CENTRO DE CIENCIAS MATEMÁTICAS

Sistemas dinámicos no lineales para estudiar, prevenir y tratar enfermedades epiteliales complejas

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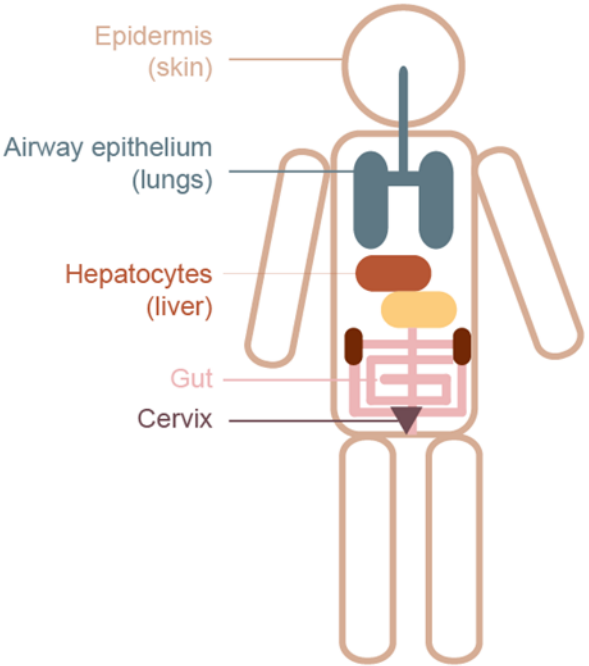
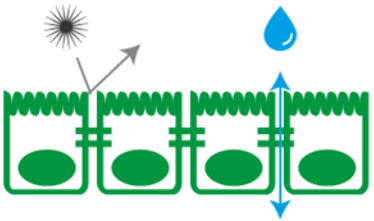
Centro de Ciencias Matemáticas
UNAM - Morelia

Febrero 2019

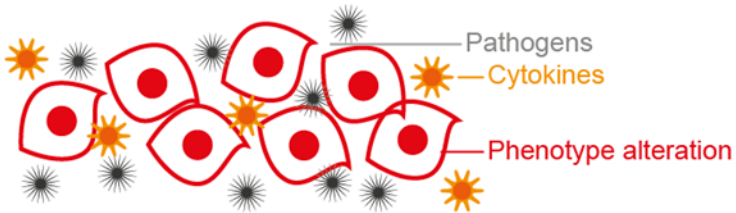
Systems Biology
CCM - UNAM

Epitelios





Regulated exchange with the environment
Protection agains aggressors



Inflammation, infection
Carcinoma

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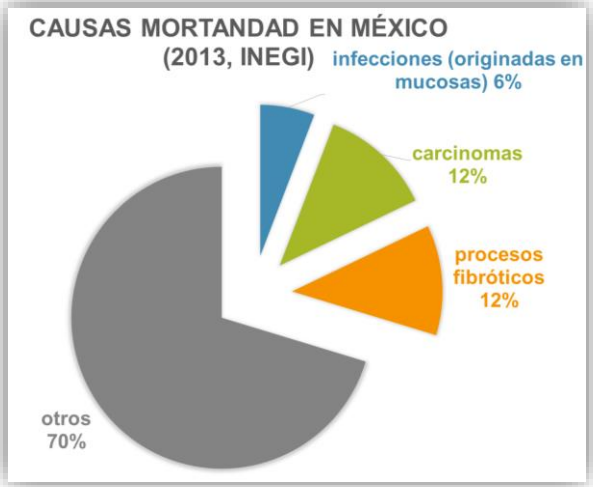
Urgencia de mejorar el entendimiento, diagnóstico, prevención y tratamiento de estas enfermedades

Muerte



Marcha atópica

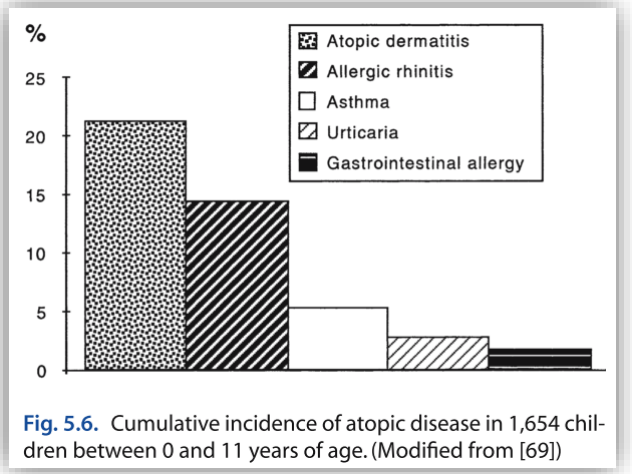


Fig. 5.6. Cumulative incidence of atopic disease in 1,654 children between 0 and 11 years of age. (Modified from [69])

Thomsen, S. F. *Eur. Clin. Respir. J.* **2,** 24642 (2015).

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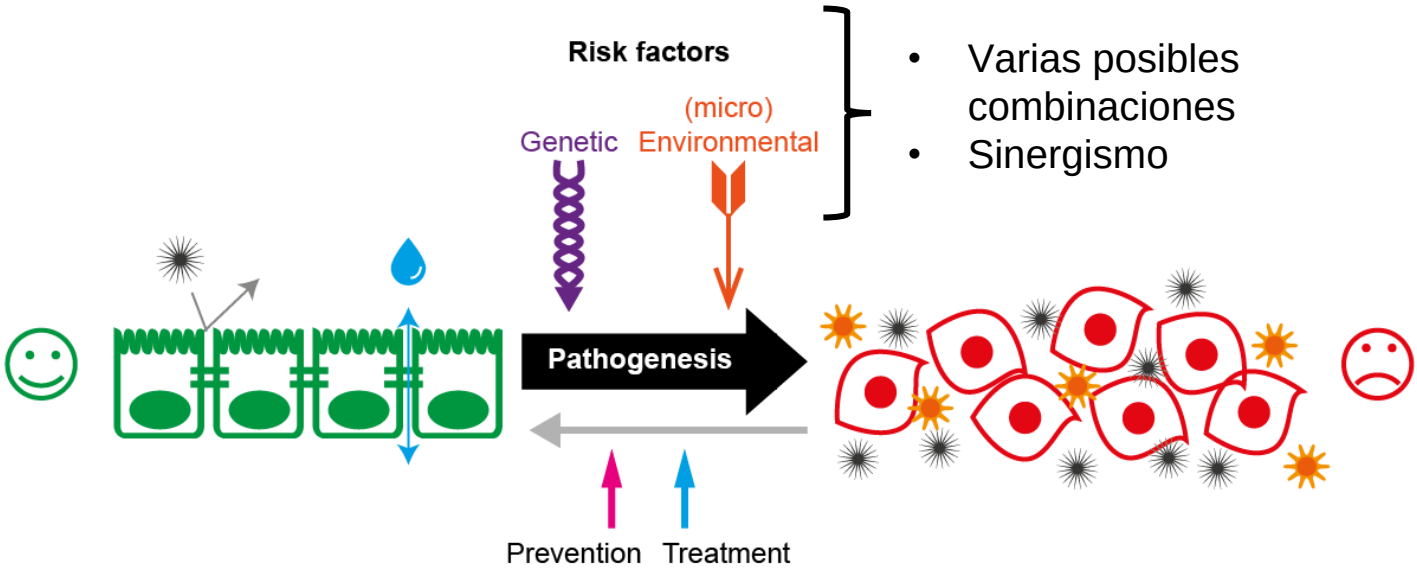
Enfermedades epiteliales complejas: retos



- Varias posibles combinaciones
- Sinergismo

- Progresión patológica gradual
- Estadios iniciales de difícil diagnóstico

Efectos secundarios no deseados

Entender, diagnosticar, prevenir, revertir (óptimamente)

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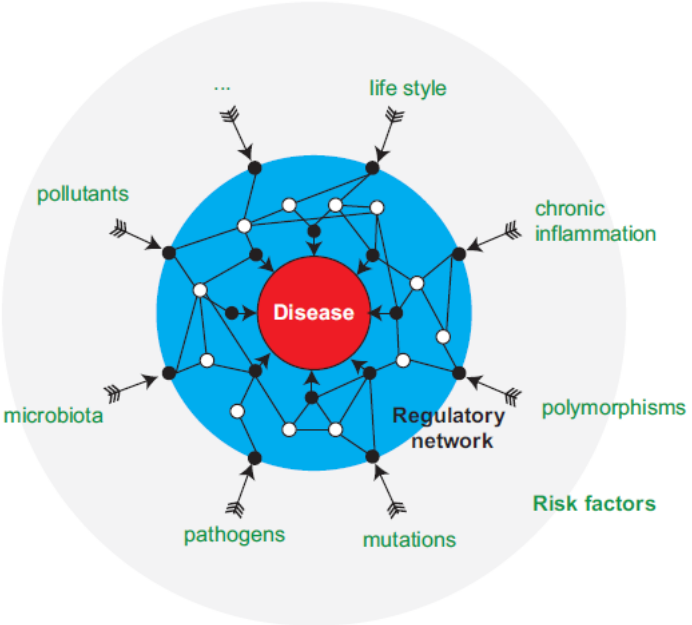
Propiedades emergentes de redes dinámicas de interacciones regulatorias



Propagación de perturbaciones / procesamiento de señales

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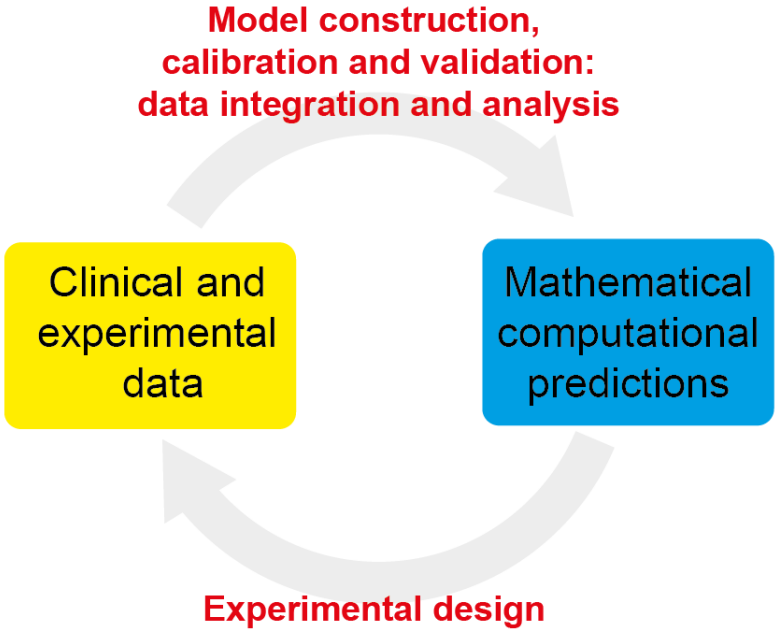
Biología de sistemas
~ biología de interacciones



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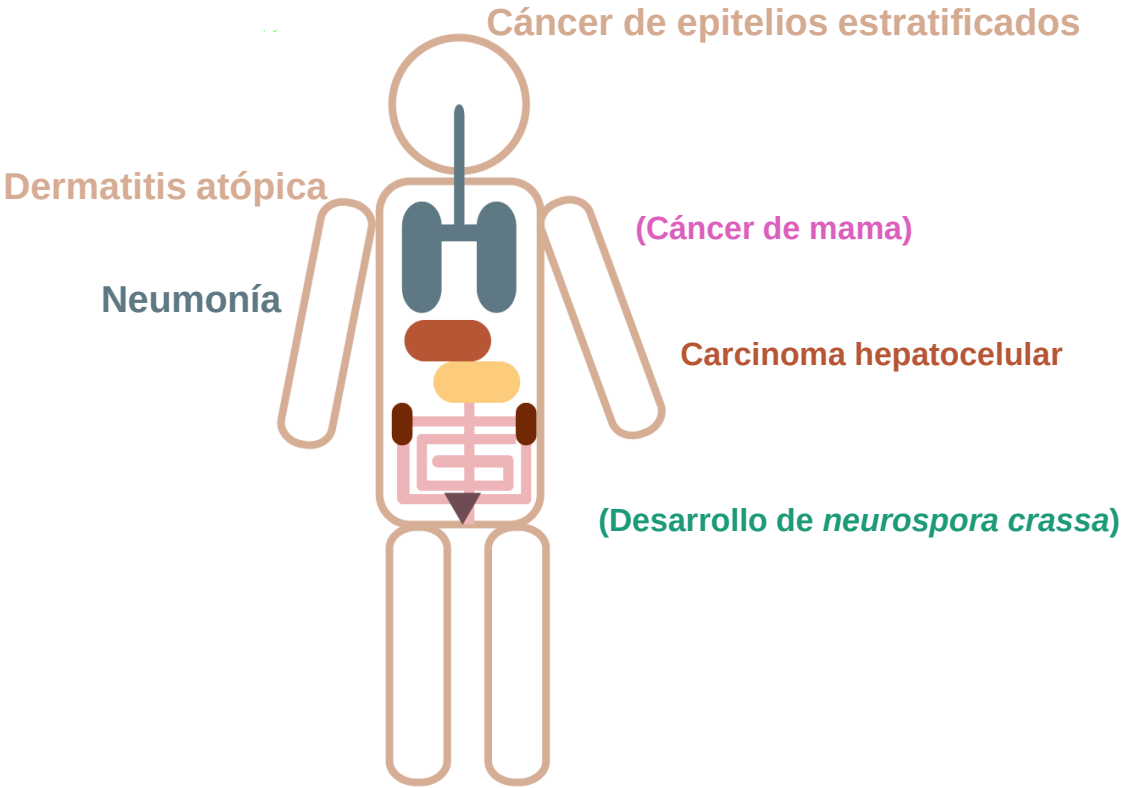

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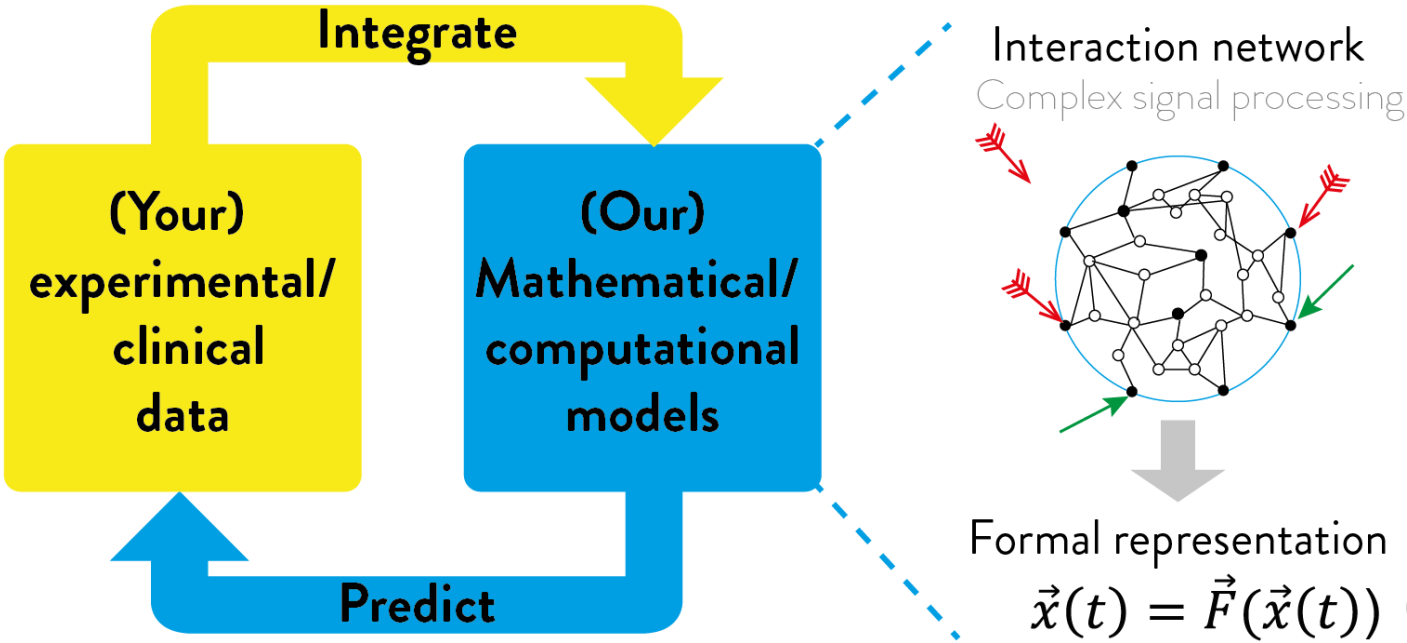
Biología de sistemas



Perspectiva integrativa, cuantitativa y dinámica

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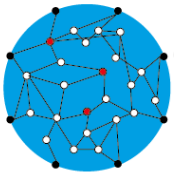
Datos empíricos

Modelos matemáticos

Integrar

Red de interacciones



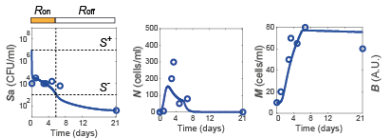
Formalizar

Sistema dinámico

$$\vec{x}(t) = \vec{F}(\vec{x}(t))$$

(Calibrar)

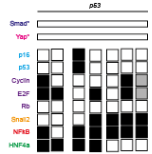
(Optimización paramétrica)

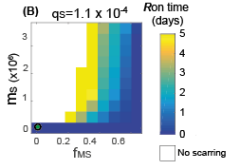


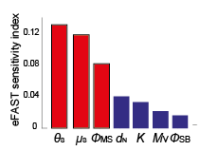
Predicciones

Análisis de perturbaciones

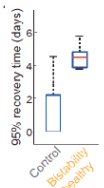
simulación de mutantes **análisis de bifurcaciones** **sensibilidad paramétrica**

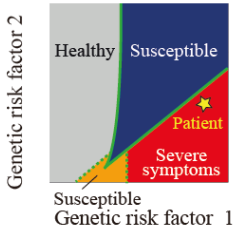


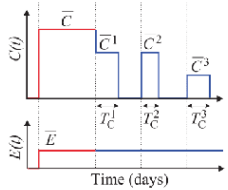




Detección temprana , estratificación **Diseño y optimización de intervenciones**







Modeling Methods for Medical Systems Biology

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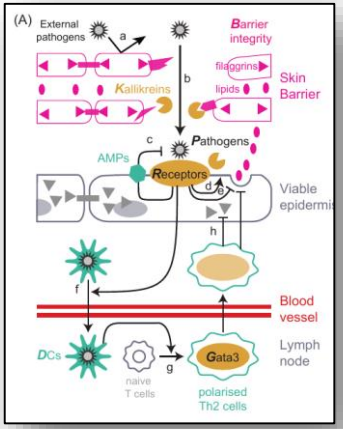
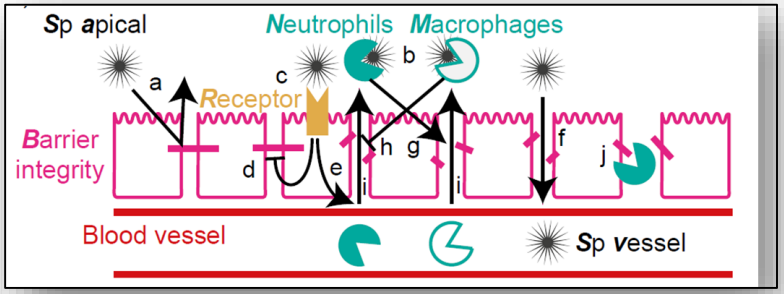
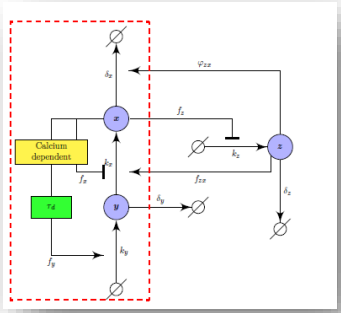
(1) Integración de la red



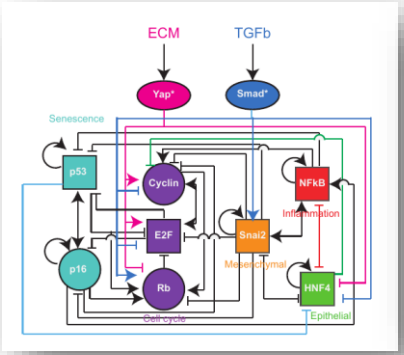
Dermatitis (JACI 2017)

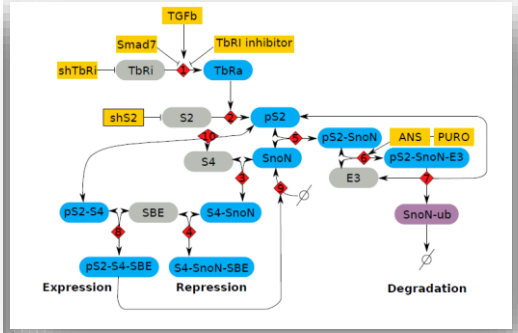


Neumonía (Frontiers in Physiology 2017)



Psoriasis y cancer de piel





Hepatocarcinoma

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(2) Formalización

$$\frac{dP(t)}{dt} = P_{env}\frac{\kappa_P}{1+\gamma_B B(t)} - \alpha_I R(t)P(t) - \delta_P P(t),$$
$$\frac{dB(t)}{dt} = \kappa_B \frac{1}{1+\gamma_R R(t)}\frac{1}{1+\gamma_G G(t)}(1-B(t)) - \delta_B K(t)B(t),$$
$$\frac{dD(t)}{dt} = \kappa_D R(t) - \delta_D D(t),$$

$$(R(t),\ K(t)) = \begin{cases} (R_{off}, K_{off}) \text{ if } P(t) < P^- \text{ or } \{P^- \le P(t) \le P^+ \text{ and } R(t^-) = R_{off}\} \\ (R_{on}, K_{on} = m_{on}P(t) - \beta) \text{ if } P(t) > P^+ \text{ or } \{P^- \le P(t) \le P^+ \\ \qquad \text{and } R(t^-) = R_{on}\} \end{cases} \quad (2)$$

$$G(t) = \begin{cases} G_{off} \text{ if } D(t) < D^+ \text{ and } G(t^-) = G_{off} \\ G_{on} \text{ if } D(t) \ge D^+ \text{ or } G(t^-) = G_{on} \end{cases} \quad (3)$$

Dermatitis (JACI 2017)

$$\frac{dS_a(t)}{dt} = \frac{\kappa_S}{\mu_S}S_a(t)(1-S_a(t)) - \frac{\theta_S}{1+\epsilon_{SB}B(t)}S_a(t) - \phi_{NS}N(t)S_a(t) - \phi_{MS}M(t)S_a(t),$$
$$\frac{dS_v(t)}{dt} = \kappa_S S_v(t) + \frac{\theta_S}{1+\epsilon_{SB}B(t)}S_a(t) - \frac{\delta_S}{K+S_v(t)}S_v(t),$$
$$\frac{dN(t)}{dt} = \alpha\frac{R(S_a(t))}{(1+\epsilon_{NB}B(t))(1+\epsilon_{NM}M(t))}N_v - \delta_N N(t),$$
$$\frac{dM(t)}{dt} = \beta\frac{N(t)}{1+\epsilon_{MB}B(t)}M_v - \delta_M M(t),$$
$$\frac{dB(t)}{dt} = \frac{\kappa_B}{1+\epsilon_{BS}R(S_a(t))}B(t)(\tilde{B}-B(t)) - \phi_{SB}R(S_a(t))B(t) - \phi_{NB}N(t)B(t).$$

$$R(S_a(t)) = \begin{cases} R_{off} & \text{if } S_a(t) < S^- \text{ or } \{S^- \le S_a(t) < S^+ \text{ and } R(S_a(t^-)) = R_{off}\}, \\ R_{on} & \text{if } S_a(t) \ge S^+ \text{ or } \{S^- \le S_a(t) < S^+ \text{ and } R(S_a(t^-)) = R_{on}\}, \end{cases}$$

Neumonía (Frontiers in Physiology 2017)

$$\dot{x}(t) = k_x f_{zx}\frac{y(t)z(t)}{1+f_x x(t)} - \delta_x \varphi_{zx} x(t)z(t) - \delta_x x(t)u(t), \quad (1.7)$$
$$\dot{y}(t) = k_y(1+f_y x(t-\tau_d)) - k_x f_{zx}\frac{y(t)z(t)}{1+f_x x(t)} - \delta_y y(t), \quad (1.8)$$
$$\dot{z}(t) = \frac{k_z}{1+f_z x(t)} - \delta_z z(t), \quad (1.9)$$

Psoriasis y cancer de piel

$$\vec{x}(t+1) = \vec{F}(\vec{x}(t))$$
$$t \in \mathbb{N}$$
$$x_i \in \{0,1\}\ \forall\ i$$

$$d\vec{y}(t)/dt = \vec{G}(\vec{y}(t), P)$$

Hepatocarcinoma

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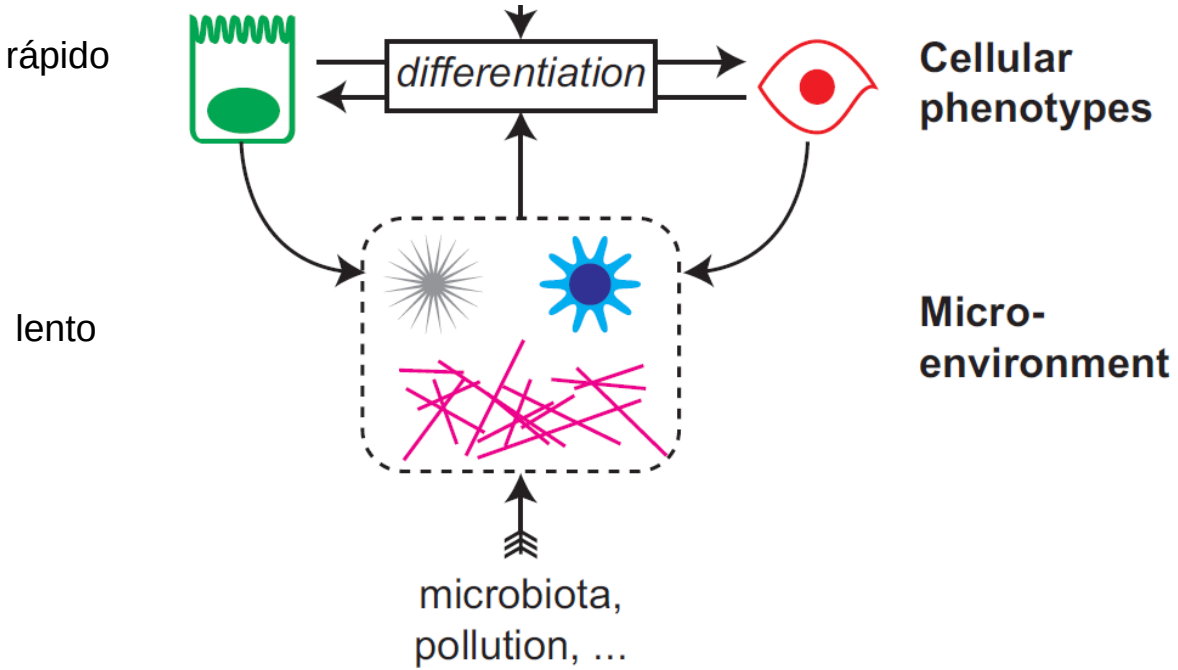
Modelos híbridos



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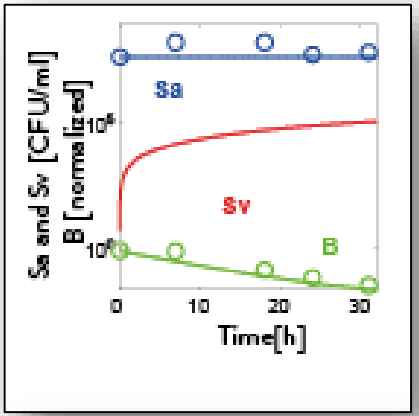
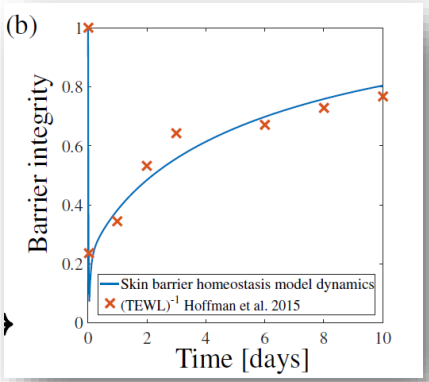
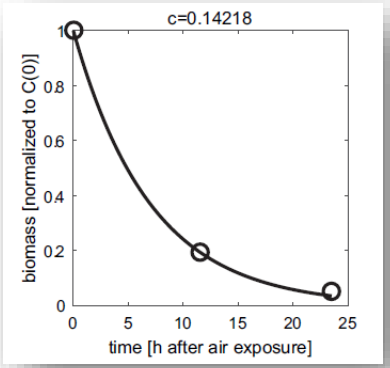
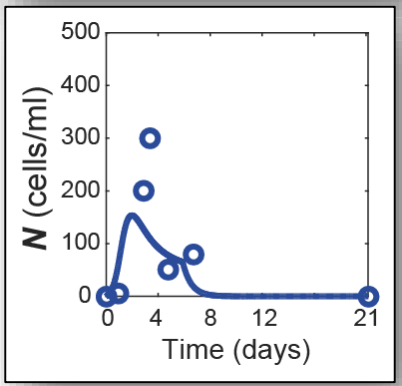
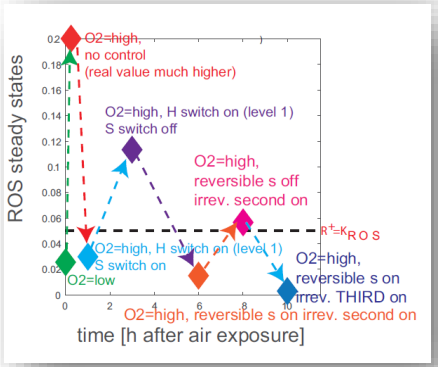
(3) Calibración (e integración) de datos

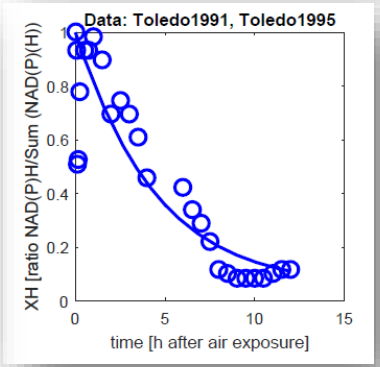












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(4) Análisis de perturbaciones

Ahora sí: a hacer predicciones y responder preguntas

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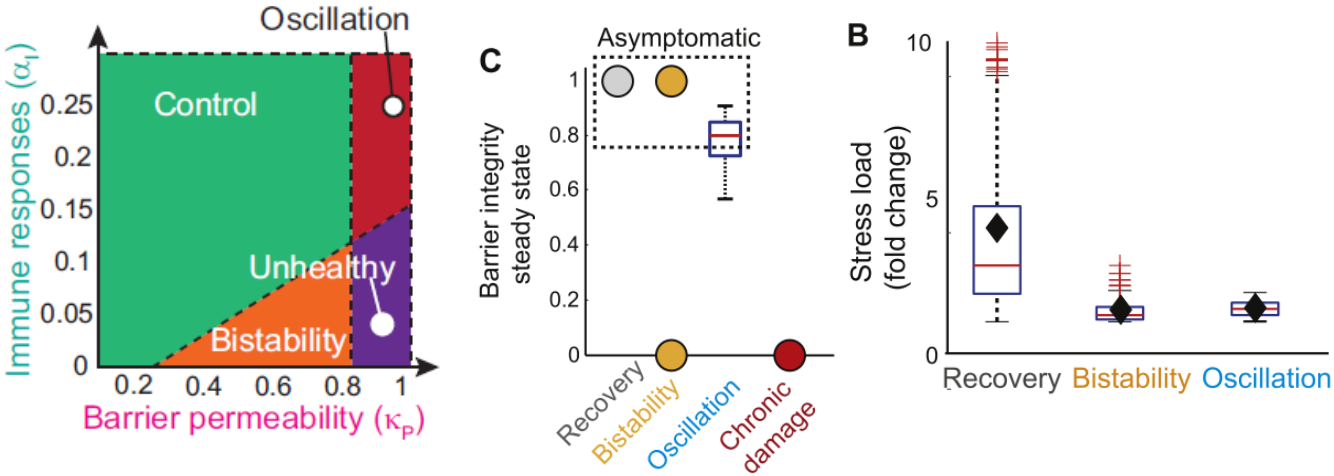
4.1 ¿Cuál es el efecto de factores de riesgo genéticos y ambientales sobre la homeostasis epitelial? (análisis de bifurcaciones)



Fenotipos asintomáticos suceptibles (dermatitis atópica)

E. Domínguez-Hüttinger et al. J. Allergy Clin. Immunol, 139, 861-72, June, 2017.

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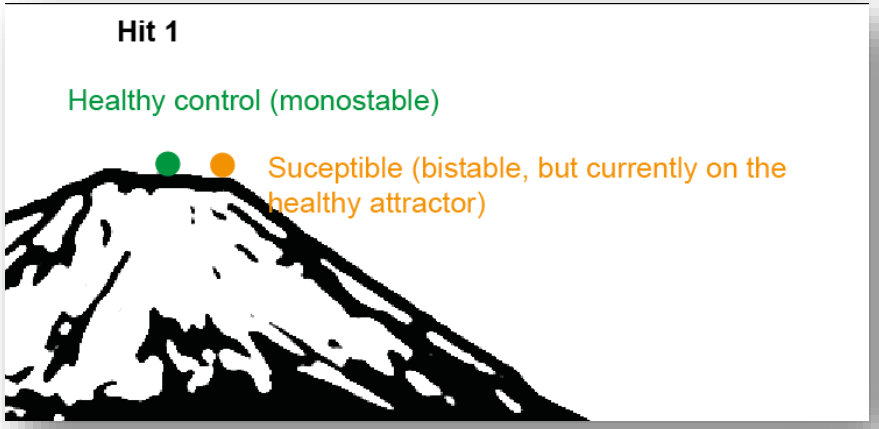
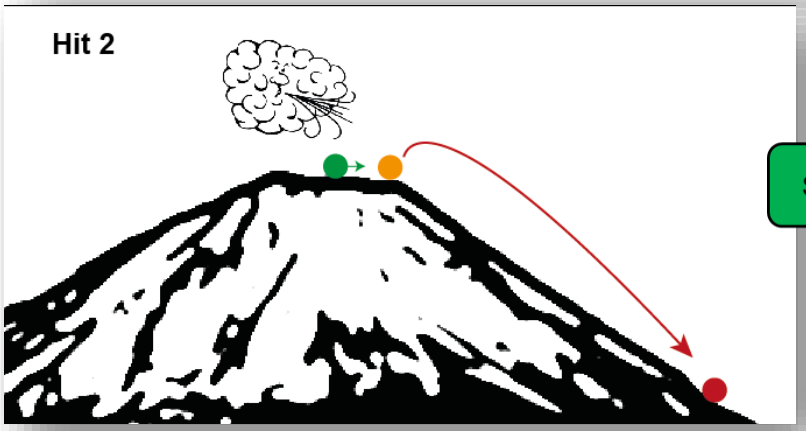
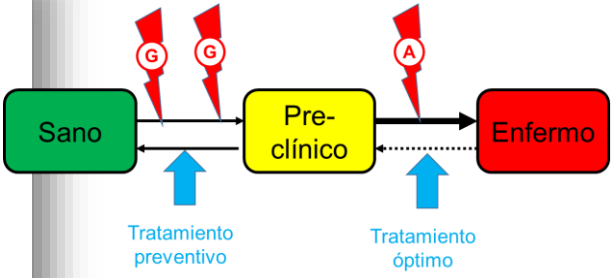
Los síntomas son producto de “dos golpes”



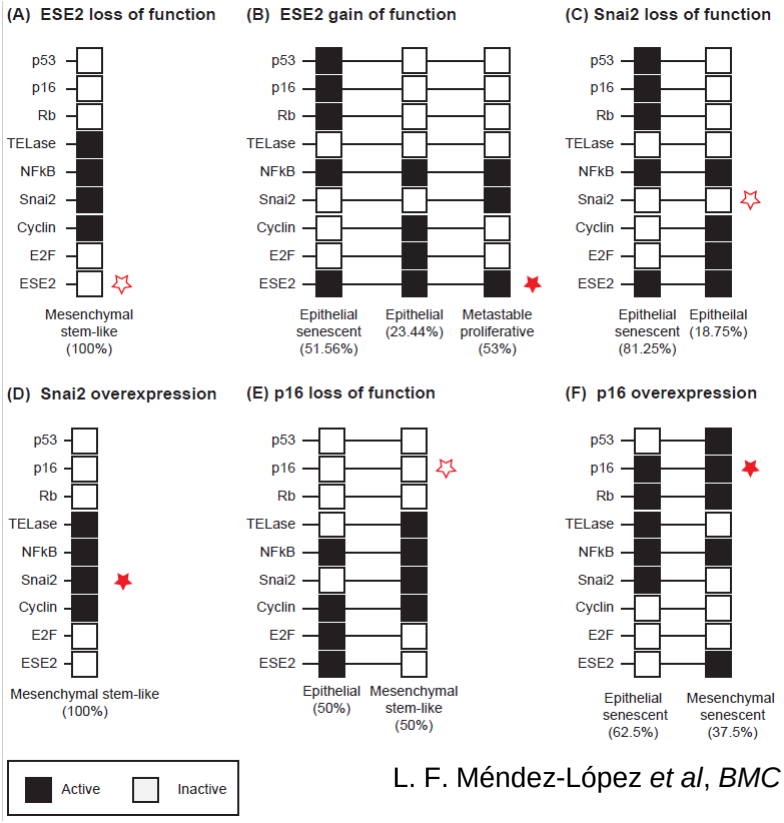
- **Primer golpe:** Factores genéticos
- **Segundo golpe:** Factores ambientales





⇨Es importante detectar las fases pre-clínicas para prevenir la “catástrofe” (transición de fase)

Efecto de mutaciones sobre la transformación maligna de epitelios



L. F. Méndez-López *et al*, *BMC Syst. Biol.* (2017)

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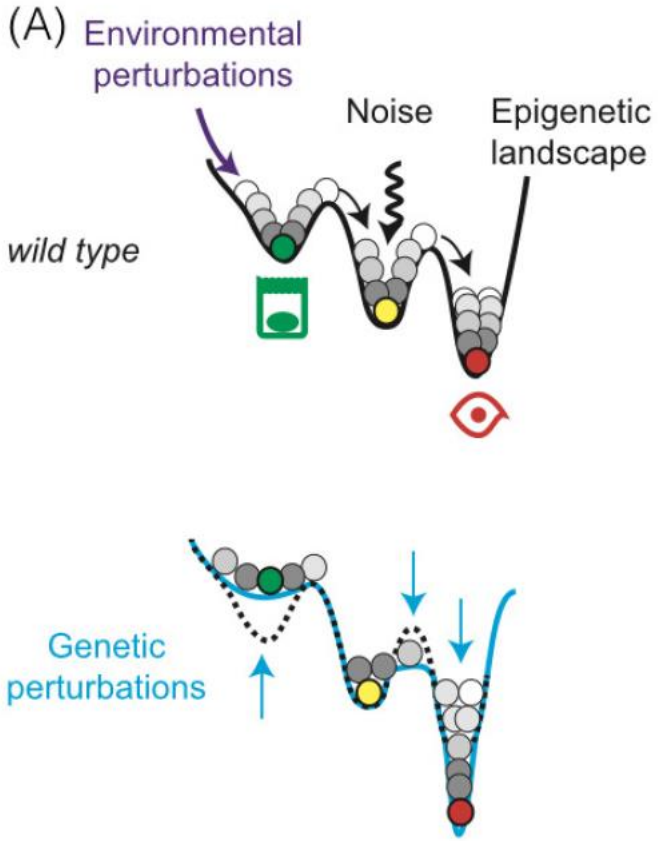

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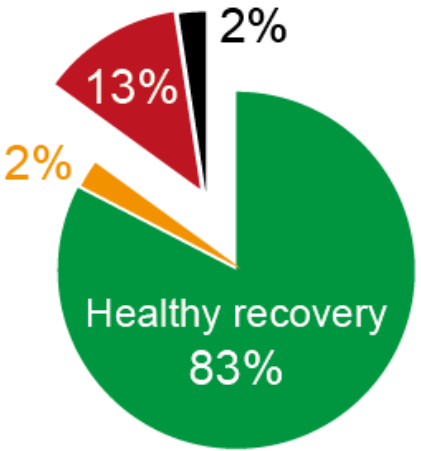
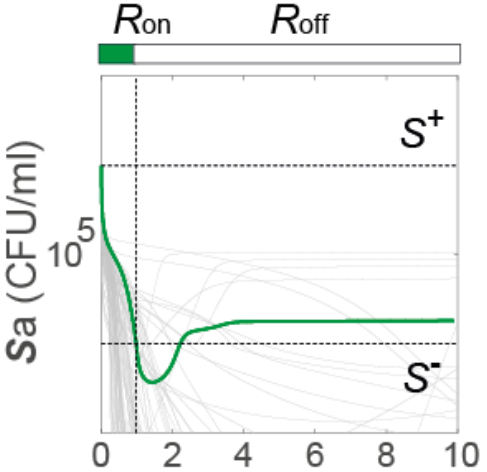
(4.2) ¿Qué tan robusta es la relación comensal entre *S pneumoniae* y la mucosa respiratoria? (análisis de perturbaciones)





E. Domínguez-Hüttinger et al. Front. Physiol., 8, 115, 1–14. March, 2017.

☺ homeostasis

☹ disbiosis

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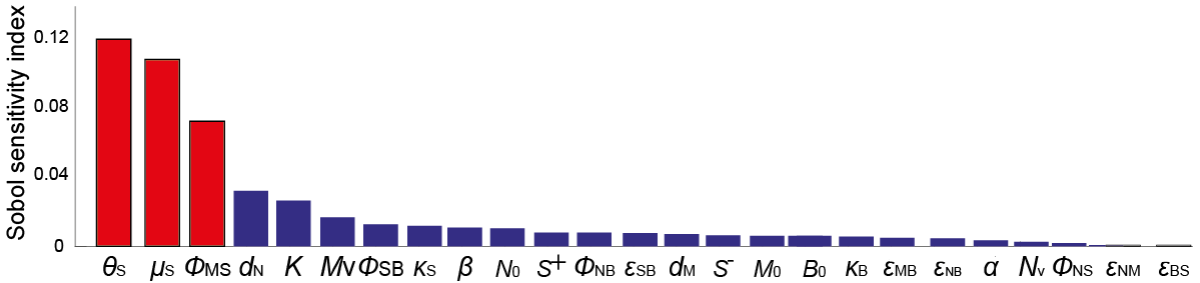
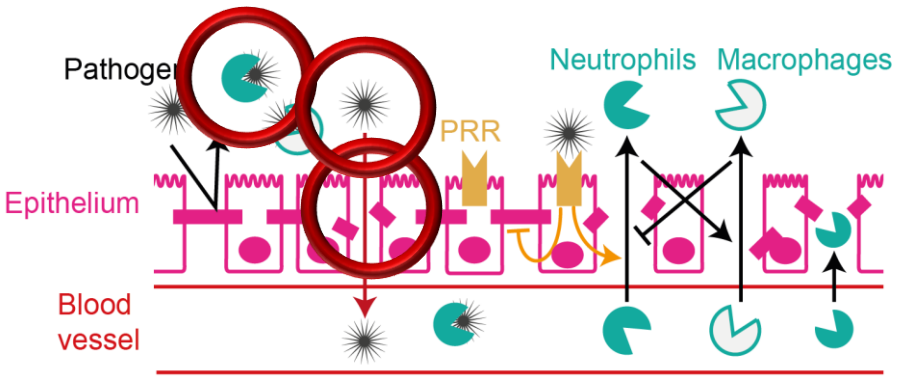
(3) ¿qué factores pueden causar disbiosis? (análisis de sensibilidad paramétrica)



E. Domínguez-Hüttinger et al. Front. Physiol., 8, 115, 1–14. March, 2017.



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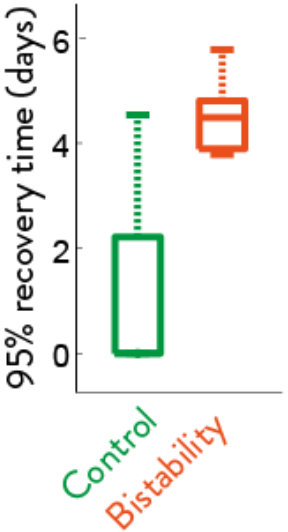
(4) ¿Cómo podemos detectar pacientes en estadíos preclínicos? (teoría de catástrofes)



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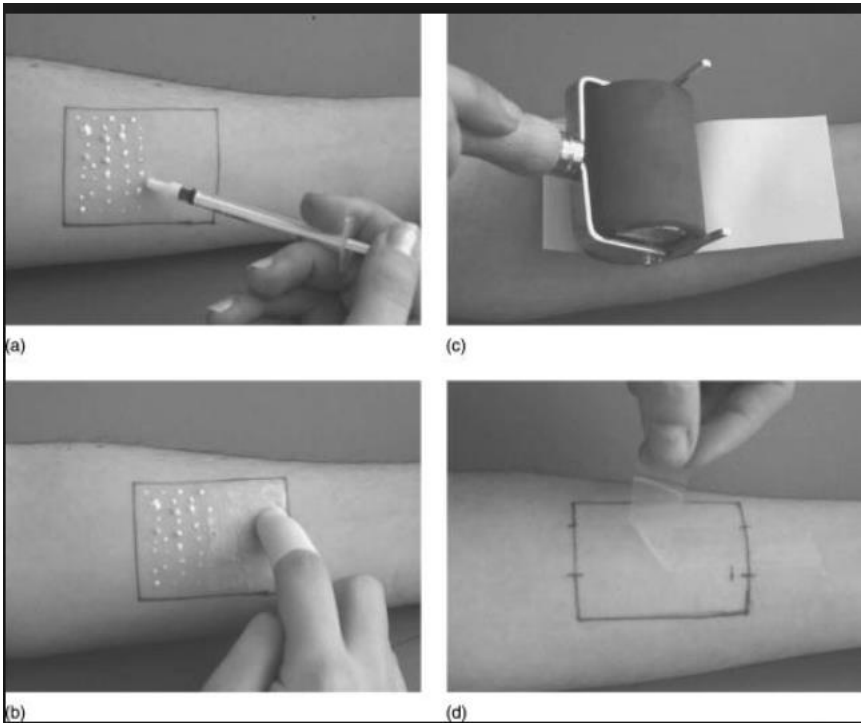

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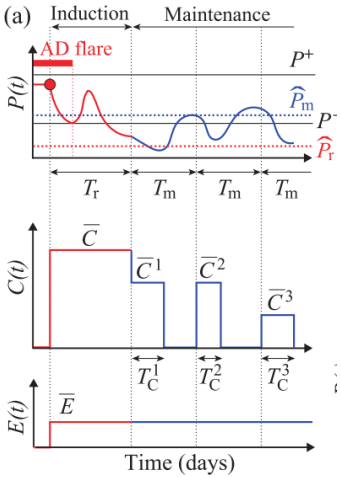
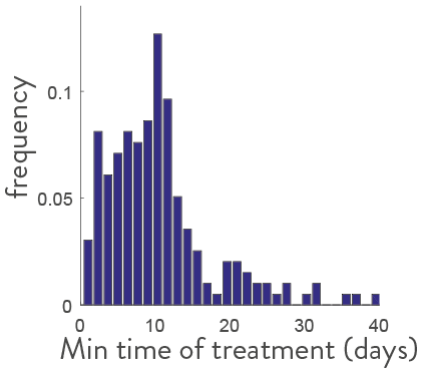
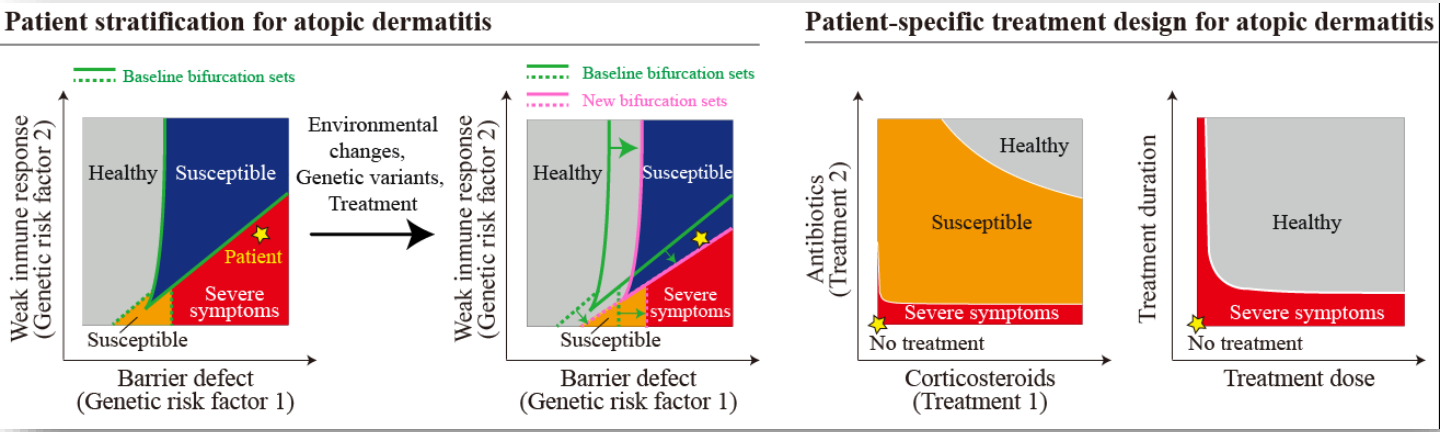
(5) Diseño, personalización y optimización de tratamientos (teoría de control).





1. P. Christodoulides et al. Phil.Trans.R. Soc. A., 375, 20160285, May, 2017.
2. E. Domínguez-Hüttinger et al. Front. Physiol., 8, 115, 1–14. March, 2017.

Estratificación de pacientes y diseño de intervenciones (teoría de bifurcaciones)



1. G. Tanaka et al. Journal of Theoretical Biology, 448: 66-79. April, 2018.

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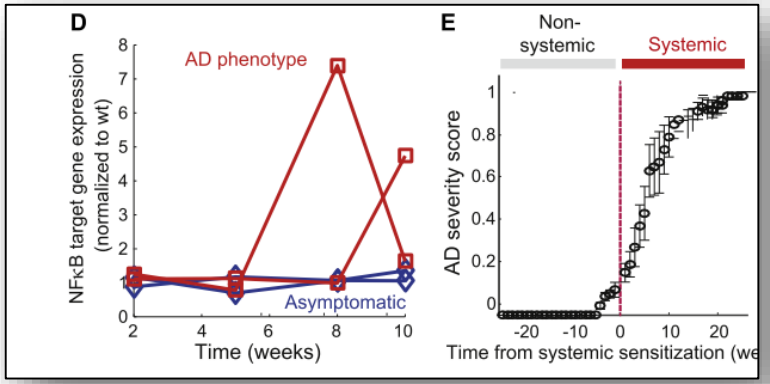
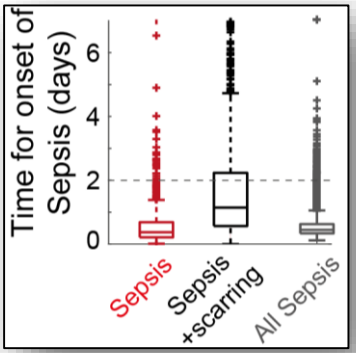
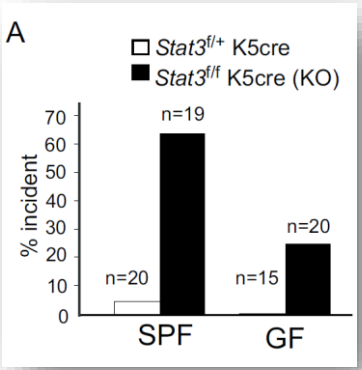
(6) Predicciones validadas experimentalmente



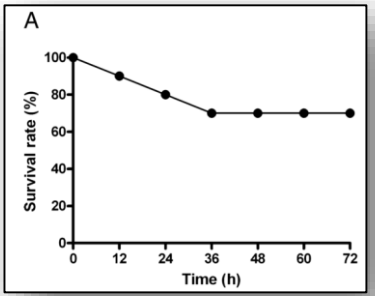
Domínguez-Hüttinger, E. et al., 2017. JACI



Domínguez-Hüttinger, E. et al., 2017. *Frontiers in physiology*

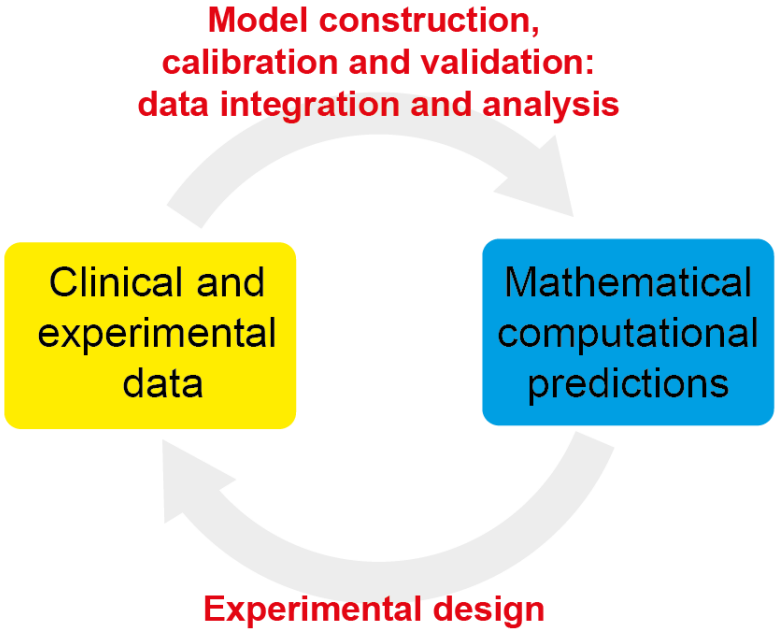


Miyauchi et al, submitted to Nature immunology



Andonegui et al, Shock 2009

Biología de sistemas
~ biología de interacciones



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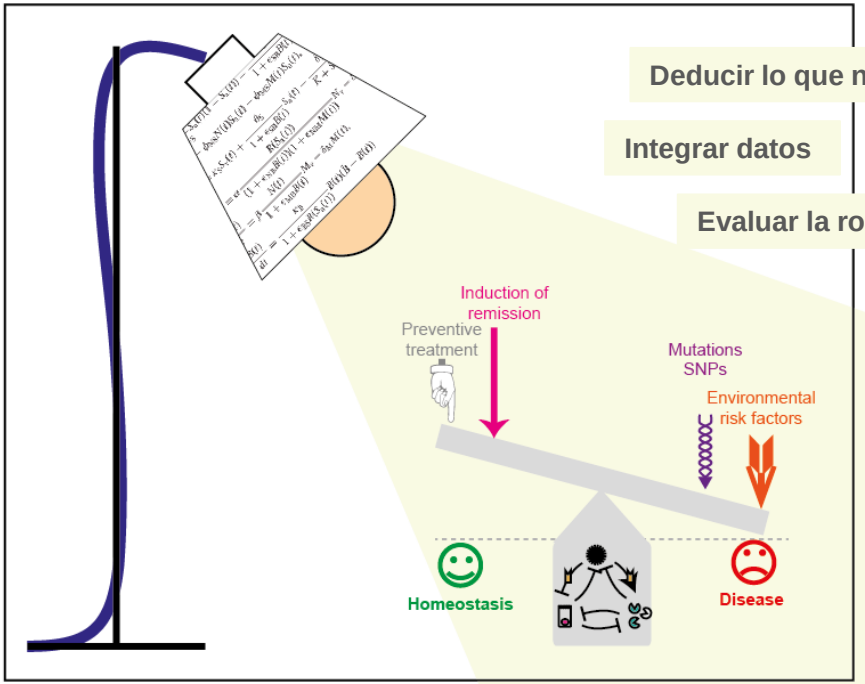
Black box (a bit more) illuminated



Deducir lo que no podemos medir

Integrar datos

Evaluar la robustez/ plasticidad del sistema

Identificar los factores de riesgo más probables

Optimización de tratamientos

Proponer marcadores tempranos

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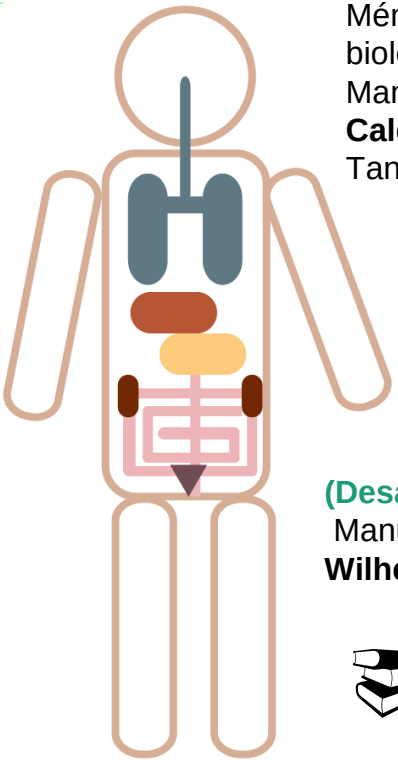
Biología de sistemas para entender, prevenir y revertir:

Dermatitis atópica

Domínguez-Hüttinger, E. et al., 2017. JACI
Domínguez-Hüttinger, E. et al., 2013. Interface Focus
Christodoulides, P., 2017. Philosophical Transactions
Tanaka, G. et al., 2018. JTB
Miyauchi et al, submitted to Nature Immunology

Neumonía

Domínguez-Hüttinger, E. et al., 2017. *Frontiers in physiology*



Cáncer de epitelios estratificados

Méndez-López 2017, BMC systems biology
Manuscrito en preparación (c **Jose Luis Caldú-Primo**, Jorge Verdusco, Reiko J Tanaka, Panayiotis Christodoulides)

Carcinoma hepatocelular

Manuscrito en preparación (c. **Francisco J Reyes Mora,** Marina Macías Silva, Rosario Pacheco Marín, Genaro Vásquez, Mathieu Hautefeuille)

(Desarrollo de *neurospora crassa*)

Manuscrito en preparación (c **Wilhelm Hansberg)**

Modeling Methods for Medical Systems Biology

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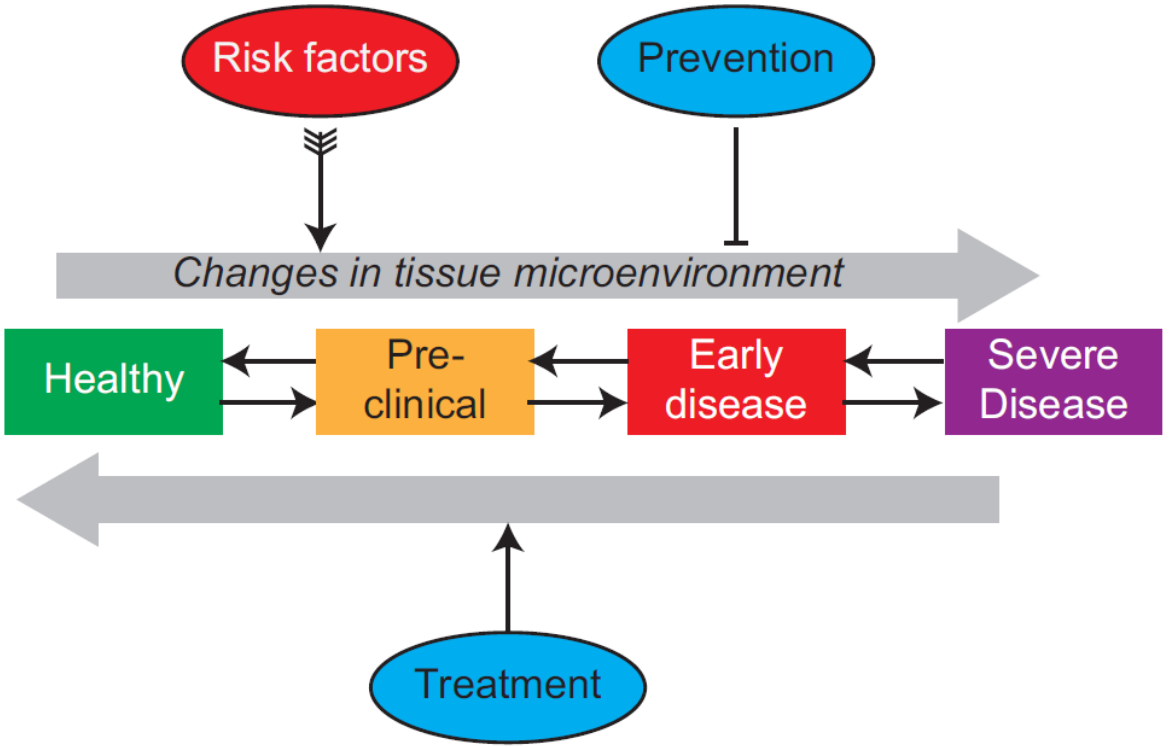

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Agradecimientos

Marina Macías Silva (IFC)
Mathieu Hautefeuille (FC)
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Rosario Pacheco (C3)
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Wilhelm Hansberg (IFC)
Elena Álvarez-Buylla (IE)

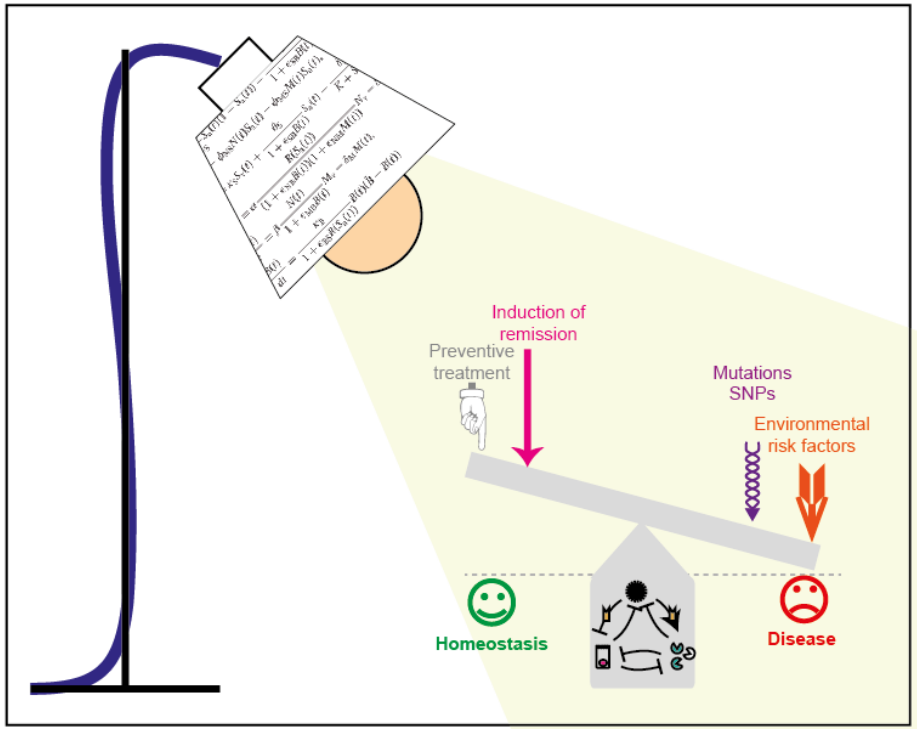
Reiko J Tanaka
Panayiotis Christodoulides

Gouhei Tanaka
Masato Kubo
Mariko Okada-Hatakeyama

Imperial College London

RIKEN

Black box (a bit more) illuminated



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