Using Multi-Scale Modeling to explore the effects of *Mycobacterium tuberculosis* on T cell responsiveness in granulomas

Jess A. Millar[1,2], JoAnne L. Flynn[3], Jennifer J. Linderman[4], Denise E. Kirschner[1,5]

(1) Computational Medicine & Bioinformatics, (2) Epidemiology, (4) Chemical Engineering, (5) Microbiology & Immunology, University of Michigan, Ann Arbor, MI.,
(3) Microbiology & Molecular Genetics, University of Pittsburgh, Pittsburgh, PA.

GOALS OF THE STUDY

- Use model to predict how Mtb interferes with T cells at the molecular level (antigen presentation) and cellular/tissue level (T cell, macrophage movement, interaction)
- Combine molecular and cellular/tissue level models to explore how they interact, look for emergent behavior

T CELLS IN MTB

- Tuberculosis (TB): Infectious disease caused by *Mycobacterium tuberculosis* (Mtb). One–third of the world's population is infected with Mtb, 2 million deaths/year[1]
- Host immune cells (macrophages and T cells) form granulomas to contain the infection
- Only ~8% T cells in granulomas respond to Mtb[2]
- It's unknown why T cell response at site of infection is low

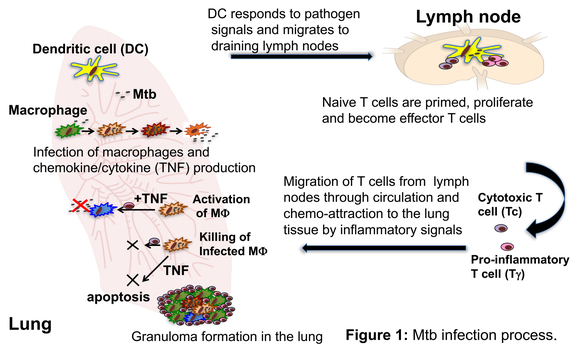
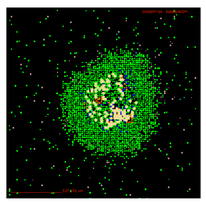


Figure 1: Mtb infection process.

MULTI-SCALE MODELING

Tissue/Cellular Model

- GranSim[3,4] captures discrete cellular dynamics between immune cells and Mtb leading to tissue scale outcomes
- Comprised of decision-making heuristics via a set of well-described interactions, calibrated using experimental data, and implemented in C++ code with Boost and FFTw libraries.



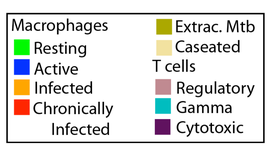
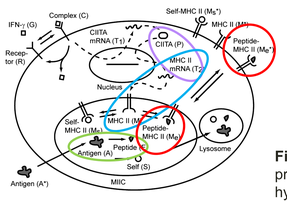


Figure 2: Example time point in GranSim and different types of agents on the grid.

Intracellular Model

- Chang *et al* 2005[5] ODE model captures Mtb-mediated down-regulation of MHC II presentation of peptides in macrophages
- Comprises 16 non-linear ODEs, solved in MatLab



Hypothesized process affected by Mtb
H1: Antigen processing
H2: MHC II maturation
H3: MHC II peptide loading
H4: MHC II transcription

Figure 3: ODE model schematic representing MHC II antigen presentation. Colored circles represent different processes hypothesized to effect antigen presentation by Mtb.

MULTI-SCALE MODELING

Integrated Multi-Scale Model

- GranSim has the ability to insert ODEs into individual agents
- Allows for observation of the interaction between tissue, cellular, and molecular scales
- Emergence of behaviors that arise from interactions between agents that would otherwise be impossible to know a priori[6]

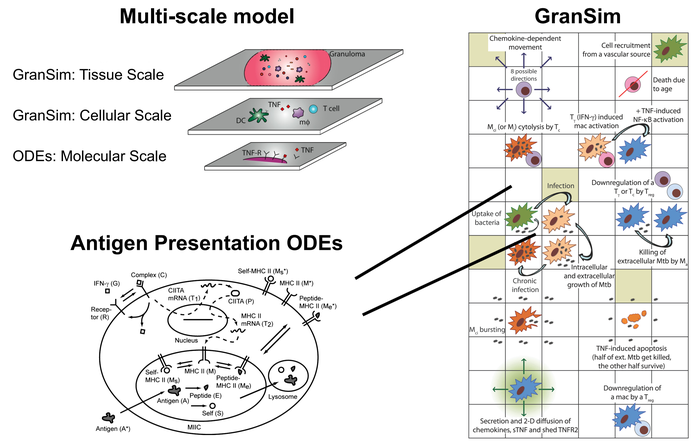


Figure 4: Model schematics of GranSim and ODEs and how they relate to each other as a multi-scale model.

ANALYSIS OF THE MODEL

Latin Hypercube Sampling

- Method for generating a near-random sample of parameter values from a multidimensional distribution
- Used to explore the entire parameter space of a model
- Parameters derived from LHS are then used to perform uncertainty analysis

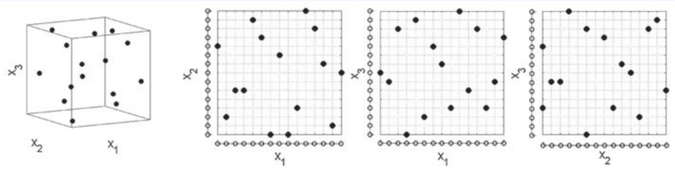


Figure 5: One-dimensional and two-dimensional projections of 3-dimensional Latin hypercube.[7]

Partial Rank Correlation Coefficient

- Measures how the uncertainty of inputs impacts model outputs (sensitivity)
- Rank transformation allows consideration of non-linear relationships
- Allows for inter and intra compartmental sensitivity analysis by varying parameters in ODEs, GranSim, or both

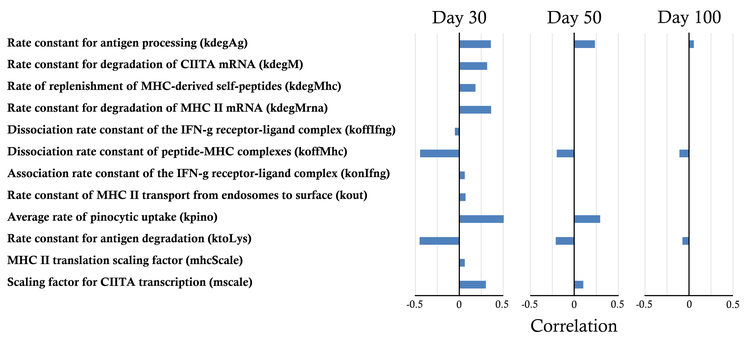
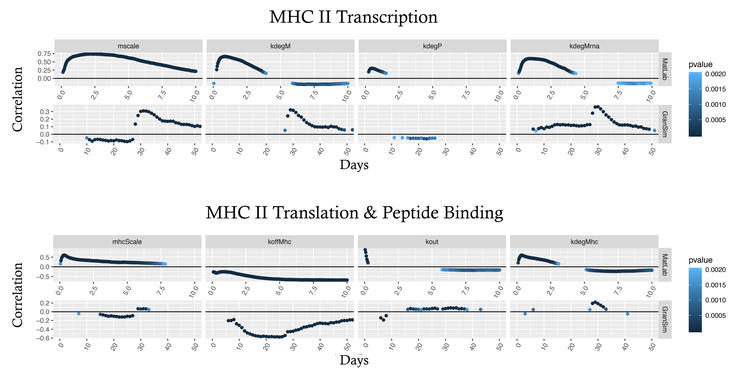


Figure 6: Partial rank correlation coefficient sensitivity analysis of ODE model parameters on Mtb peptide-MHC II complexes.

RESULTS OF UNCERTAINTY & SENSITIVITY ANALYSIS

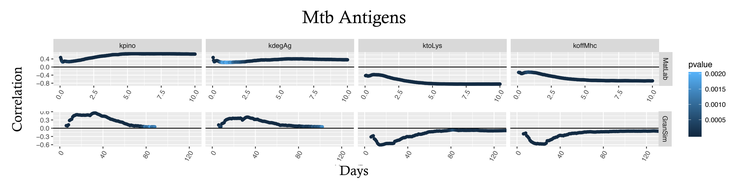
1. MHC II transcription and translation are most influential during first 50 days of infection

- The molecular dynamics change when placed inside agents in GranSim
- The effect on Mtb peptide-MHC II complexes is delayed until 30 days post infection in GranSim, when T cells are deployed
- Increases seen most with CIITA transcription, degradation rate of CIITA mRNA, and degradation rate of MHC class II mRNA
- Decreases seen with dissociation rate of peptide-MHC complexes



2. Mtb antigen uptake and processing are most influential through first 100+ days of infection

- In GranSim, influence on Mtb peptide-MHC II complexes peaks around day 25, tapers 100+ days post infection
- Increases seen with pinocytic uptake and antigen processing
- Decreases seen with antigen degradation and dissociation rate of Mtb peptide-MHC II complexes



DISSCUSSION / CONCLUSIONS

- Intervention in Mtb infection could possibly consist of finding ways to decrease Mtb antigen degradation and lowering dissociation rates of Mtb peptide-MHC II complexes

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