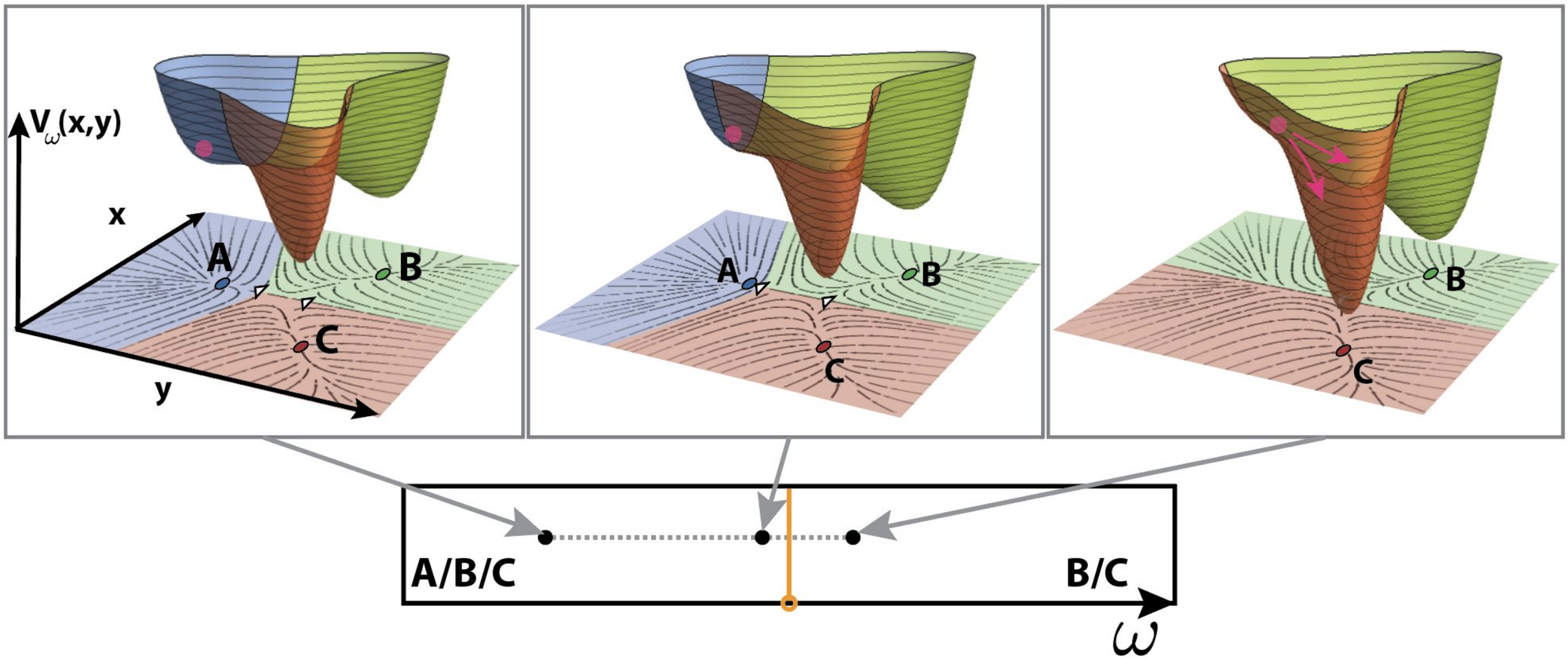




Waddington's landscape: from a simple metaphor to a mathematical formalism



Waddington's landscape: from a simple metaphor to a mathematical formalism



Waddington's landscape: from a simple metaphor to a mathematical formalism

PNAS PNAS PNAS

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

This contribution is part of the special series of Inaugural Articles by members of the National Academy of Sciences elected in 2009.

Contributed by Eric Dean Siggia, February 6, 2012 (sent for review November 28, 2011)

Developmental signaling networks are composed of dozens of components whose interactions are very difficult to quantify in an embryo. Geometric reasoning enumerates a discrete hierarchy of phenotypic models with a few composite variables whose parameters may be defined by in vivo data. Vulval development in the nematode *Caenorhabditis elegans* is a classic model for the integration of two signaling pathways; induction by EGF and lateral signaling through Notch. Existing data for the relative probabilities of the three possible terminal cell types in diverse genetic backgrounds as well as timed ablation of the inductive signal favor one geometric model and suffice to fit most of its parameters. The model is fully dynamic and encompasses both signaling and commitment. It then predicts the correlated cell fate probabilities for a cross between any two backgrounds/conditions. The two signaling pathways are combined additively, without interactions, and epistasis only arises from the nonlinear dynamical flow in the landscape defined by the geometric model. In this way, the model quantitatively fits genetic experiments purporting to show mutual pathway repression. The model quantifies the contributions of extrinsic vs. intrinsic sources of noise in the penetrance of mutant phenotypes in signaling hypomorphs and explains available experiments with no additional parameters. Data for anchor cell ablation fix the parameters needed to define Notch autocrine signaling.

(5) shows that even differentiation can be reversed. Yet they have provided a useful guide to experiments.

These concepts admit a natural geometric representation, which can be formalized in the language of dynamical systems, also called the geometric theory of differential equations (Fig. 1). When the molecular details are not accessible, a system's effective behavior may be represented in terms of a small number of aggregate variables, and qualitatively different behaviors enumerated according to the geometrical structure of trajectories or topology. The fates that are accessible to a cell are associated with attractors—the valleys in Waddington's "epigenetic landscape" (6)—to which neighboring trajectories converge. The set of points that tend to a given attractor forms its basin of attraction, and the state of commitment of a cell can be defined by its position relative to the basins of different fates. Along the boundaries between basins of attraction are saddle points, where the flow splits between two attractors, marking a "decision point" between different outcomes. Certain fates become accessible only at a particular time during development, so one should think of a landscape that changes over time. The external signals to which cells respond during competence transiently shift the boundaries between attractors, biasing trajectories toward one fate or other.

The appeal of this type of mathematics for developmental biology was recognized long ago (7) because the description is phenotypic and the mathematical concepts are formulated without reference to parameters. However, the applications never went

eLIFE elifesciences.org

RESEARCH ARTICLE

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

Abstract Models of cell function that assign a variable to each gene frequently lead to systems of equations with many parameters whose behavior is obscure. Geometric models reduce dynamics to intuitive pictorial elements that provide compact representations for sparse in vivo data and transparent descriptions of developmental transitions. To illustrate, a geometric model fit to vulval development in *Caenorhabditis elegans*, implies a phase diagram where cell-fate choices are displayed in a plane defined by EGF and Notch signaling levels. This diagram defines allowable and forbidden cell-fate transitions as EGF or Notch levels change, and explains surprising observations previously attributed to context-dependent action of these signals. The diagram also reveals the existence of special points at which minor changes in signal levels lead to strong epistatic interactions between EGF and Notch. Our model correctly predicts experiments near these points and suggests specific timed perturbations in signals that can lead to additional unexpected outcomes.

DOI: https://doi.org/10.7554/eLife.30743.001

Corrected 28 February 2019. See full text.

RESEARCH

RESEARCH ARTICLE SUMMARY

NEURODEVELOPMENT

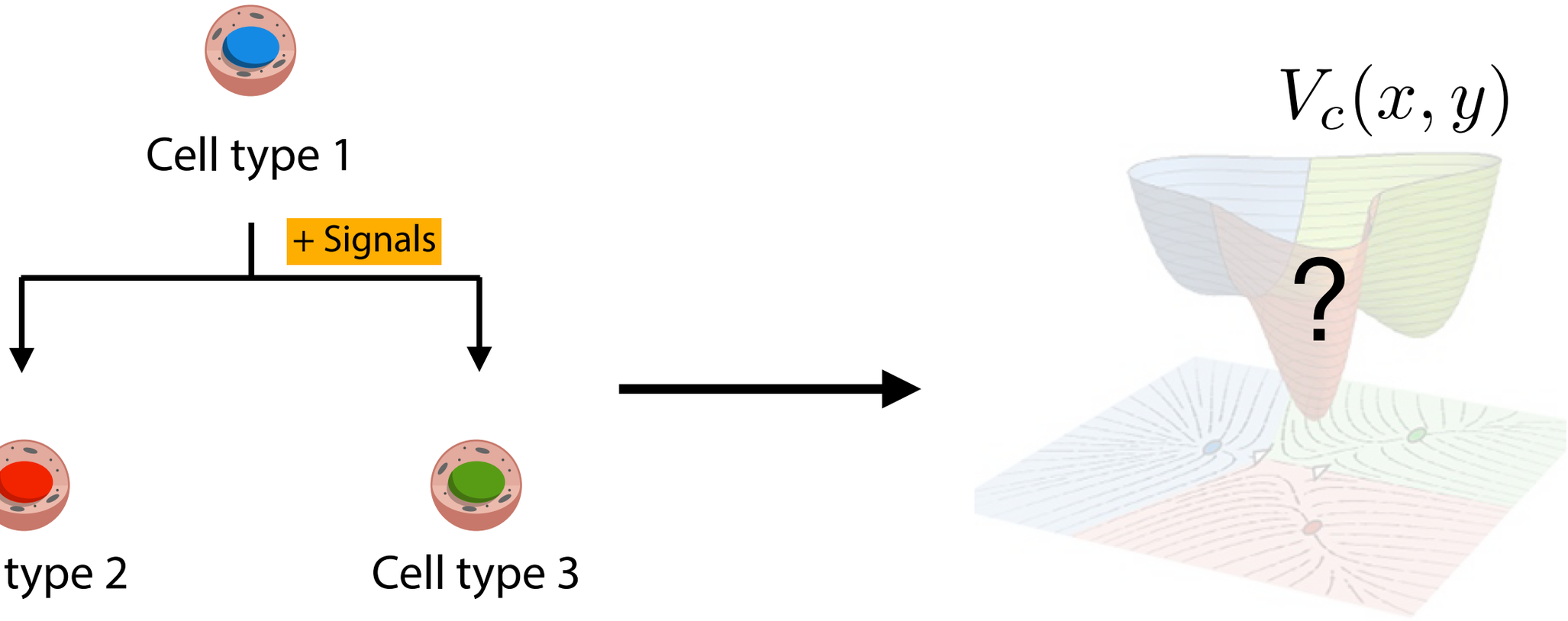
Self-organized Notch dynamics generate stereotyped sensory organ patterns in *Drosophila*

Francis Corson,* Lydie Couturier, Hervé Rouault, Khalil Mazouni, François Schweisguth*

INTRODUCTION: Spatial patterning in developing multicellular organisms relies on positional cues and cell-cell interactions. Stereotyped sensory organ arrangements in *Drosophila* are commonly attributed to a prepattern that defines regions of neural competence. Notch-mediated interactions then isolate sensory organ precursor (SOP) cells from among the competent cells. In support of this view, prepattern factors direct the expression of proneural factors in discrete clusters and determine the location of large bristles on the dorsal thorax. However, no such prepattern is known to establish the proneural stripes that give rise to finer-bristle rows.

RATIONALE: By analogy with reaction-diffusion systems, we wondered whether Notch-mediated cell-cell interactions might organize a pattern of proneural stripes. To explore a possible role for Notch in proneural patterning, we generated fluorescent reporters for the proneural factors Achaete and Scute, the ligand Delta, and the Notch early-response factor E(spl)m3-HLH, which antagonizes proneural activity. We observed expression of these reporters in live and fixed samples throughout early pupal development. In parallel, we developed a mathematical model for Notch-mediated patterning. In this abstract model, the dynamics of a cell is expressed in terms of just two variables, for the state of the cell and the level of signal it receives. The model incorporates a series of plausible assumptions that govern its patterning behavior: Cells, which adopt the SOP fate in the absence of signal and the alternative, epidermal fate under high enough signal, exhibit a bistable response under intermediate signal levels. Inhibitory signaling from a cell varies nonlinearly with cell state and reaches beyond immediate neighbors.

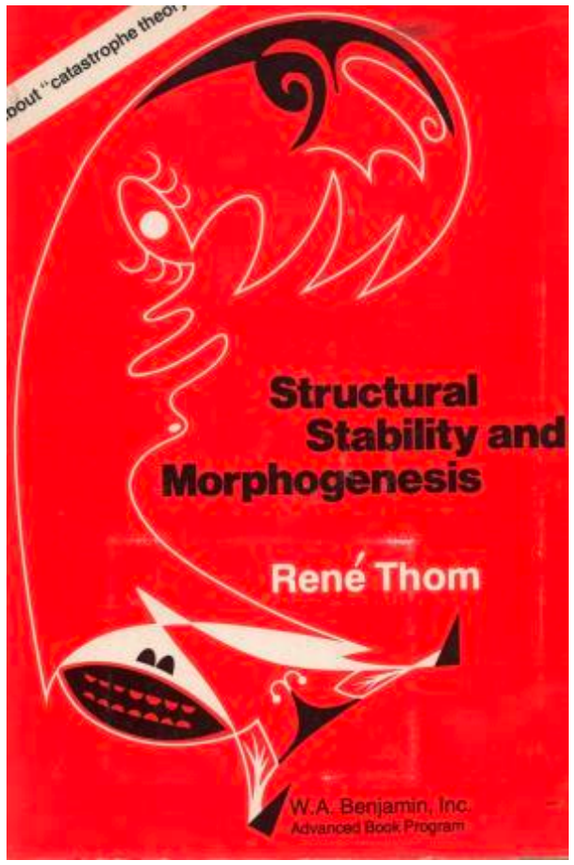
Open question: how to tailor a landscape to a process

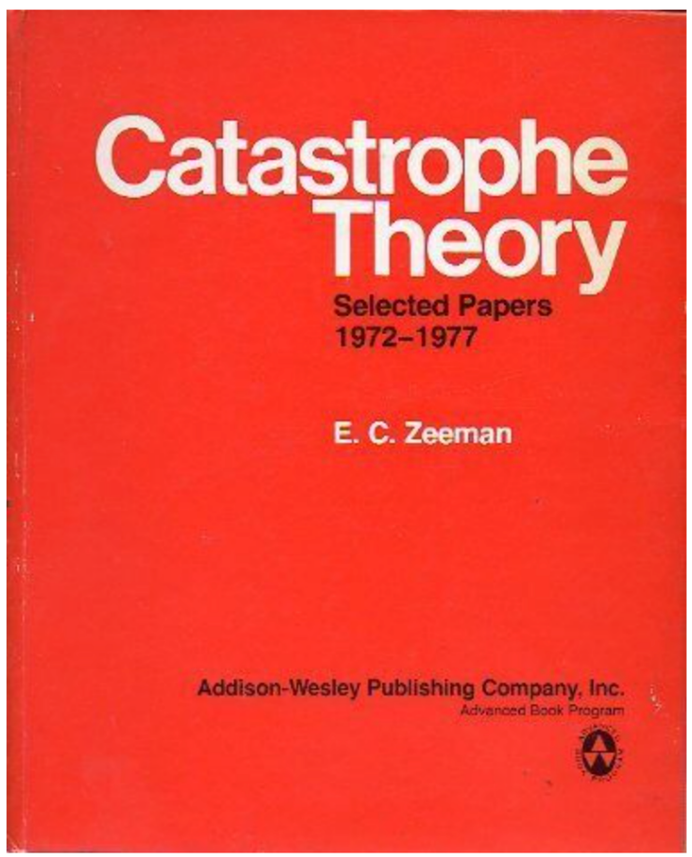


Catastrophe Theory (CT), a *new* approach

René Thom

Christopher Zeeman





Catastrophe Theory (CT), a *new* approach

Thom's classification theorem

Typically an r-parameter family of smooth functions $\mathbb{R}^n \to \mathbb{R}$, for any n and for all $r \leq 5$, is structurally stable, and is equivalent around any point to one of the following forms:

- **Non critical:** $V(u) = u_1$
- **Nondegenerate critical, or Morse:** $V(u) = u_1^2 + \cdots + u_i^2 - u_{i+1} - \cdots - u_n^2$
- **Cuspoid catastrophes**
  - **Fold:** $V(u,t) = u_1^3 + t_1 u_1 + (M)$
  - **Cusp:** $V(u,t) = \pm(u_1^4 + t_2 u_1^2 + t_1 u_1) + (M)$
  - **Swallowtail:** $V(u,t) = u_1^5 + t_3 u_1^3 + t_2 u_1^2 + t_1 u_1 + (M)$
  - **Butterfly:** $V(u,t) = \pm(u_1^6 + t_4 u_1^4 + t_3 u_1^3 + t_2 u_1^2 + t_1 u_1) + (M)$
  - **Wigwam:** $V(u,t) = u_1^7 + t_5 u_1^5 + t_4 u_1^4 + t_3 u_1^3 + t_2 u_1^2 + t_1 u_1 + (M)$
- **Umbilic Catastrophes**

(M) Morse function of the form $u_2^2 + \cdots + u_i^2 - u_{i+1}^2 - \cdots - u_n^2$, $2 \leq i \leq n$

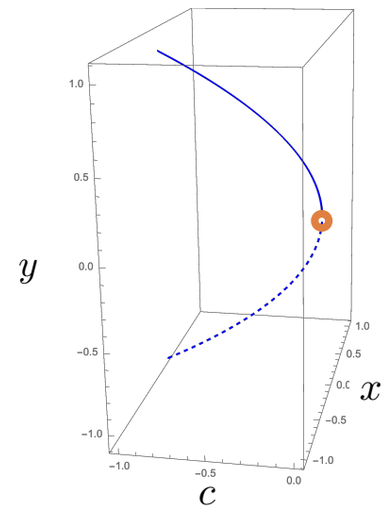
Example: Fold catastrophe

$$V(x, y, c) = y^3/3 + x^2/2 + cy$$

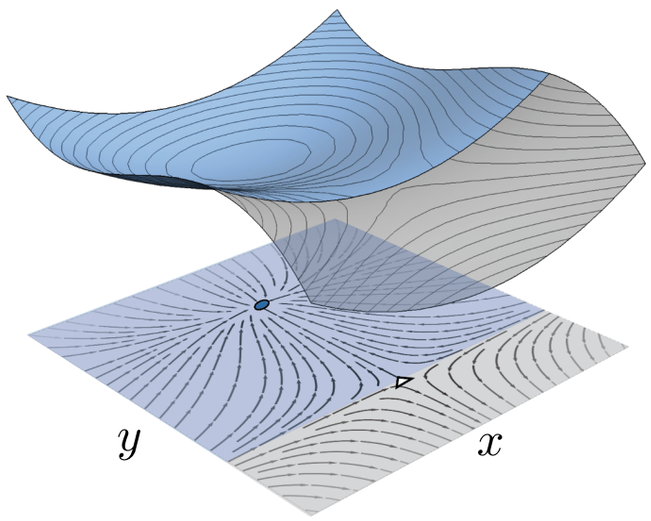
$$\mathcal{M} = \{(x, y, c) \in \mathbb{R}^2 \times \mathbb{R} : x = y^2 + c = 0\}$$

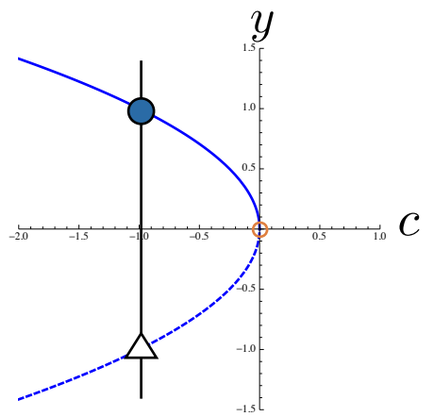
$$\mathcal{S} = \{(x, y, c) \in \mathbb{R}^2 \times \mathbb{R} : x = y = c = 0\}$$

$$\mathcal{B} = \{c = 0\}$$



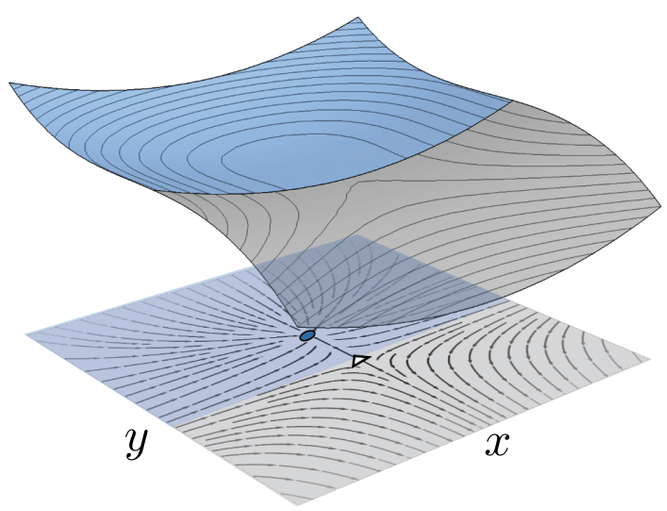
$V(x, y, -1)$

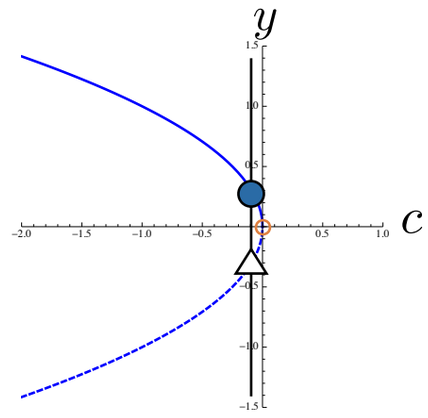




2 CPs 1 CP 0 CPs

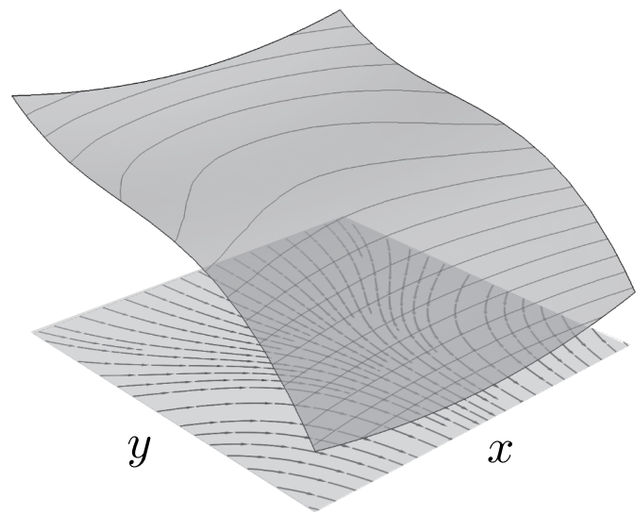
$V(x, y, -0.1)$

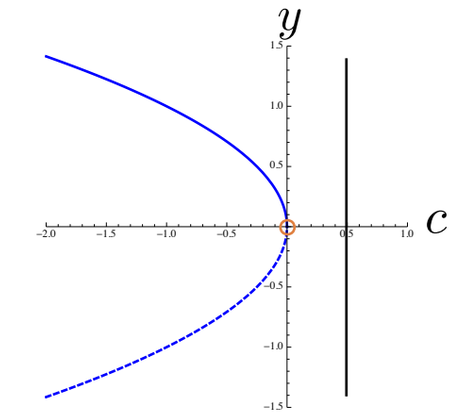




2 CPs 1 CP 0 CPs

$V(x, y, 1)$





2 CPs 1 CP 0 CPs

Method

1.- **Characterise the cell types** and signals present in the biological process, **and the transitions that can be observed** in the data.

2.- Using Catastrophe and Dynamical Systems Theory, **enumerate the landscapes** that contain the desired number of attractors and transitions.

3.- **Build the landscapes by gluing elementary catastrophes**.

4.- Write the **control parameters as functions of the biological signals**.

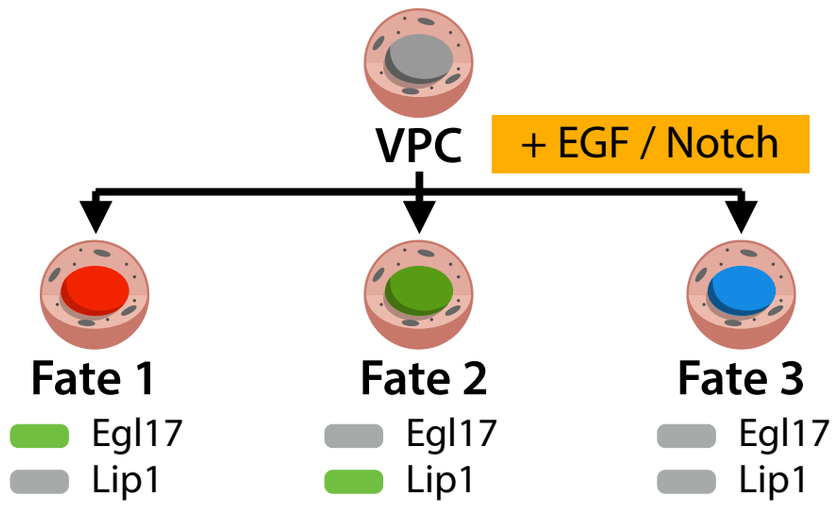
5.- Use a parameter fitting method to **fit the models to the data**. Discard the landscapes that are not consistent with the data.

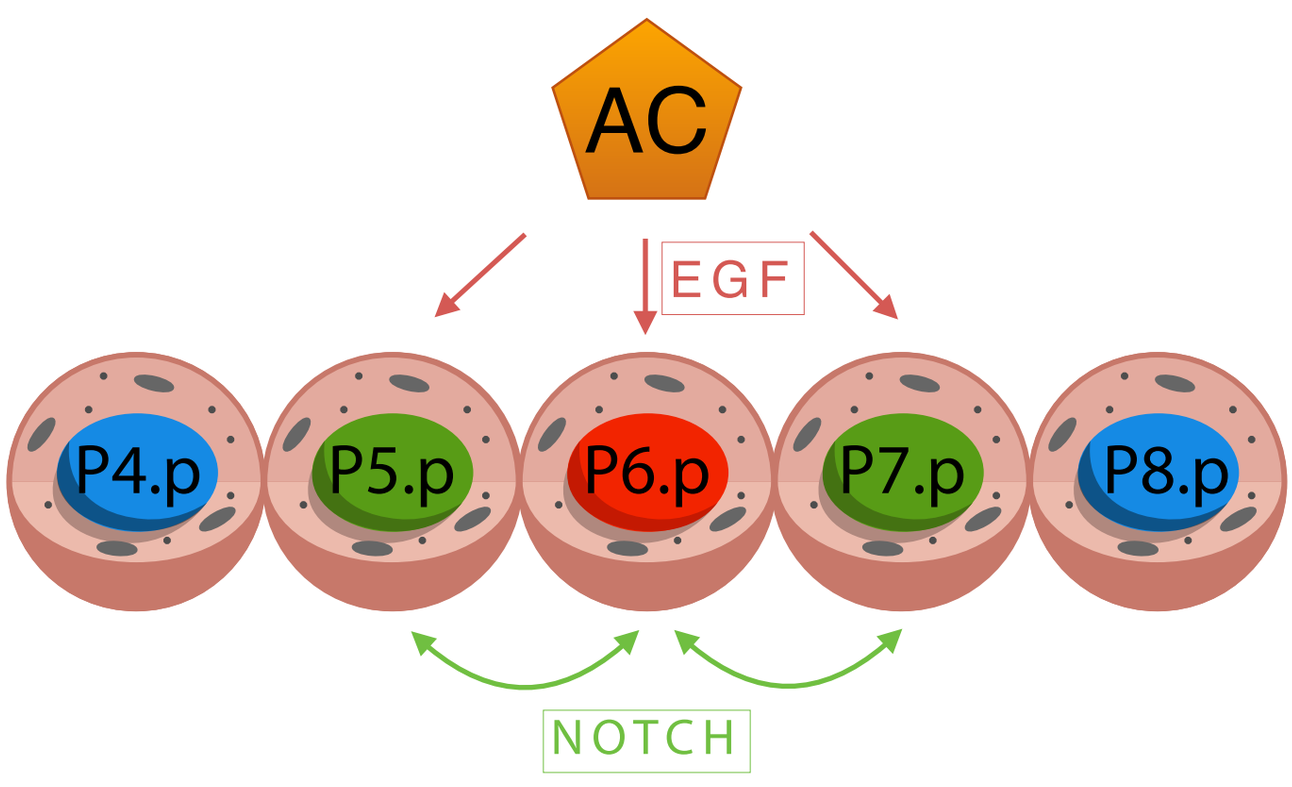
6.- **Validate the model and make predictions**.

An example of cell state transitions: *C. elegans* vulval development

David A. Rand (University of Warwick)

Aryeh Warmflash (Rice University)





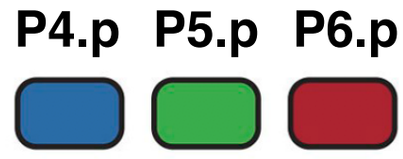
Primary fate: Inner vulva

Secondary fate: Outer vulva

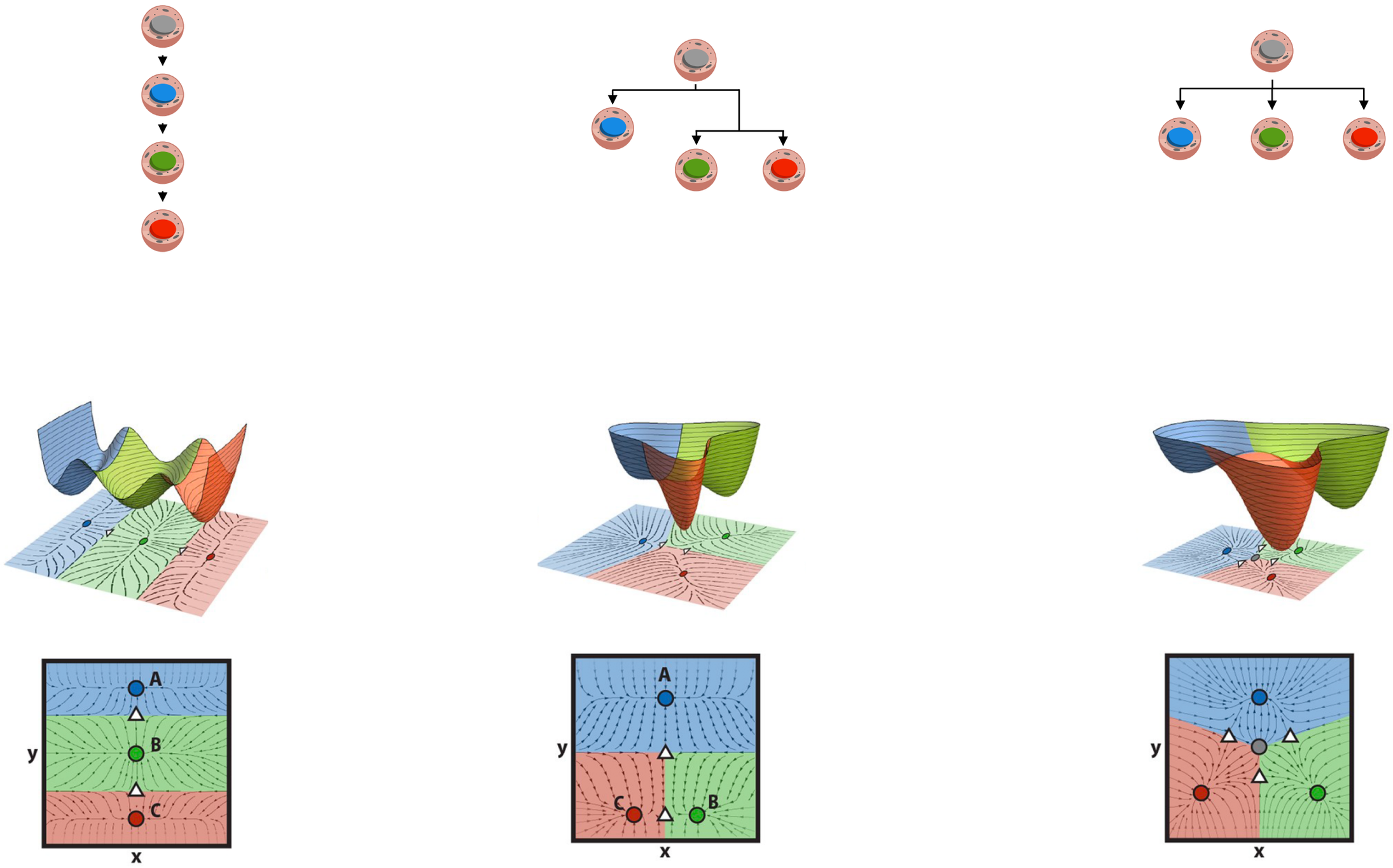
Fate 3: Non vulval

Available data consists of probability of patterns for different signaling perturbations

	Experiment	VPC fates (% 1°, 2° 3°)		
		P4.p	P5.p	P6.p
	Wild-type outcomes under reduced signalling			
(1)	Wild type	0, 0, 100	0, 100, 0	100, 0, 0
(2)	*let-23* mosaic		wild type	
	(no EGF receptors in P5/7.p)			
(3)	Half dose of *lin-3*		wild type	
	(Half EGF ligand)			
(4)	Half dose of *lin-12*		wild type	
	(Half Notch receptor)			

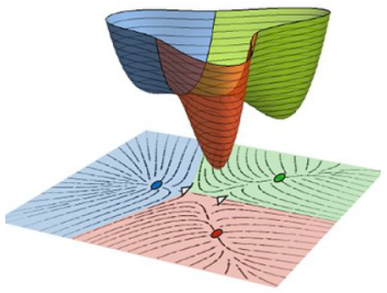


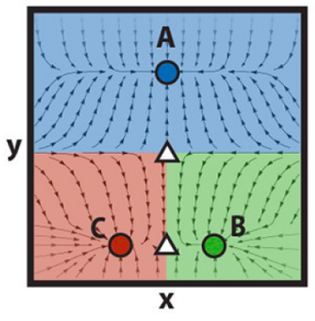
Model design: Three landscape topologies are possible for a process involving three fates

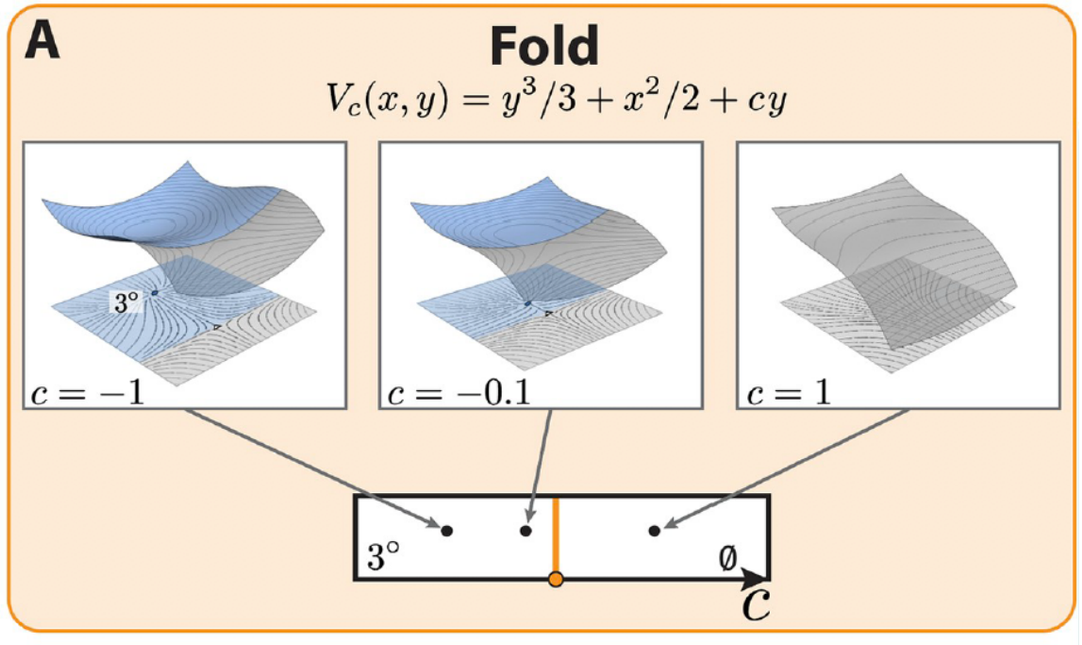


Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Model construction: Using CT we can build the simplest landscape with the desired features

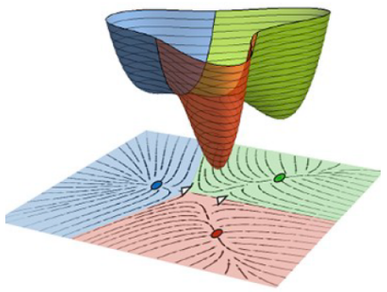


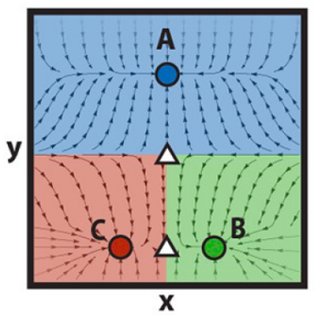


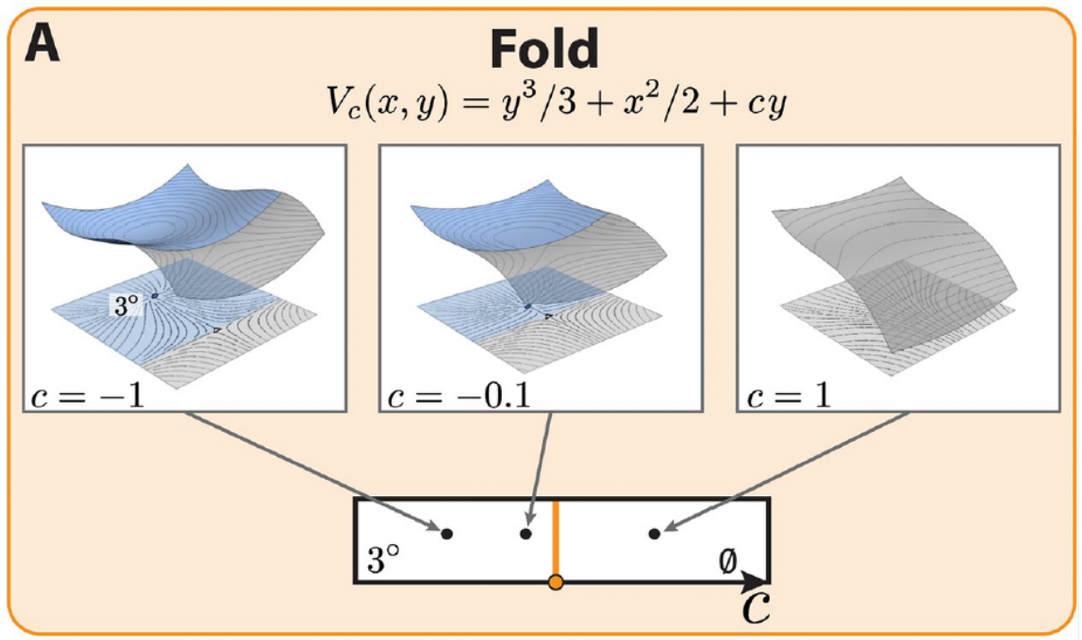


Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

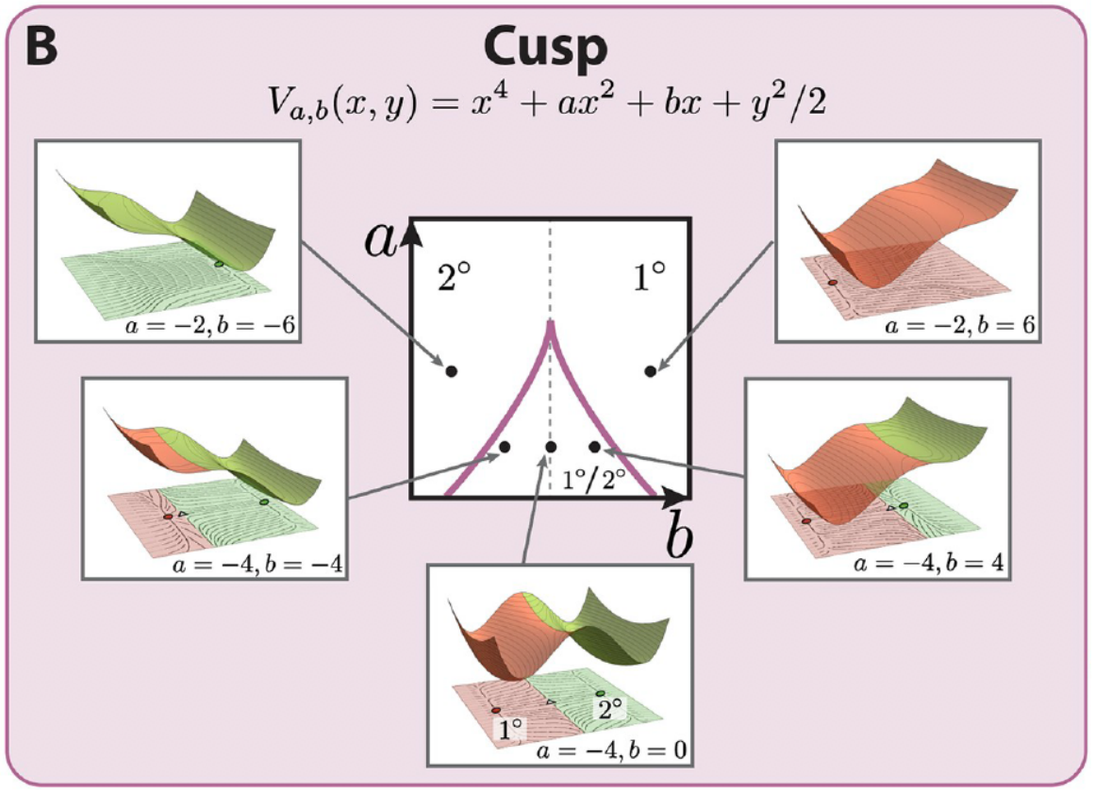
Model construction: Using CT we can build the simplest landscape with the desired features





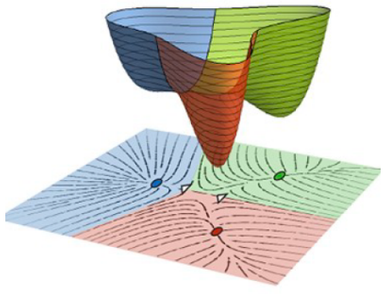


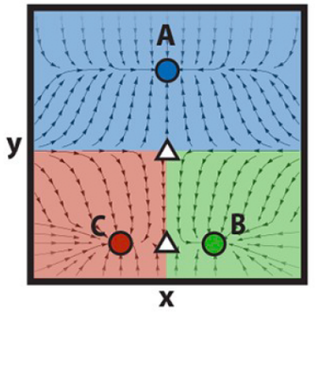
+



Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Model construction: Piecing together the fold and the cusp catastrophes we can construct the right flow



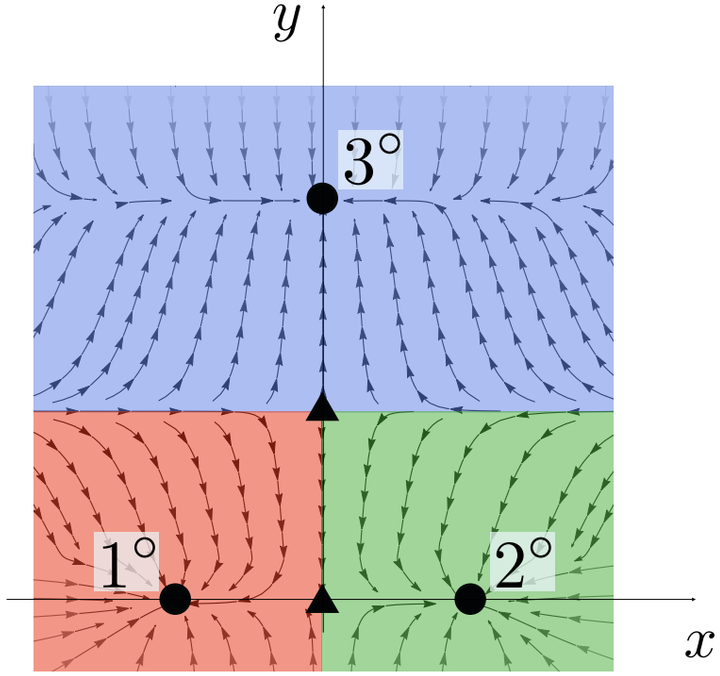


$$\begin{cases} \dot{x} &= H(-y)f_{\text{cusp}}(x,a,b) - (1-H(-y))x = f_1(x,y,a,b,c,M) \\ \dot{y} &= yf_{\text{fold}}(y-M,c) = f_2(x,y,a,b,c,M), \end{cases}$$

$$H(y) = 0, \text{if } y < 0$$

$$H(y) = 1, \text{if } y \geq 0$$

Control parameters: a, b, c

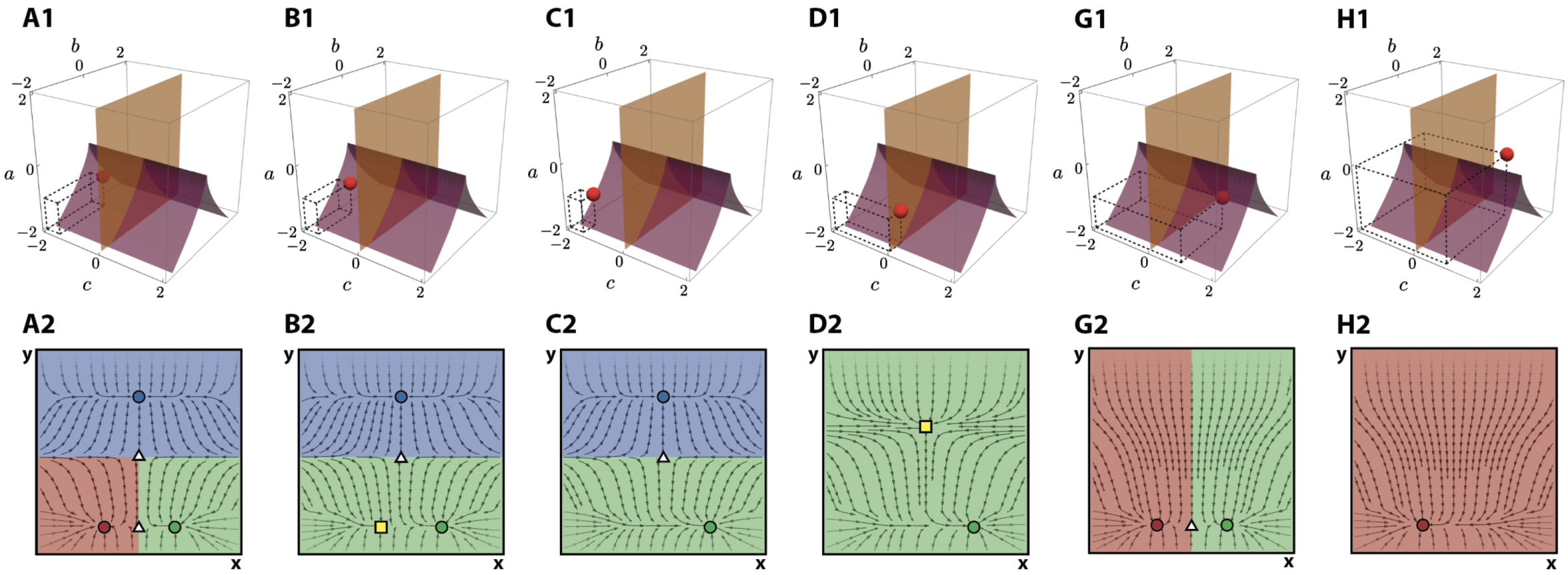


Heteroclinic flip

Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

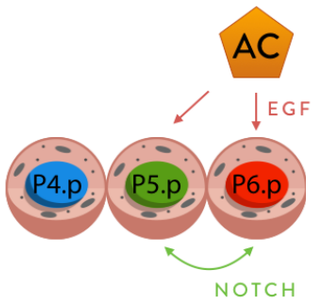
Building the model using CT allows for a deep understanding of the allowed transitions

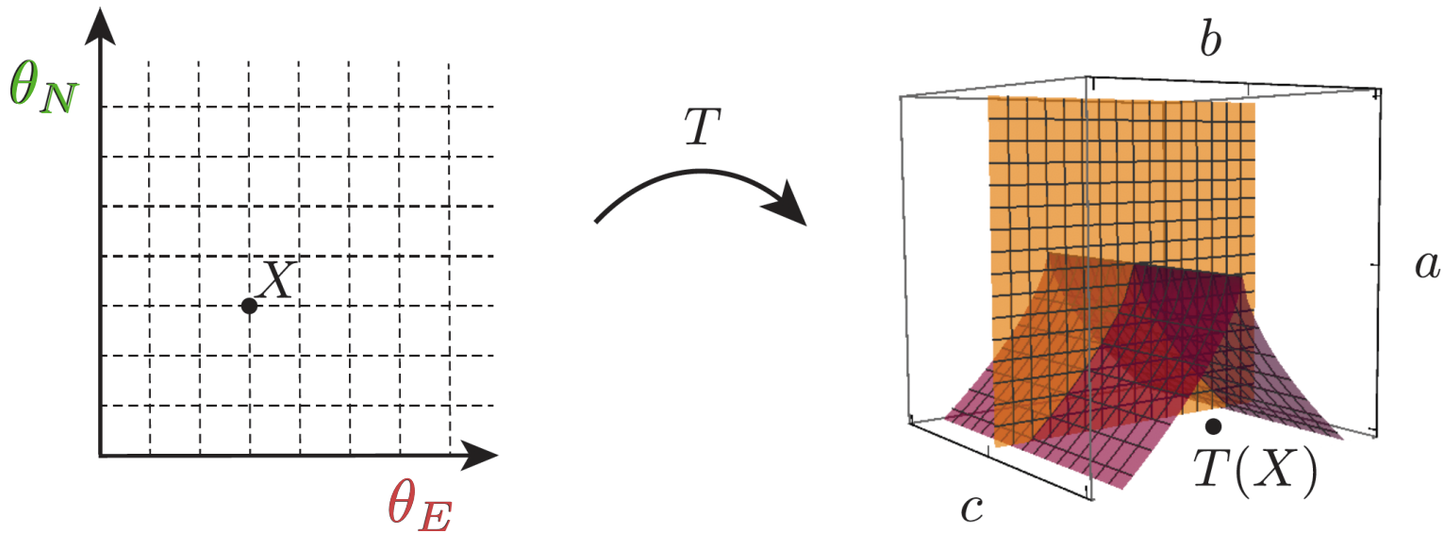
$$\mathcal{B} = \{(a, b, c) \in \mathbb{R}^3 : 8a^3 + 27b^2 = 0\} \cup \{(a, b, 0) : a, b \in \mathbb{R}\}$$



Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

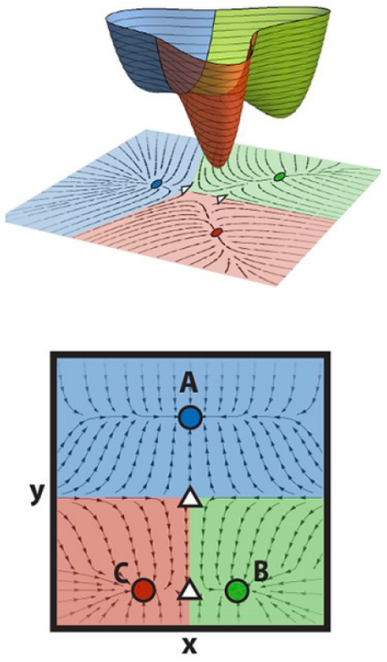
Modelling the effect of biological signals through the control parameters to control cell state transitions





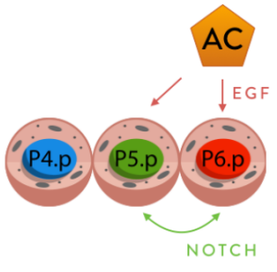
Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Modelling the effect of biological signals through the control parameters to control cell state transitions



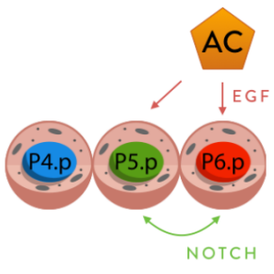
Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Adding white noise, we can simulate experiments

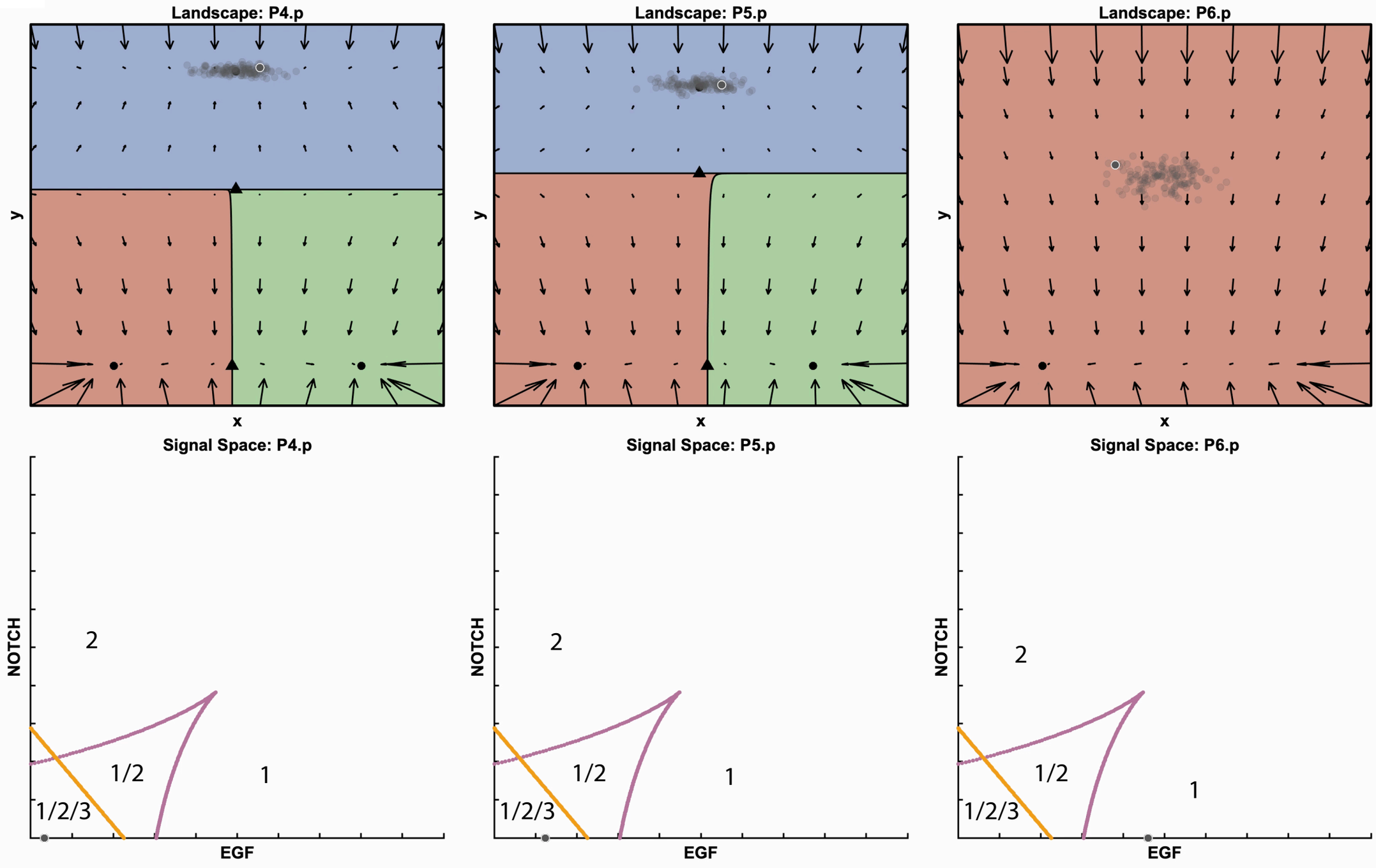


Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Adding white noise, we can simulate experiments

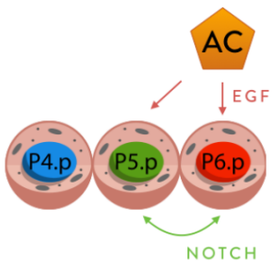


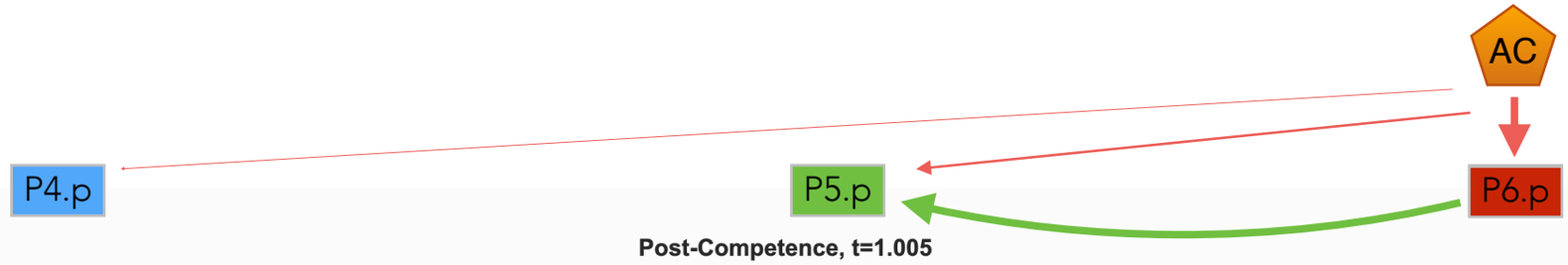
Competence, t=0.45



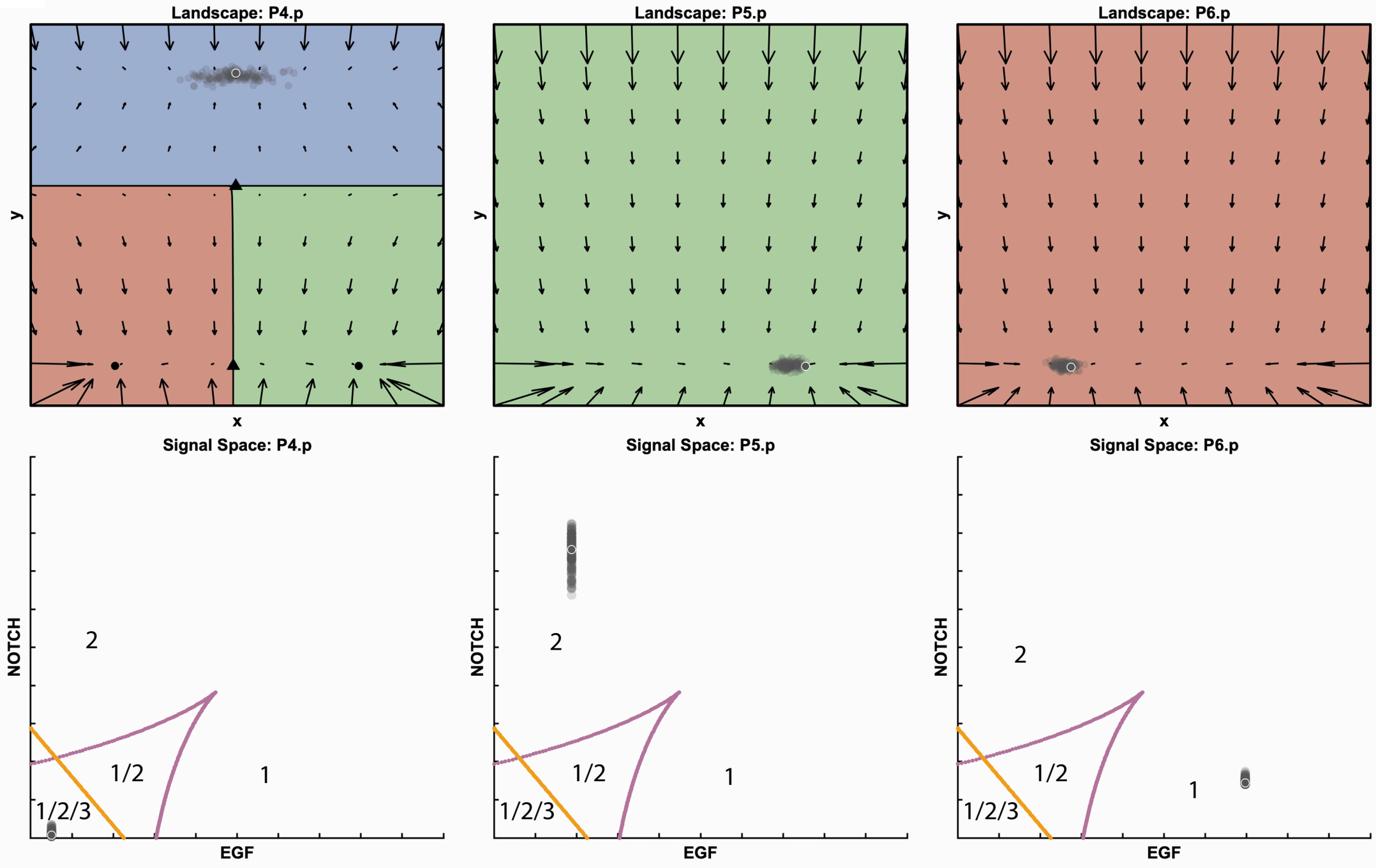
Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Adding white noise, we can simulate experiments



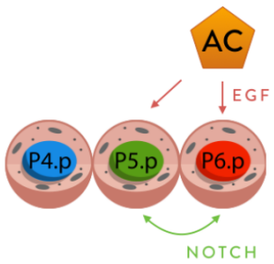


Post-Competence, t=1.005



Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Model fitting: We use approximate Bayesian computation (ABC) to fit a set of available data



Data

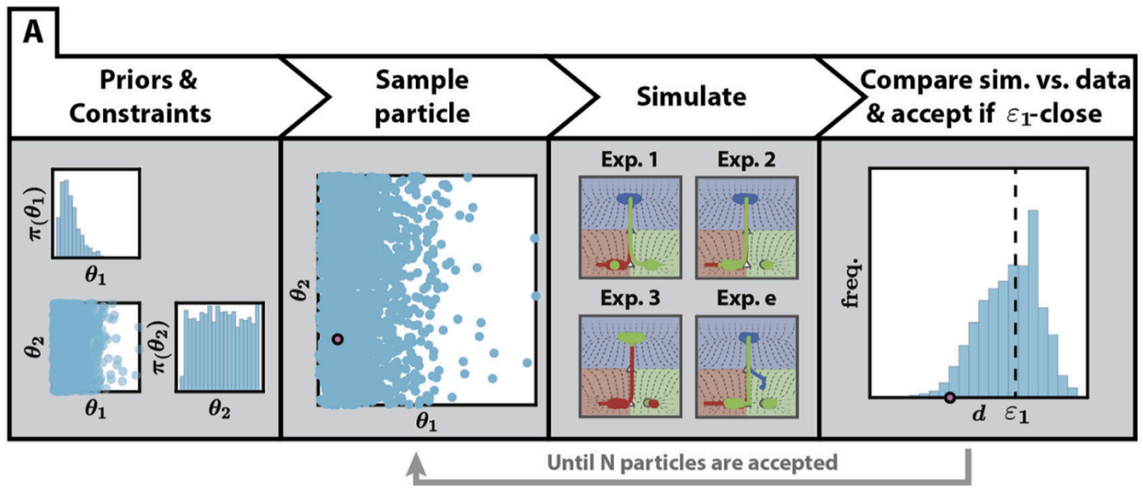
A

	Data		
	P4.p	P5.p	P6.p
WT Patterns WT let-23 mosaic Half dose lin-3 Half dose lin-12			
Notch null, 2ACs (2xWT EGF)			
No Notch signaling			

B

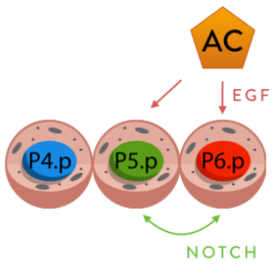
EGF overexpression	18 / 46 / 36 ; 46 / 55 ;

Fitting (ABC)

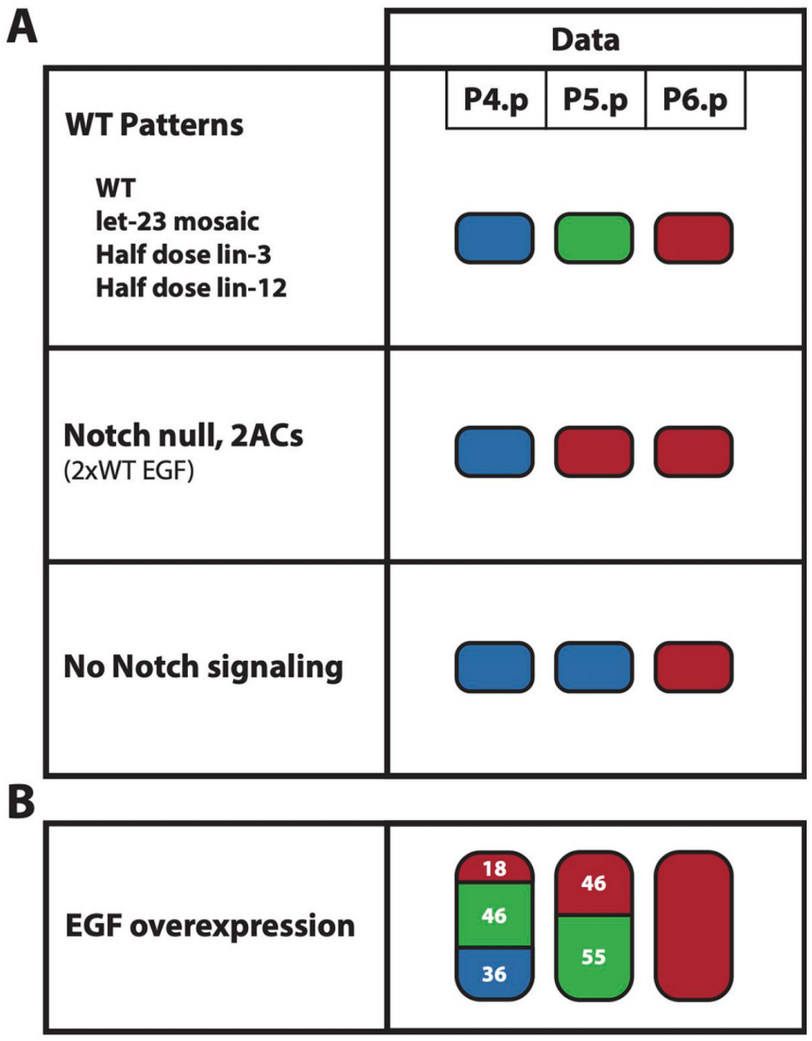


Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

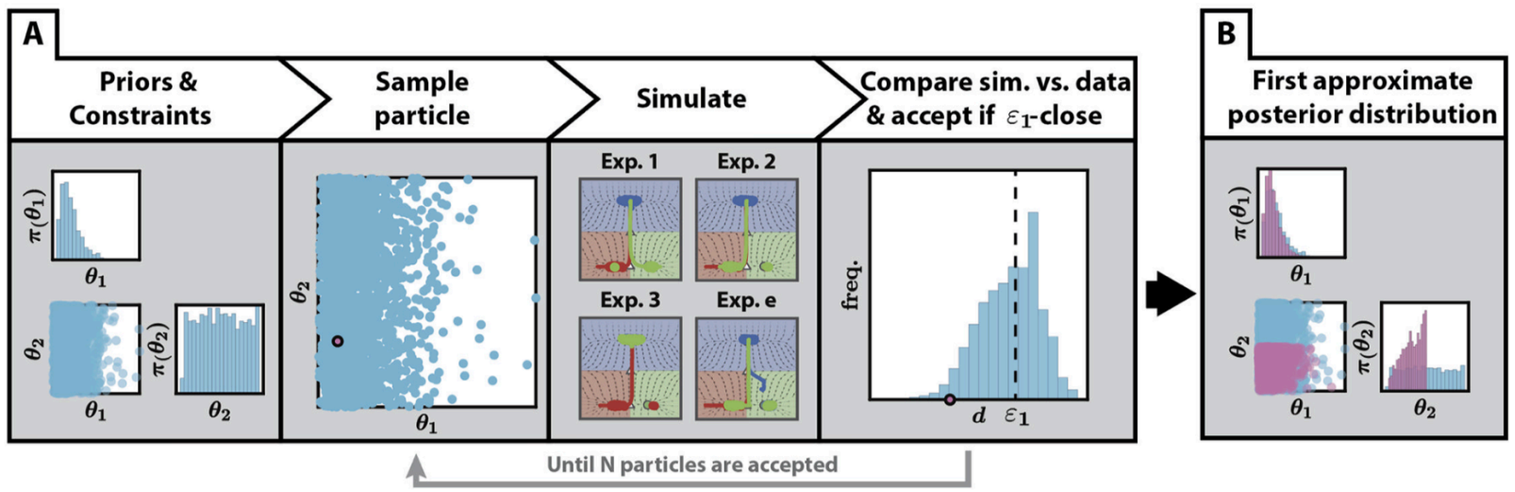
Model fitting: We use approximate Bayesian computation (ABC) to fit a set of available data



Data

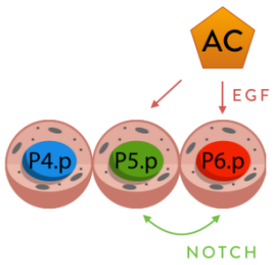


Fitting (ABC)

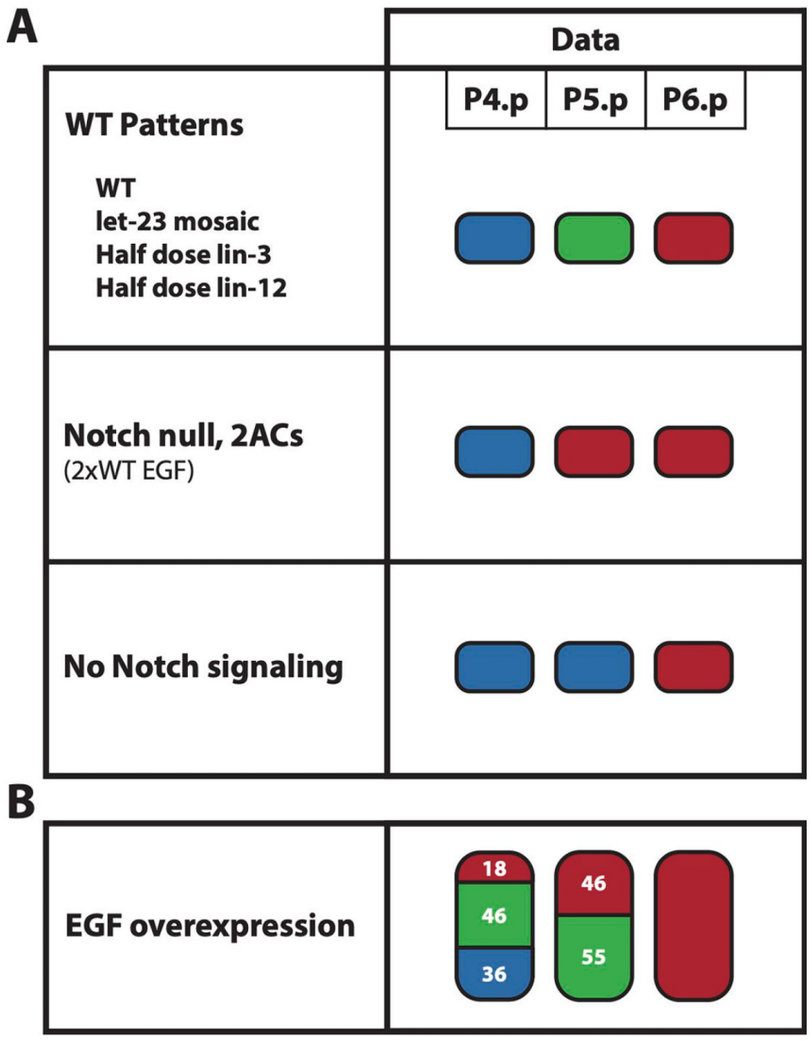


Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

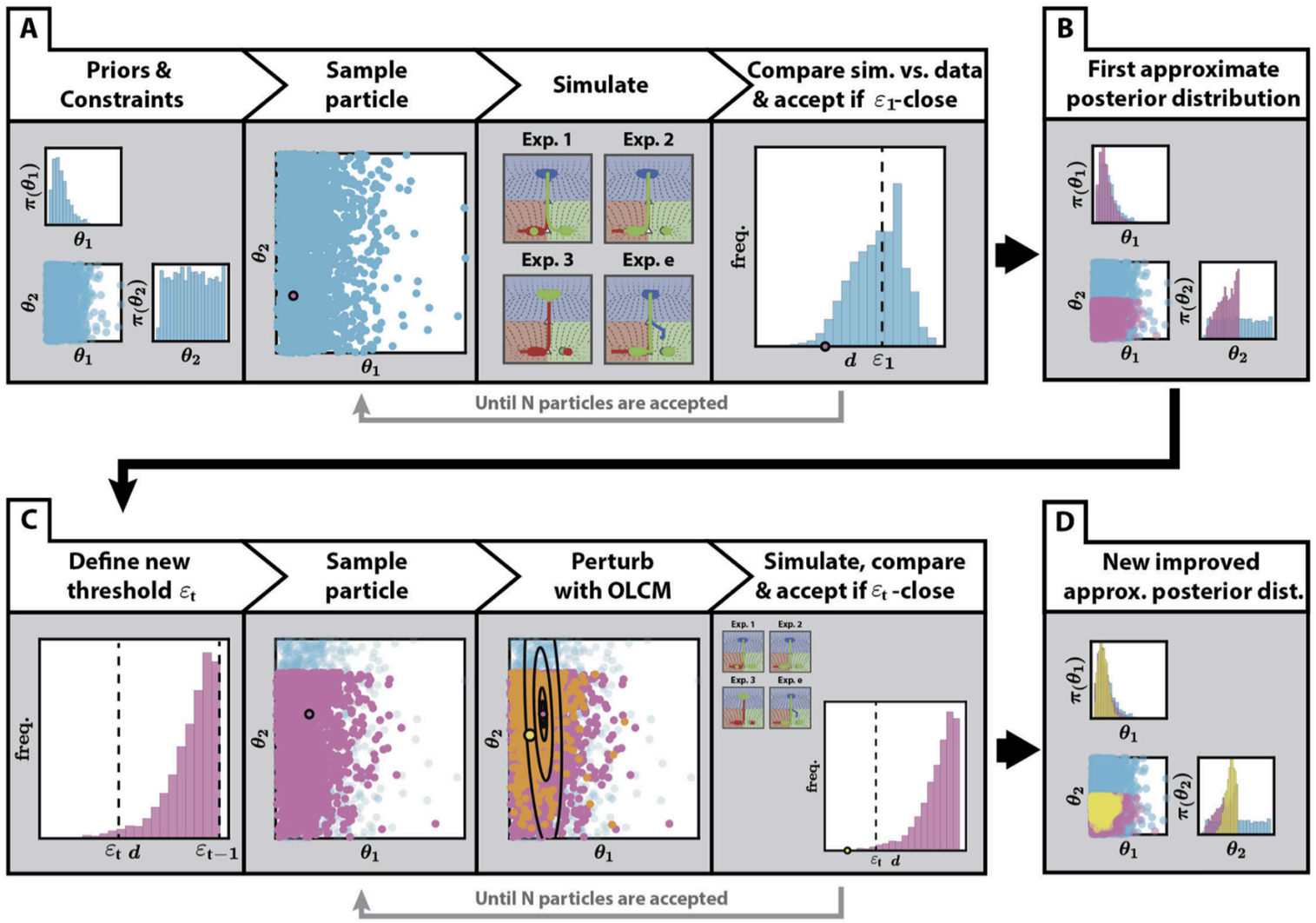
Model fitting: We use approximate Bayesian computation (ABC) to fit a set of available data



Data

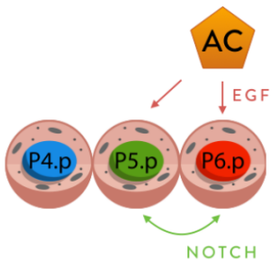


Fitting (ABC)

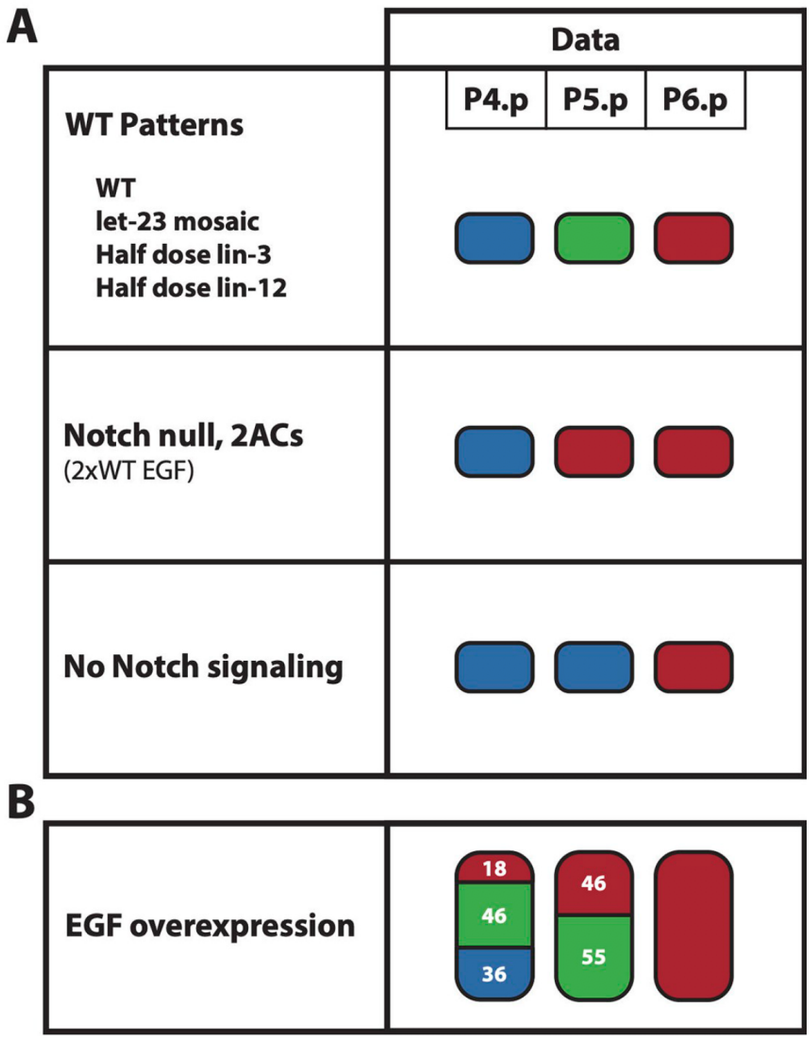


Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

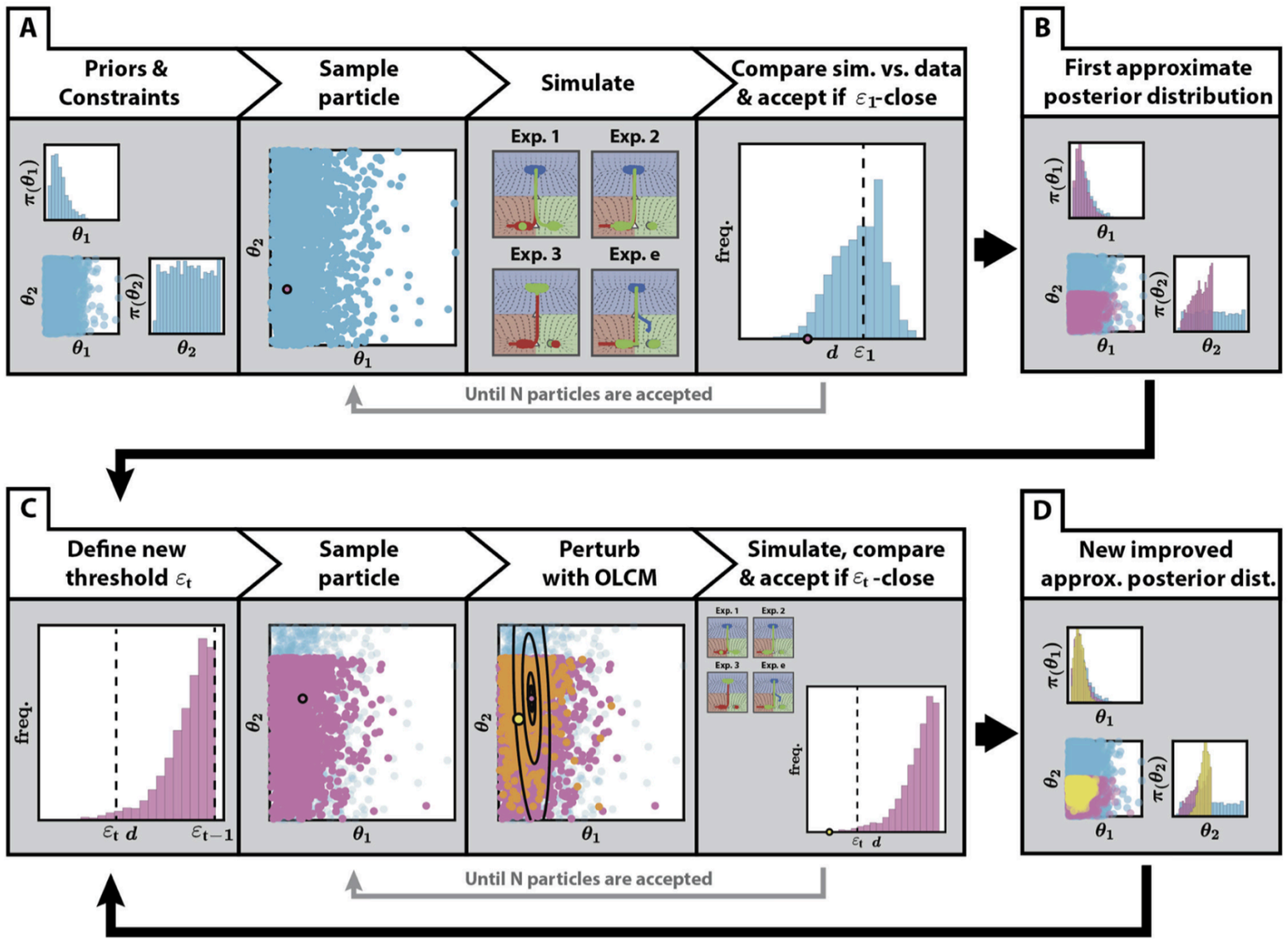
Model fitting: We use approximate Bayesian computation (ABC) to fit a set of available data



Data

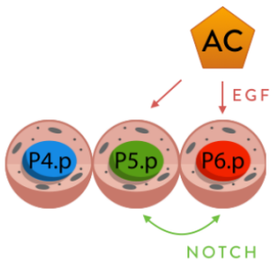


Fitting (ABC)



Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

Model fitting: We use approximate Bayesian computation (ABC) to fit a set of available data



A

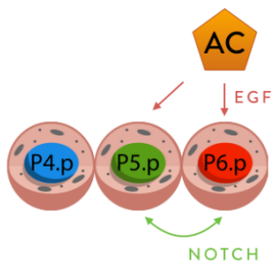
	Data	Simulations
WT Patterns **WT** **let-23 mosaic** **Half dose lin-3** **Half dose lin-12**	P4.p P5.p P6.p	P4.p P5.p P6.p
Notch null, 2ACs (2xWT EGF)		
No Notch signaling		

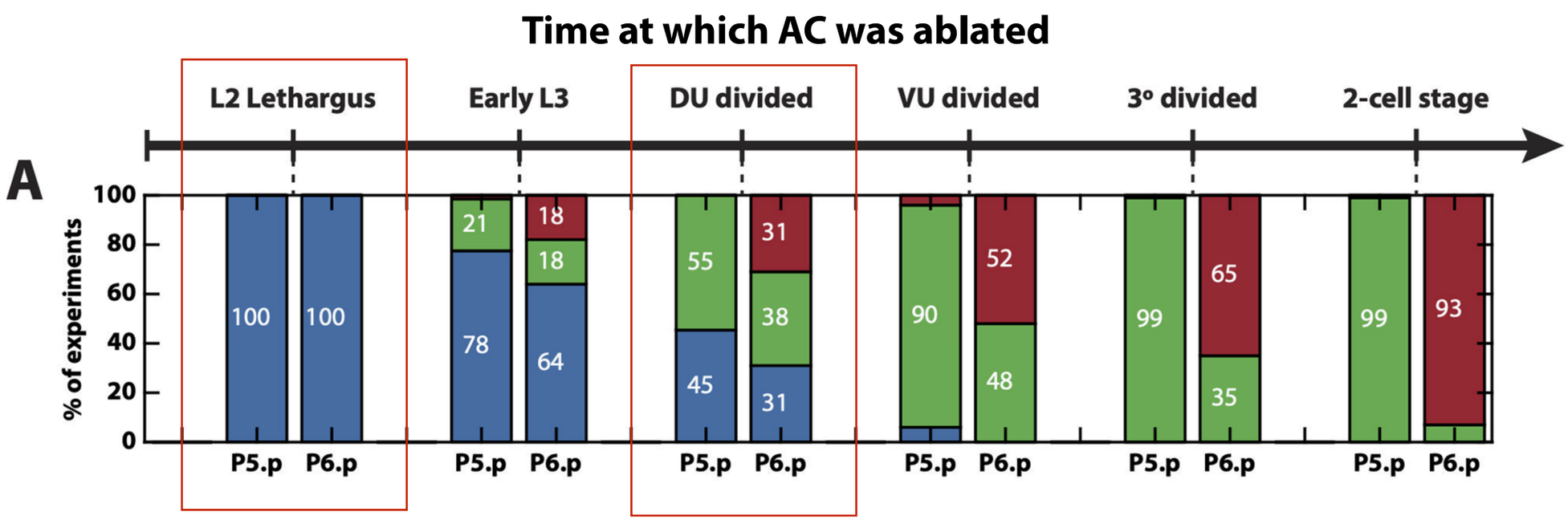
B

EGF overexpression	18 / 46 / 36 ; 46 / 55 ;	13 / 46 / 41 ; 42 / 57 ;

Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

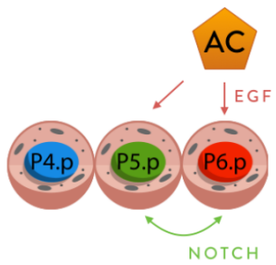
Using fitted parameters we can validate the model with remaining data

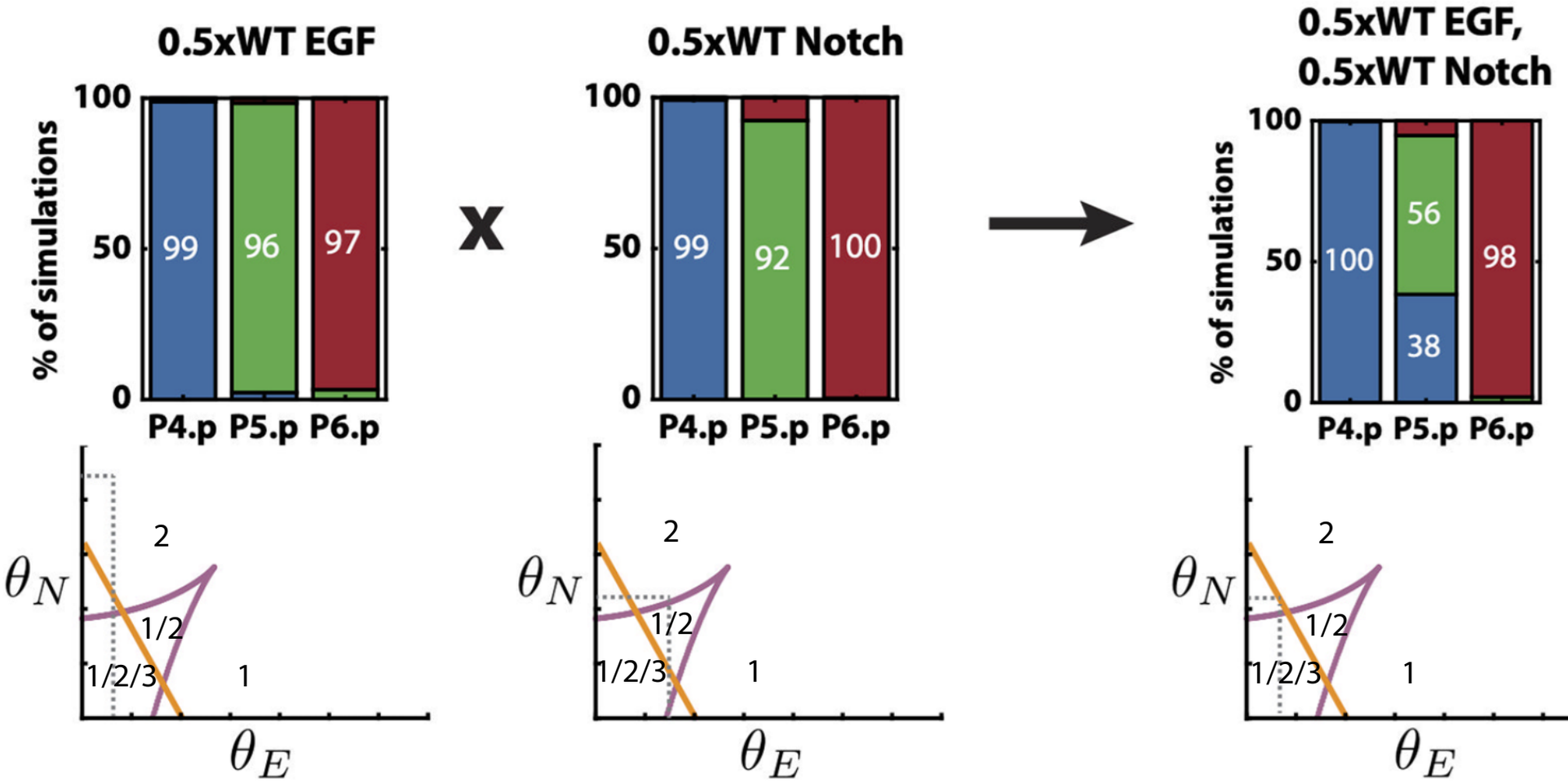




Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

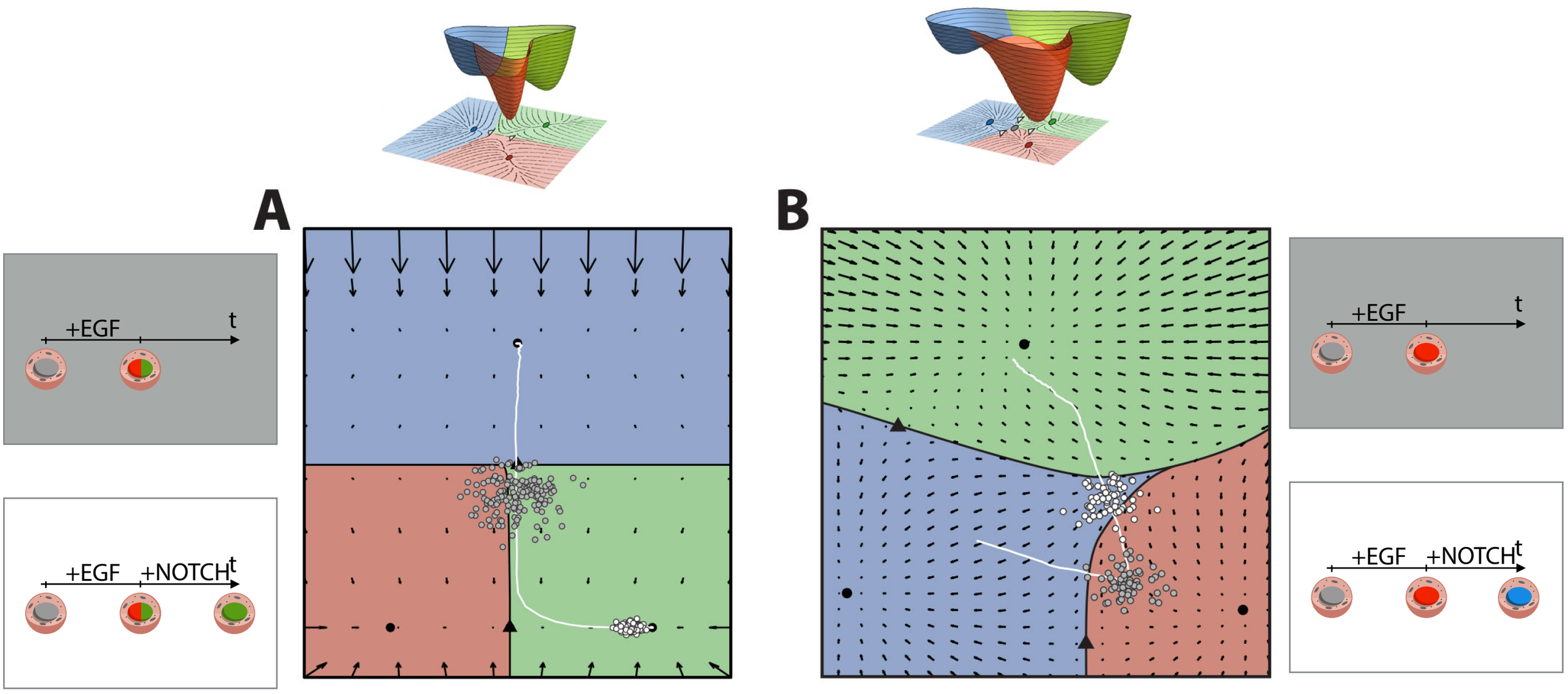
Using fitted parameters we can validate the model with remaining data and make new predictions





Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

New predictions can differentiate between the two proposed landscape models



Camacho-Aguilar E, Warmflash A, Rand DA (2021) Quantifying cell transitions in C. elegans with data-fitted landscape models. PLoS Comput Biol 17(6): e1009034. https://doi.org/10.1371/journal.pcbi.1009034

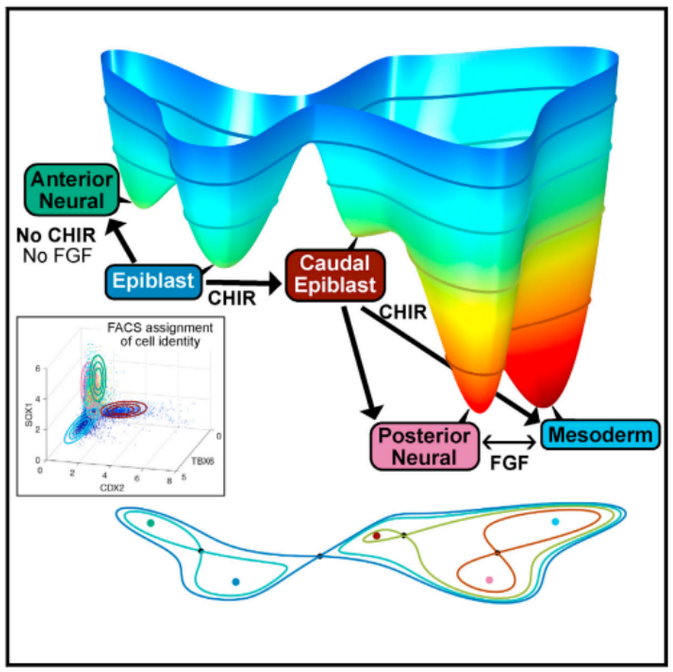
More research on landscape models…

Article

Cell Systems

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

Graphical abstract



Authors

Meritxell Sáez, Robert Blassberg, Elena Camacho-Aguilar, Eric D. Siggia, David A. Rand, James Briscoe

Correspondence

d.a.rand@warwick.ac.uk (D.A.R.), james.briscoe@crick.ac.uk (J.B.)

In brief

Fate decisions in developing tissues involve cells transitioning between discrete cell states. We developed an approach to construct a dynamical landscape from quantitative gene expression data, in which the development of a cell is represented by a trajectory through the landscape. Applying it to pluripotent stem cells exposed to different combinations of signaling factors accurately predicted cell fate outcomes. This revealed two distinct architectures for the way cells make a binary choice between one of two fates.

Highlights

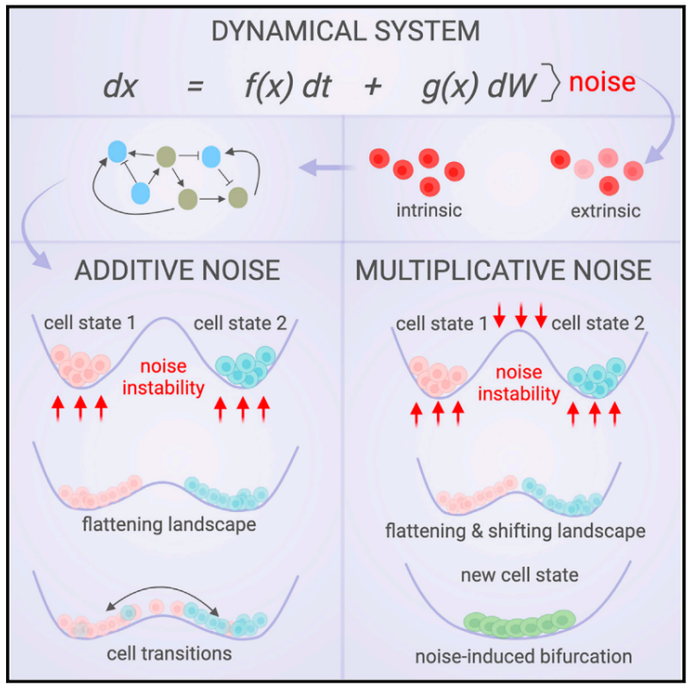
- Quantified effect of signaling on fate decisions in an *in vitro* differentiation system
- Constructed a Waddingtonian-like dynamical landscape model from the quantitative data

Synthesis

Cell Systems

Noise distorts the epigenetic landscape and shapes cell-fate decisions

Graphical abstract



Authors

Megan A. Coomer, Lucy Ham, Michael P.H. Stumpf

Correspondence

mstumpf@unimelb.edu.au

In brief

Waddington's epigenetic landscape provides a conceptual tool and, increasingly, analytical framework for the study of cell differentiation. While the role of noise in cell biology has been amply documented, the repercussions of stochasticity on the landscape and the differentiation dynamics has received only scant attention. Here, we show that noise shapes the landscape profoundly and is even capable of changing qualitative features of the cell differentiation dynamics. It also limits our ability to learn regulatory processes from single-cell data.

Highlights

- Additive and multiplicative noise have distinct effects on the epigenetic landscape
- Changes in the number of cell fate choices are altered by multiplicative noise only

Cell fate transitions in murine trunk development

James Briscoe

Robert Blassberg

(Francis Crick Institute)

David A. Rand

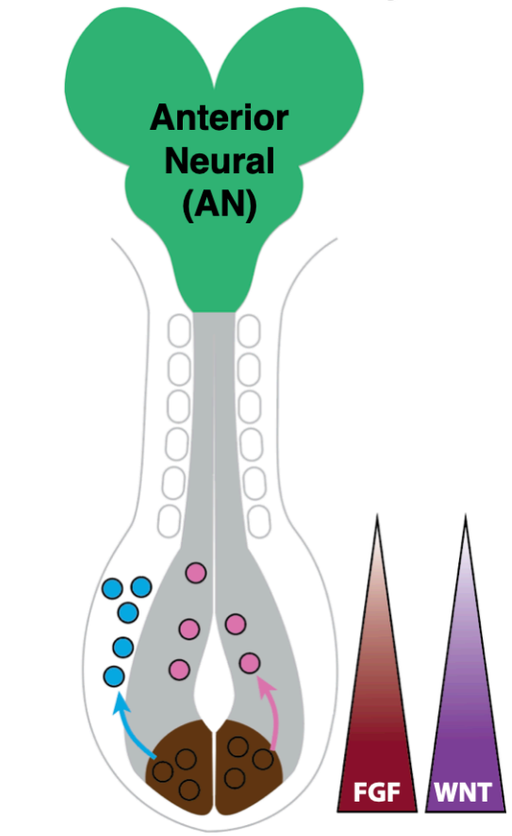
Meritxell Saez

(University of Warwick)

Eric D. Siggia

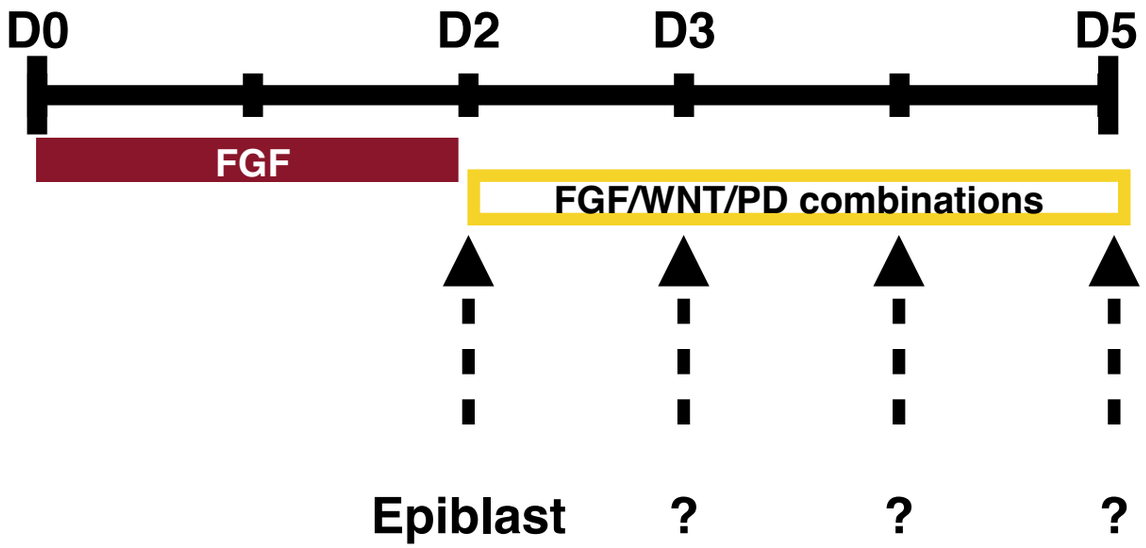
(Rockefeller Univ.)

E8.5 mouse embryo

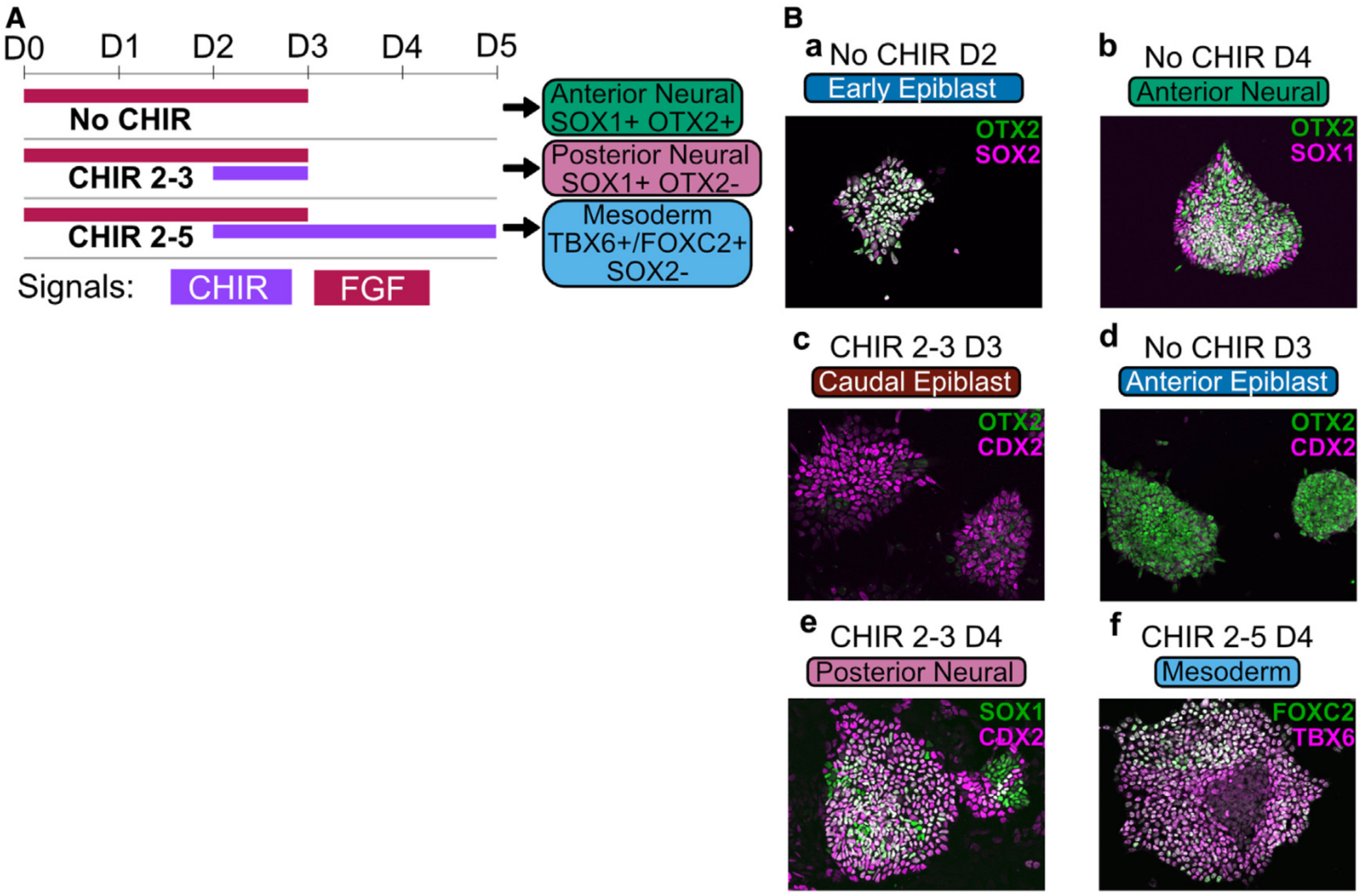


- Caudal epiblast
- Posterior neural
- Posterior mesoderm

In vitro

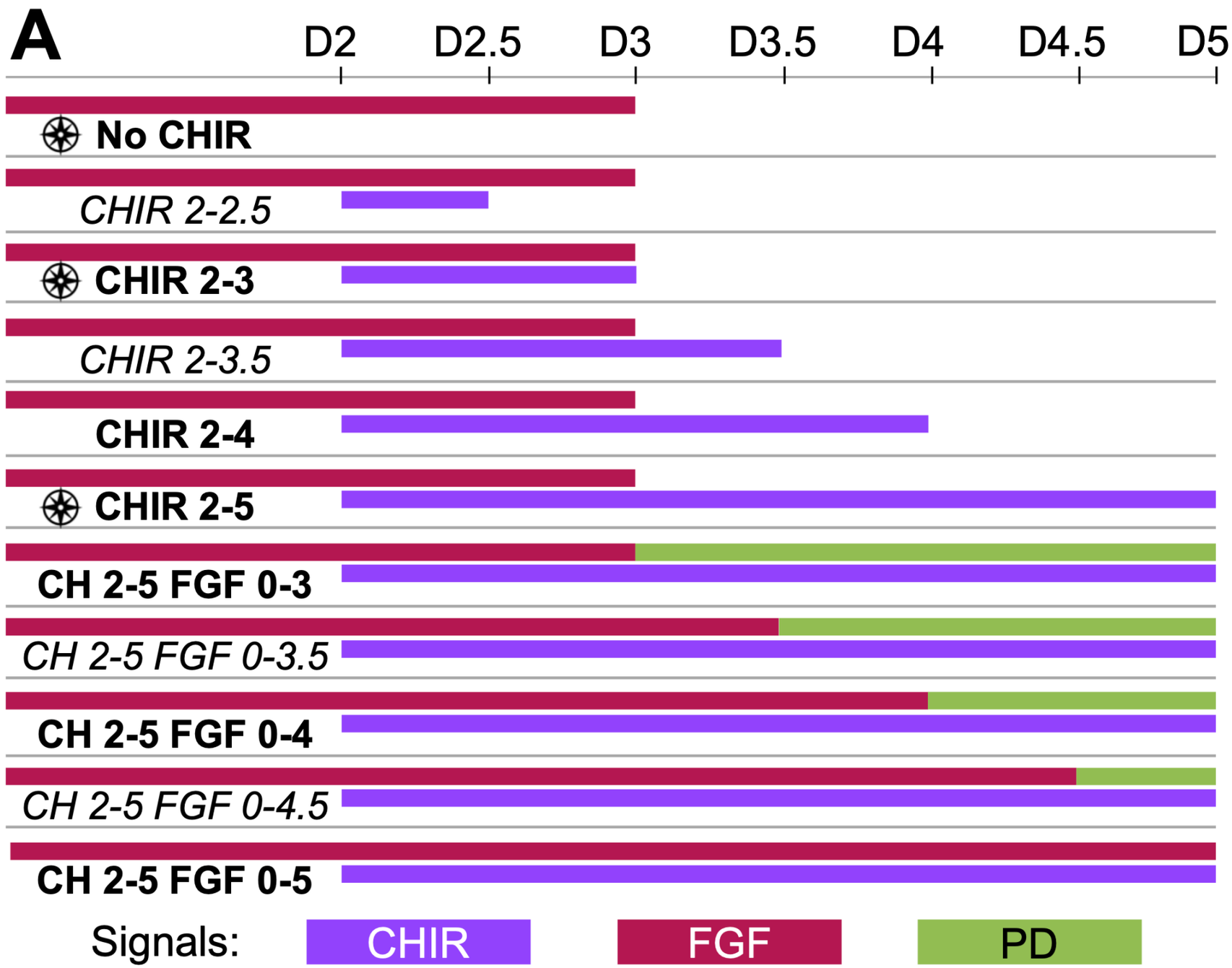


Data is no longer cell fates but gene expression



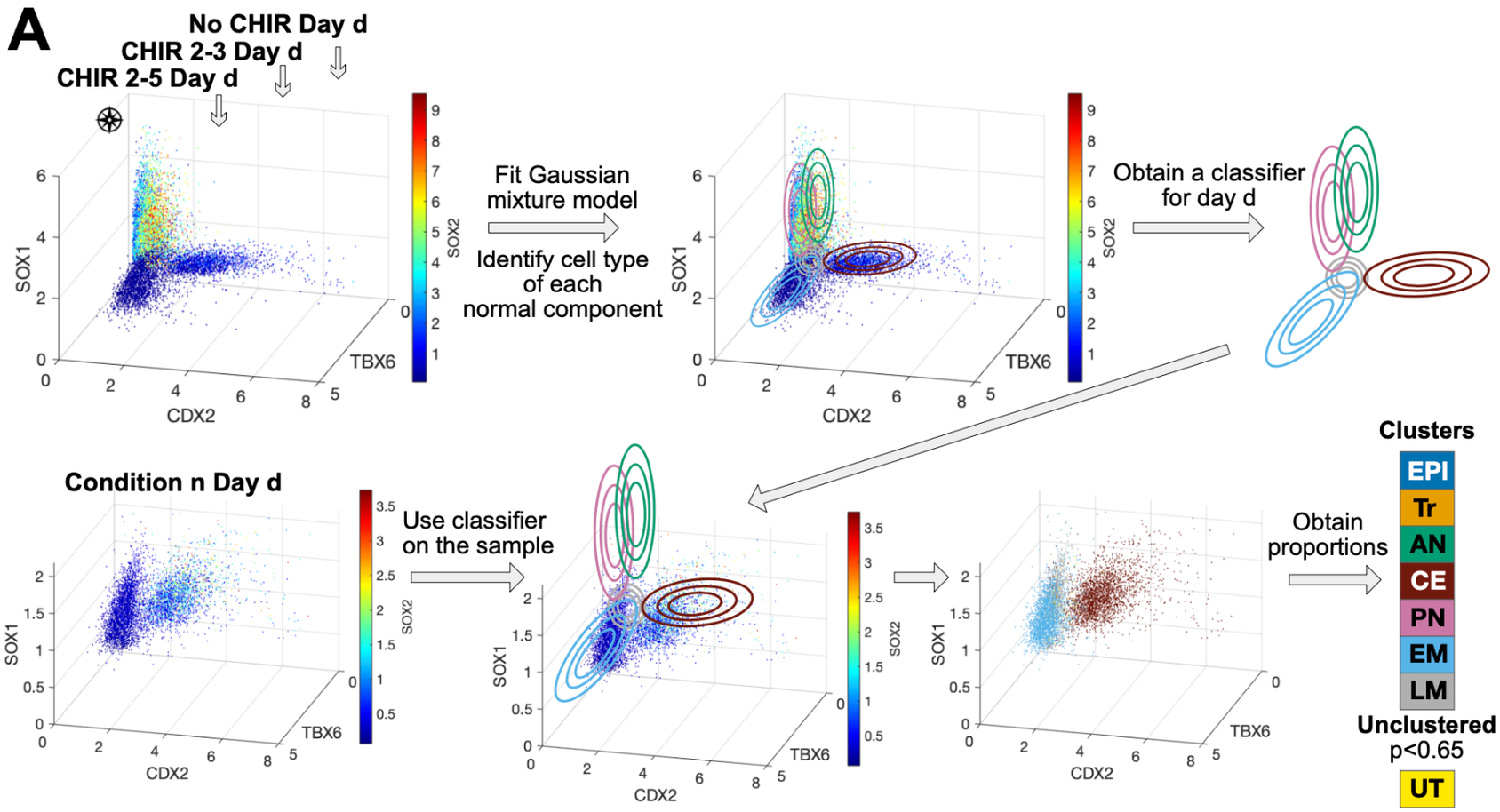
Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

The experimental setting allowed for many signaling combinations



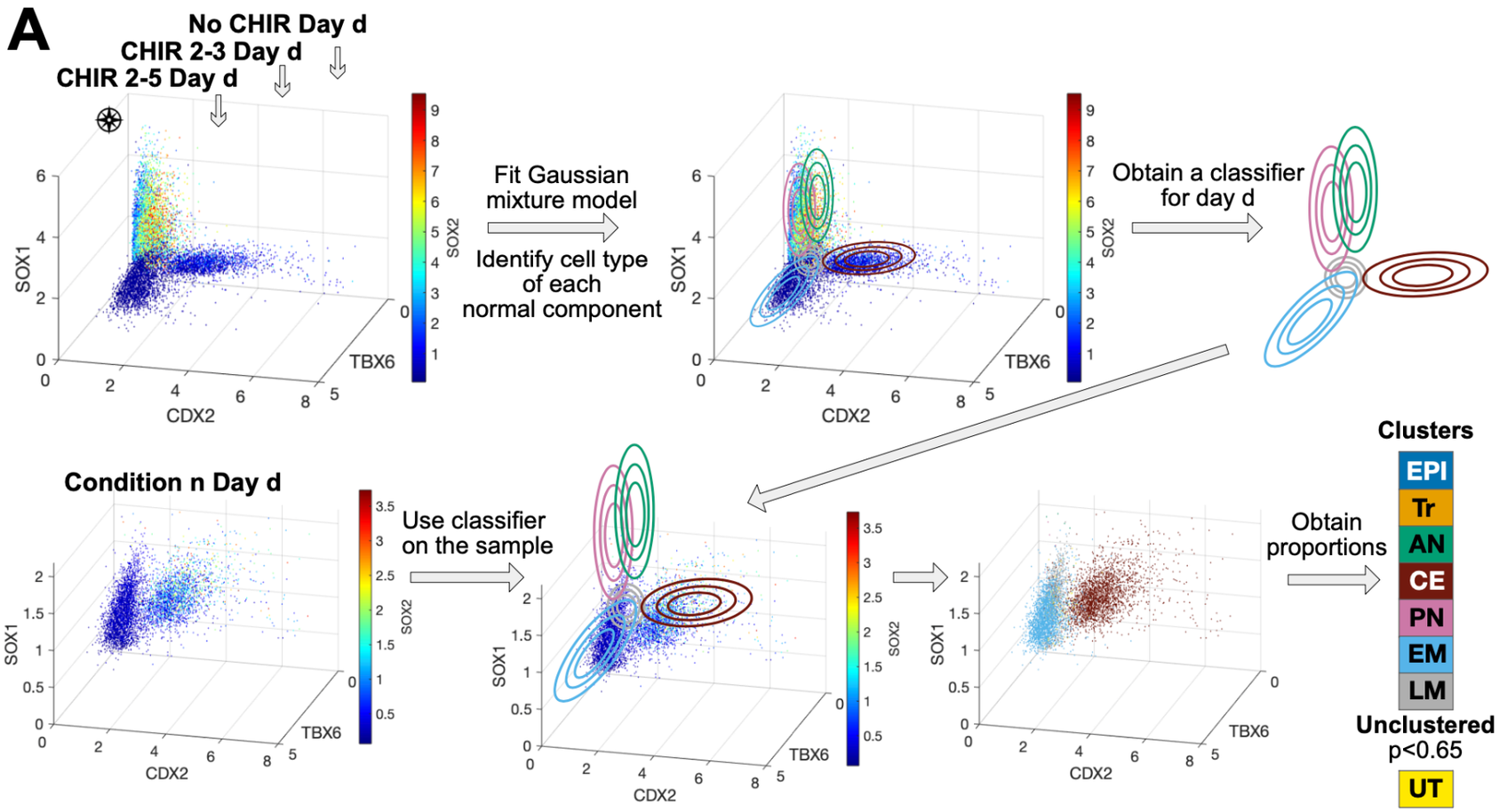
Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Statistical approach to classify cell fates



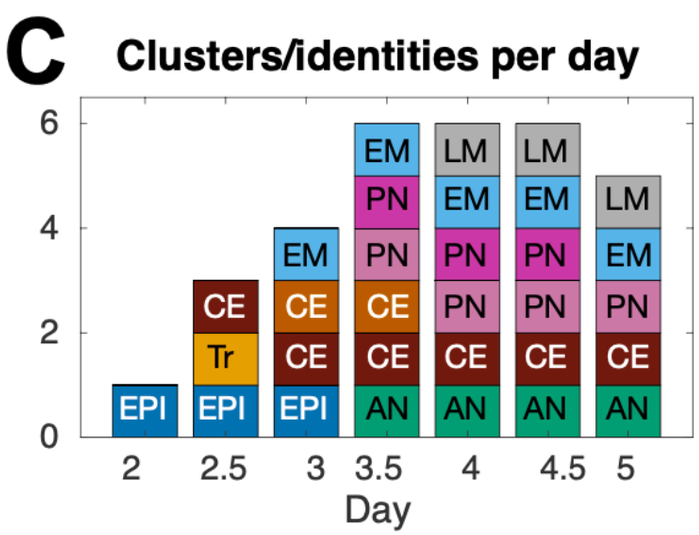
Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Statistical approach to classify cell fates



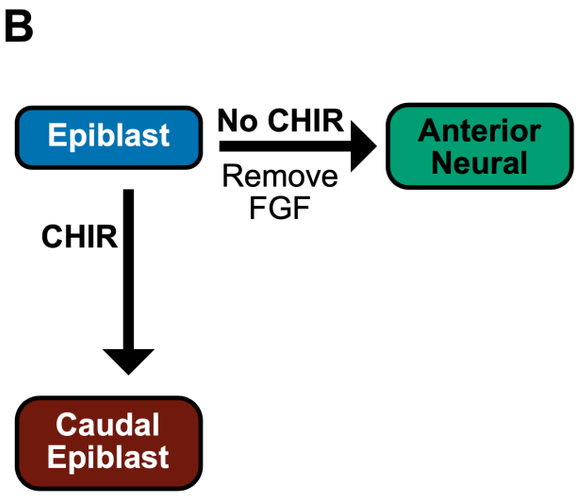
D

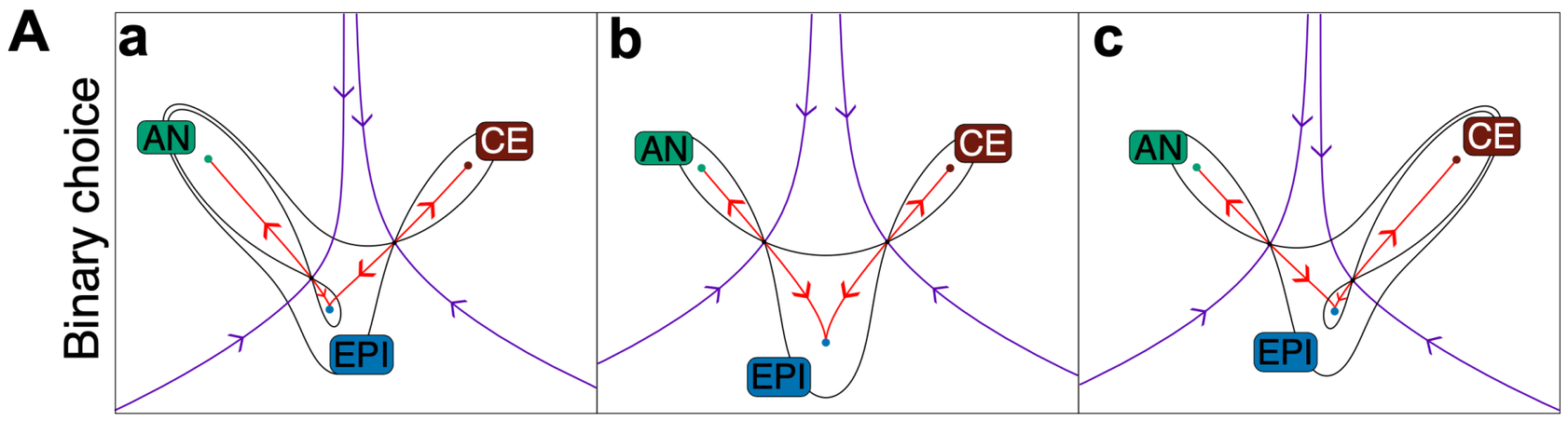
	BRA	CDX2	SOX1	SOX2	TBX6	OTX2	FOXC2
EPI				++		+	
Tr				+		+	
AN			+	++		+	
CE	(+)	+					
PN		(+)	++	+			
EM	(+)				+		
LM							+

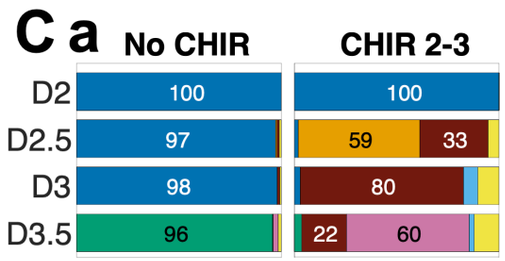


Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Cell differentiation is governed by two distinct binary cell fate decisions

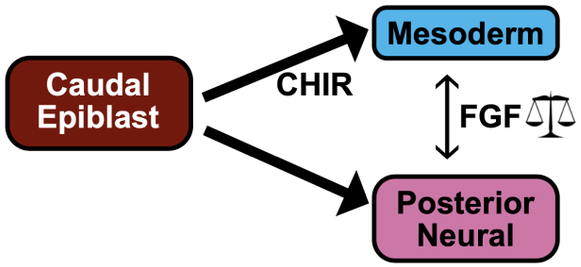


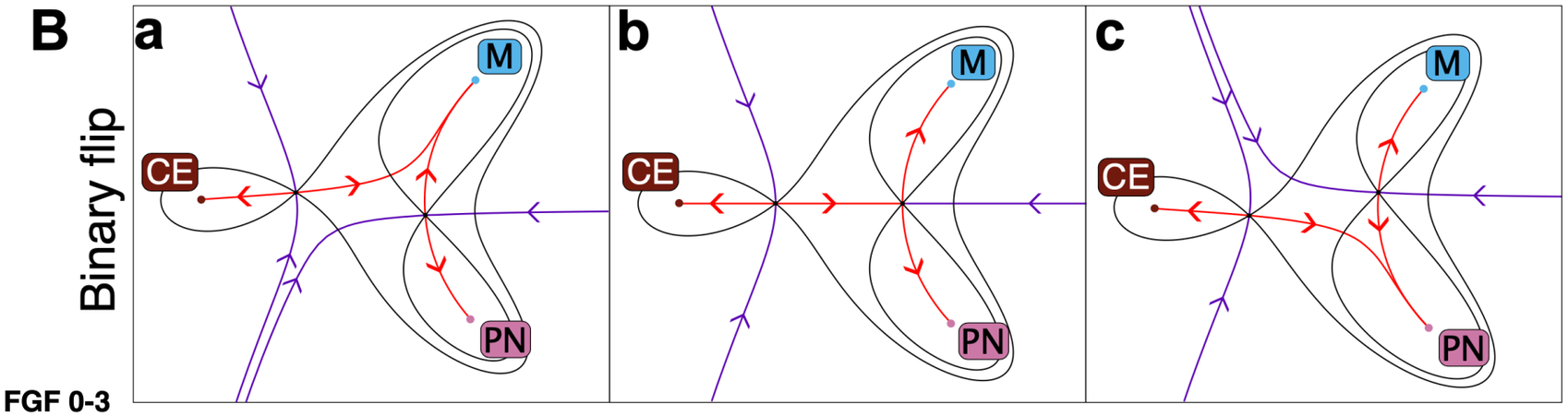


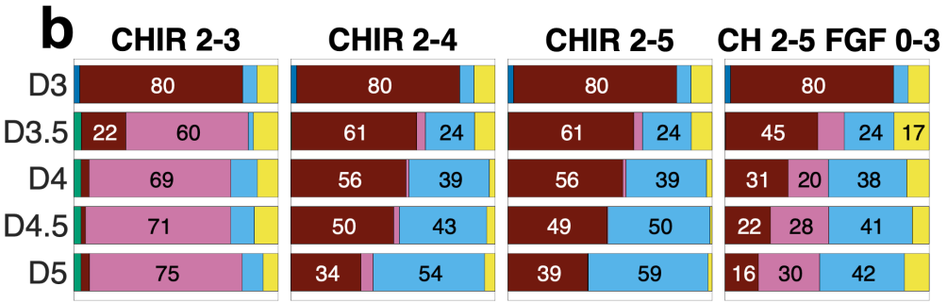


Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Cell differentiation is governed by two distinct binary cell fate decisions



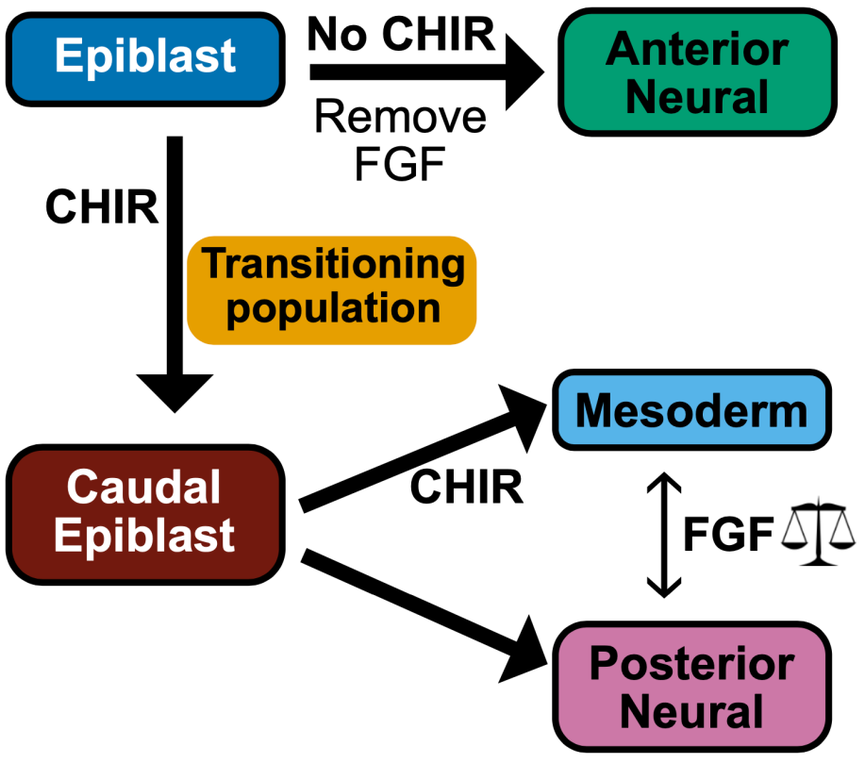




Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

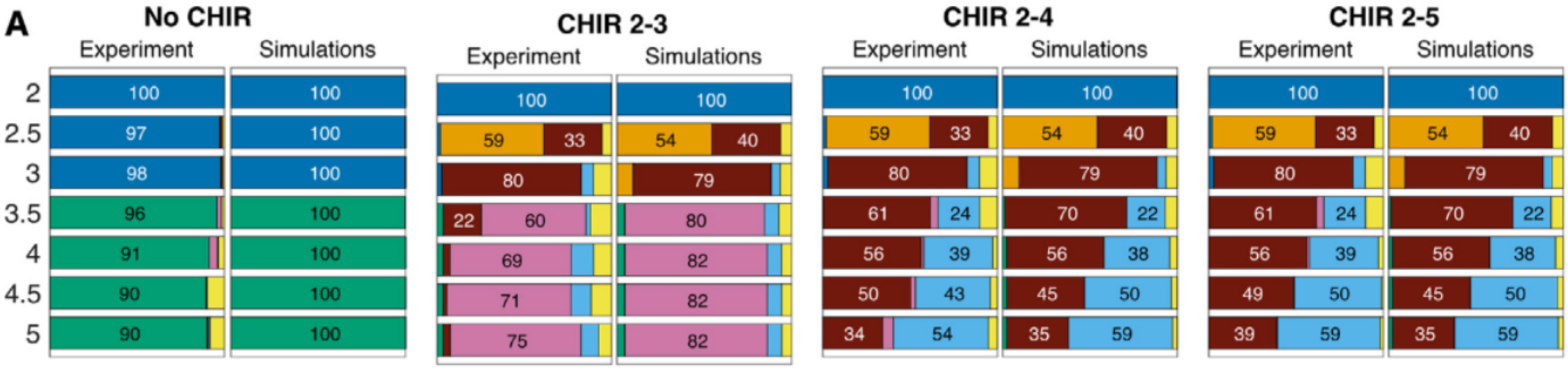
The final model merges the two binary fate decisions

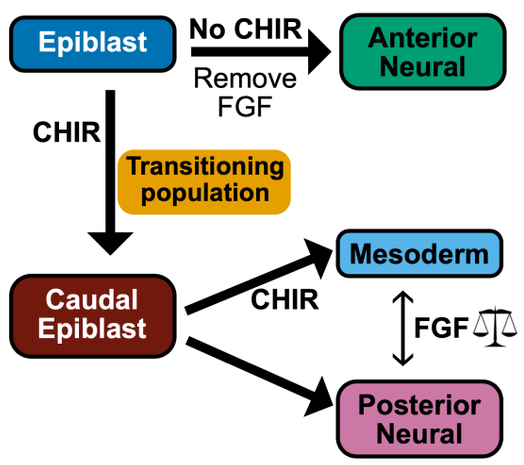
B

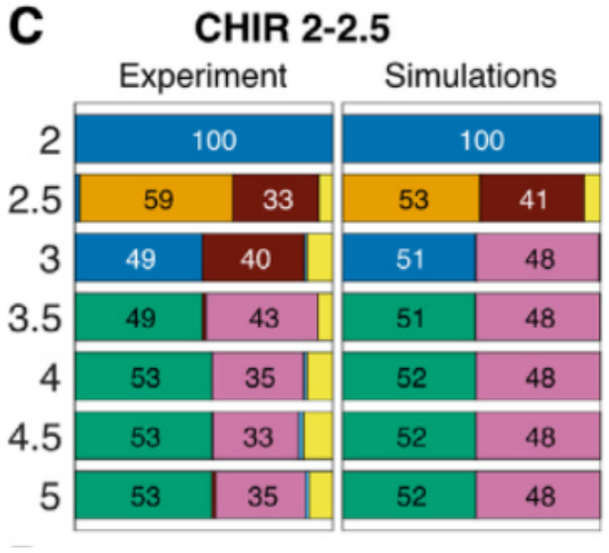


Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Fitted landscape captures cell fate decisions

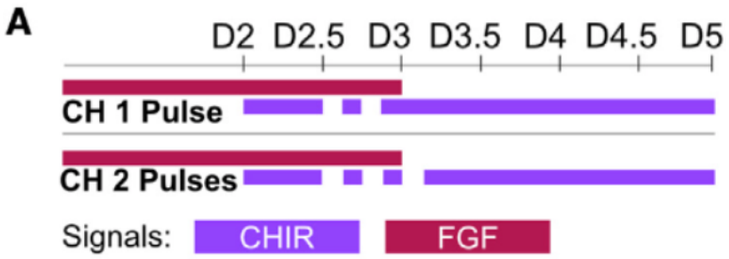


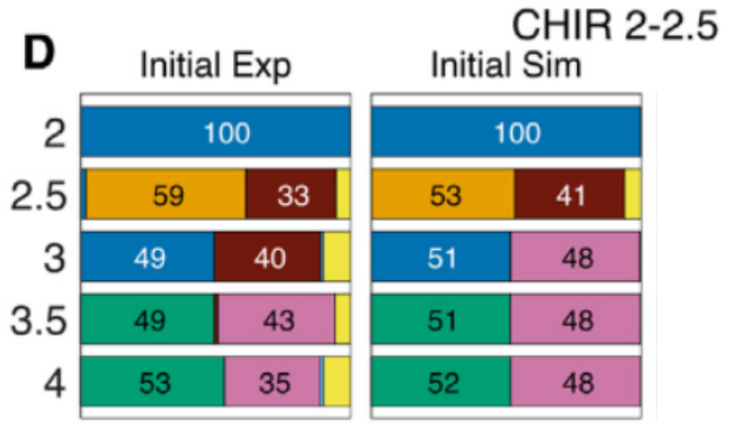




Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

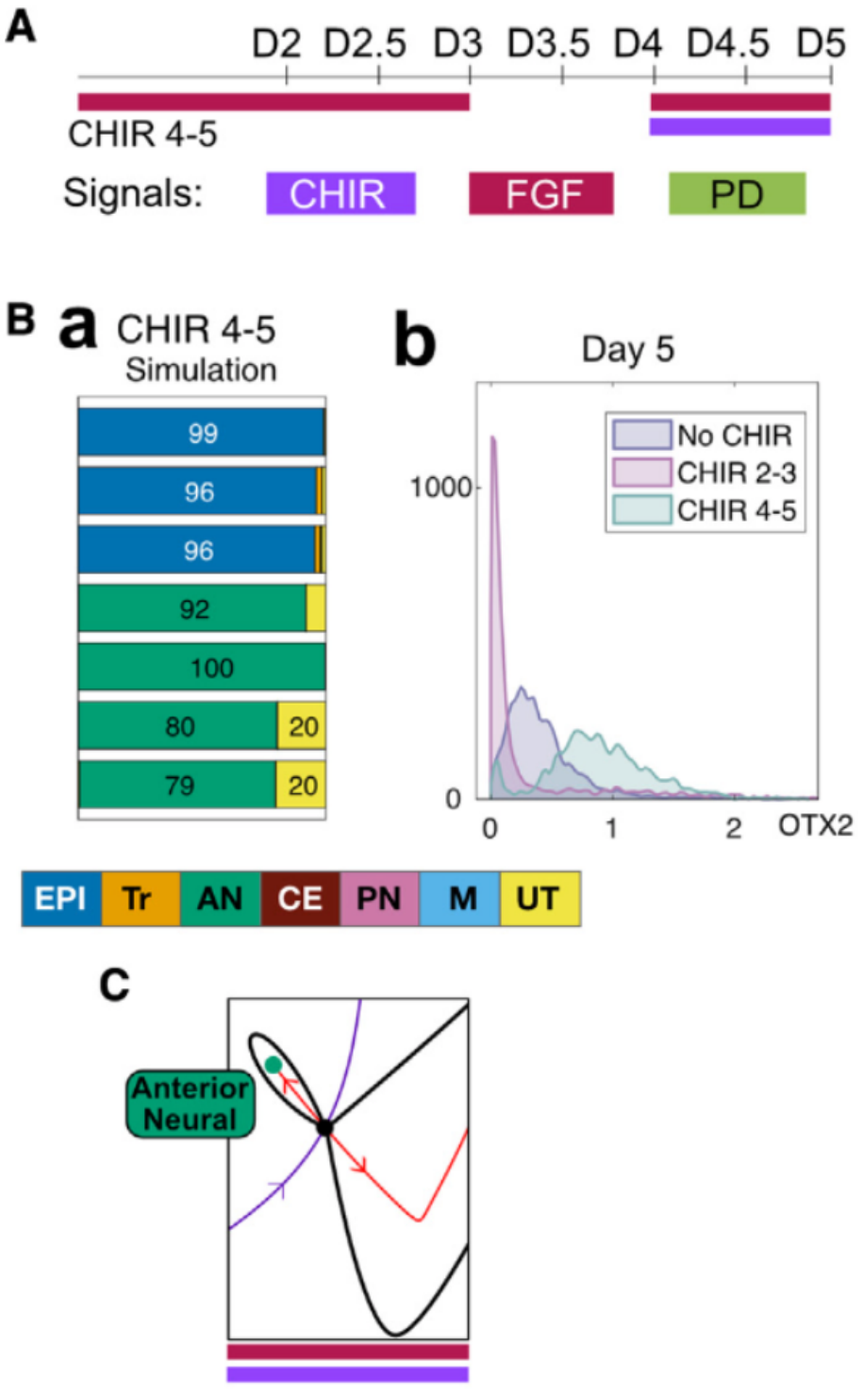
Refined model accurately recapitulates experimental data





Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Quantitative predictions test the accuracy of the landscape



Sáez M*, Blassberg R*, Camacho-Aguilar E*, Siggia ED, Rand DA, Briscoe J. (2022) Statistically derived geometrical landscapes capture principles of decision-making dynamics during cell fate transitions. Cell Systems Sep 11:S2405-4712(21)00336-7. doi: 10.1016/j.cels.2021.08.013

Thanks to…

David A. Rand
Giorgos Minas

Eric D. Siggia
Francis Corson

Michael Stumpf

James Briscoe
Robert Blassberg
Meritxell Saez

Warmflash Lab

Aryeh Warmflash
Miguel Ángel Ortiz Salazar
Cecilia Guerra
Xiangyu Kong
Idse Heemskerk (curr. U. Michigan)
Joseph Massey
Sapna Chhabra
Lizhong Liu
George Britton
Eleana Rizou
Ye Zhu
Siqi Du
Alena Streletskaia
Luisa Rezende
Sumin Yoon
Grace Wang
Kevin Chen

WARWICK
THE UNIVERSITY OF WARWICK

UKRI Engineering and Physical Sciences Research Council

NSF

RICE UNIVERSITY

NIH National Institutes of Health
Turning Discovery Into Health

THE Welch FOUNDATION

SIMONS FOUNDATION

Thanks to…

CABD

Centro Andaluz de Biología del Desarrollo

CSIC
Consejo Superior de Investigaciones Científicas

Excelencia María de Maeztu
Agencia Estatal de Investigación

Sy(stem)s Developmental Biology Lab

systemsdevbiolab.com

Elena Camacho-Aguilar
Principal Investigator

Andrea Theodorou
Lab Technician

Grace Wang
Undergraduate Student (Co-supervised with Dr. Aryeh Warmflash)

Irene Carrero Castro
MSc Student (Co-supervised with Dr. Fernando Casares)

ALiS
Adaptable Living Systems

alis.es

Fernando Casares
(CABD)

Luciano Marcon
(CABD)

Juan Poyatos
(CNB)