Imperial College London

Dual feedbacks in inflammatory and infectious disease

CDS@20

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Biological Control design principles

- Fast, rough + Slow, detailed regulation
- Use of a pair of competing signals for target setting

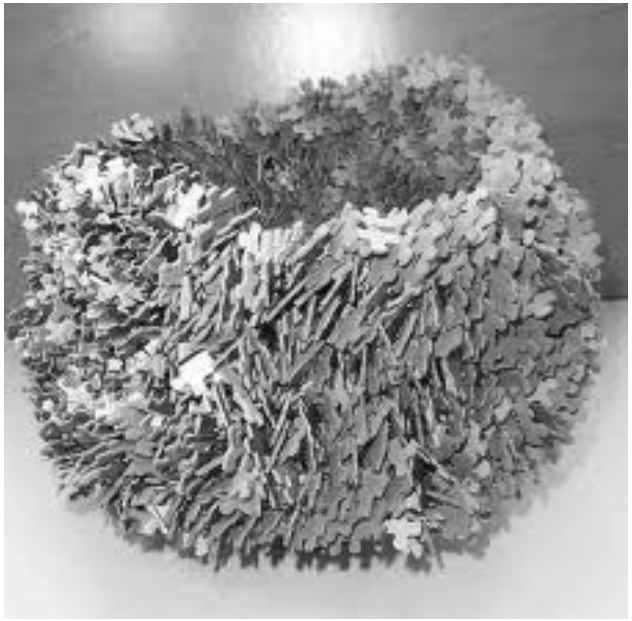
Key mechanisms for
effective diagnosis and treatment

Health vs Disease

- Balanced positive and negative feedbacks
- Different spatial/temporal scales

Modelling approach

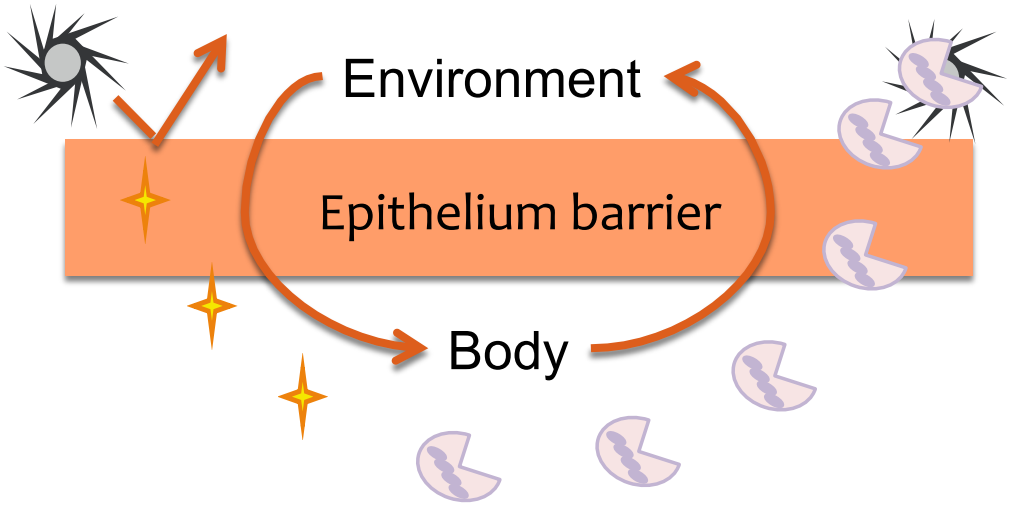
Experimental data



Minimal explanatory models

- Transferable tools and insights
- Common design principles

Inflammatory and infectious disease

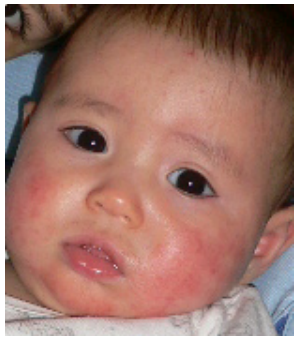


- Skin – Atopic eczema
- Upper respiratory airway – Bacterial infection
- Lung – Fungal infection

Skin: Atopic Dermatitis (eczema)

<u>High Socio-economic Impact</u>

- ~30% children; > 5million people in UK
- Treatment cost: $3.8 billion/year in US
- 3-fold increase in last 30 years



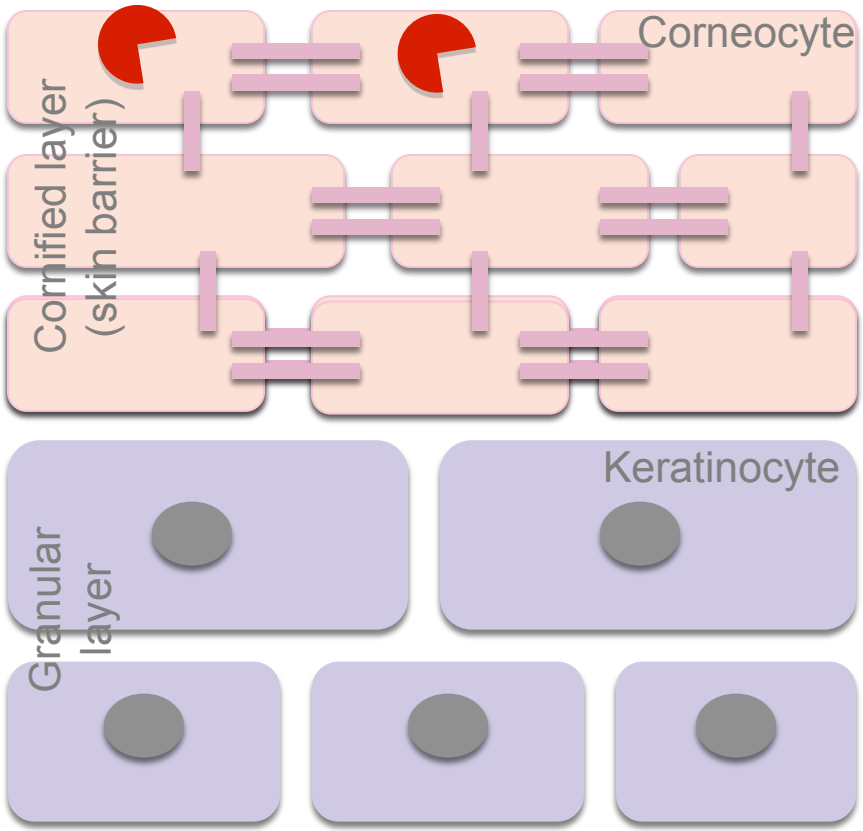
<u>Characteristic Symptoms</u>

- ✓ Red, itchy eczema caused by allergens
- ✓ Persistence & aggravation of inflammation
- ✓ Skin vulnerable to infection

<u>Benefits for Modelling</u>

- Abundant yet fragmented knowledge
- Morphological appearance

Skin Barrier Homeostasis

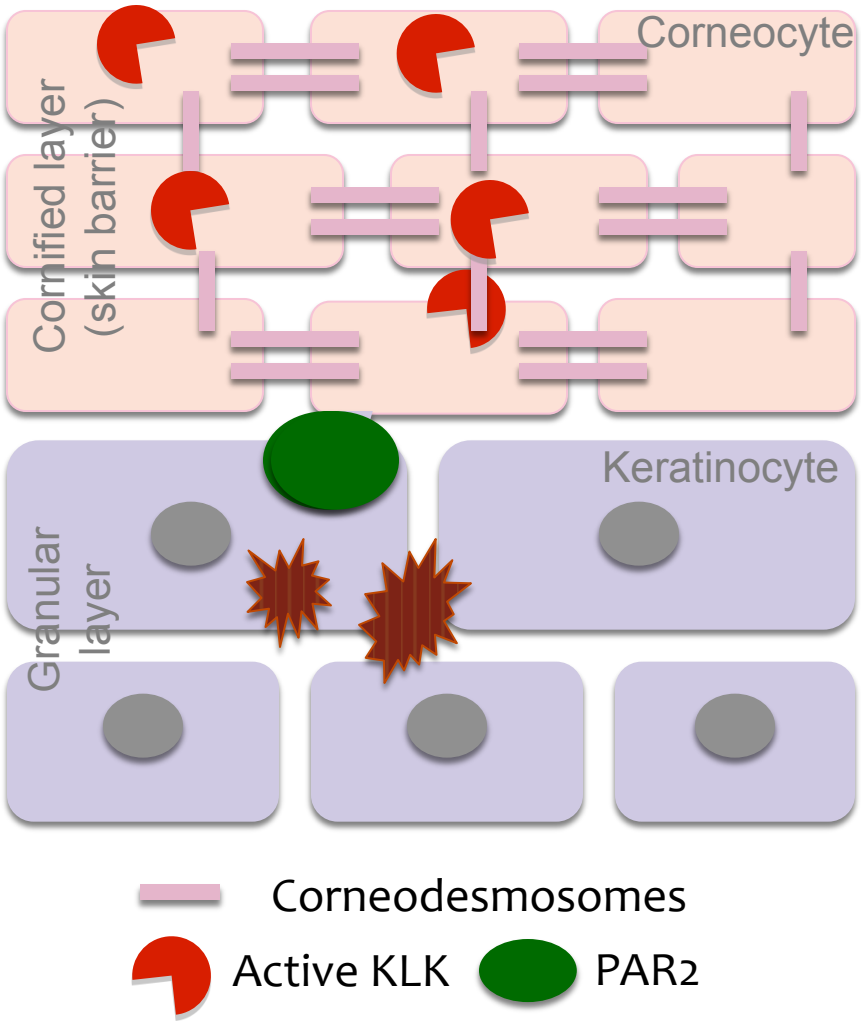


Corneodesmosomes

Active KLK (protease)

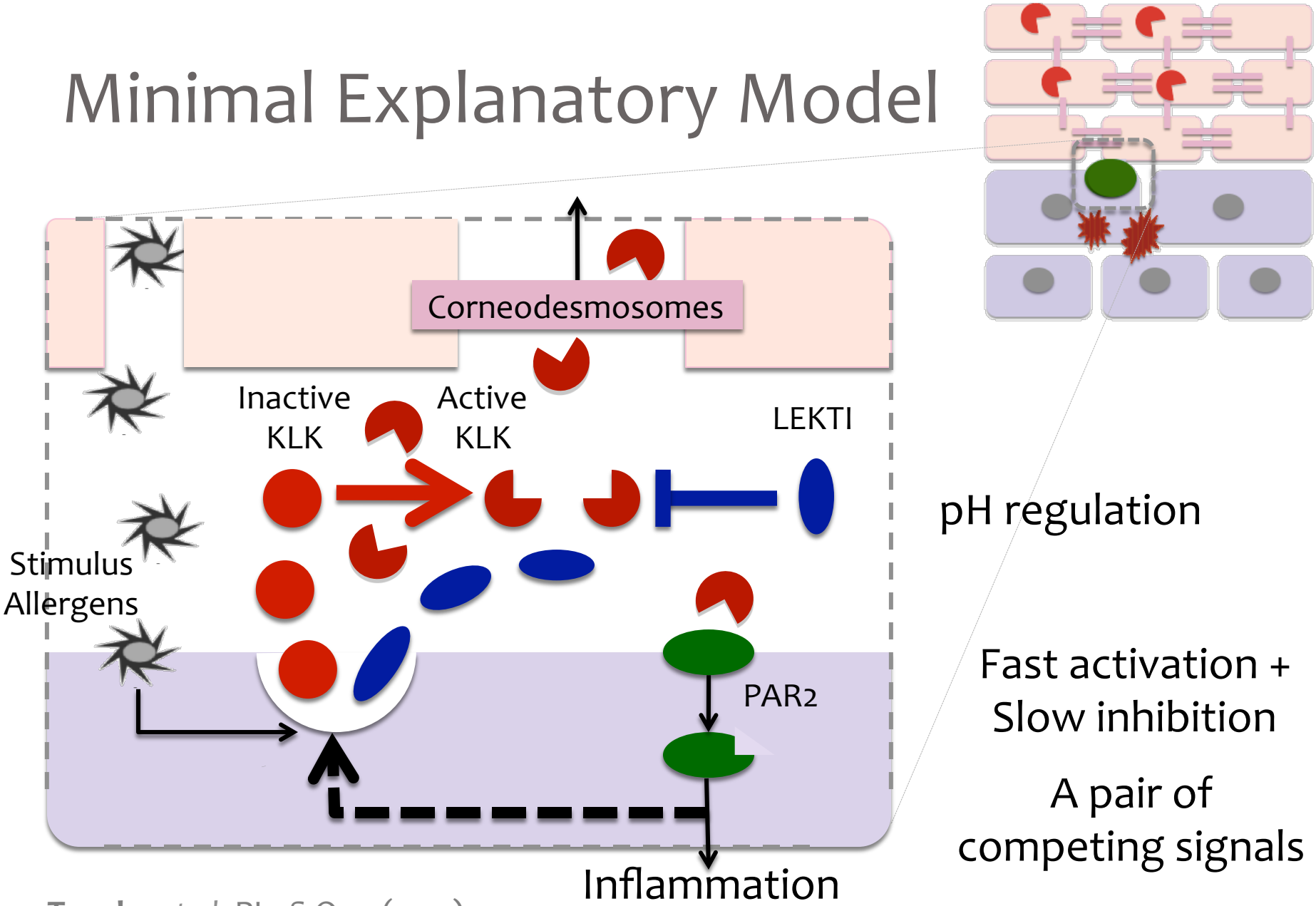
Defective Skin Barrier in atopic eczema

Excessive KLK activity



Inflammation

Minimal Explanatory Model



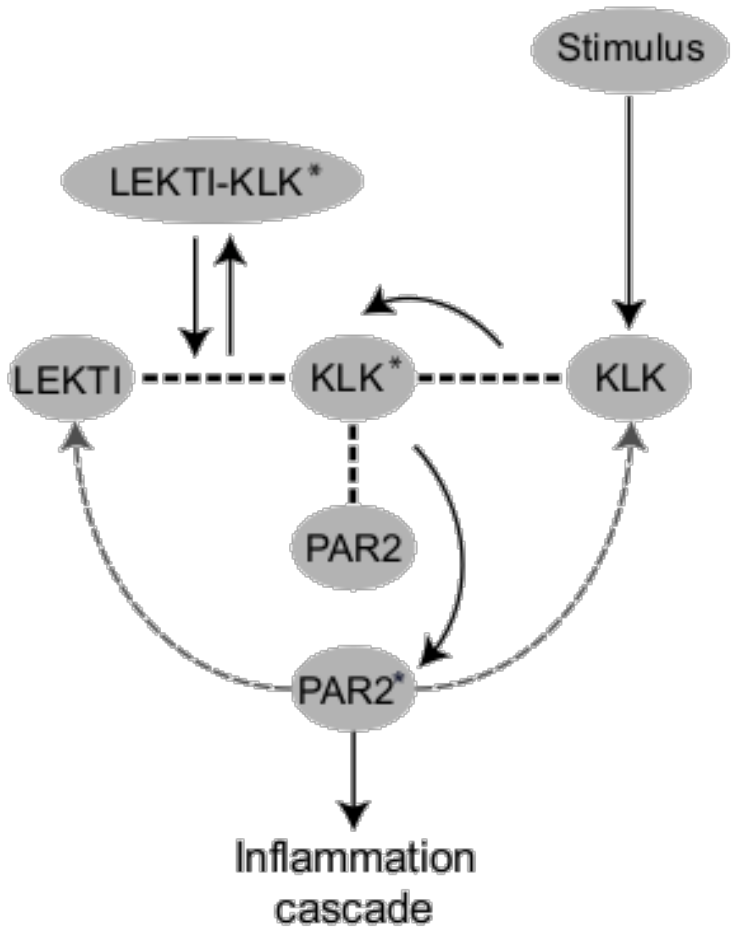
pH regulation

Fast activation + Slow inhibition

A pair of competing signals

Tanaka *et al*. PLoS One (2011)

Mathematical Model



$$\frac{d[\mathrm{L}-\mathrm{K}^*]}{dt} = k_a[\mathrm{K}^*][\mathrm{L}] - k_d[\mathrm{L}-\mathrm{K}^*] - \delta_{LK}[\mathrm{L}-\mathrm{K}^*]$$

$$\frac{d[\mathrm{L}]}{dt} = -k_a[\mathrm{K}^*][\mathrm{L}] + k_d[\mathrm{L}-\mathrm{K}^*] - \delta_L[\mathrm{L}] + t_L(m_L + f_L[P^*])$$

$$\frac{d[\mathrm{K}^*]}{dt} = -k_a[\mathrm{K}^*][\mathrm{L}] + k_d[\mathrm{L}-\mathrm{K}^*] + k\frac{[\mathrm{K}^*][\mathrm{K}]}{[\mathrm{K}]+C_K} - \delta_{K^*}[\mathrm{K}^*]$$

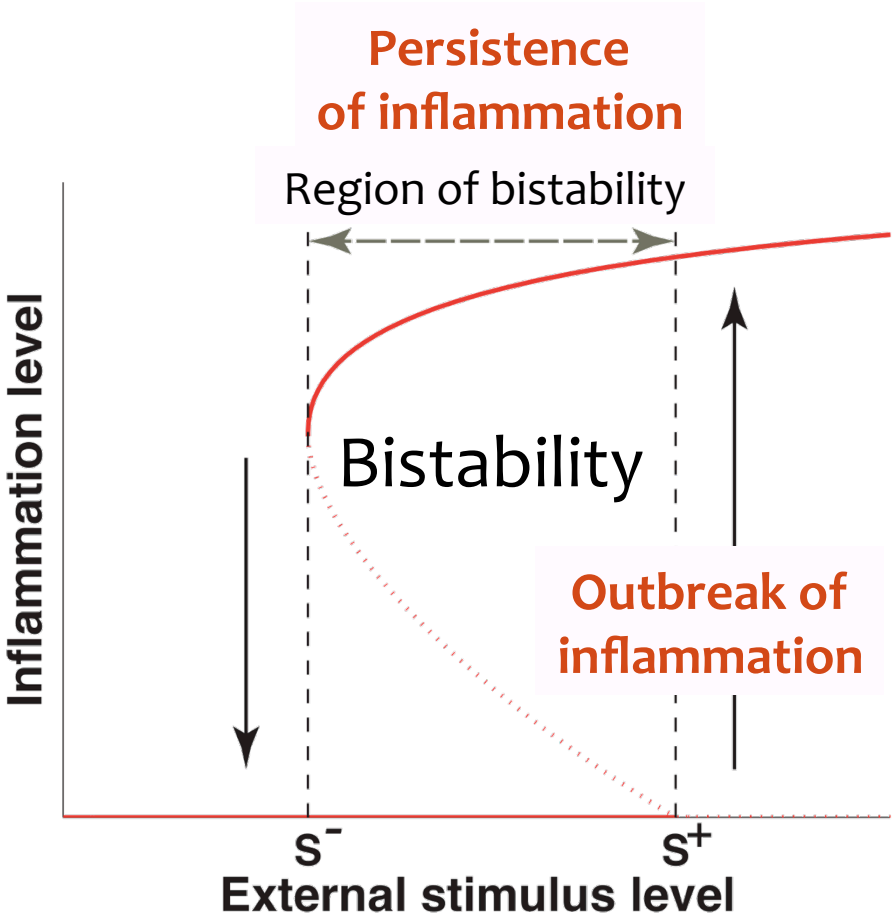
$$\frac{d[\mathrm{K}]}{dt} = -k\frac{[\mathrm{K}^*][\mathrm{K}]}{[\mathrm{K}]+C_K} - \delta_K[\mathrm{K}] + m_K + f_K[P^*] + f_{KS}S$$

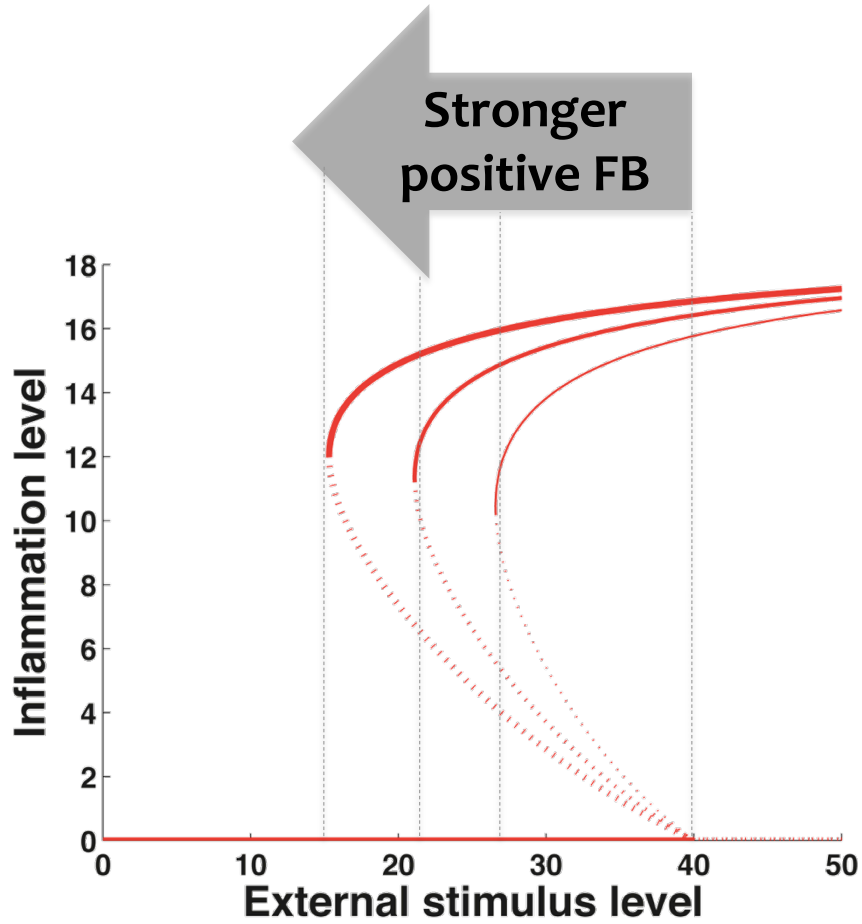
$$\frac{d[\mathrm{P}]}{dt} = -k_P\frac{[\mathrm{K}^*][P]}{[P]+C_P} - \delta_P[\mathrm{P}] + m_P$$

$$\frac{d[\mathrm{P}^*]}{dt} = -k_P\frac{[\mathrm{K}^*][\mathrm{P}]}{[P]+C_P} - \delta_{P^*}[\mathrm{P}^*]$$

Tanaka *et al*. PLoS One (2011)

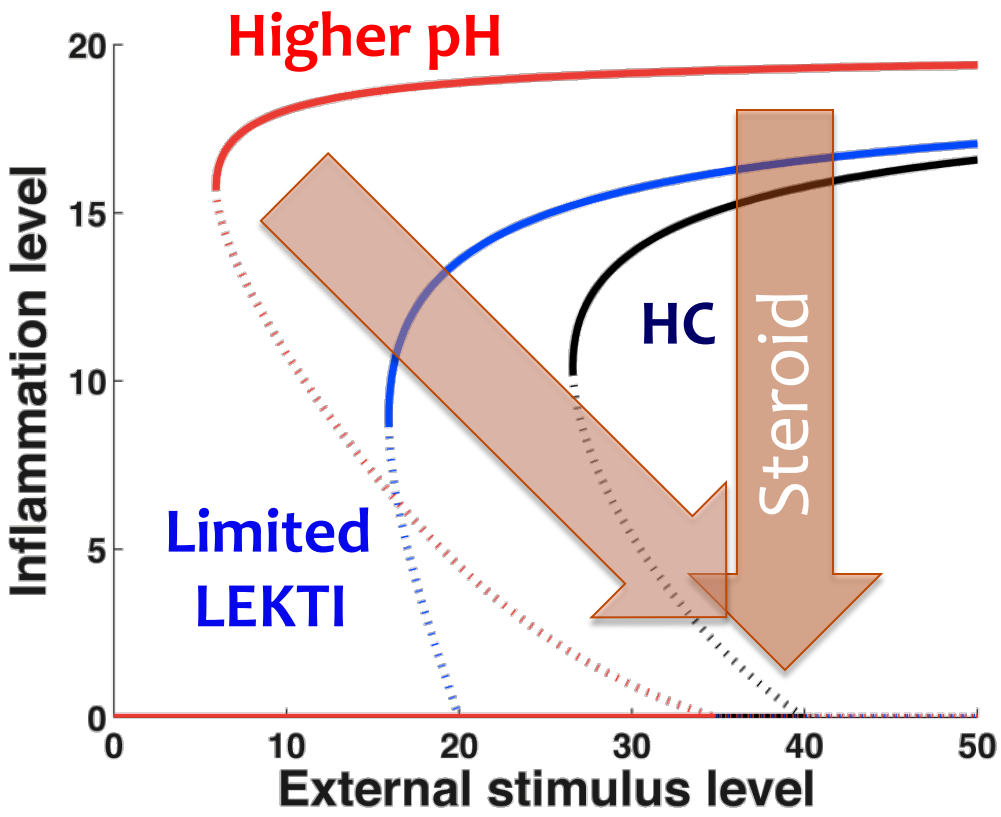
Bistable switch





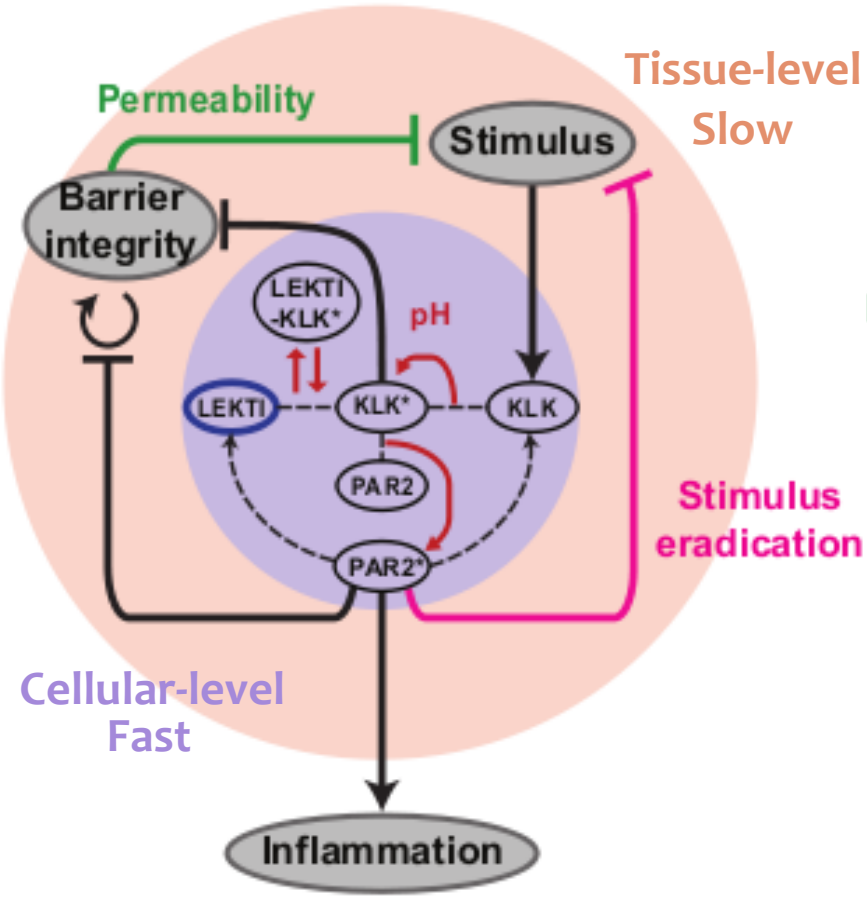
Tanaka *et al*. PLoS One (2011)

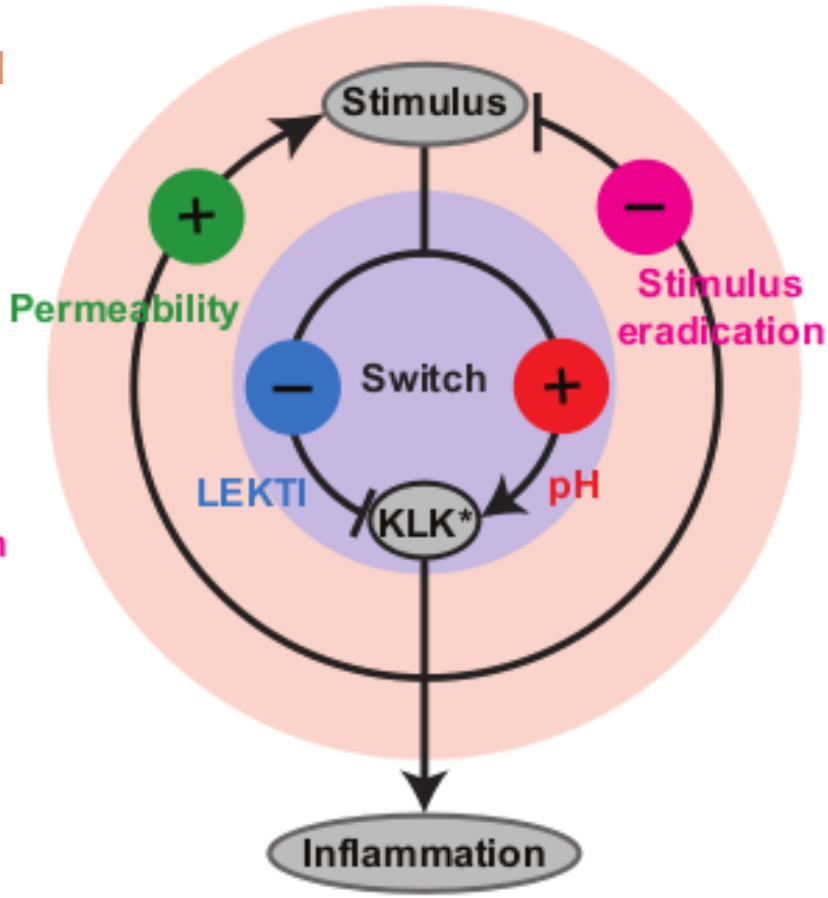
Vulnerability of eczema skin



Tanaka *et al*. PLoS One (2011)

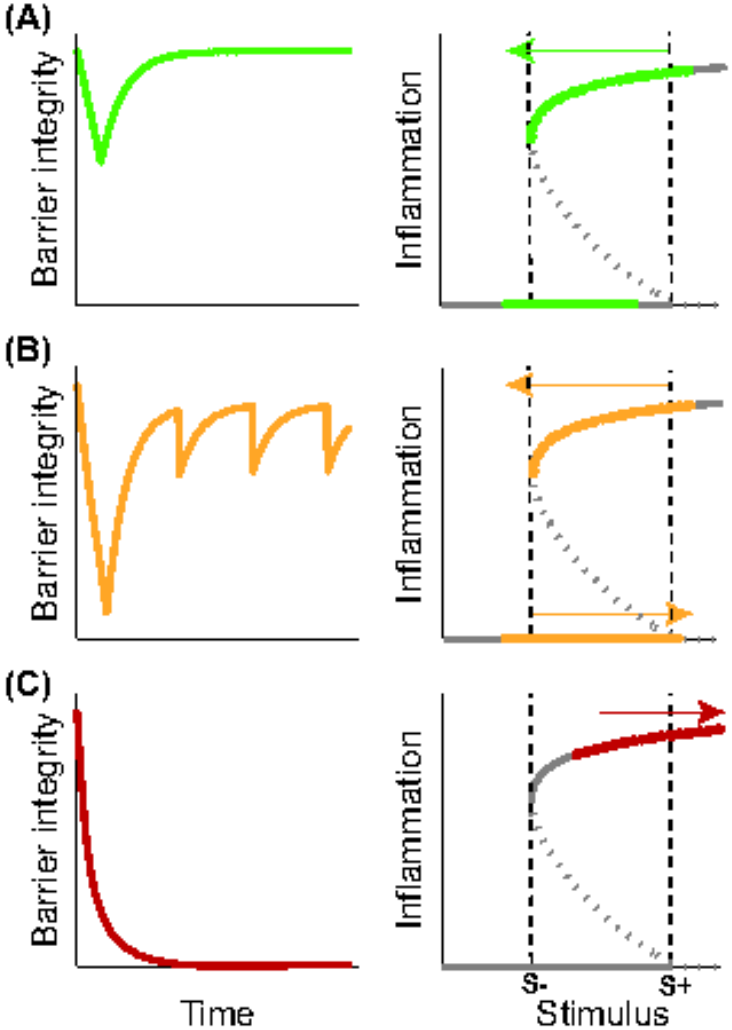
Model for Multi-scale regulation

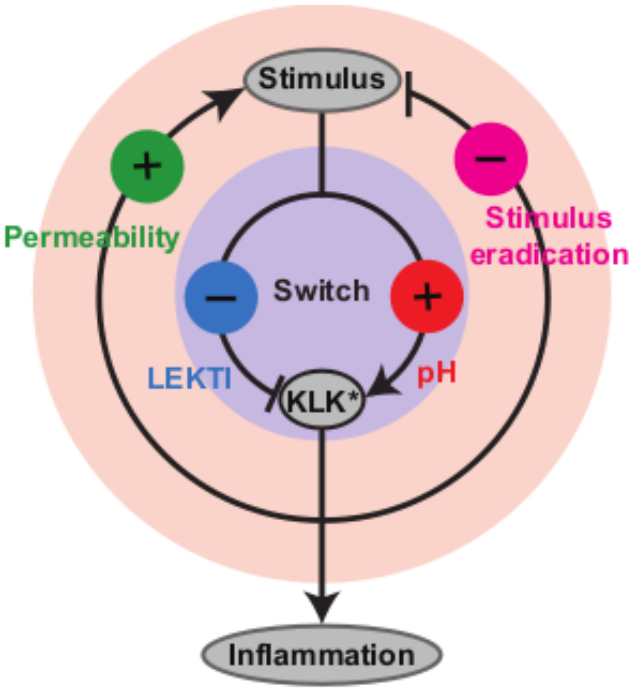




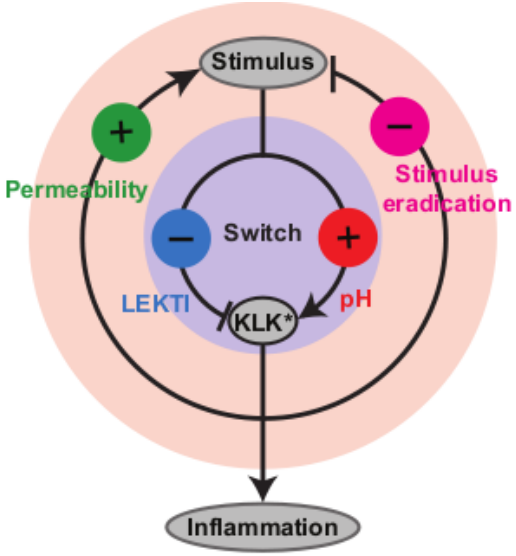
Domínguez-Hüttinger *et al*. Interface Focus (2013)

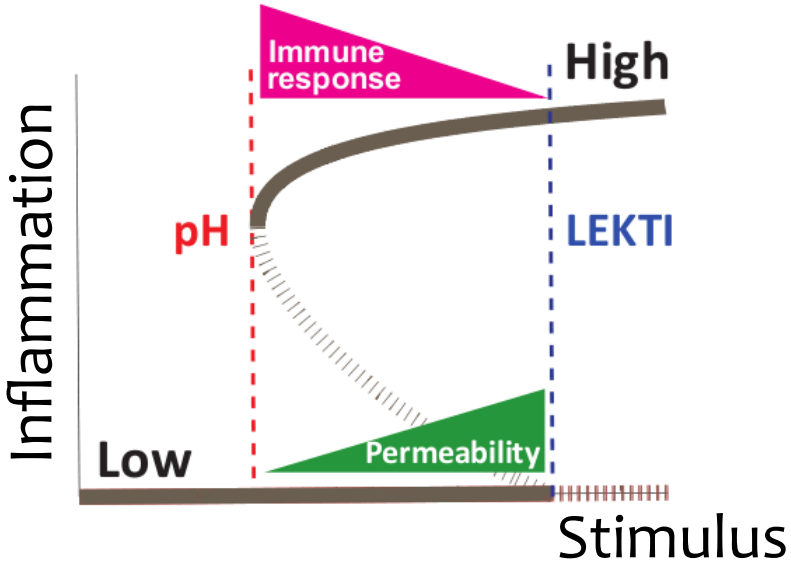
Simulation Results
- Possible behaviours -





Domínguez-Hüttinger *et al*. (2013)

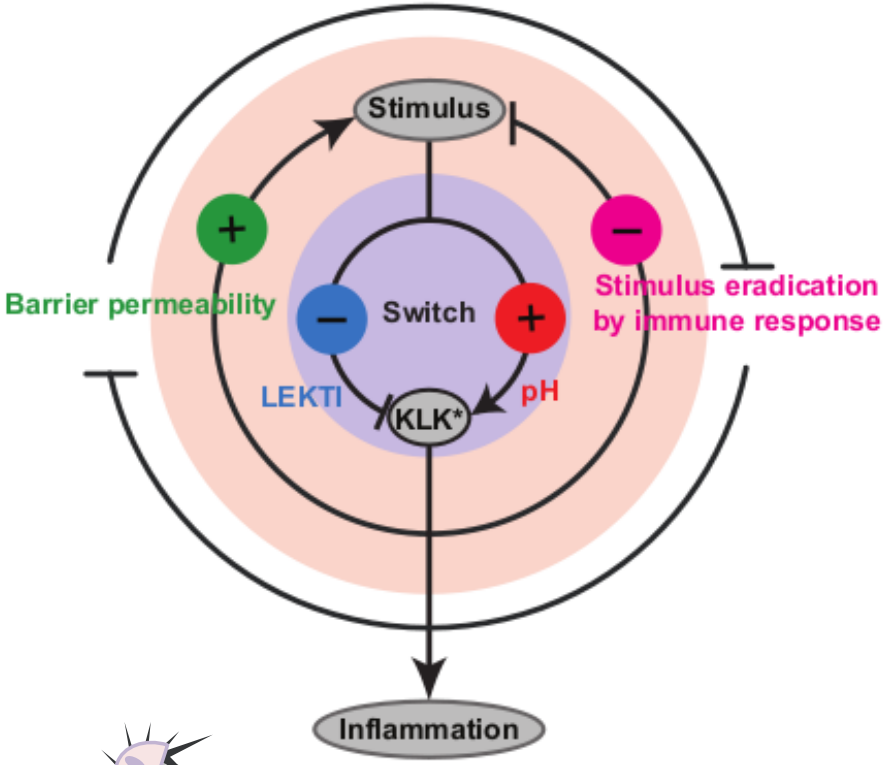


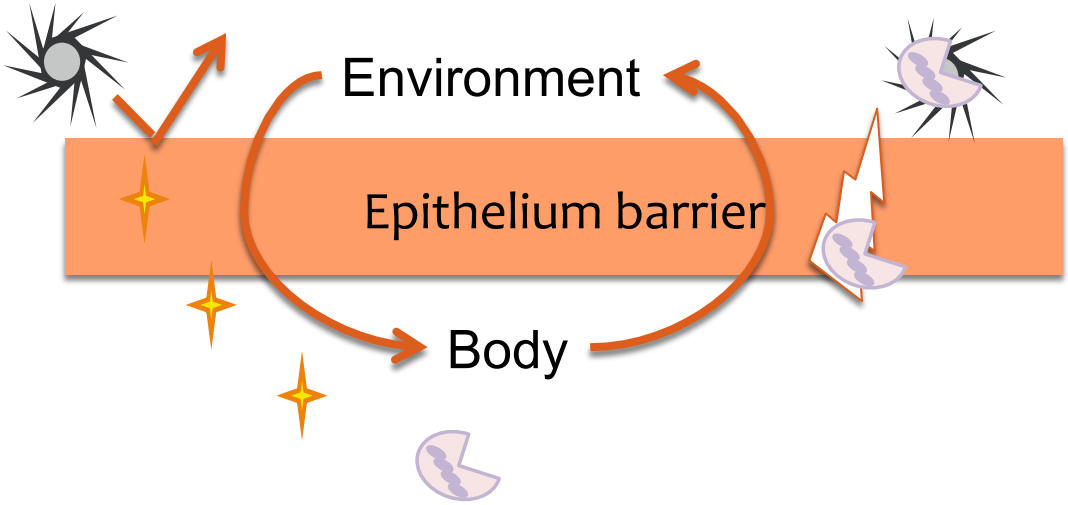


Risk factors	Cellular-level Dose-response	Tissue-level Dynamics
LEKTI deficiency	Low threshold for inflammation outbreak	Oscillatory behaviour in barrier/inflammation
High permeability (Filaggrin deficiency)		
High pH	Persistent inflammation	Chronic damage in barrier/inflammation
Weak immune response		

Further interplay

- Barrier function
- Immune responses





Conclusion: AD model

Successful synergy: Control + Biology + Medicine

- A mathematical model for AD – multi-scale regulation
  - Inflammation outbreak by a defective skin barrier
  - More susceptibility to external stimulus
  - Stronger persistence of inflammation
  - Oscillatory behaviour and chronic damage
  - Combination of multiple risk factors
- Loss of balanced feedback – **Drug target**
- Different causes for AD – **Personalized treatment**
- Further development of model – Adaptive immunity
- On-going collaboration with several dermatologists

Biological control design principles

Health vs Disease

- Balanced positive and negative feedbacks
- Different spatial-temporal scales
- Inflammatory/infectious disease

Biological necessity

Efficiency

Homeostasis - Disease

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