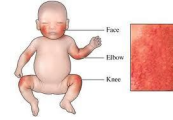


Modelling Atopic Dermatitis using Petri Nets

Dr Marta E Polak
BioPPN
Hamburg June 2012

Atopic Dermatitis – impact on patient life



- Rash
- Extensive itch
- Uncontrolled scratching
- Skin infections
- Sleep disturbance

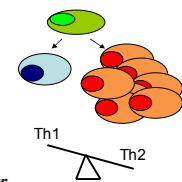


- Problems with concentration
- Aesthetic concerns
- Dietary restrictions
- Stress
- Depression

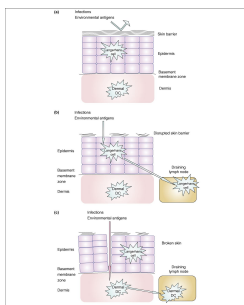
Atopic Dermatitis - treatment

- Limited options
- Unspecific
- Relief in symptoms
- Side effects – immunosuppressants, steroids

Aberrant polarisation of immune responses in AD



Role of keratinocytes



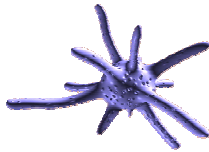
- skin barrier: physical, immunological, chemical
- Genetic abnormalities => Th2
- Removal of barrier => Th2
- Colonisation by S.A. => Th2
- Can sense the antigen
- Produce cytokines, incl TNFα and TSLP, IL-31, IL-33

Staphylococcus Aureus



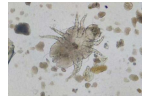
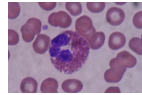
- Releases toxins: SEA & SEB => Th2
- Induces infiltration of T cells
- Induces degranulation of Mast cells
- Enhances presentation of antigen to Th2 cells
- Contains LTA => Th2

Dendritic cell

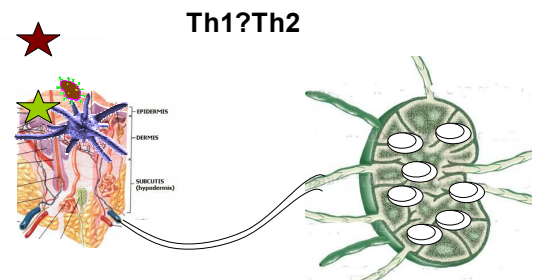
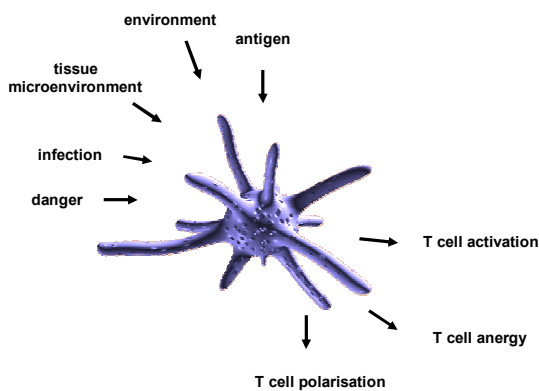


- Antigen Presenting Cells
- Ability to prime naïve T cells
- Ability to polarise naïve T cells
- In AD: LC & IDEC: high in FcεR1
- LC => prime Th2
- Tissue resident sentinels
- orchestrate the immune reaction

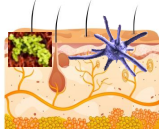
Other factors



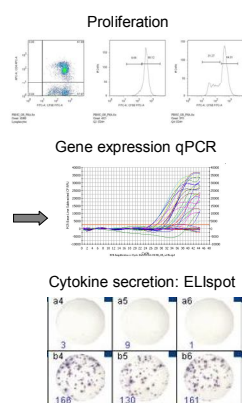
- Eosinophils: high level in blood and in skin => Th2
- Allergens = proteases = tissue damage => Th2
- Scratching = tissue damage => Th2



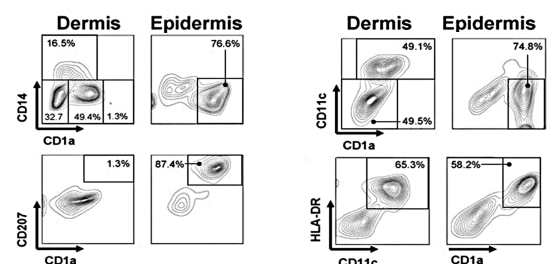
<http://www.eczemacenter.nm>



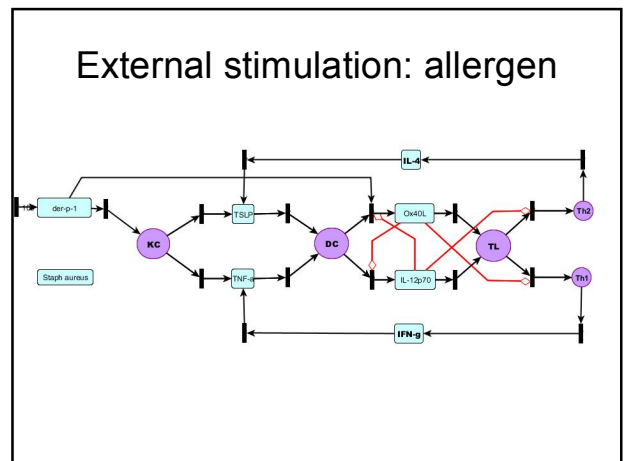
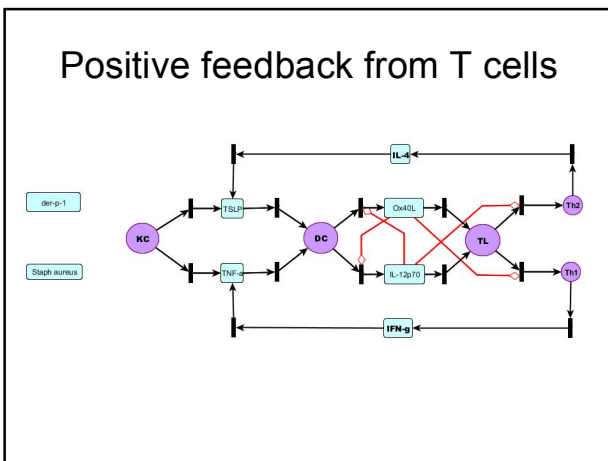
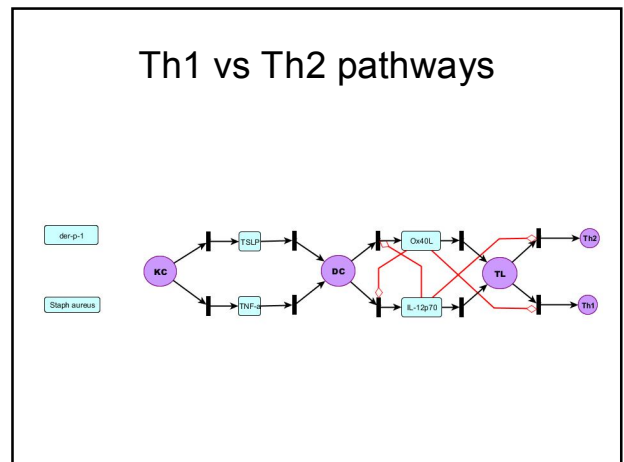
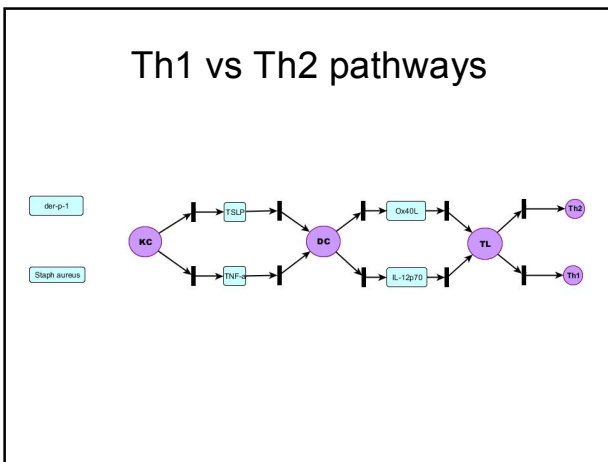
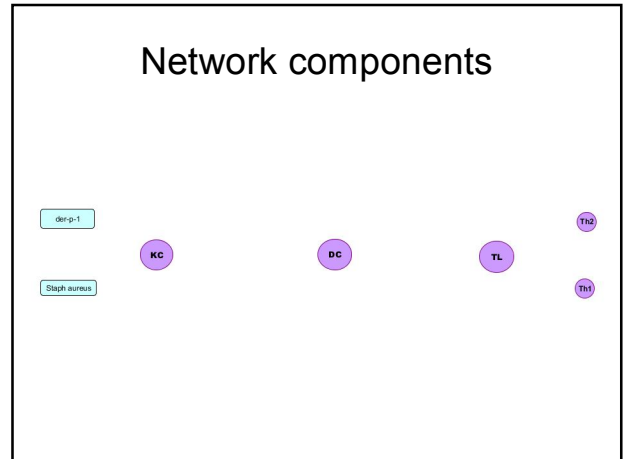
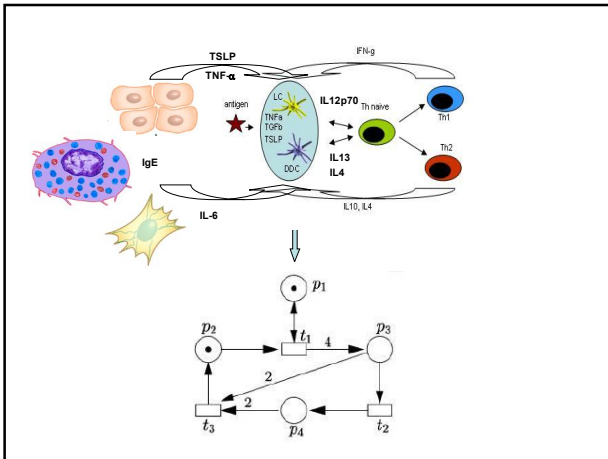
http://www2.cedarcrest.edu/academic/bio/hale/bioT_EID/lectures/staph.html



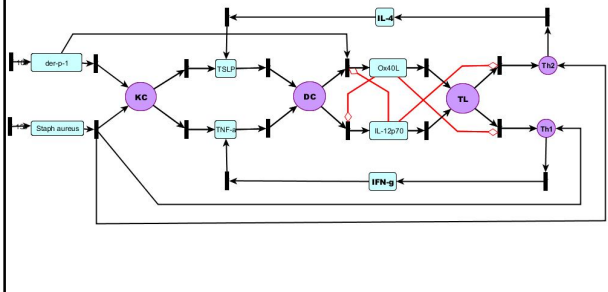
Subpopulations of DC in different skin compartments



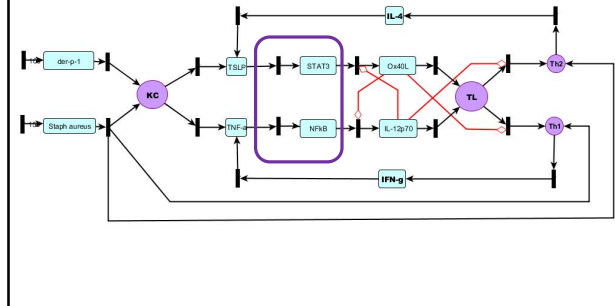
Polak ME et al J Invest Dermatol. 2012 Jun;132(6):1636-44.



External stimulation: *Staphylococcus Aureus*



Th1 vs Th2 in DCs



Biolayout Express and SPN

OPEN ACCESS Freely available online

PLOS COMPUTATIONAL BIOLOGY

The Signaling Petri Net-Based Simulator: A Non-Parametric Strategy for Characterizing the Dynamics of Cell-Specific Signaling Networks

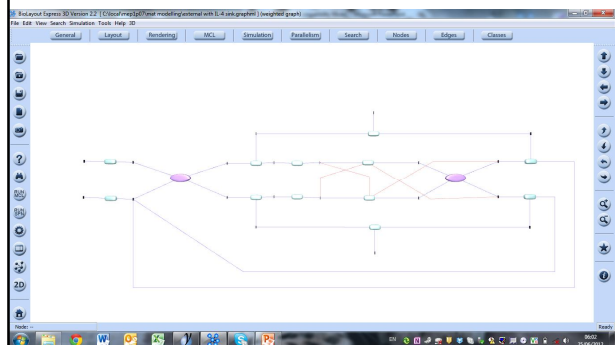
Derek Ruths^{1*}, Melissa Muller², Jen-Te Tseng², Luay Nakhleh¹, Prahlaad T. Ram²

¹Department of Computer Science, Rice University, Houston, Texas, United States of America, ²Department of Systems Biology, University of Texas M. D. Anderson Cancer Center, Houston, Texas, United States of America

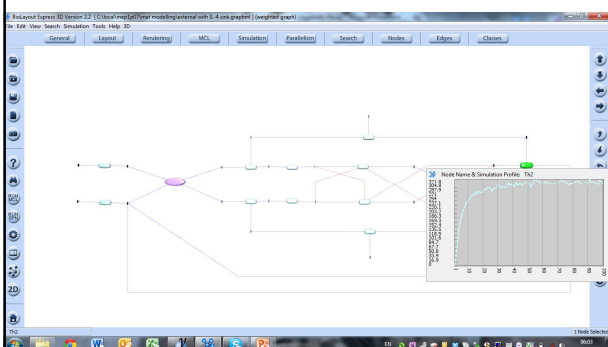
Simulation:

- PN executed multiple times
- Firing sequence given by a signalling even generator
- Two-level time scale to randomise order of transition firing
- Within one time block each transition is fired only once, in random order

Simulations

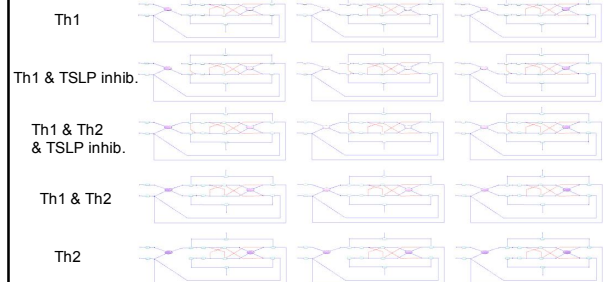


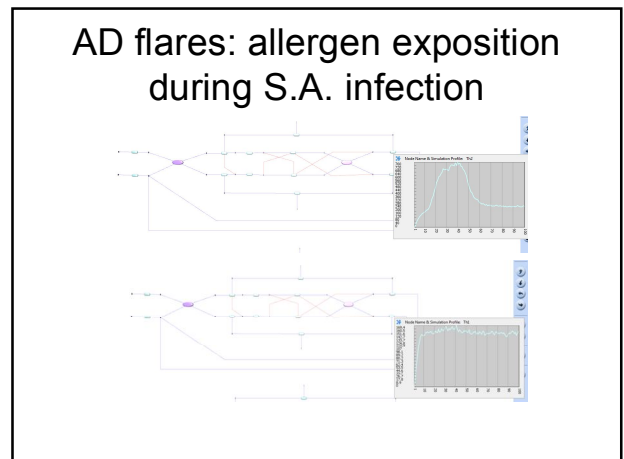
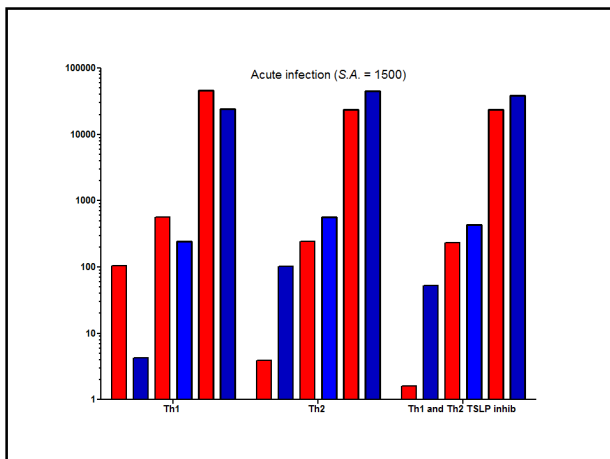
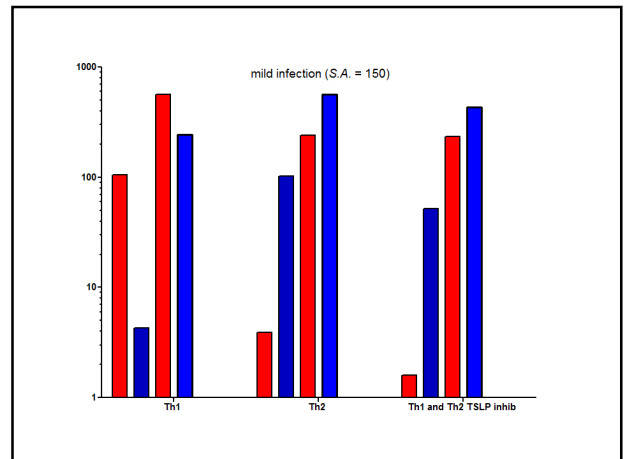
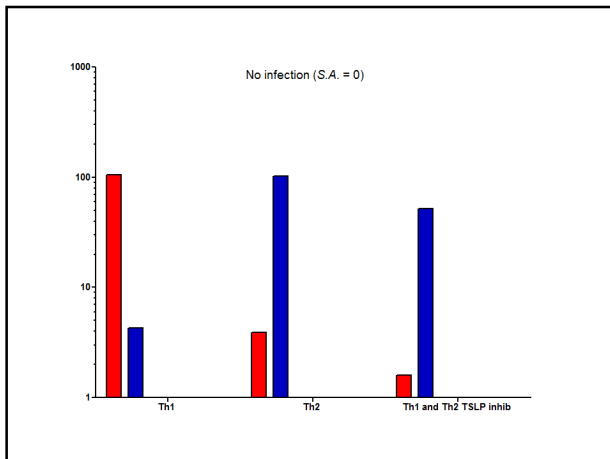
Simulations



Model analysis

der-p-1 = 100 No S.A. S.A. = 150 S.A. = 1500





Questions:

- Are PN a suitable tool to model AD (or any other cell-to-cell interactions)?
- How much data/information is necessary to construct a reasonable model?
- How much information is necessary to validate the model?
- What is the measure of correct model predictions?
- At what level of advancement such a model can give meaningful predictions?



Thank you for your attention

