Modeling and analysis of T cell differentiation

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NSF Expeditions in Computing

Abstract

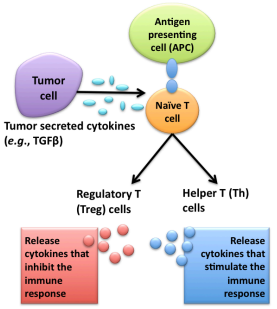
Peripheral naïve T-cells differentiate into several effector phenotypes and their relative phenotype proportions critical for immune-related pathologies.

Logical model of T-cell differentiation is developed for studying selection of regulatory (Treg) vs. helper (Th) cell fate.

Model results accurately recapitulate existing experimental results, provide novel insights into the system and suggest directions for new experiments.

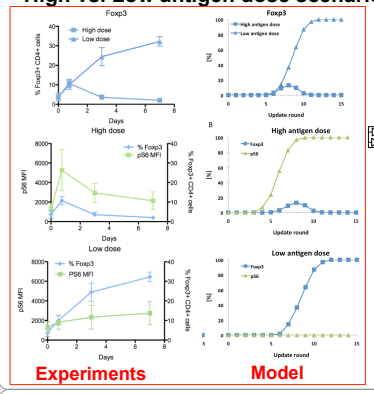
Motivation

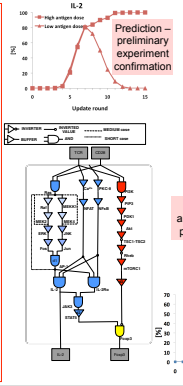
Mechanisms involved in dendritic cell-mediated expansion of Treg vs. Th cells are not well understood.

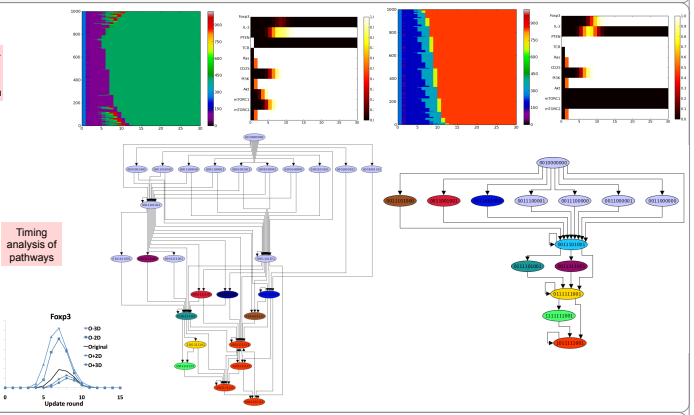


Results

High vs. Low antigen dose scenario

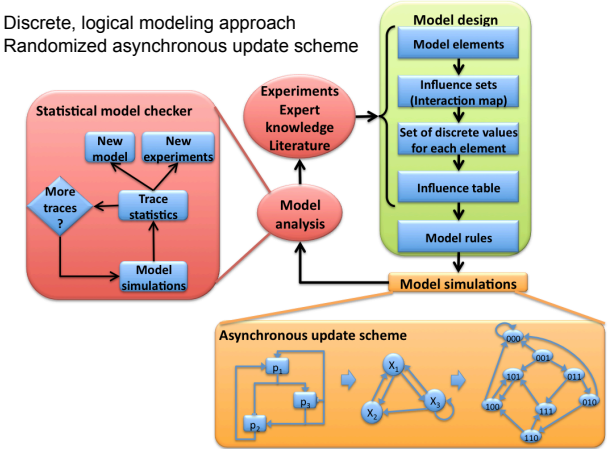




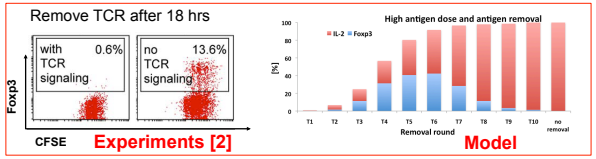


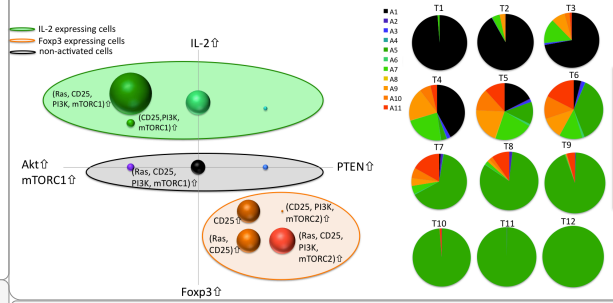
Modeling and Analysis Methodology

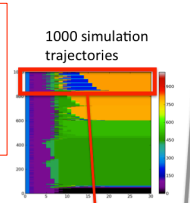
Discrete, logical modeling approach
Randomized asynchronous update scheme

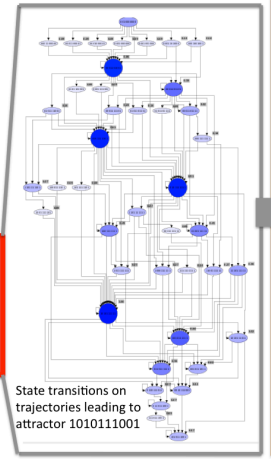


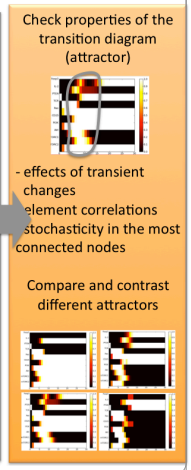
Antigen removal scenario











T Cell Differentiation Model

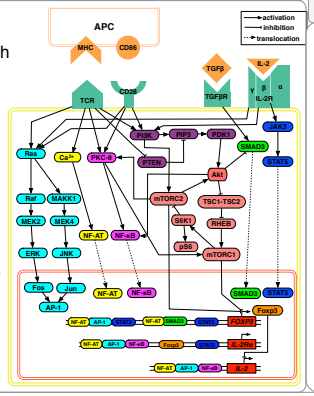
Presentation of antigen by dendritic cells (APC) initiates signaling pathways through TCR and CD28 resulting in the activation of transcription factors AP-1, NFAT and NFκB

Growth factor signaling from TGFβR and IL-2R results in activation of transcription factors SMAD3 and STAT5, respectively

The transcription factors converge on the genes for Foxp3, IL-2 and IL-2Rα and initiate protein expression

PI3K signaling via TCR and CD28 results in activation of mTORC1 via the Akt pathway which is antagonized by PTEN

mTORC1 and mTORC2 inhibit Foxp3 expression



Discussion

Methods
- Logical models easily constructed, simulated and refined
- Model behavior sensitive to composition of rules
- Decisions for rule composition highlighted need for future experiments

Results
- Important experimental results reproduced:
  - Transient Foxp3 expression for high antigen dose
  - Treg expansion under: prolonged low antigen dose, antigen removal, Akt/mTORC pathway inhibition
  - pS6 expression negatively correlates with Treg cell fate
- Race between Foxp3 induction by STAT5 and inhibition by mTORC1 activation controls final expression levels
- Analysis identifies PTEN, STAT5 and Akt/mTOR axis as critical nodes and pathways requiring further experimental evidence
  - PTEN regulation not well understood but critical for fate decision
  - Relative levels of mTORC1 and mTORC2 very important for Foxp3 expression
  - STAT5 may be necessary for Foxp3 expression in most cases

Future Directions

Experiments
- Differential PTEN expression in Treg and Th cells
- Presence and relative levels of mTORC1 and mTORC2 at different antigen doses and their correlation with Foxp3 expression/inhibition
- Presence of Smad3 at low antigen dose
- Relative time of activation of CD25 vs. STAT5

Modeling
- Model with three instead of two levels
- Interactions of multiple cell types
- Knock-outs, knock-ins and inhibitors
- Updating biochemically fast and slow events differently

References

1 Turner *et al. J Immunol (2009) vol. 183 (8) pp. 4895-903*
2 Sauer *et al. PNAS (2008) vol. 105 (22) pp. 7797*
3 Delgoffe *et al. Immunity (2009) vol. 30 (6) pp. 832-44*
4 Albert *et al. (2008) Source Code for Biology & Medicine*