Multi-scale mathematical modelling of epithelial tissues to uncover the mechanisms of onset, progression, prevention and reversion of complex diseases

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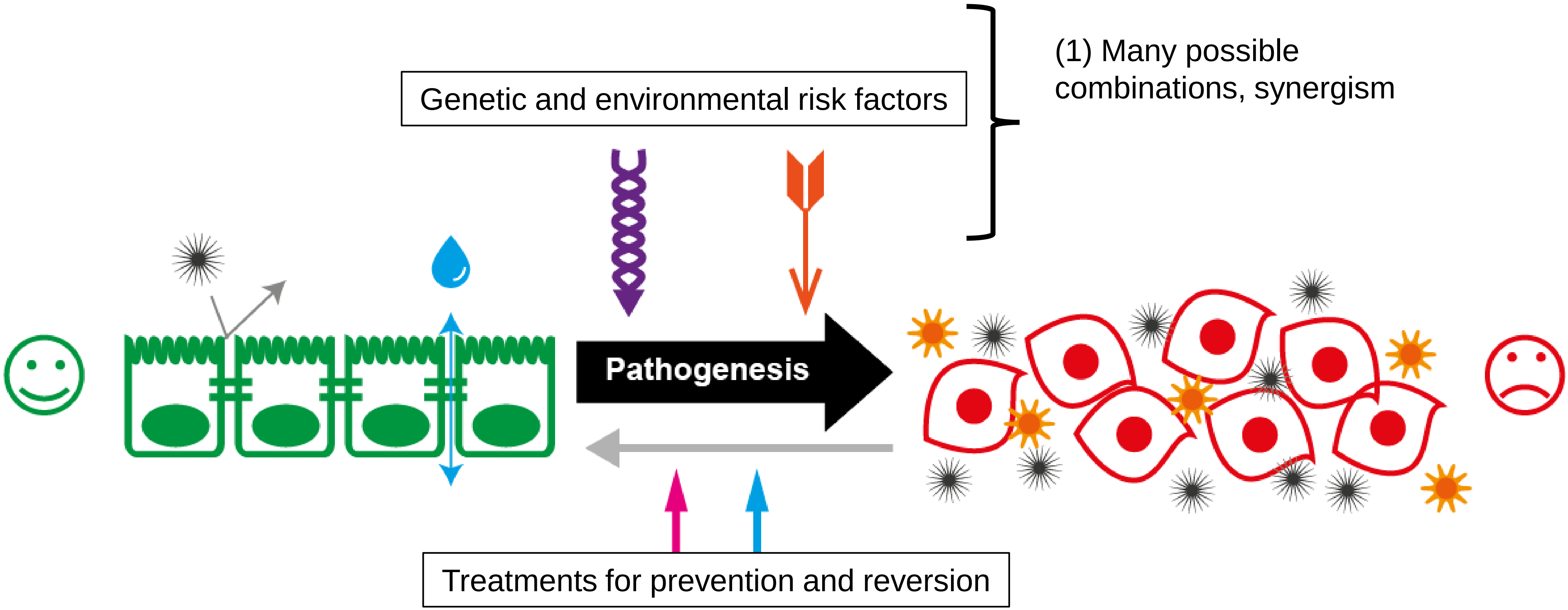
On the menue today:

Systems biology for the analysis of Complex epitheilal tissue diseases:

What? Why? How?

Complex epithelial tissue diseases: challenges

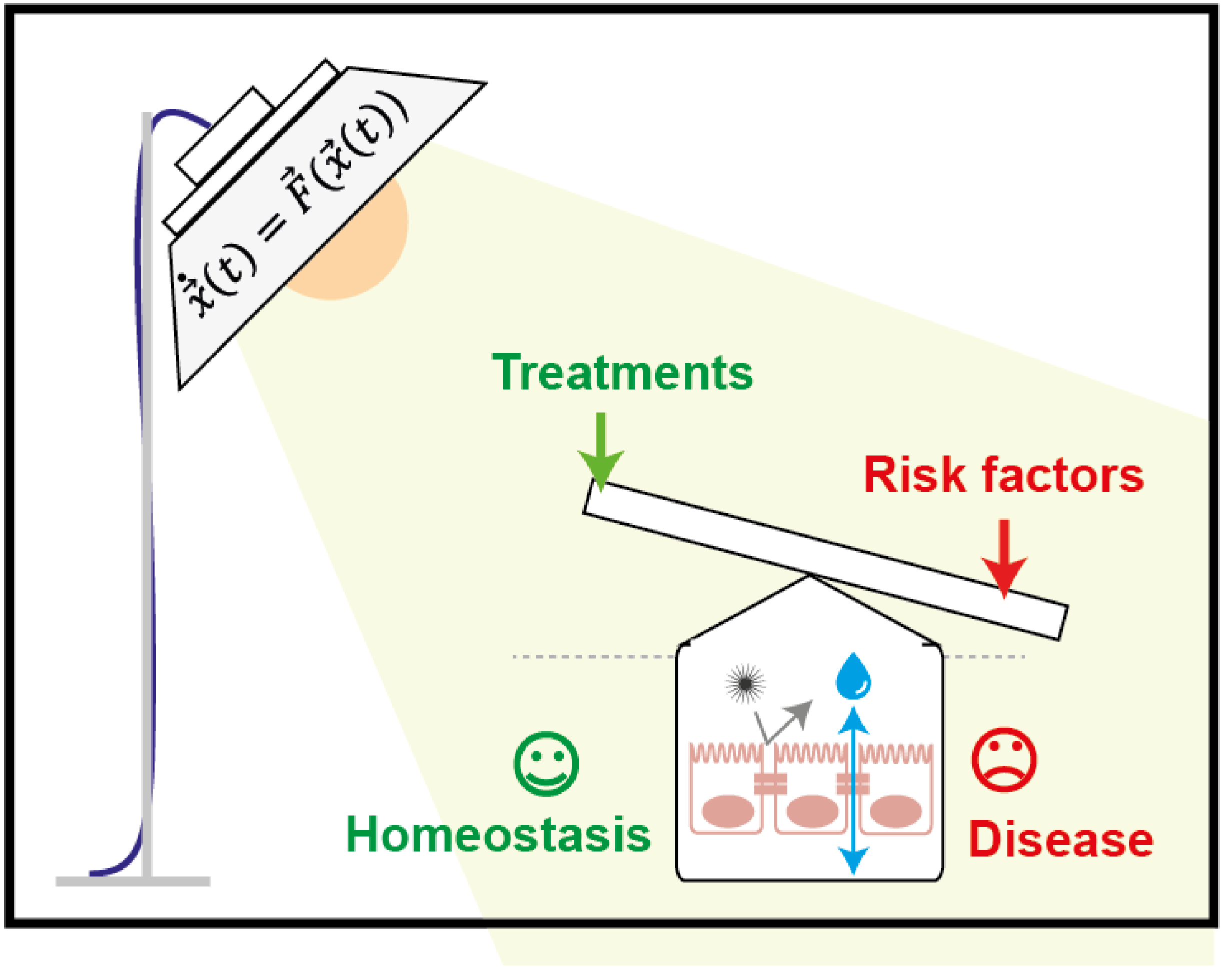


(2) **Pathogenic mechanisms are unclear**

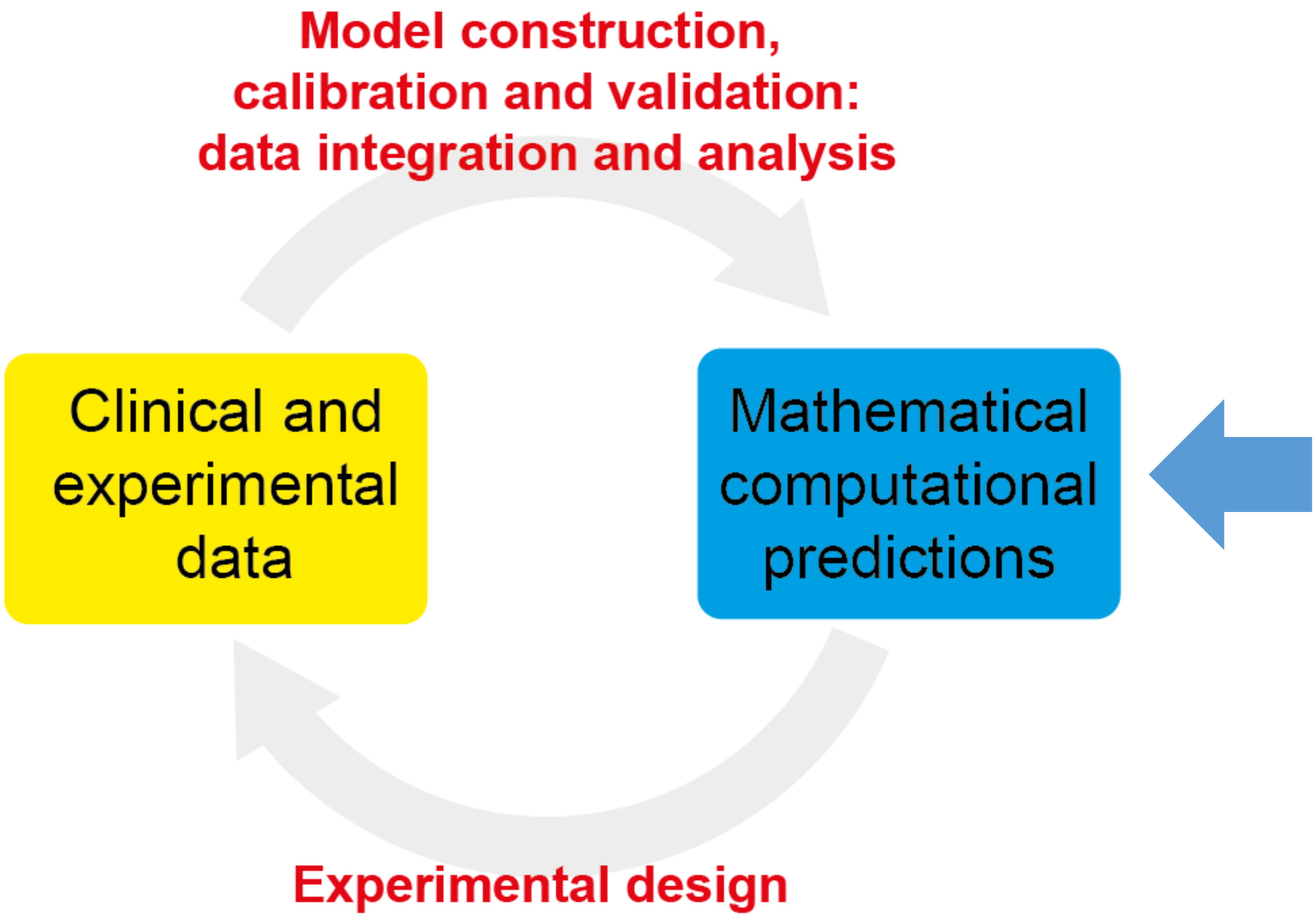
(3) Slow pathological progression

(4) Negative side effects of treatments that are often ineffective

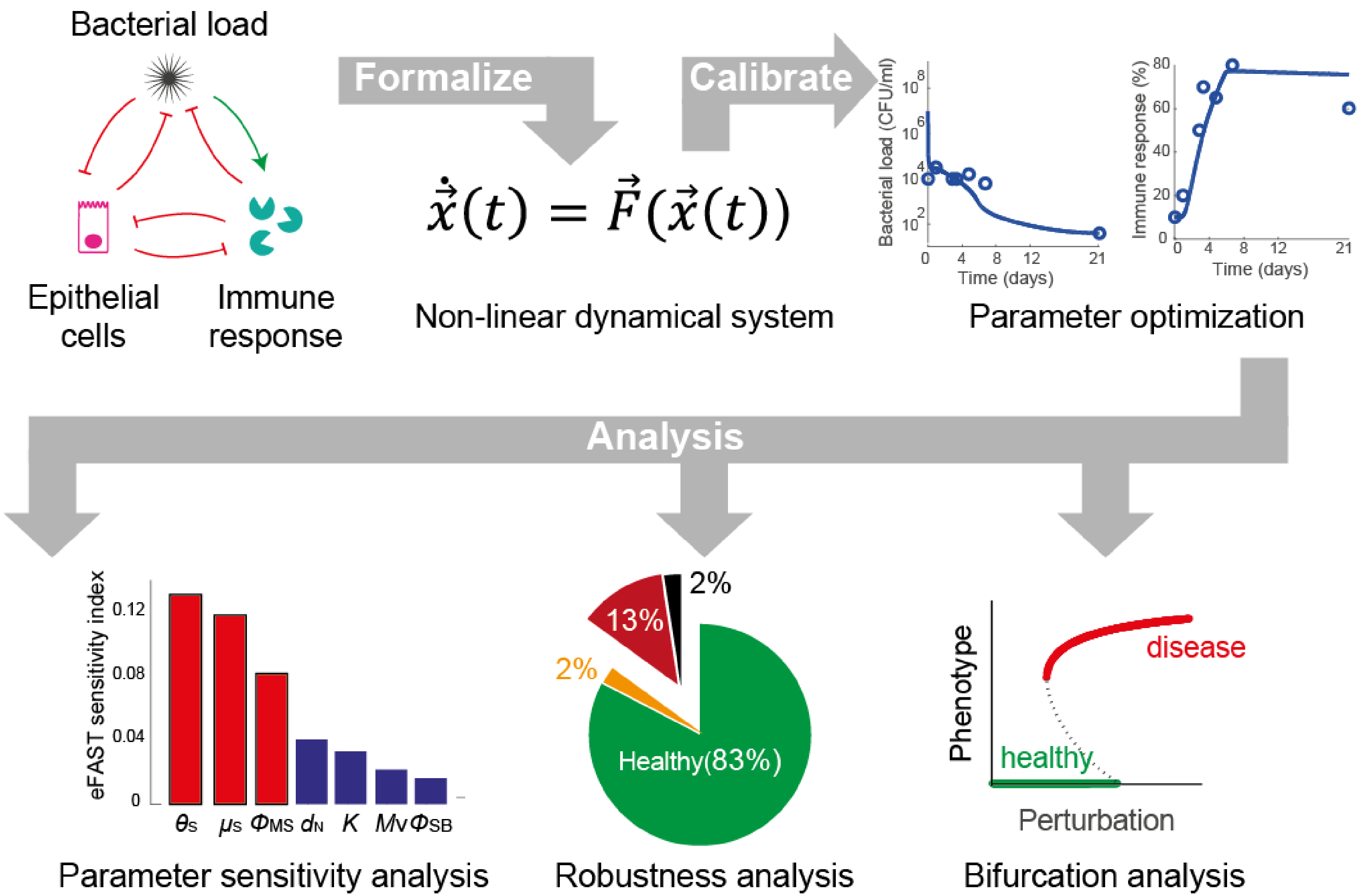
How can we understand, diagnose,prevent and revert)?


$\dot{\vec{x}}(t) = \vec{F}(\vec{x}(t))$
Treatments
Risk factors
Homeostasis
Disease

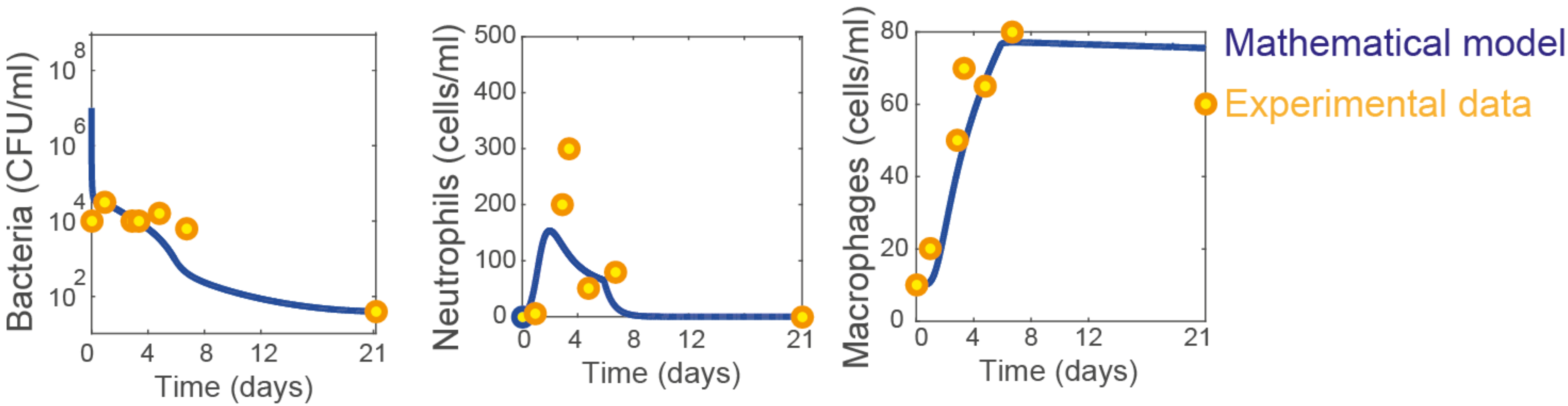
What is systems biology?



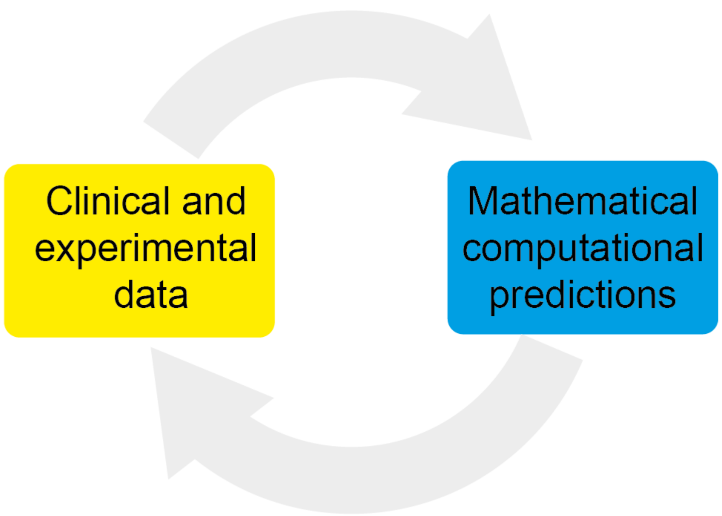
Systems biology pipeline



Model to agree with experimental data



Adapted from Domínguez-Hüttinger, E. et al., 2017. *Front. Physiol.* 8: 115

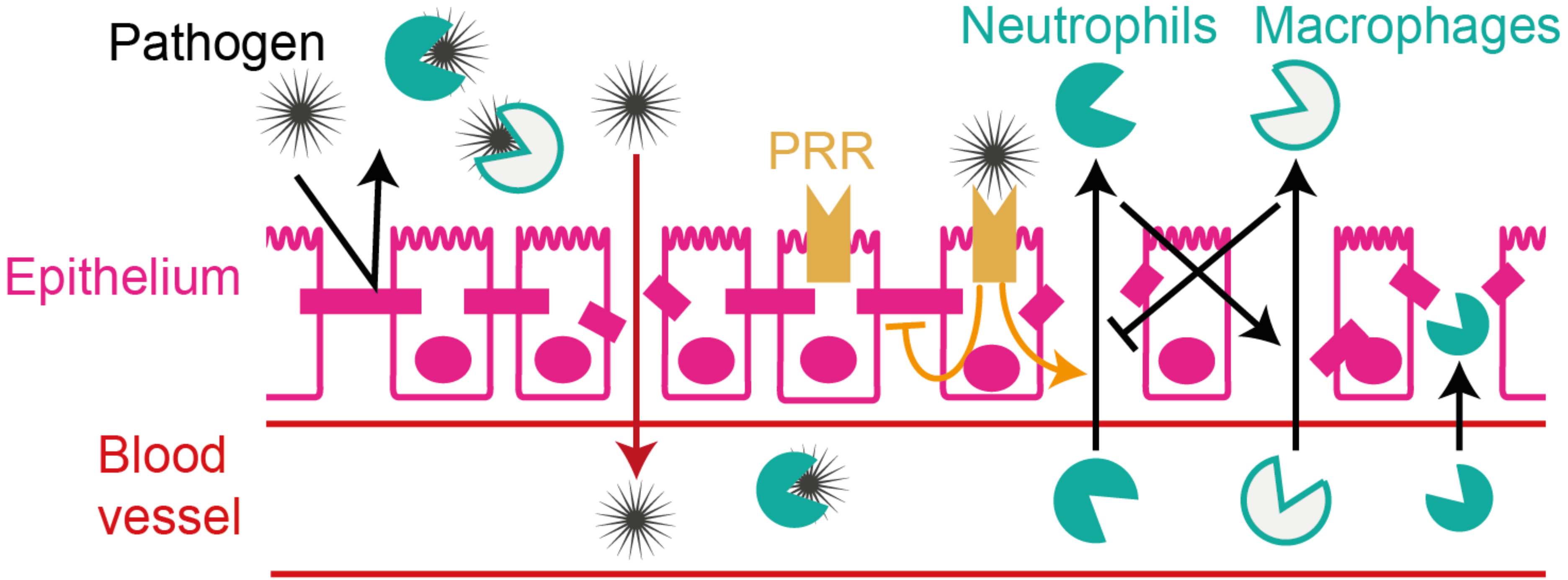


(What?)

Why?

(How?)

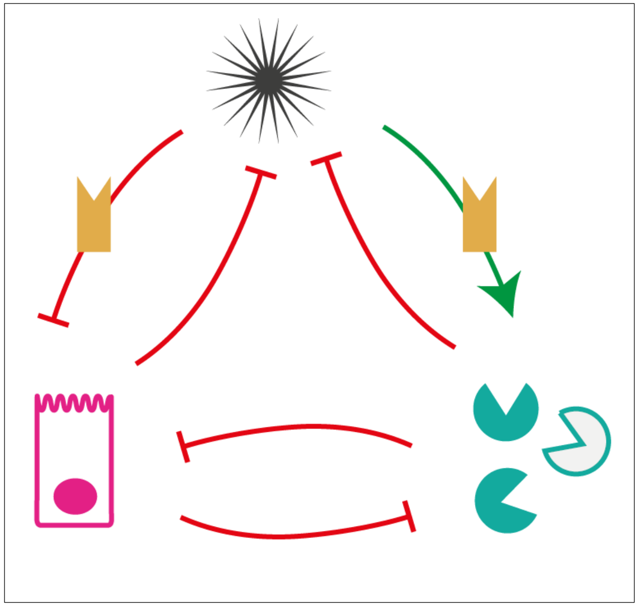
Our working example:



System of interacting pathogens, immune cells and epithelial tissue.

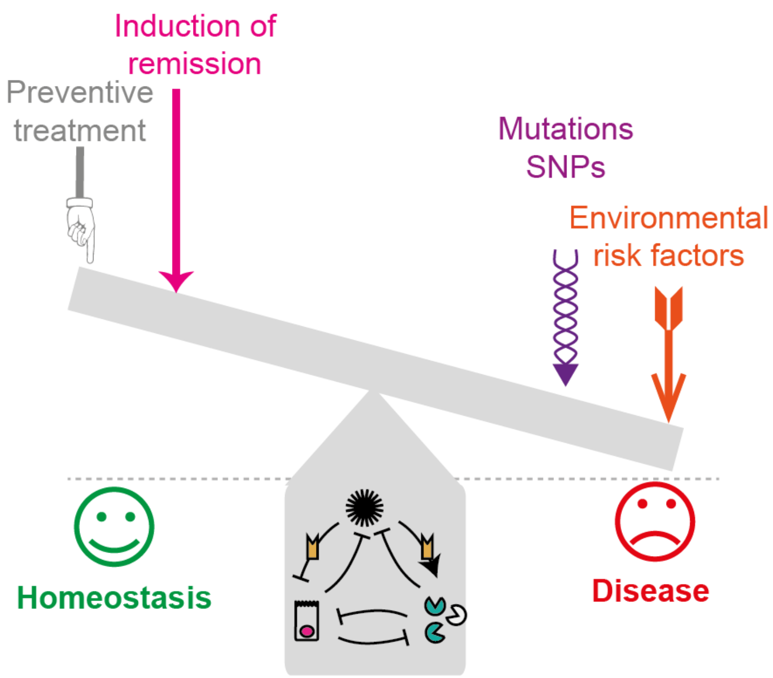
Figure adapted from:
Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

Key clinically relevant quesitons



- What is the (clinical) **outcome** of this system?
- How is it affected by genetic or environmental **risk factors**?
- How can systemic infection be **prevented**?
- How could the risk of antibiotics resistance be **minimized**?

What are the challenges?



Complex and non-linear

- Synergy between risk factors (network-as-buffer)
- Negative side effects of treatments (propagation of disturbances)

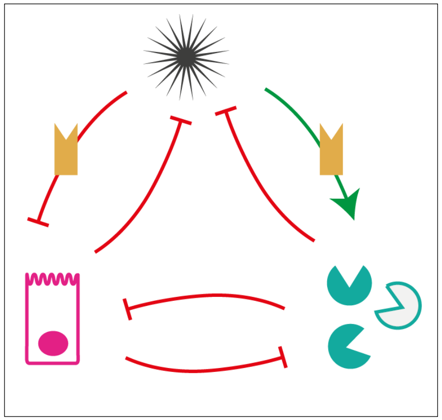
Dynamical

- Multiple processes co-ocurring at different (temporal) scales
- Disease progression

Quantitative:

- Dose-dependency of qualitative transitions
- Need for opimization of treatments

How can systems biology help?



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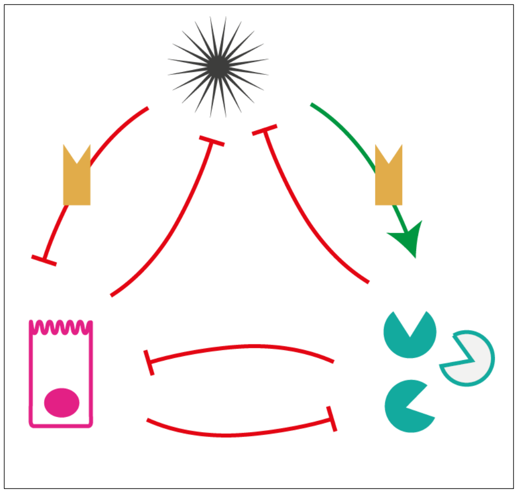
- Simulate what can´t be measured
- Perturbation analysis (of risk factors)
- Optimization of treatments
- Predicting the infectious dynamics
- Identify vulnerable patient cohorts

What?

Why?

How?

Step 1: Formalization



=

$$\frac{dS_a(t)}{dt} = \frac{\kappa_S}{\mu_S} S_a(t)(1 - S_a(t)) - \frac{\theta_S}{1 + \epsilon_{SB} B(t)} S_a(t) - \phi_{NS} N(t) S_a(t) - \phi_{MS} M(t) S_a(t),$$

$$\frac{dS_v(t)}{dt} = \kappa_S S_v(t) + \frac{\theta_S}{1 + \epsilon_{SB} B(t)} S_a(t) - \frac{\delta_S}{K + S_v(t)} S_v(t),$$

$$\frac{dN(t)}{dt} = \alpha \frac{R(S_a(t))}{(1 + \epsilon_{NB} B(t))(1 + \epsilon_{NM} M(t))} N_v - \delta_N N(t),$$

$$\frac{dM(t)}{dt} = \beta \frac{N(t)}{1 + \epsilon_{MB} B(t)} M_v - \delta_M M(t),$$

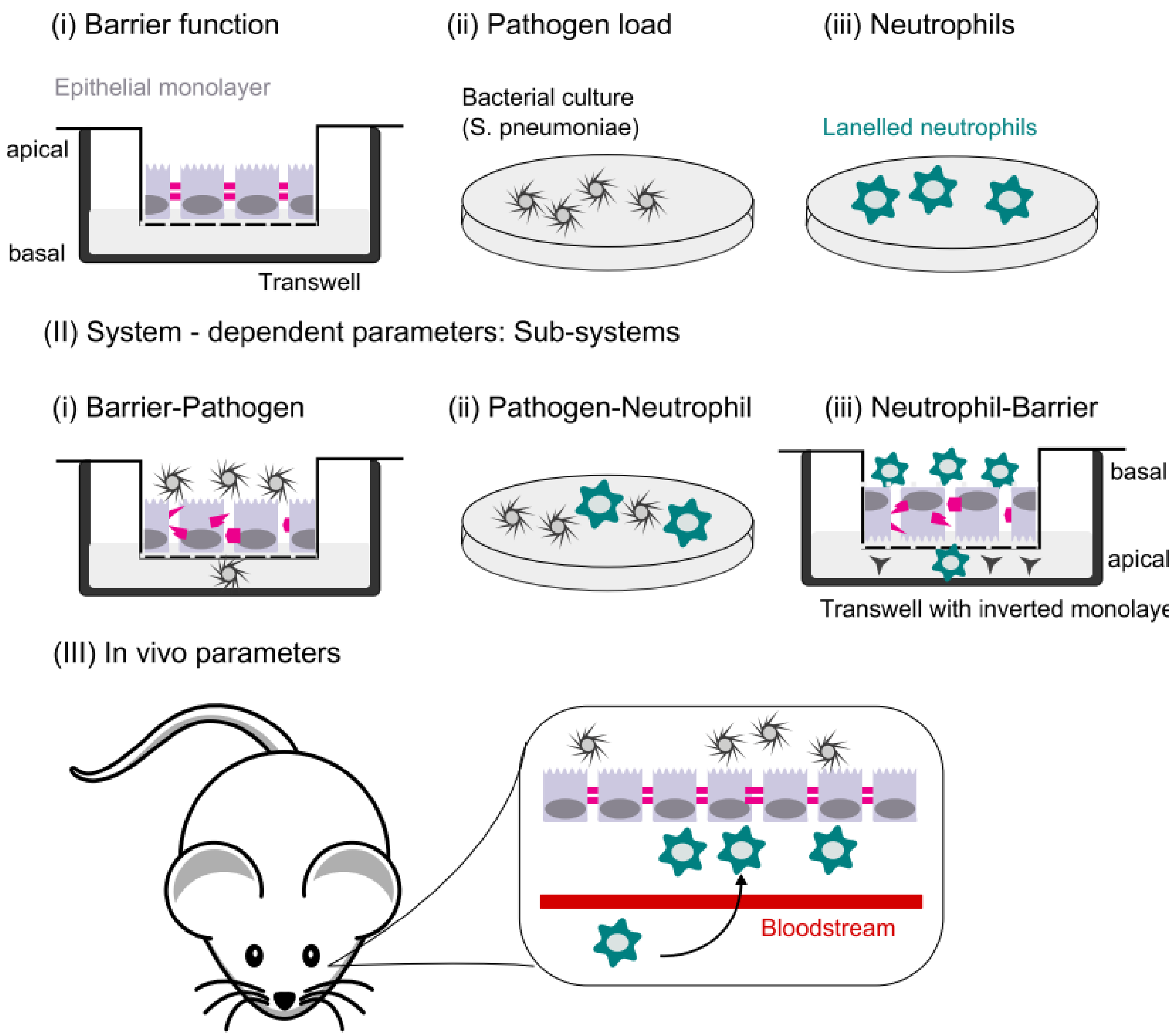
$$\frac{dB(t)}{dt} = \frac{\kappa_B}{1 + \epsilon_{BS} R(S_a(t))} B(t)(\tilde{B} - B(t)) - \phi_{SB} R(S_a(t)) B(t) - \phi_{NB} N(t) B(t).$$

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

Non-linear network
of feedback interactions:
A dynamical system

Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

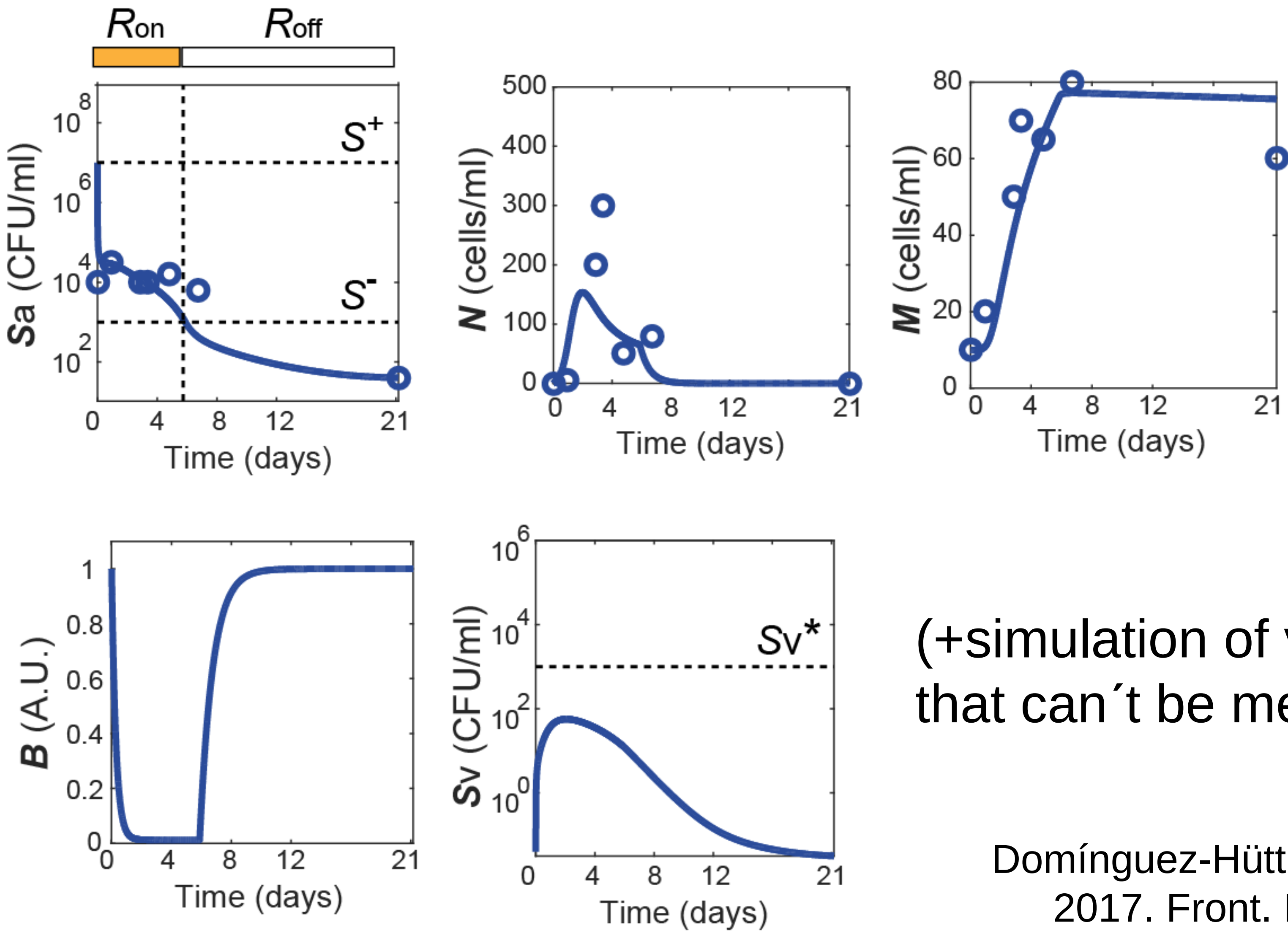
Integration of experimental data



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

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

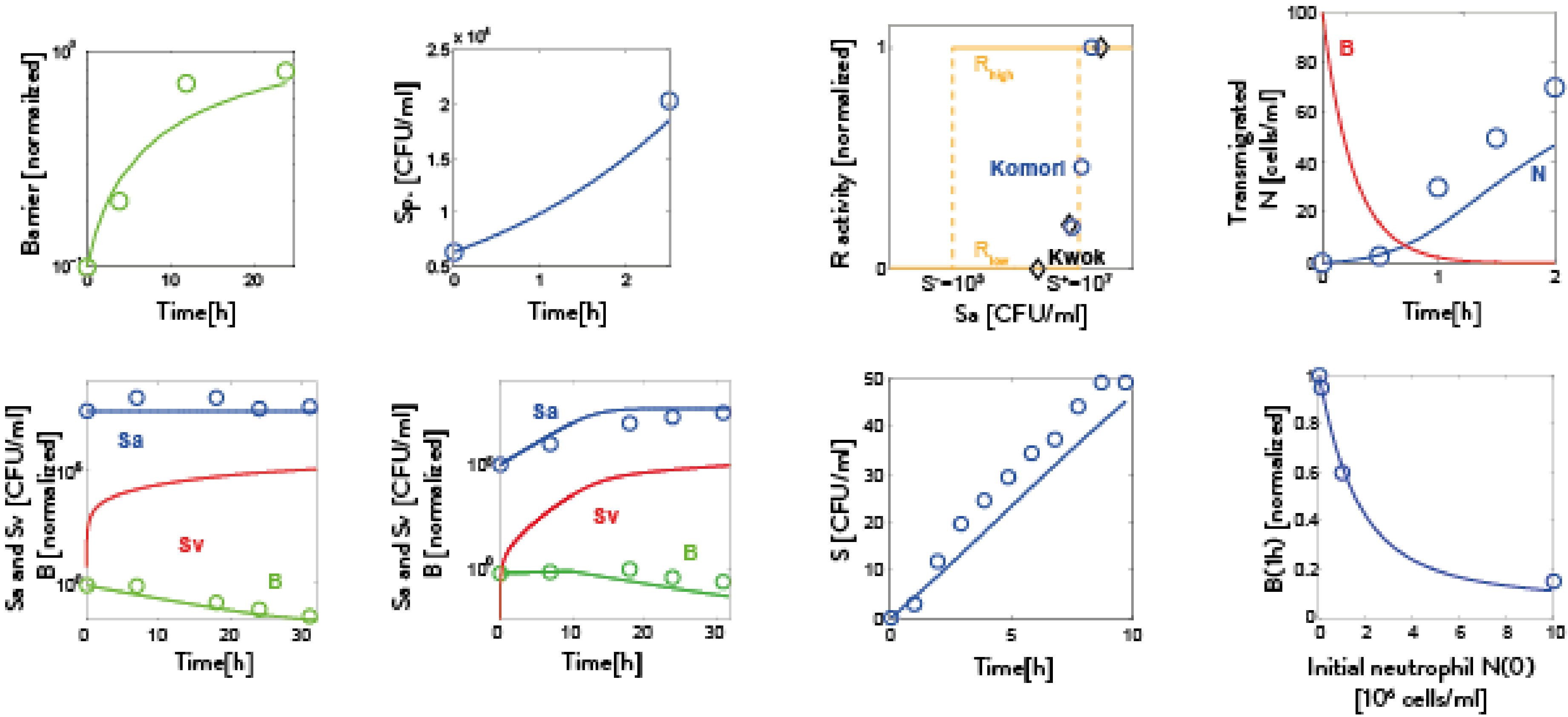
Step 2: Parametrization and validation



(+simulation of variables that can´t be measured)

Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

(cont. Parametrization and validation)



(model agrees with 13 independent datasets)

Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

Step 3: Model analysis
(a) Perturbation analysis

Question: How robust is the system?

- How much do we have to hit the system until the functionality is lost?
- Quantification of the fragility of the system.

(a) Perturbation analysis

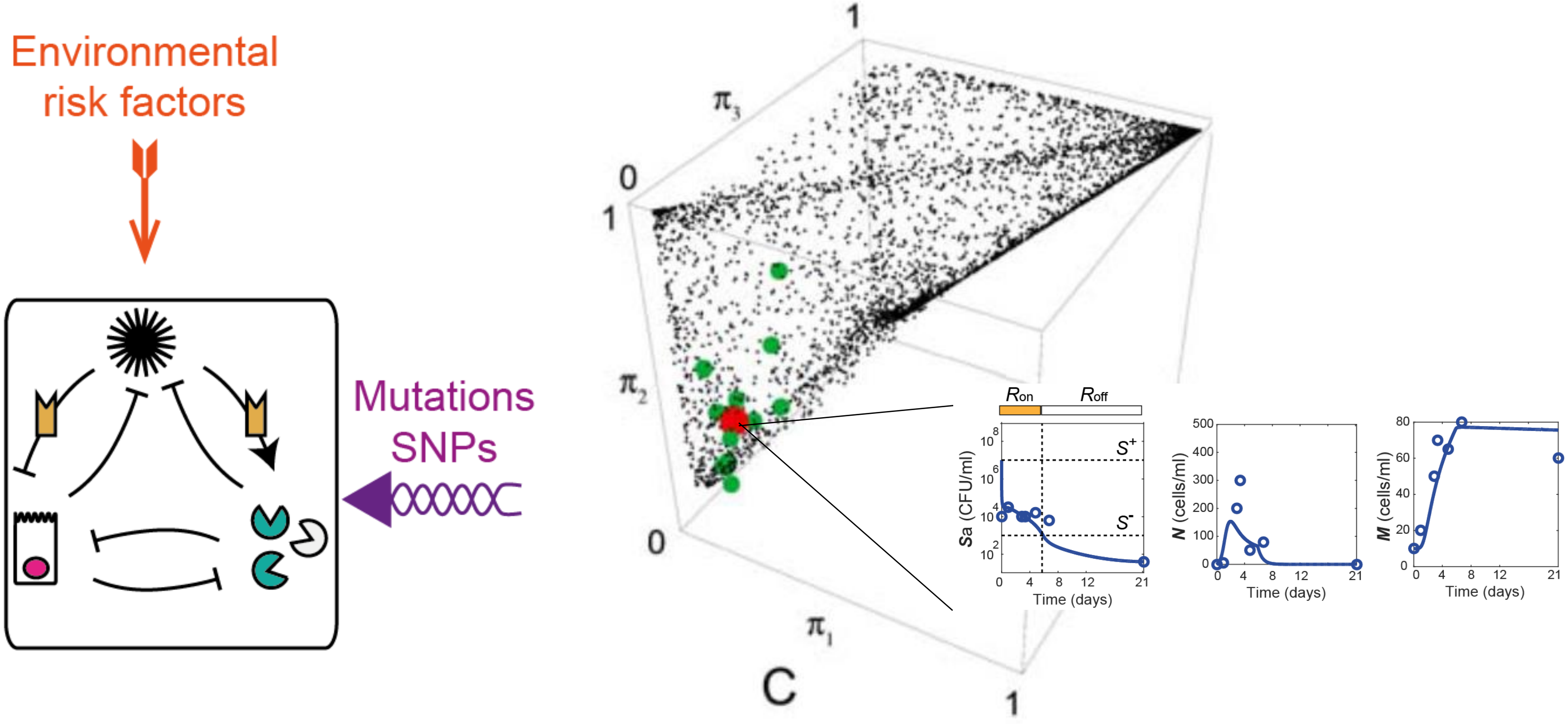
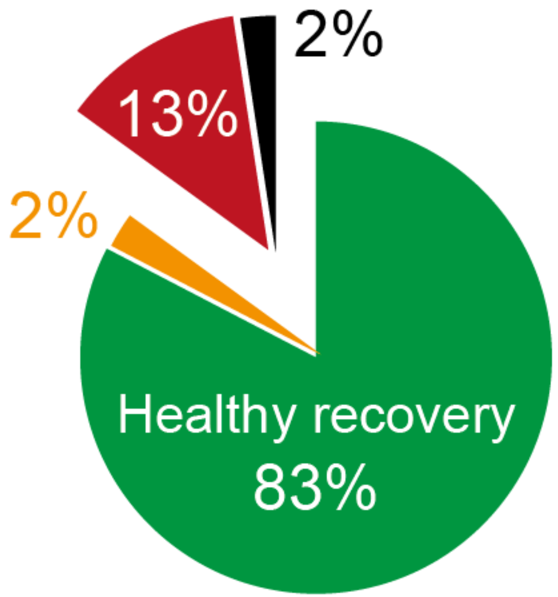
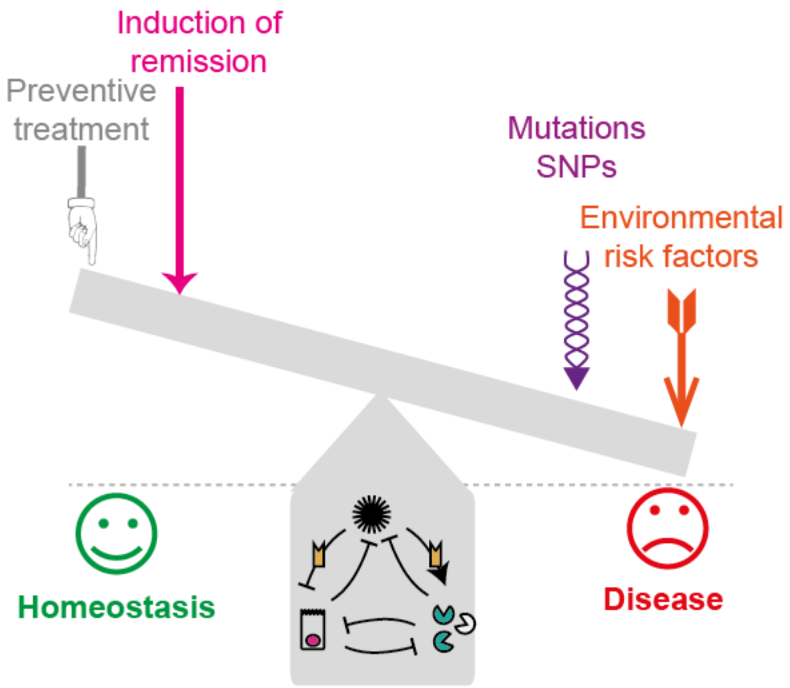


Figure adapted from
Mayo, A.E. et al., 2006. *LoS Biology*, 4(4), pp.555–561.

Homeostasis: a robust property of the system





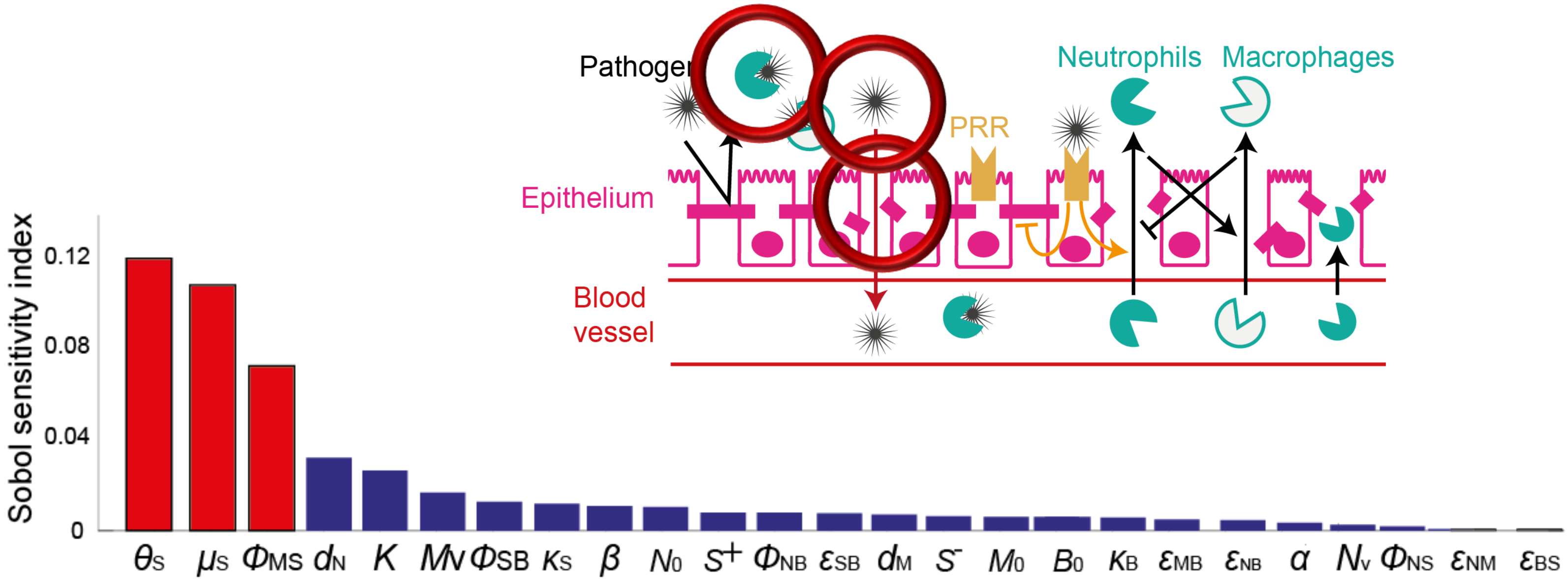
Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

Step 3: Model analysis
(b) Sensitivity analysis

Question: What causes the loss of homeostasis?

- Computational tolos to identify the changes in parameters that are most likely to result in disease

Mechanisms of dysbiosis



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Most sensitive parameters:

- rate of bacterial transmigration through the barrier (θS),
- bacterial carrying capacity (μS),
- killing rate of bacteria by macrophages (φMS)

Less sensitive:

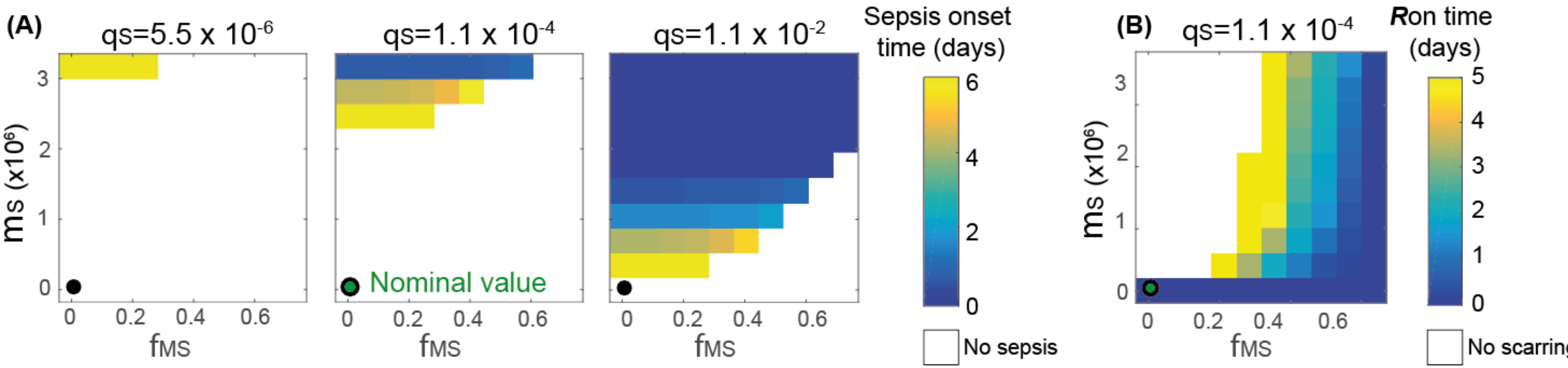
- propensity to develop sepsis (Sv)
- unresolved host responses (R)

Step 3: Model analysis
(c) Bifurcation analysis

Question:

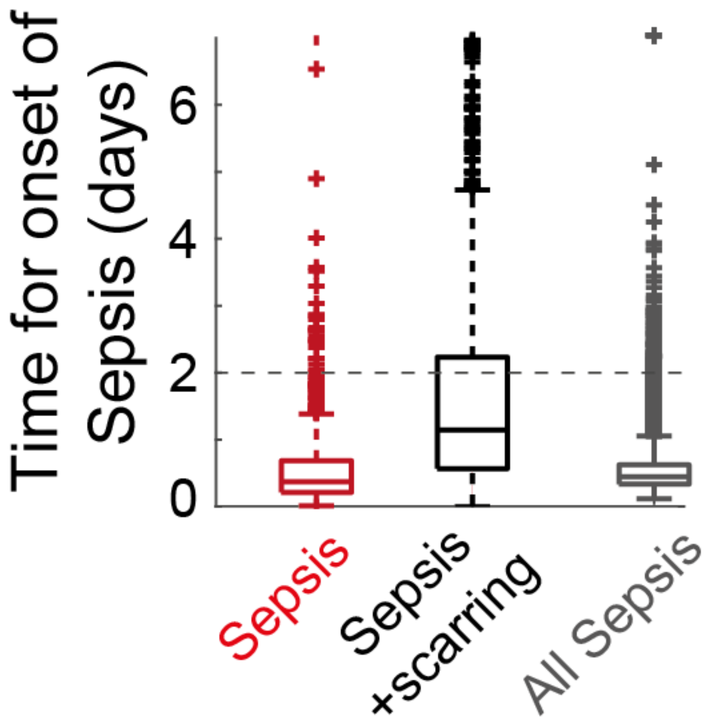
How do the the risk factors affect the infectious dynamics?

Step 3: Model analysis
(c) Bifurcation analysis



Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

Step 4: Checking consistency of predicitons with experimental data



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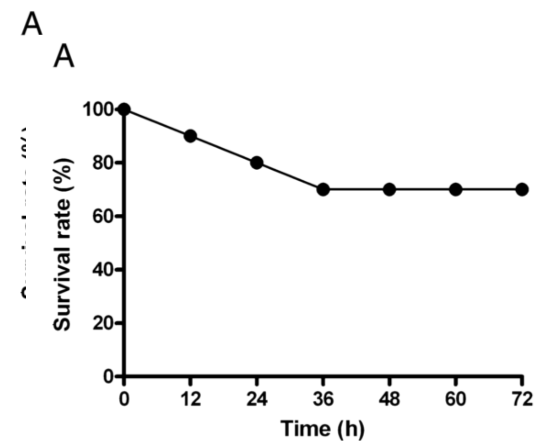
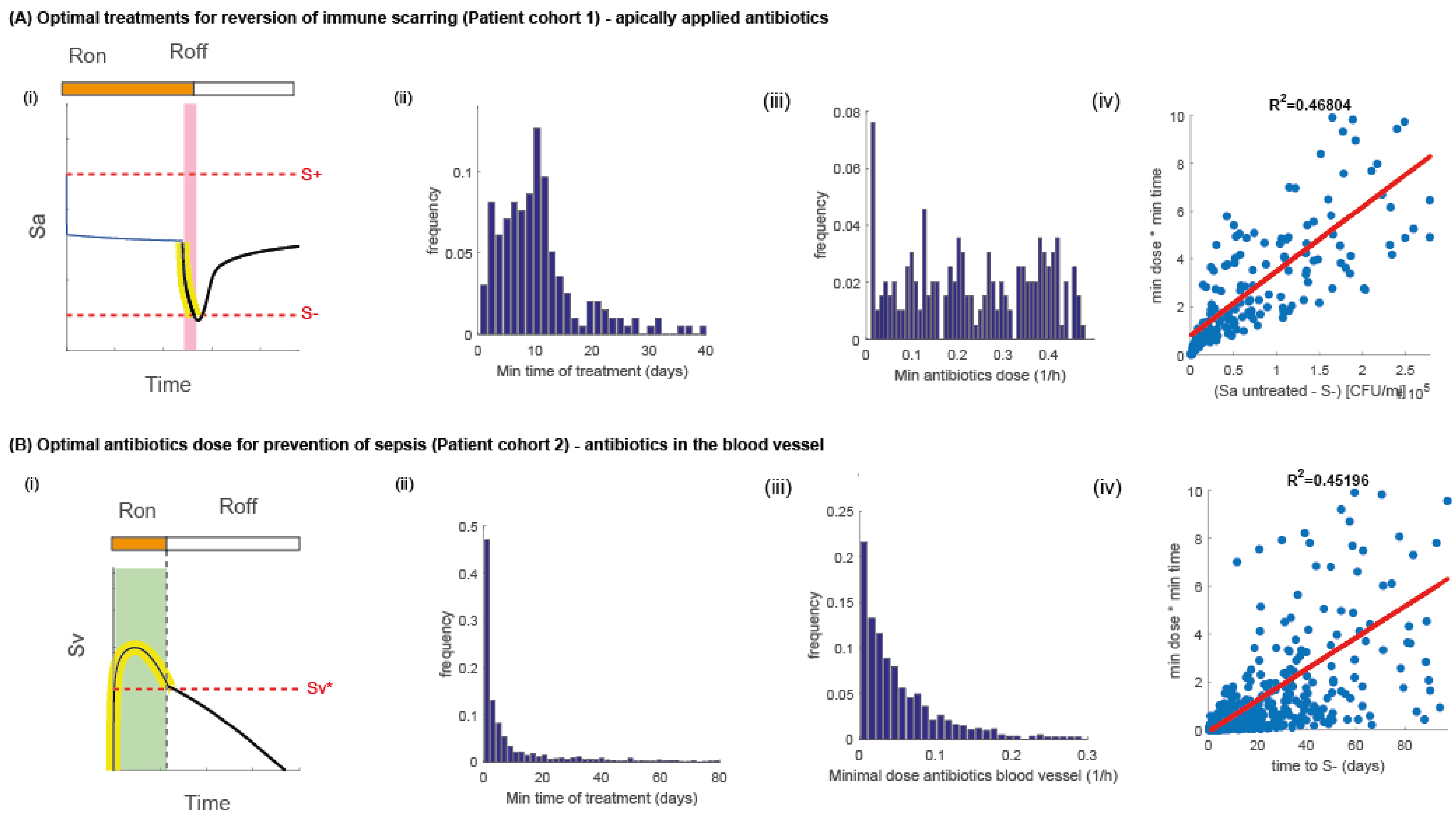


Consistent with experimental data: Andonegui et al, Shock 2009

Using the model for treatment optimization



Domínguez-Hüttinger, E. et al., 2017. Front. Physiol. 8:115.

Tackling antibiotics resistance!

From description to **prediction**

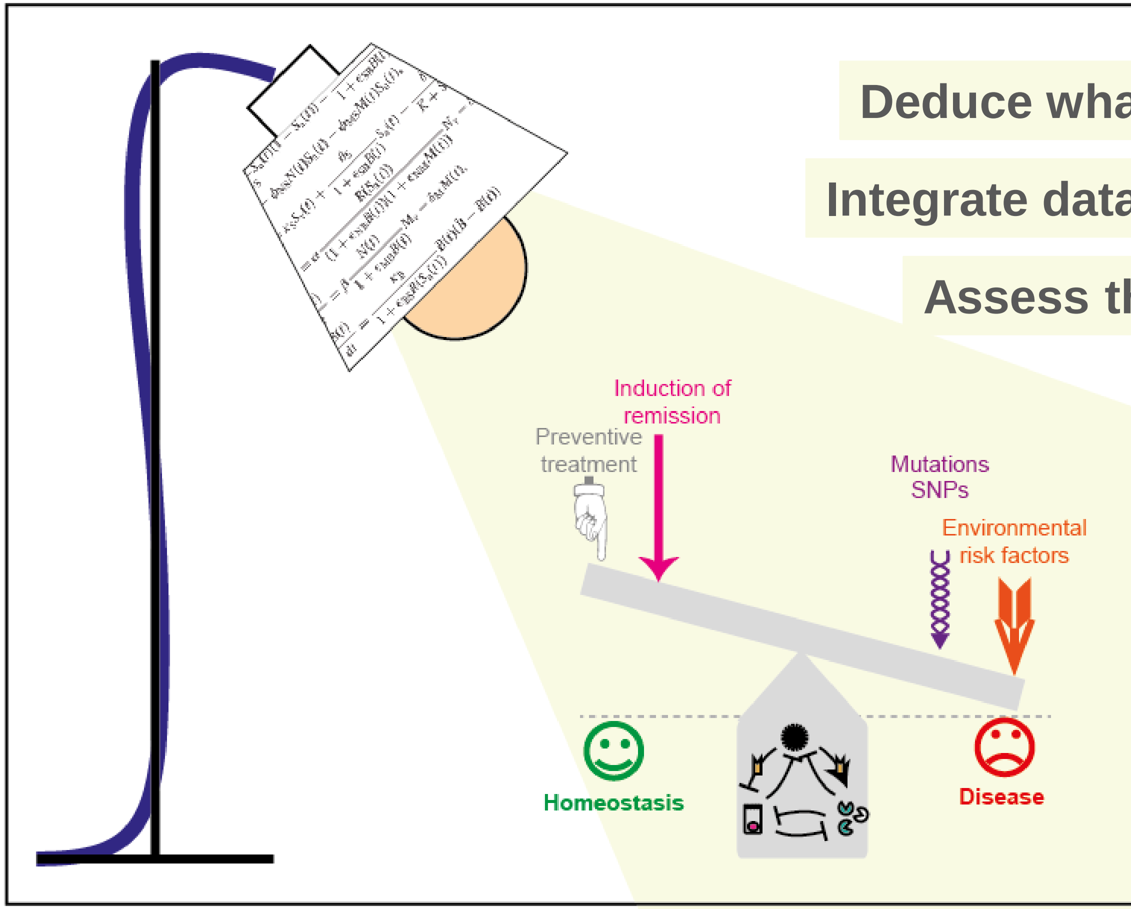
Robustness assessment


Prevention of
catastrophes

Design of optimal treamtents

Conclusions

Black box (a bit more) illuminated



Deduce what can´t be measured

Integrate data

Assess the robustness of the system

Identify the most likely risk factors for dysbiosis

Optimize treatments

Predict infectious dynamics

Systems biology to understand, prevent and optimally treat complex epithelial tissue diseases

frontiers in Physiology

ORIGINAL RESEARCH
published: 02 March 2017
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Check for updates

Mathematical Modeling of *Streptococcus pneumoniae* Colonization, Invasive Infection and Treatment

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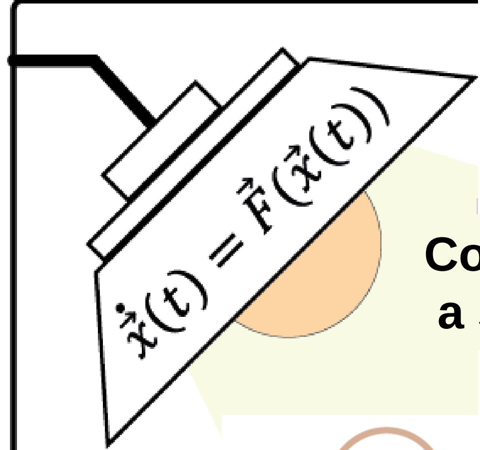
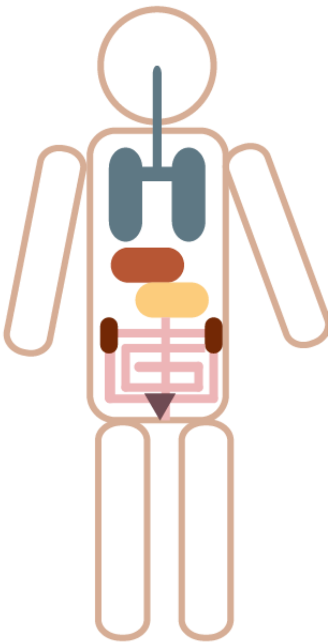


Complex epithelial tissue diseases – a systems biology perspective



1. Guillem Hurault, E. Domínguez-Hüttinger, …, R. J. Tanaka et al., 2020, CEA
2. G. Tanaka, E. Domínguez-Hüttinger, …, R. J. Tanaka. *Journal of Theoretical Biology,* 448: 66-79
3. P. Christodoulides, …, E. Domínguez-Hüttinger, …, R. J. Tanaka. 2017. *Phil.Trans.R. Soc. A.*, 375: 20160285.
4. E. Domínguez-Hüttinger, …, R. J. Tanaka, 2017. Front. Physiol., 8: (115), pp.1–14.
5. F. Méndez-López, …, E. Domínguez-Hüttinger, … E. Álvarez-Buylla, 2017. BMC Syst Biol., 11(24), pp.1–15.
6. E. Domínguez-Hüttinger, …, R. J. Tanaka. 2017. J. Allergy Clin. Immunol 139:1861-72.
7. M. D. A. van Logtestijn, E. Domínguez-Hüttinger, …, R. J. Tanaka. 2015. PLoS ONE 10(2):e0117292.
8. Domínguez-Hüttinger E., …, R.J. Tanaka. 2013. Interface Focus 3:20120090
9. Elena R. Álvarez-Buylla Roces, …, Elisa Domínguez-Hüttinger, and Mariana Esther Martínez-Sánchez. *Modeling Methods for Medical Systems Biology - Regulatory Dynamics Underlying the Emergence of Disease Processes.* Editorial: Springer. Serie: Advances in Experimental Medicine and Biology (2018)

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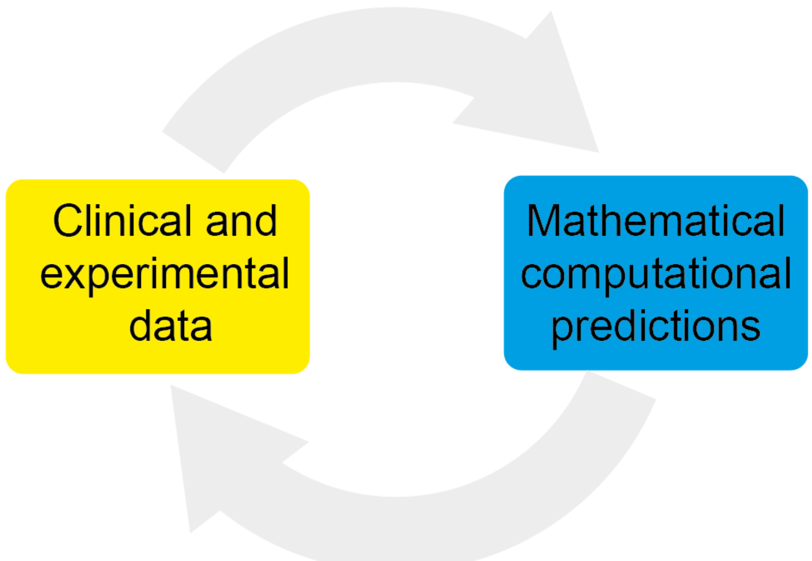

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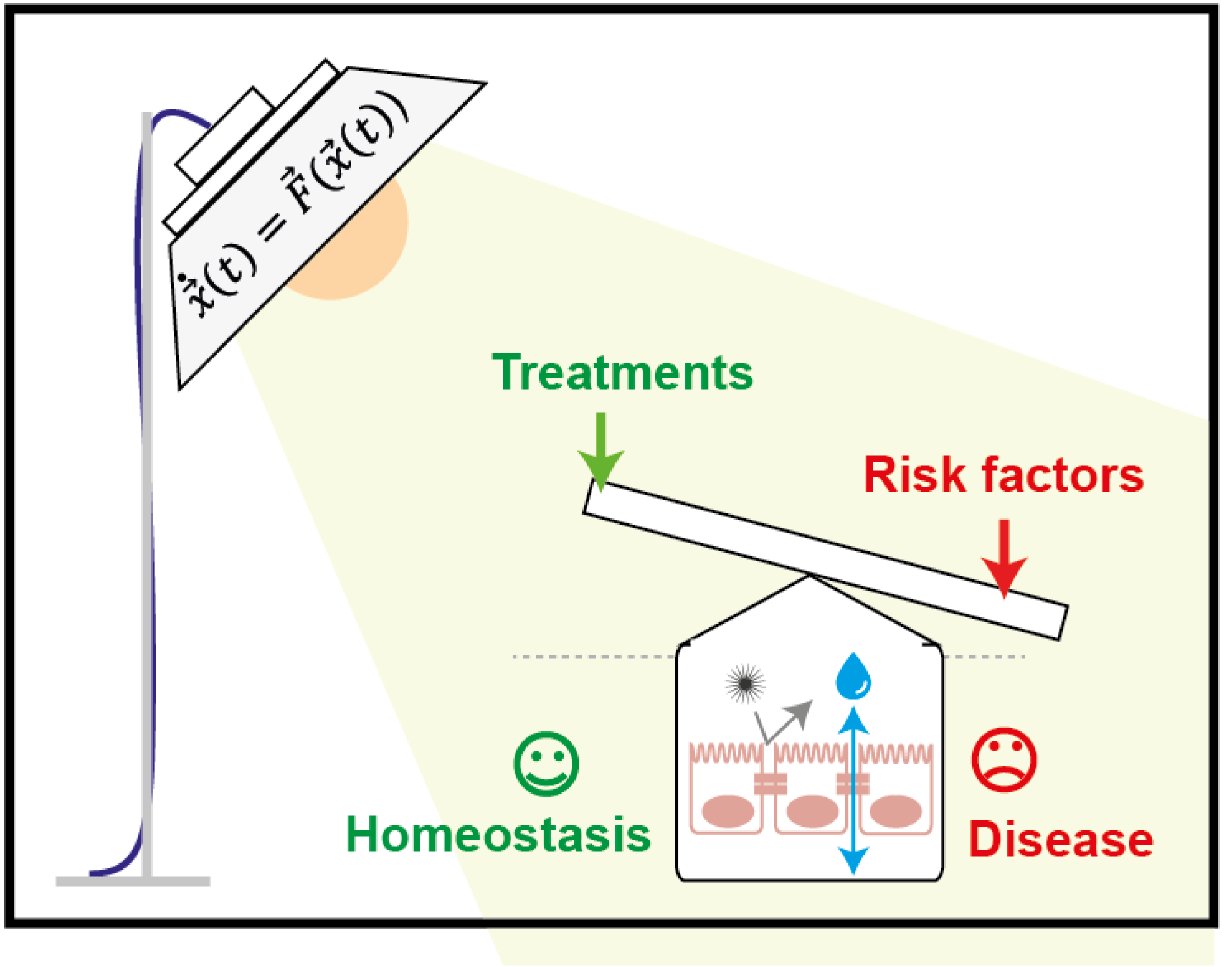

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