

Systems Biology



# Modelos suaves a trozos de sistemas biológicos multi-escala

Elisa Domínguez Hüttinger

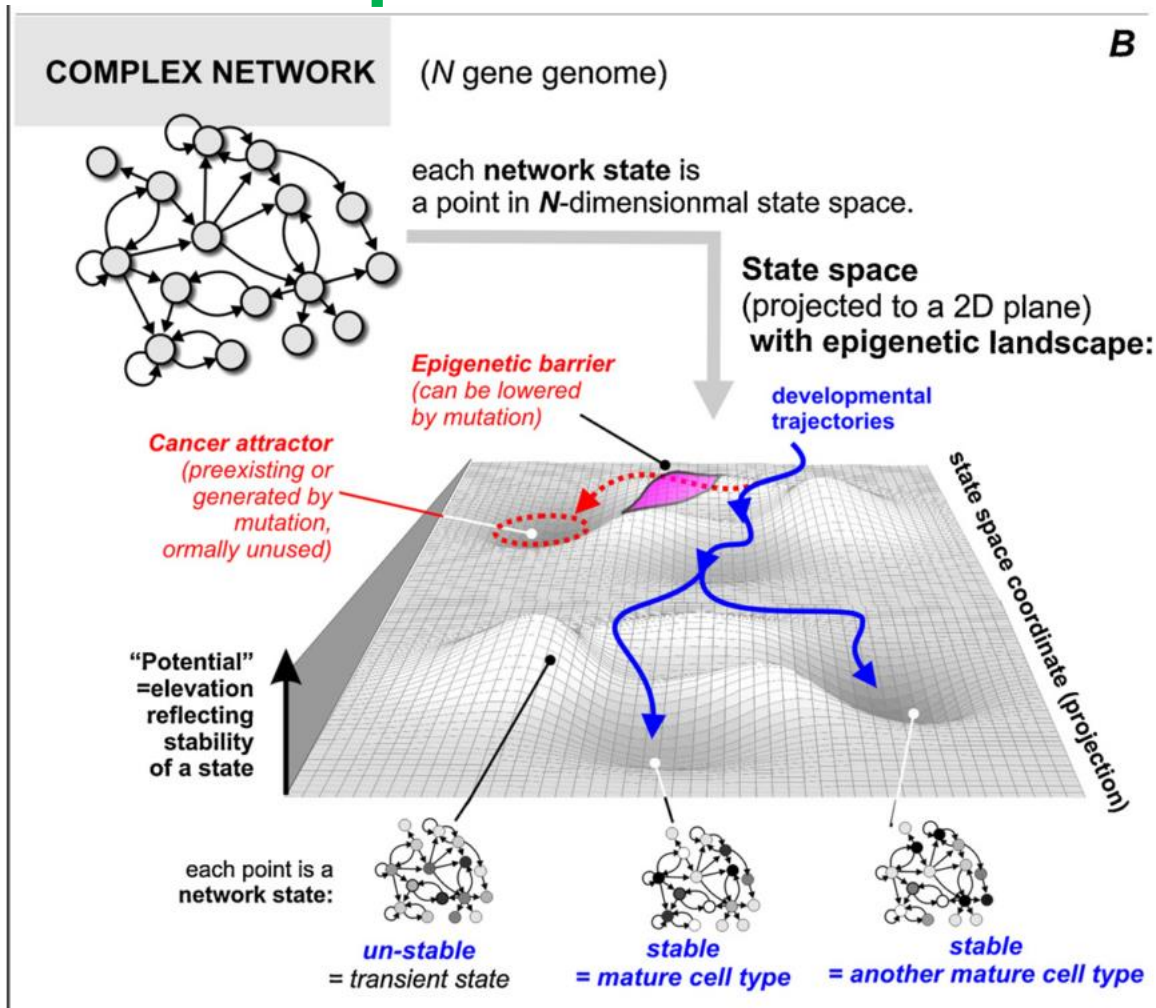
IIBO, UNAM

A photograph of a stage with red curtains pulled back, revealing a wooden floor. The scene is dimly lit, with a spotlight effect on the floor.

Primer acto:

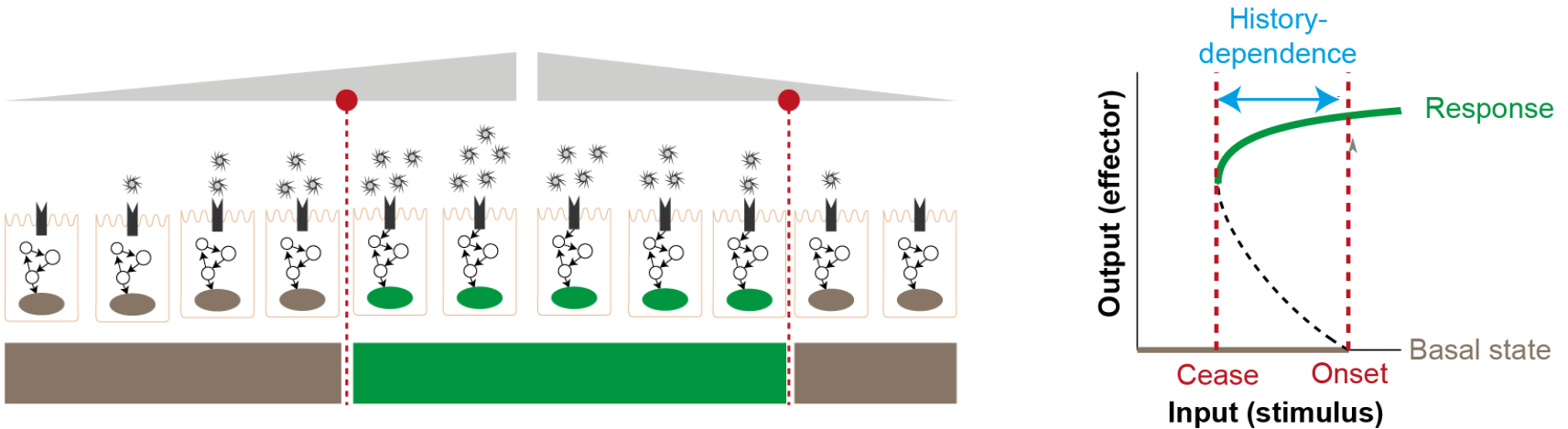
Multi-**estabilidad**  
y fragmentación  
del espacio fenotípico

# Fenotipos como atractores



S. Huang, I. Ernberg, and S. Kauffman, "Cancer attractors: A systems view of tumors from a gene network dynamics and developmental perspective," *Semin. Cell Dev. Biol.*, vol. 20, no. 7, pp. 869–876, 2009.

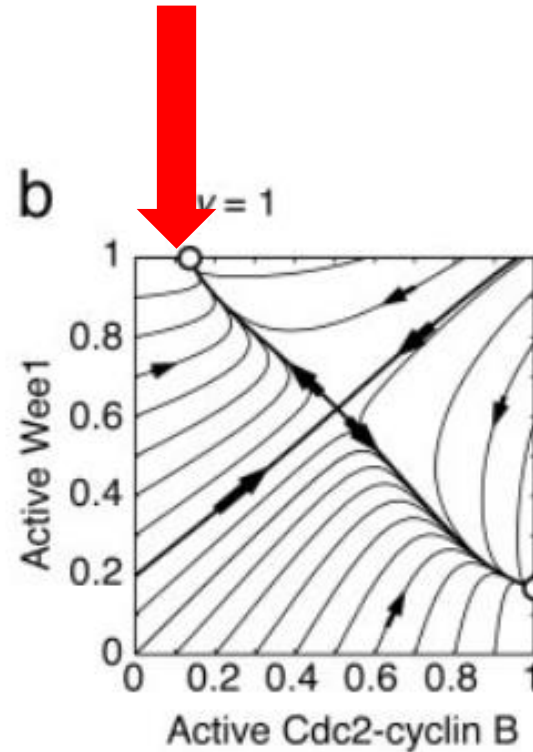
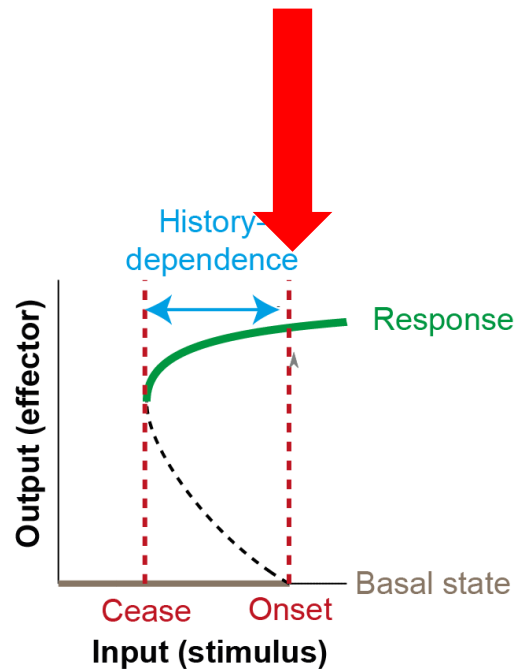
# Biestabilidad: El caso más sencillo de multi-estabilidad:



## Comportamiento tipo umbral

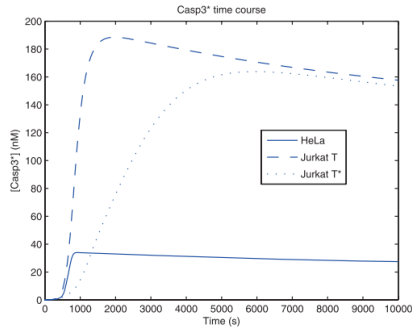
Decisiones fenotípicas abruptas en respuesta a estímulos (ambientales) continuos. Memoria

# Umbrales paramétricos y en el espacio fase



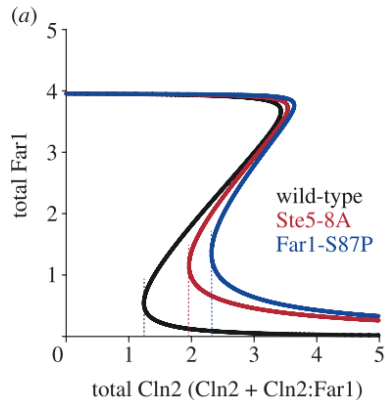
Angeli D, Ferrell JE, Sontag ED. Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems. PNAS 2004;101:1822–7.

# Una gran gama de decisiones fenotípicas están reguladas por redes que generan biestabilidad



- **Apoptosis:**

- Harrington HA, et al Theor Biol Med Model 2008 [cited 2012 Jun 22];5:26.
- Eissing T. J Biol Chem 2004;279.

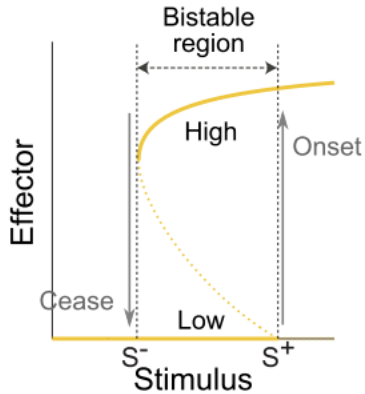


- **Entrada al ciclo celular:**

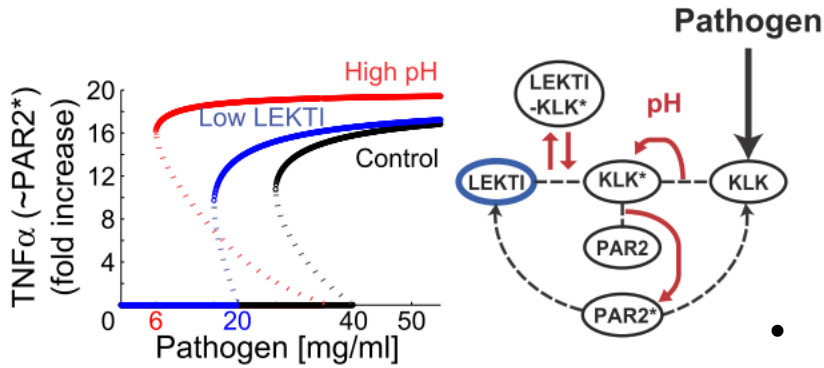
- Zhang, T., Schmierer, B., & Novak, B. (2011). Open Biology, 1, 110009–110009.

# Respuesta inmune ante estímulos ambientales

(A) Bistability

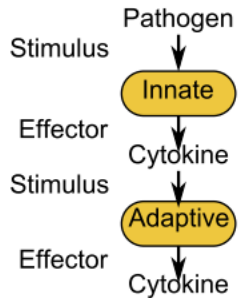


(C) Protease dependent innate immune reactions

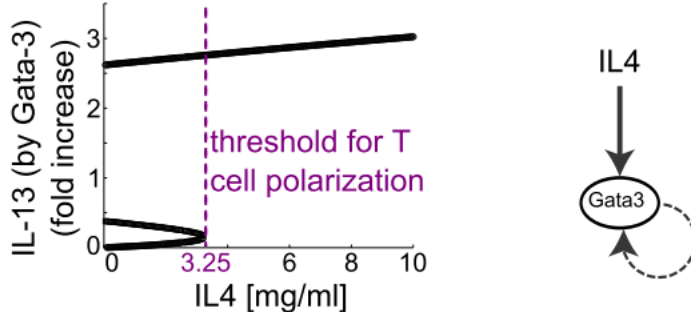


• Tanaka RJ et al PLoS One 2011

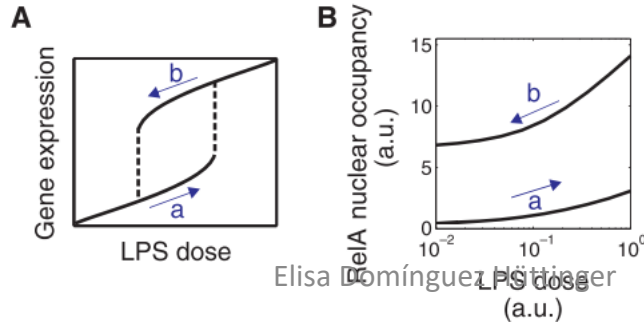
(B) Control of immune responses



(D) Gata-3 dependent adaptive immune responses



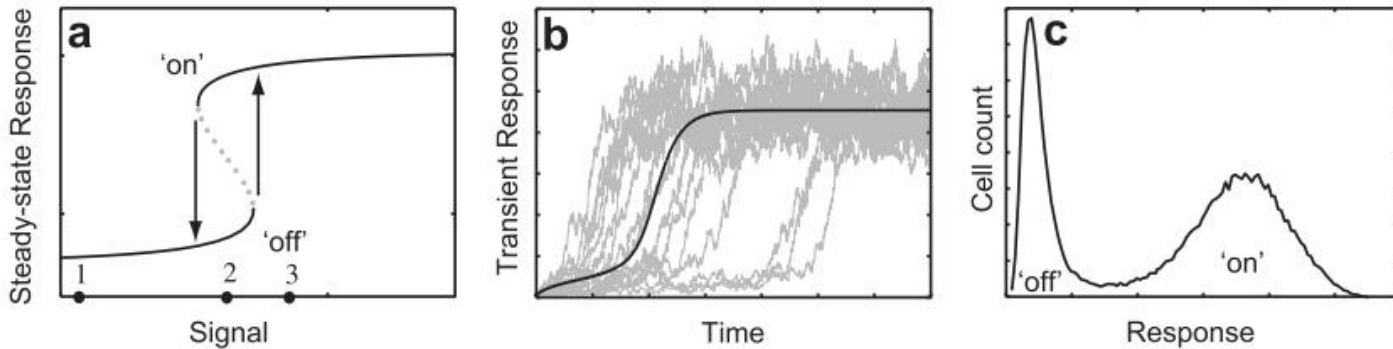
• Höfer T et al, 2002;99:9364–8.



• Sung MH, et al Sci Signal 2014;7:ra6.

# ¿Cómo se observa experimentalmente?

*O, ¿Qué sugiere que haya bi-estabilidad?*  
*Single cell: Distribuciones bimodales*

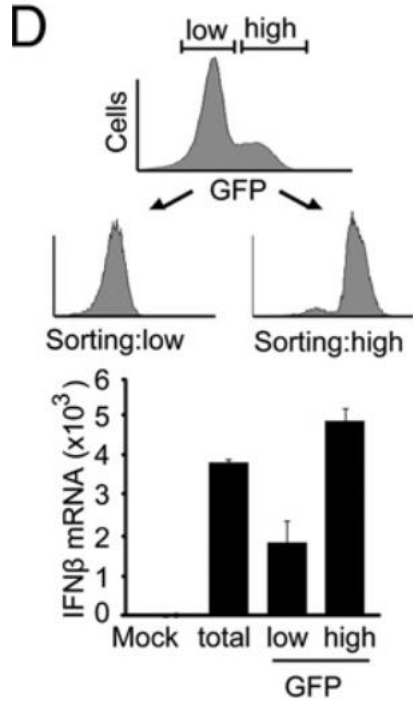


Tiwari A, Ray JCJ, Narula J, Igoshin O a. Bistable responses in bacterial genetic networks: designs and dynamical consequences. 2011, 31:76–89.

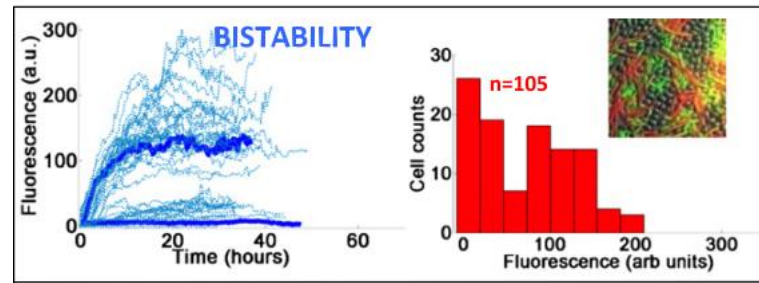
## Fragmentación del espacio fenotípico



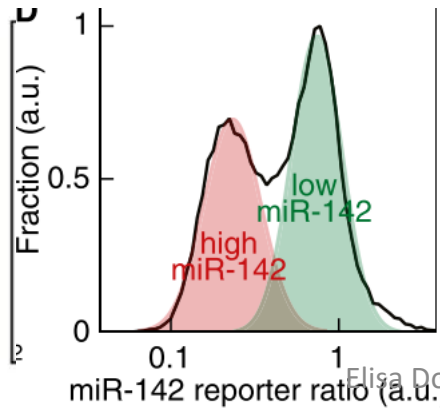
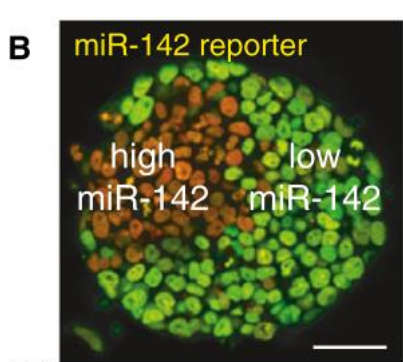
# Ejemplos de distribuciones bimodales



- Hwang S et al. Biphasic RLR – IFN-  $\beta$  Response Controls the Balance between Antiviral Immunity and Cell Damage. *J Immunol* 2013;190:1192–200.



- Espinar L, Dies M, Cagatay T, Suel GM, García-Ojalvo J. Circuit-level input integration in bacterial gene regulation. *PNAS* 2013;110.

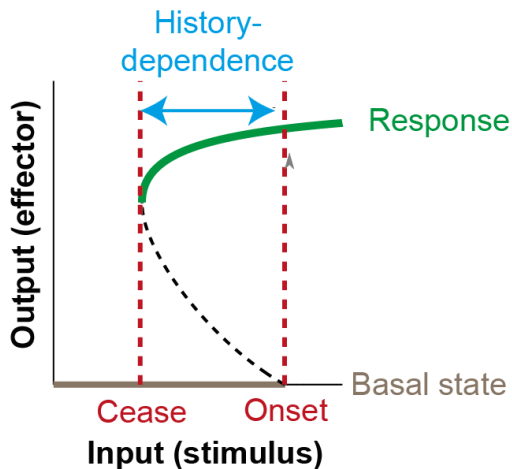


- Sladitschek HL, Neveu PA. The bimodally expressed microRNA miR- 142 gates exit from pluripotency. *Mol Syst Biol* 2015;1–16.

**Notas:** --Reproducción *in silico* de estas distribuciones: Versión estocástica  
 -- no todos los sistemas bimodales son biestables  
 -- To T-L, Maheshri et al, Science 2010

**¿Convencidos de la relevancia de un *switch*?**

# Diagramas de bifurcaciones: Suposición general: soluciones de **equilibrio**



$$\frac{d\bar{x}}{dt} = f(\bar{x}, input)$$

Encontrar las raíces **estables**  $x_1^{SS}, x_2^{SS}, \dots, x_n^{SS}$ , que satisfacen  $0 = f(x_k^{SS})$

(Más info: Strogatz S. Nonlinear dynamics and chaos. 2000.)

Análisis de cambios cualitativos en respuesta a  
**cambios en el parámetro de bifurcación**

# Grind.R

<http://theory.bio.uu.nl/rdb/grind.html>

The screenshot shows the homepage of the Grind.R website. At the top, there is a navigation bar with the University of Utrecht logo and the text 'Theoretical Biology & Bioinformatics'. Below this is a menu with 'About us', 'Education', 'Research', and 'Contact'. The main content area features a header image of a microscope slide with various yeast species names. Below the image is a profile for Rob J. de Boer, including a photo and a list of links: 'Home | Research | Publications | Books | Software | CV'. The 'Grind' section contains a detailed description of the software, its capabilities, and a list of functions: 

- `run()` integrates model numerically and provides a time plot or a trajectory in the phase plane.
- `phase()` draws nullclines and separatrices a vector field or phase portrait.
- `newborn()` finds steady states using the Newton-Raphson method and can provide the Jacobian with its eigenvalues and eigenvectors.
- `continue()` continues a steady state along a parameter, thus providing a bifurcation diagram.
- `fit()` fits an ODE model to data by estimating its parameters, and depicts the result as a bplot.

The text also mentions that the `run()` function will plot() from the database Rynkebeek, the `fit()` function will modify from fit, and `newborn()` and `continue()` will modify() from the respective package. It notes that `grind.R` functions have several options with well-chosen defaults (also for the state (x) and parameters (p) of the system), such that they are typically well-behaved when no options are provided. Using `library()` one can easily create webpages for analysing particular models using sliders for changing parameters (see a [LaTeX version example](#)). A note states that `grind.R` is in our course for biology students at Utrecht University because it allows them to easily analyse mathematical models, see their dynamical behavior on the screen, and export high quality graphics for reports. Researchers may also like `grind.R` because it allows them to easily define and study simple ODE models, add differential statements, read and write, and perform nonlinear parameter estimation while fitting several data sets simultaneously having unique and shared parameters (using the state of the art environment R). A footer note mentions that a tutorial, the `grind.R` script and a number of examples can be downloaded from the [tutorials](#). The final note states that `grind.R` is basically an extension of an earlier program called `GRIND`, the installation instructions of `GRIND` are still available on the [web page](#) for `GRIND`. See the [page](#) for a translation of `GRIND` commands into `Grind`.

On the right side of the page, there is a 'Research groups' section with a list of groups: 'De Boer group', 'Snel group', 'Hogeweg group', 'Kamir group', 'Hamman group', 'Tea Tusscher group', 'Dutilh group', and 'Bontrou group'. A 'CONTACT' button is located at the bottom right of the main content area.

## Ejercicio 1:

Analizando la “forma normal biológicamente plausible de un sistema bi-estable”

### 1 Construcción y análisis de un sistema multiestable - equivalente continuo

Las células T se diferencian de manera irreversible. Este proceso es controlado por el regulador transcripcional maestro, Gata3, que es inducido por citocinas pro-inflamatorias, como IL4. En 2002, Höfer *et al* [1] propusieron el primer modelo matemático que describe este proceso, con un modelo matemático muy sencillo, representado en la ecuación [1]

$$\frac{d[\text{Gata3}(t)]}{dt} = \alpha[\text{IL4}] + \frac{\kappa_G[\text{Gata3}(t)]^2}{1 + [\text{Gata3}(t)]^2} - \kappa[\text{Gata3}(t)]. \quad (1)$$

Considerando los parámetros nominales de [1] ( $\alpha = 0.02$ ,  $\kappa_G = 5$ ,  $\kappa = 1$ ):

1. Describe con tus palabras las reacciones consideradas en este modelo. **Hint:** Puedes empezar dibujando a Gata3 como nodo de una red, con aristas de entrada y de salida.
2. Integra numéricamente la ecuación [1] considerando diferentes condiciones iniciales  $\text{Gata3}(0)$ , primero para un valor de  $\text{IL4}=1$ , y posteriormente, para  $\text{IL4}=5$ . Discute tus resultados.
3. Construye el diagrama de bifurcación de Gata3 (estado estacionario) en función del parámetro de bifurcación  $\text{IL4}$  (considerando el rango  $\text{IL4} = [0, 10]$ ). Puedes hacerlo de manera analítica, usando `Mathematica`, o numérica, usando `Grind.R`. Discute tus resultados.
4. ¿qué diferencias/similitudes encuentras con la ecuación 1 de [2]?

A minimal model of an ecosystem showing hysteresis describes the change over time of an 'unwanted' ecosystem property  $x$ :

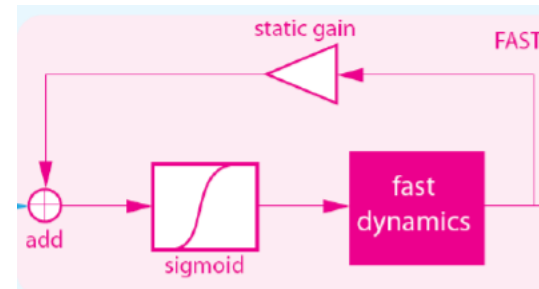
$$dx/dt = a - bx + rf(x) \quad (1)$$

The parameter  $a$  represents an environmental factor that promotes  $x$ . The remainder of the equation describes the internal dynamics:  $b$  represents the rate at which  $x$  decays in the system, whereas  $r$  is the rate at which  $x$  recovers again as a function  $f$  of  $x$ . For lakes, one can think of  $x$  as nutrients suspended in phytoplankton causing turbidity, of  $a$  as nutrient loading, of  $b$  as nutrient removal rate and of  $r$  as internal nutrient recycling<sup>12</sup>. For desertification, one could interpret  $x$  as barren soil,  $a$  as vegetation destruction,  $b$  as recolonization of barren soil by plants and  $r$  as erosion by wind and runoff<sup>58</sup>.

For  $r = 0$ , the model has a single equilibrium at  $x = a/b$ . The last term, however, can cause alternative stable states, for example, if  $f(x)$  is a function that increases steeply at a threshold  $h$ , as in the case of the Hill function:

$$f(x) = x^p / (x^p + h^p)$$

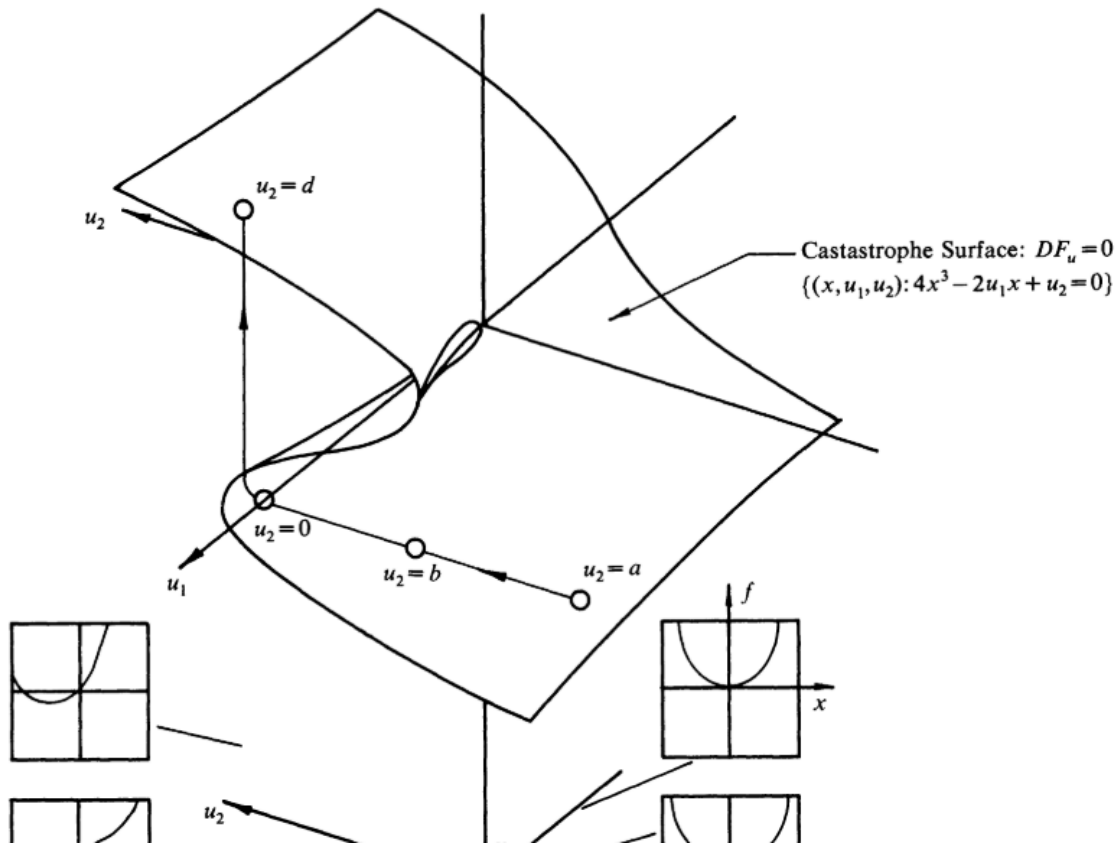
where the exponent  $p$  determines the steepness of the switch occurring around  $h$ . Notice that (1) can have multiple stable states only if the maximum  $\{rf'(x)\} > b$ . Thus, steeper Hill functions (resulting



**Table 1 Characteristics of some major ecosystem state shifts and their causes**

Ecosystem	State I	State II	Events inducing shift from I to II	Events inducing shift from II to I	Suggested main causes of hysteresis	Factors affecting resilience
Lakes	Clear with submerged vegetation	Turbid with phytoplankton	Killing of plants by herbicide Killing of <i>Daphnia</i> by pesticide	Killing of fish Low water level	Positive feedback of plant growth Trophic feedbacks	Nutrient accumulation
Coral reefs	Corals	Fleshy brown macroalgae	High water level Killing of coral by hurricane Killing of sea urchins by pathogen	Unknown	Prevention of coral recolonization by unpalatable adult algae	Nutrient accumulation Climate change Fishing
Woodlands	Herbaceous vegetation	Woodlands	Fires Tree cutting	Killing of grazers by pathogen Hunting of grazers	Positive feedback of plant growth Inedibility of adult trees	Overgrazing Climate change
Deserts	Perennial vegetation	Bare soil with ephemeral plants	Climatic events Overgrazing by cattle	Climatic events	Positive feedback of plant growth	Climate change
Oceans	Various	Various	Climatic events	Climatic events	Physical	Fishing Climate change

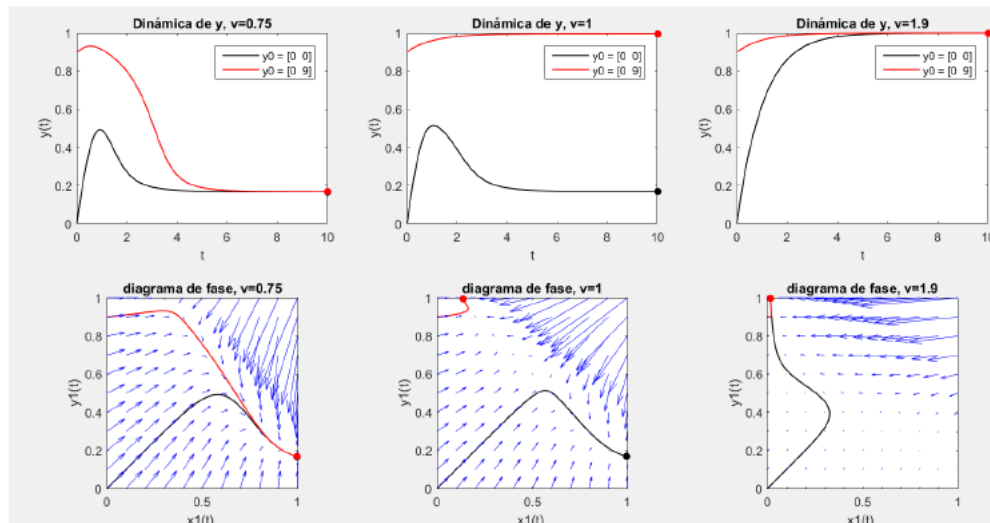
# Notas sobre reversibilidad



Auer JW. Mathematical Prelimiaries to Elementary Catastrophe Theory. Math Mag 1980;53:13–20.

# Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems

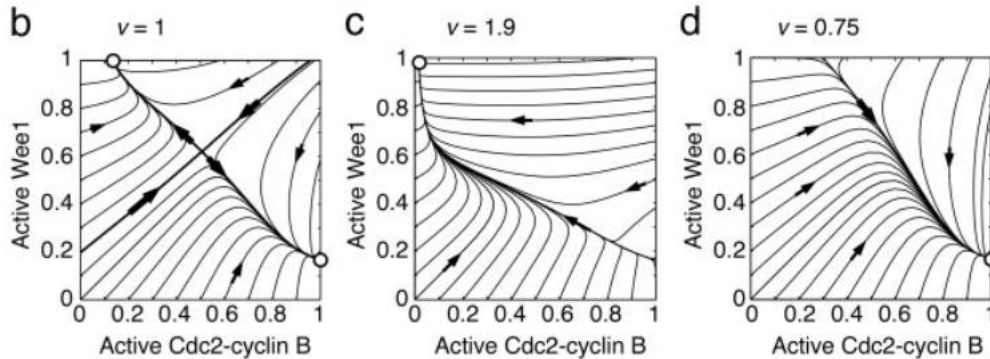
David Angeli\*, James E. Ferrell, Jr.<sup>†</sup>, and Eduardo D. Sontag<sup>‡§</sup>



(Figuras hechas en matlab: PracticaAngeli.m; lo mismo obtendrán con Practica\_2\_ODEs\_Angeli.r).

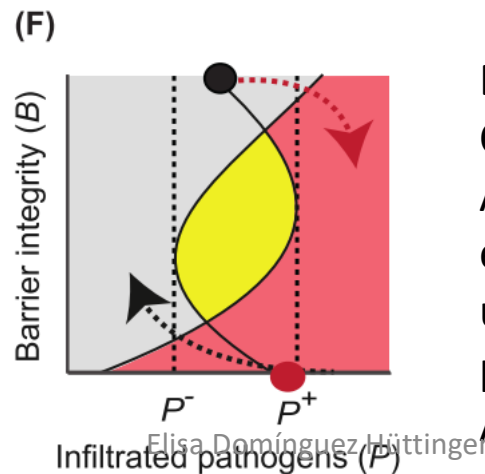
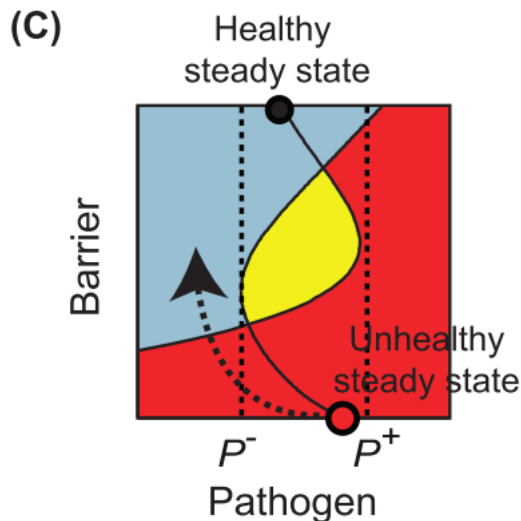


# Cuencas de atracción (tamaño, posición de separatriz) cambian conforme cambia el parámetro de bifurcación




- Cuencas de atracción (tamaño, posición de separatriz) cambian conforme cambia el parámetro de bifurcación

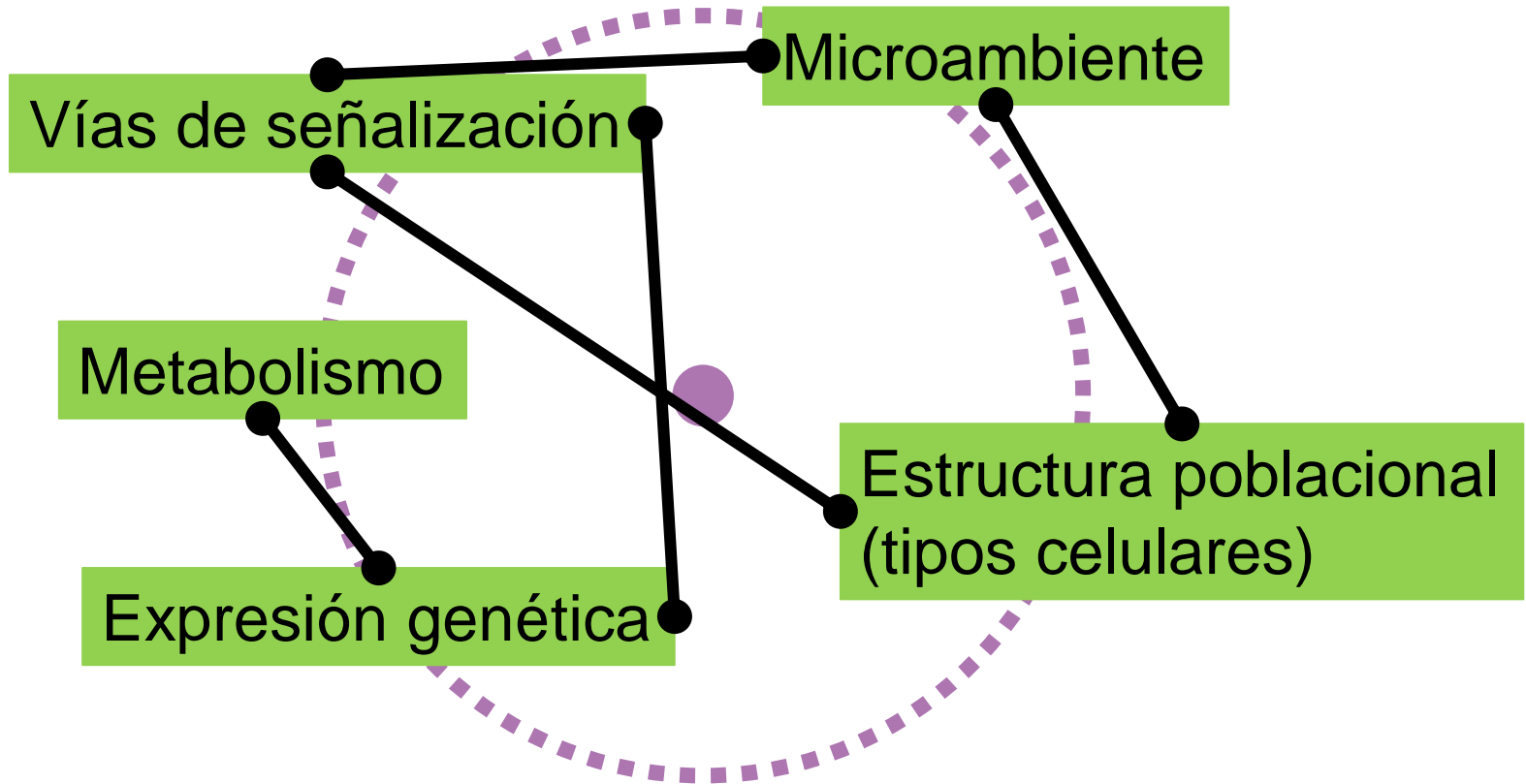
Angeli D, Ferrell JE, Sontag ED. Detection of multistability, bifurcations, and hysteresis in a large class of biological positive-feedback systems. PNAS 2004;101:1822–7.



Domínguez-Hüttinger E, Christodoulides P, Miyauchi K, Irvine AD, Okada-hatakeyama M, Kubo M, et al. “Double switch” mechanisms underlying onset, progression and prevention of atopic dermatitis. J Allergy Clin Immunol 2016; accepted

A photograph of a stage with red curtains pulled back, revealing a wooden floor. The scene is dimly lit, with a spotlight effect on the floor.

**Segundo acto:**  
**¿qué media el cambio en el  
parámetro de bifurcación?**

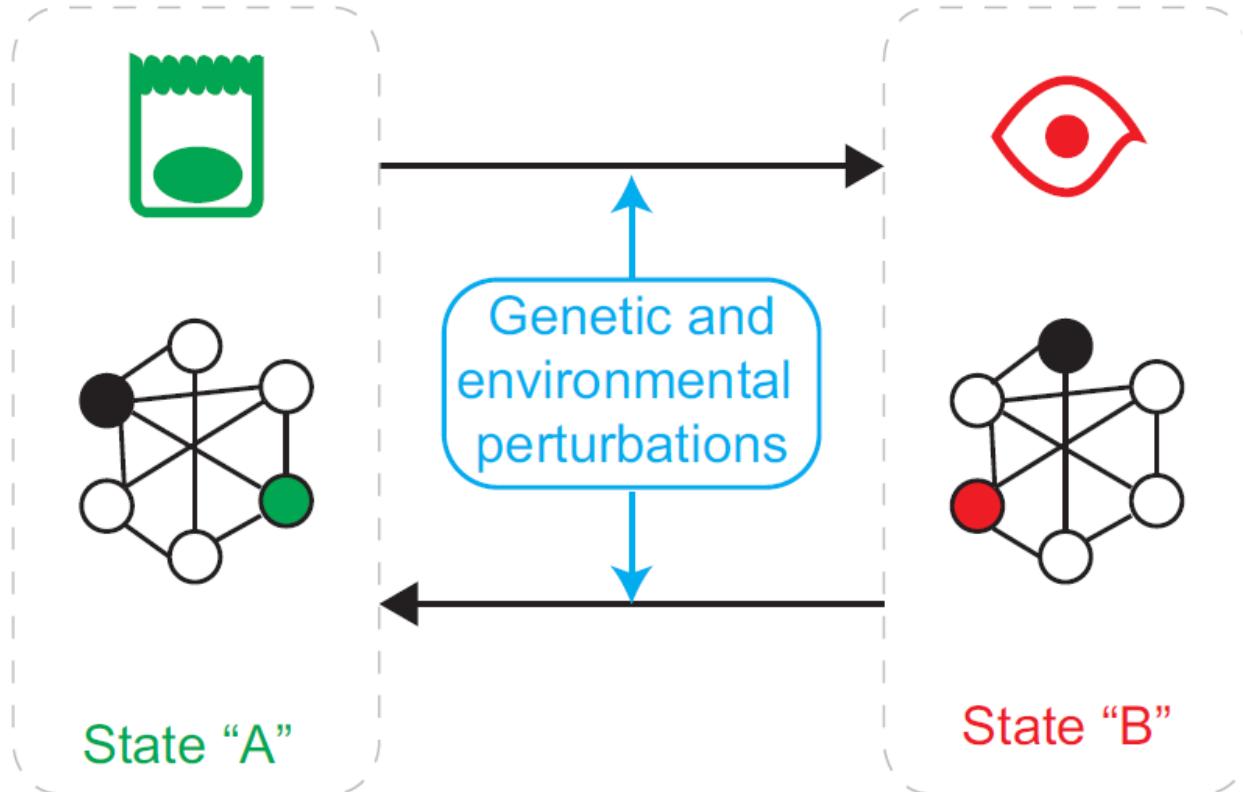


# Plasticidad fenotípica

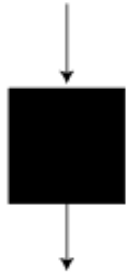
Decisiones fenotípicas (abruptas\*) en respuesta a medios ambientes cambiantes

Cellular phenotype

Underlying biochemical interaction network



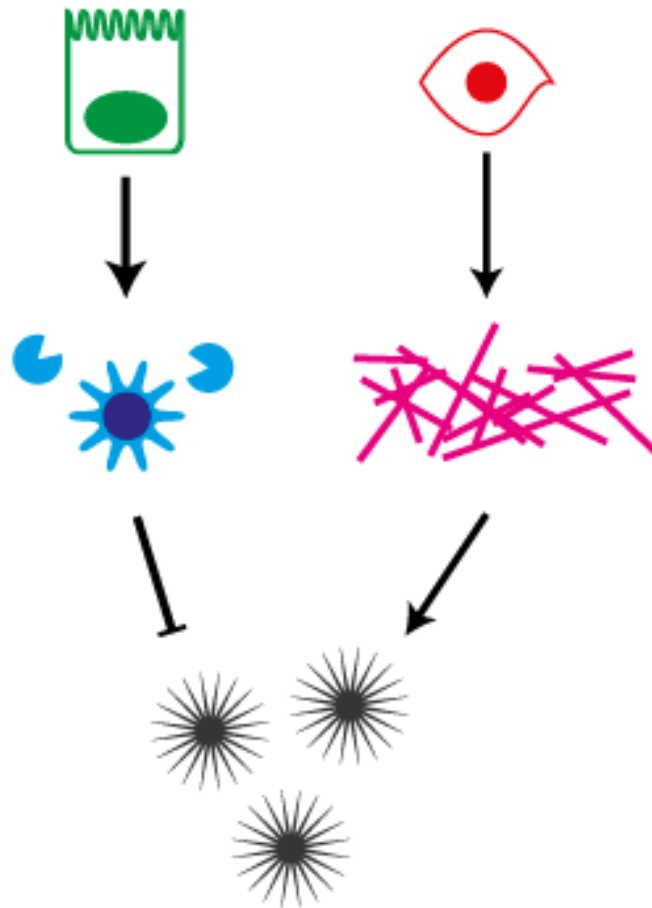
Input (stimulus)



Output: Phenotype

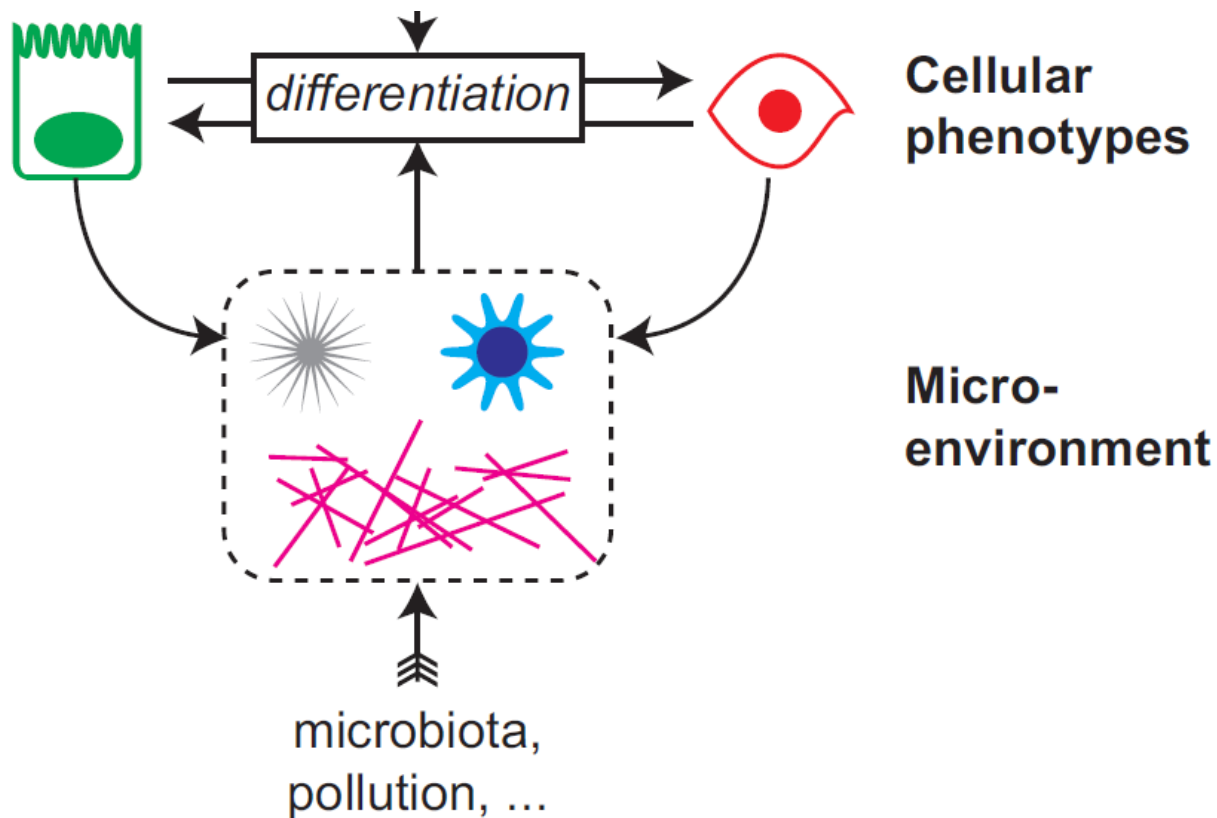
# Medio ambiente depende del fenotipo

(\*estructura fenotípica, propiedades colectivas)



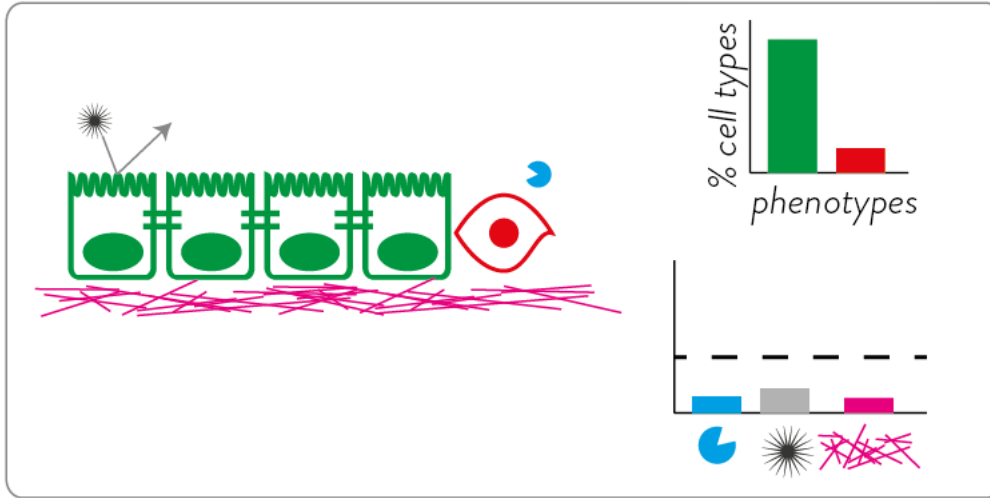
# Interacciones dinámicas entre fenotipo Y medio ambiente

*De principio a fin*

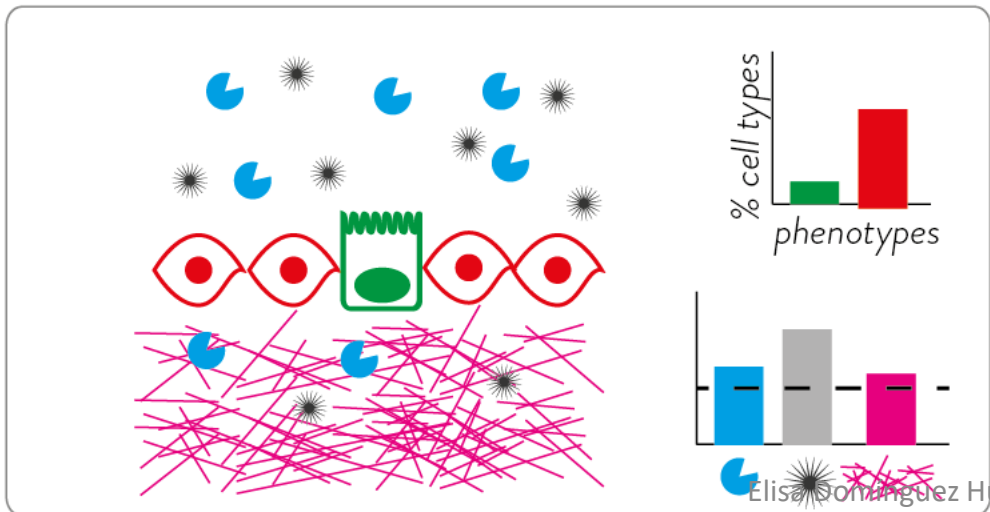


Reto:

# De descripción a explicación y predicción



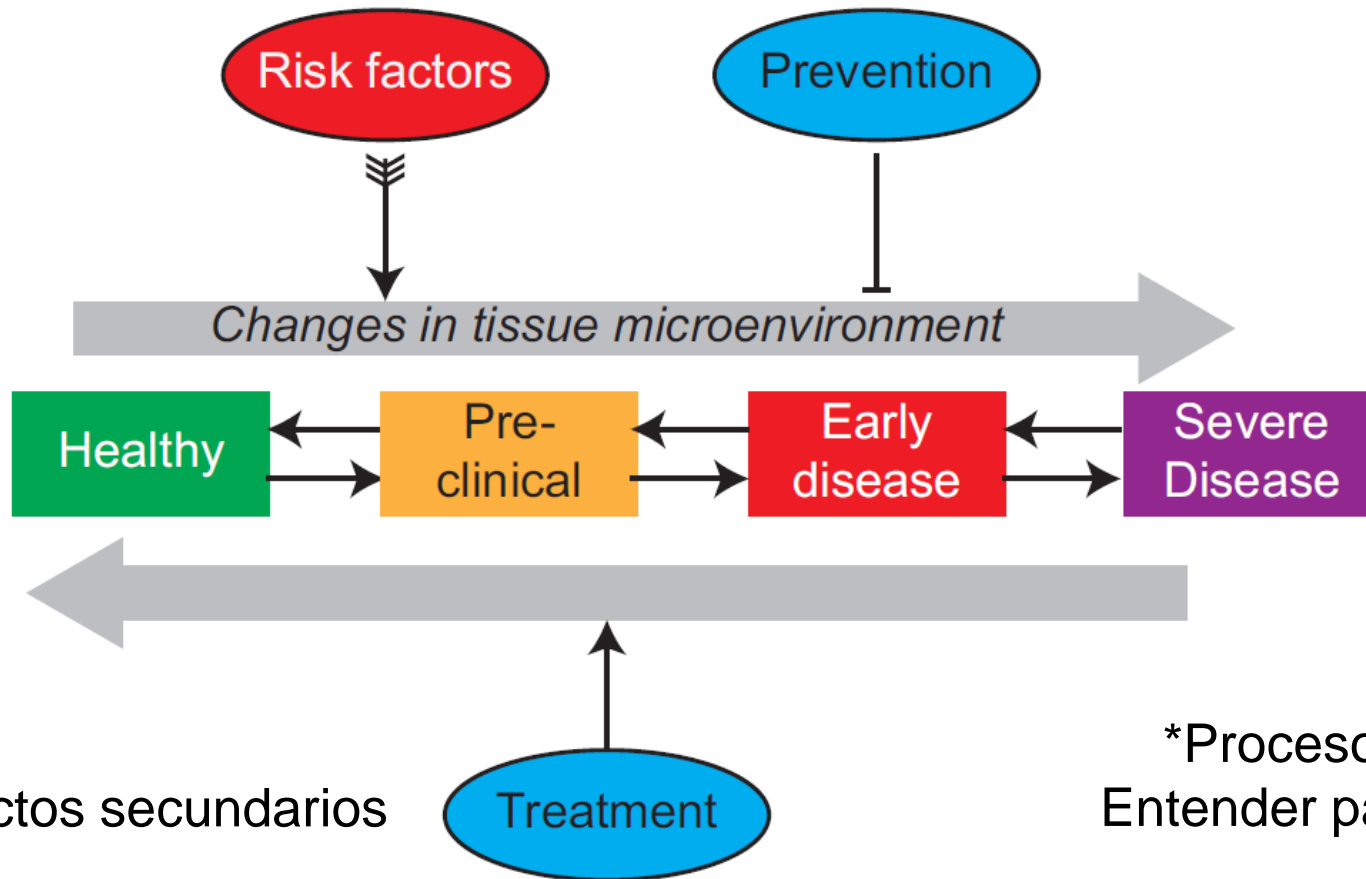
“Sano”



“Patológico”

# Relevancia clínica

Progresión de enfermedades:  
resultado de interacciones dinámicas entre fenotipos y microambientes

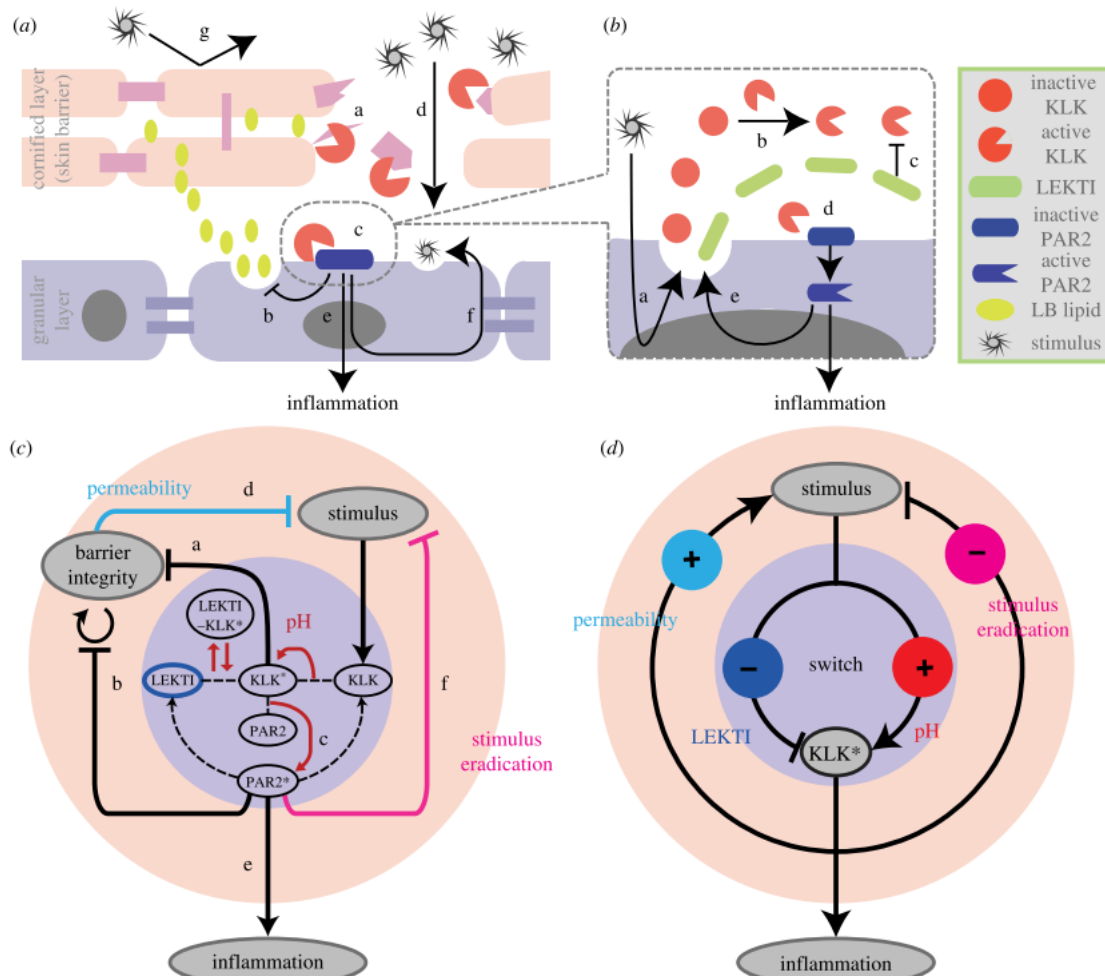


\*\*\* Efectos secundarios

\*Proceso **dinámico**:  
Entender para prevenir

\*\* Caracterización de estadios pre-clínicos: diagnóstico temprano

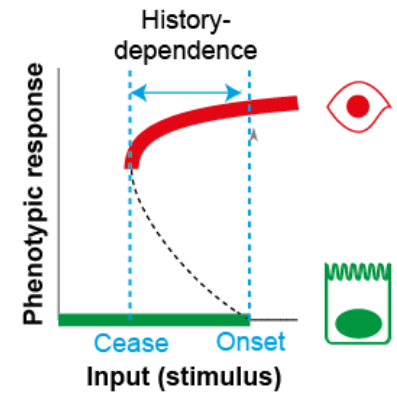
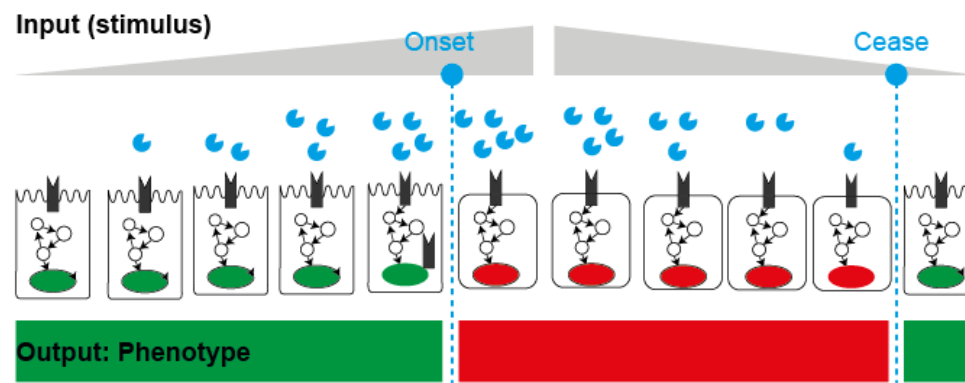
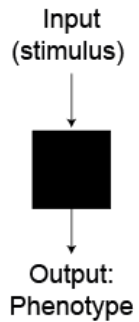




E. Domínguez-Hüttinger, M. Ono, M. Barahona, and R. J. Tanaka, “Risk factor-dependent dynamics of atopic dermatitis : modelling multi-scale regulation of epithelium homeostasis,” *Interface Focus*, vol. 3, no. February, p. 20120090, 2013.

# Ingrediente 1: Decisiones fenotípicas - abruptas y estacionarias

## Cellular decision-making



## Nota técnica:

### → Problema de matemático:

Dificultad de obtener una solución analítica de los puntos de equilibrio (sistemas con altos grados de no linealidad, i.e. polinomios de grado alto... Teorema de Abel (no hay solución para polinomios de grado mayor a 5)

→ Solución de ingeniero: Aproximación fenomenológica la solución algebraica

$$E(\tau) = \begin{cases} E_{low} & \text{if } (S(\tau) < S^-) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x < \tau) = E_{low}\} \\ E_{high} & \text{if } (S(\tau) > S^+) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x < \tau) = E_{high}\}. \end{cases}$$

# Ingrediente 2: Fenotipo modifica al microambiente

$$\dot{S}(\tau) = \begin{cases} F_{low}(S) & \text{if } E(\tau) = E_{low} \\ F_{high}(S) & \text{if } E(\tau) = E_{high}, \end{cases}$$



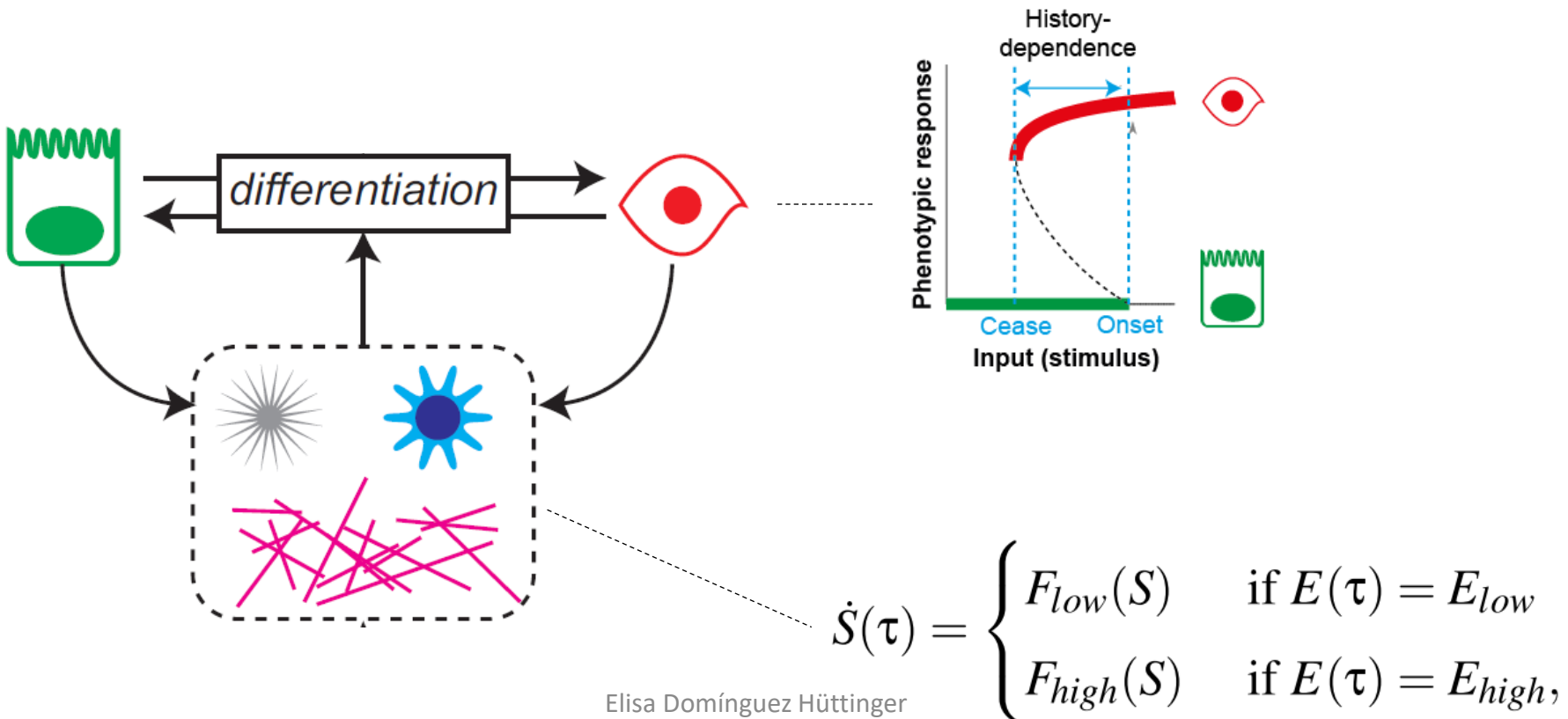
XOR



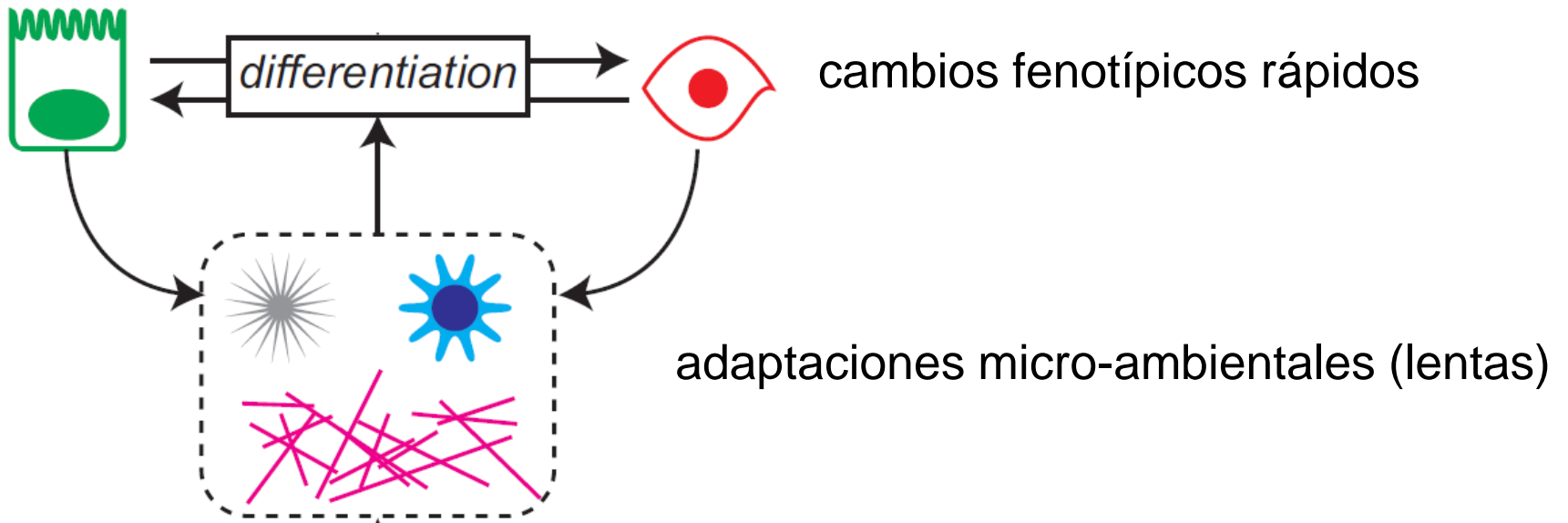
Formalismo: Ecuaciones diferenciales híbridas  
(Piecewise Affine Functions)  
*Poblaciones homogéneas*

# Ingrediente 3: acople fenotipo-microambiente

$$E(\tau) = \begin{cases} E_{low} & \text{if } (S(\tau) < S^-) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x < \tau) = E_{low}\} \\ E_{high} & \text{if } (S(\tau) > S^+) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x < \tau) = E_{high}\} \end{cases}.$$



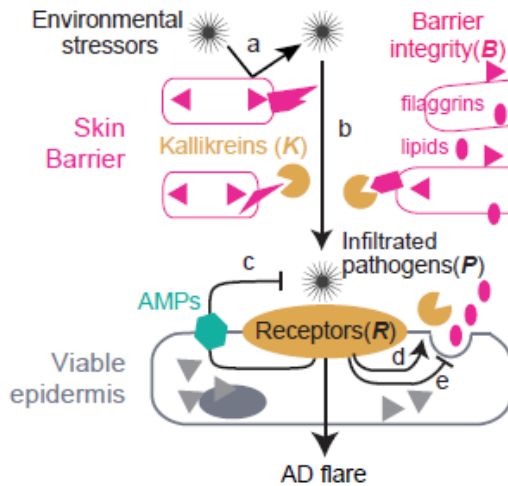
# Modelos multi-escala



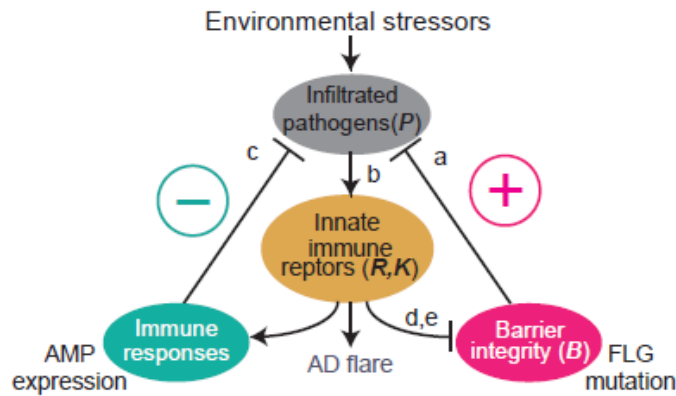
## Ejercicio 2:

Analizando un sistema híbrido – aproximación de diagrama de bifurcaciones por análisis de puntos focales e integración numérica con funciones localizadoras de eventos

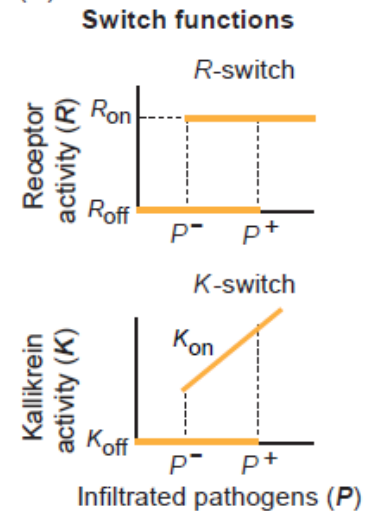
(A)



(B)



(C)



$$\frac{dP(t)}{dt} = \underbrace{P_{env} \frac{\kappa_P}{1 + \gamma_B B(t)}}_{\text{Infiltración de patógenos}} - \underbrace{\alpha_I R(t) P(t)}_{\text{muerte por antibióticos naturales}} - \underbrace{\delta_P P(t)}_{\text{muerte natural}}, \quad (2a)$$

$$\frac{dB(t)}{dt} = \underbrace{\frac{\kappa_B}{1 + \gamma_R R(t)} (1 - B(t))}_{\text{recuperación (representación fenomenológica)}} - \underbrace{\delta_B K(t) B(t)}_{\text{degradación por proteasas}} \quad (2b)$$

$$(R(t), K(t)) = \begin{cases} (0, 0) & \text{if } P(t) < P^- \text{ or } P^- \leq P(t) \leq P^+ \text{ and } R(t^-) = R_{off}, \\ (R_{on}, K_{on} = m_{on} P(t) - \beta) & \text{if } (P(t) > P^+) \text{ or } (P^- \leq P(t) \leq P^+ \text{ and } R(t^-) = R_{on}) \end{cases} \quad (3)$$

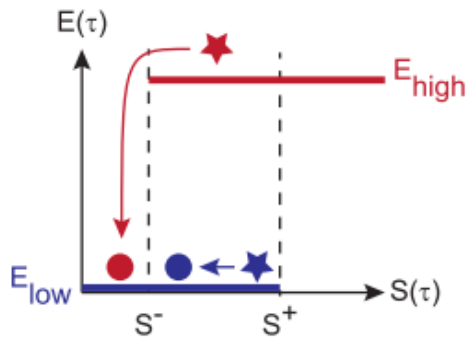
- El acople entre las ecuaciones diferenciales [2] y la ecuación algebraica [3] corresponde a un sistema híbrido, que presupone una separación de escalas temporales. ¿Cuáles son las variables del modelo que se asumen que cambian significativamente (de hecho, infinitamente) más rápido que las otras? ¿Es válida esta aproximación, asumiendo que se sabe que  $S(t)$  y  $B(t)$  cambian mucho más lentamente (de días a semanas) que  $R(t)$  y  $K(t)$  (minutos a horas)?
- ¿Por qué decimos que la recuperación de la barrera está modelada de manera fenomenológica? ¿Qué tipo de sistemas biológicos presentan (auto)recuperación, y cómo los modelarías? **Hint:** piensa en la adaptación perfecta.
- La ecuación [3] es una aproximación fenomenológica de un diagrama de bifurcación bi-estable. Haz un esquema de este diagrama de bifurcación, anotando los parámetros de bifurcación  $P^+$ ,  $P^-$ . ¿Qué tipo de sistemas biológicos presentan bi-estabilidad? Da un ejemplo de un modelo mecanista que presente este comportamiento.
- ¿Qué comportamientos cualitativos puede presentar el sistema híbrido, dado por ecuaciones [2] y [3]? ¿De qué depende? (**Hint:** piensa en los puntos focales de los sub-sistemas)
- Explora los efectos de alteraciones de  $\kappa_P$  y  $\alpha_I$  sobre el comportamiento a largo plazo del sistema híbrido. **Hint:** Usa  $\mathbb{R}$  para variar sistemáticamente los valores de estos dos parámetros de bifurcación,  $\kappa_P = [0, 1]$  y  $\alpha_I = [0, 0.3]$ . Empieza por escribir un *pseudocódigo*, en el que anotes cada uno de los pasos de tu algoritmo. Considera los parámetros  $P_{env} = 95$ ,  $\gamma_B = 1$ ,  $\delta_P = 1$ ,  $\kappa_B = 0.5$ ,  $\gamma_R = 10$ ,  $\delta_B = 0.1$ ,  $R_{on} = 16.7$ ,  $P^+ = 40$ ,  $P^- = 26.6$ ,  $m = 6.71$  y  $\beta = 6.71$
- Considera los parámetros:
  - $\kappa_P = .6$ ,  $\alpha_I = 0.25$
  - $\kappa_B = 0.6$ ,  $\alpha_I = 0.0325$
  - $\kappa_B = 0.9$ ,  $\alpha_I = 0.25$
  
  - $\kappa_B = 0.9$ ,  $\alpha_I = 0.0325$

Y las condiciones iniciales  $P(0) = 41$  o  $P(0) = 55$ ; y  $B(0) = 1$ . Dado tu análisis anterior, ¿qué comportamientos cualitativos esperas?

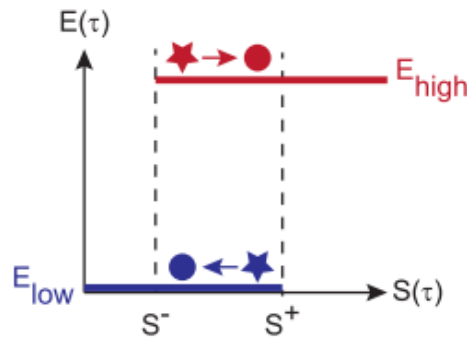


# Análisis de la estructura multi-escala, basado en la estabilidad de los puntos focales

(i) Homeostasis



(iii) Bistability



**Focal points**

●  $S_{ss}^{high}$

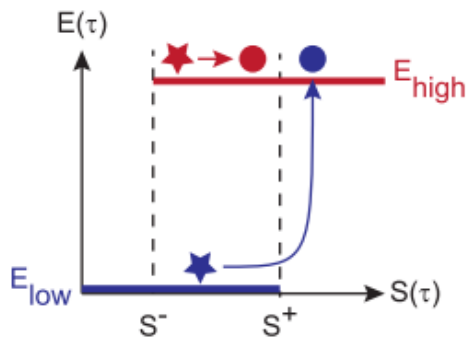
●  $S_{ss}^{low}$

**Initial conditions**

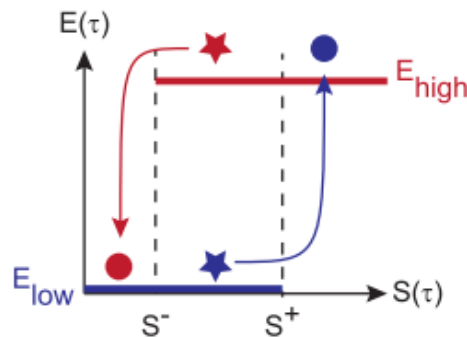
★  $S^{high}(0)$

★  $S^{low}(0)$

(ii) Chronic inflammation



(iv) Oscillations



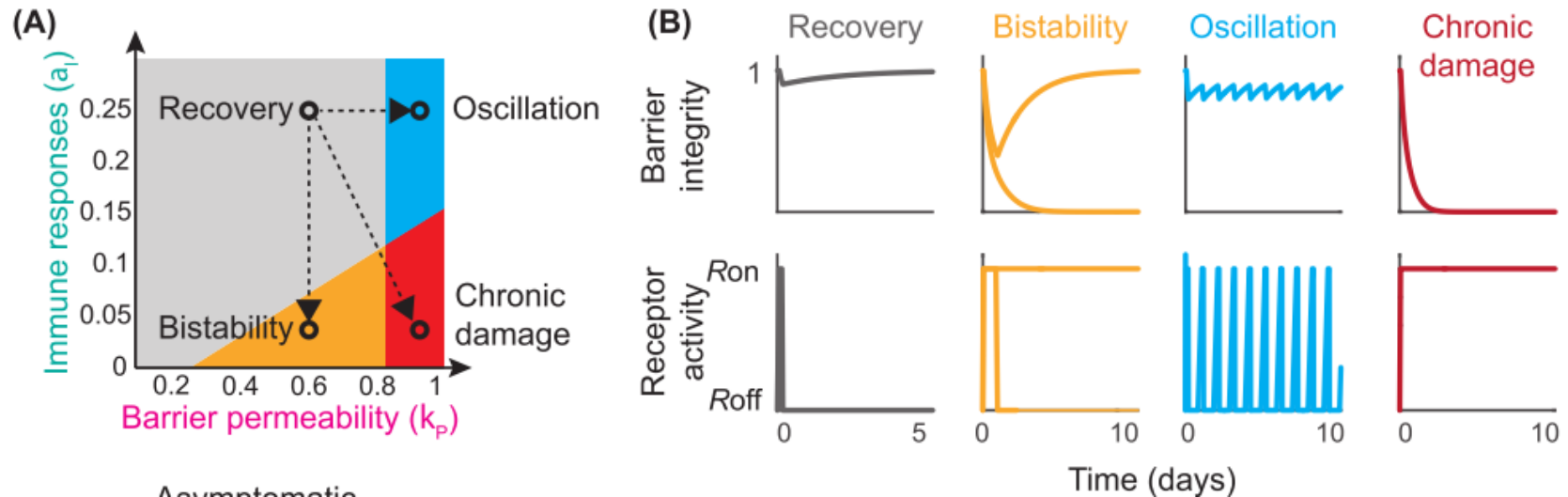
Domínguez-Hüttinger  
E;2015

**Basado en:**

Oyarzún D, Chaves M, Hoff-  
Hoffmeyer-Zlotnik M.JTB 2012 ;  
295:139–53.

$$E(\tau) = \begin{cases} E_{low} & \text{if } (S(\tau) < S^-) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x < \tau) = E_{low}\} \\ E_{high} & \text{if } (S(\tau) > S^+) \text{ or } \{S(\tau) \in [S^-, S^+] \text{ and } E(x < \tau) = E_{high}\}. \end{cases}$$

# Dinámicas emergentes de este tipo de estructuras (bifurcaciones emergen de la bifurcación - **Fragmentación del espacio fenotípico**)



E. Domínguez-Hüttinger, P. Christodoulides, K. Miyauchi, A. D. Irvine, M. Okada-hatakeyama, M. Kubo, and R. J. Tanaka, "Mathematical Modeling of Atopic Dermatitis Reveals 'Double switch' Mechanisms Underlying Four Common Disease Phenotypes," *J. Allergy Clin. Immunol.*, accepted.

Algunas puertas sólo se pueden acceder una vez que se ha atravesado otra puerta... (desde cierto espacio)



Convex and Concave. [M.C. Escher](#), 1955

# Decaimientos lentos y memoria.



Hokusai



Caspar David  
Friedrich



Turner