Moving Toward a Whole Host Modeling Framework For Tuberculosis

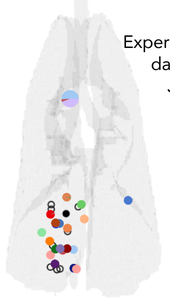
Louis R Joslyn[1,2], Jennifer J Linderman[1], Denise E Kirschner[2]
[1]Department of Chemical Engineering, University of Michigan, Ann Arbor, MI
[2]Department of Microbiology & Immunology, University of Michigan, Ann Arbor, MI

The need for a new TB modeling framework

- Granulomas – collections of immune cells that surround *Mycobacterium tuberculosis* (Mtb) -- are the hallmark of Mtb infection, which kills 3 individuals per minute.
- Some granulomas control bacterial growth. Others cannot and lead to bacterial dissemination: new granulomas form within lungs/lymph nodes or spread to airways.
- Bacterial dissemination is associated with poorer host outcomes and transmission.
- It is challenging to address dissemination experimentally and our previous models of granuloma formation focus on events within a single granuloma.
- **We need a new TB modeling framework to address host-level events like dissemination**

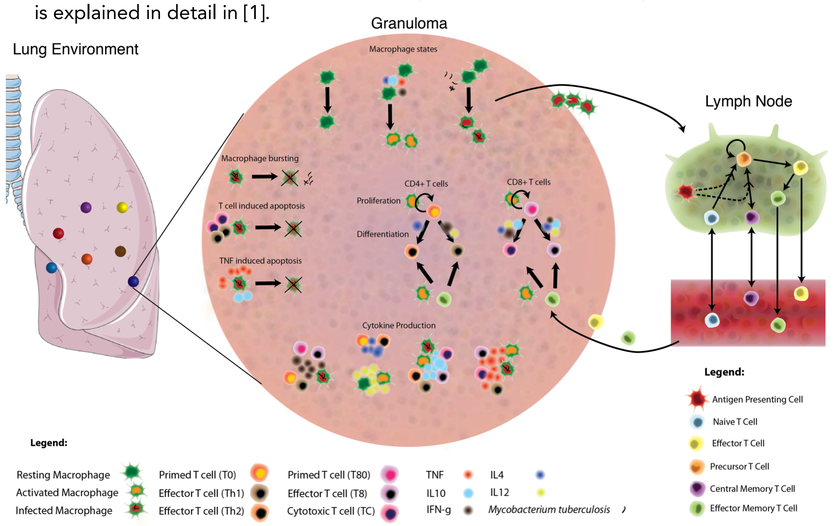
Building a multi-scale computational model of Mtb infection with multiple granulomas

Simulation of NHP lung with Mtb infection



Experimental NHP lung, data provided by JoAnne Flynn

We have developed a whole host computational model of Mtb infection across multiple granulomas in the lung and cellular dynamics in lymph node and blood. Each colored circle represents the location of a granuloma within the lung. Our new model is explained in detail in [1].



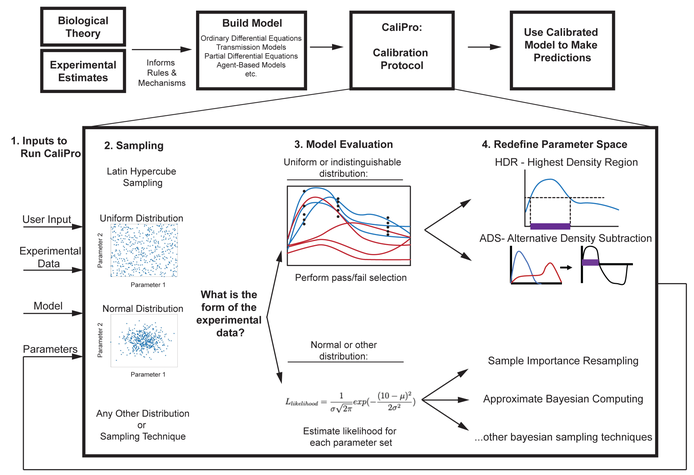
Each granuloma is represented by a system of 22 nonlinear ODEs that track key characteristics of granulomas including cells, cytokines and bacteria across time [1].

Linking lung to blood and lymph node compartments

CD4 & CD8 specific & non-specific T cells and Antigen Presenting Cells (APCs) are represented in the lymph node and blood compartments by a system of 35 ODEs [2]. These ODEs are linked to each granuloma within the lung environment in two ways:

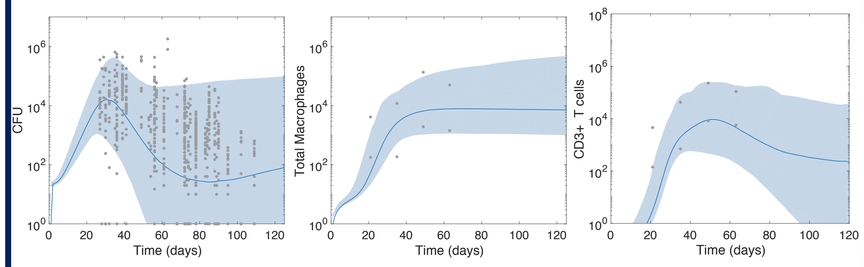
1) A small percentage (5 to 30%) of infected macrophages become APCs within the lymph node compartment per time step (24 hours).
2) CD4+ & CD8+ Effector and Effector Memory T cells are recruited to granulomas based on TNF and activated macrophage concentrations within each granuloma at each timestep (24 hours).

Calibrating multi-scale models with *CaliPro*

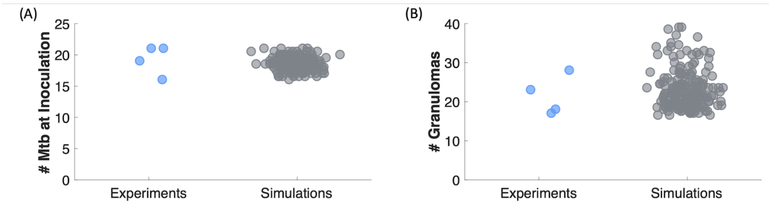


Finding a robust, calibrated parameter space for multi-scale models is often performed manually and can take weeks due to lack of automated protocols and vast initial parameter space. *CaliPro* is our newly developed protocol that quickly identifies a robust parameter space -- where a range of distinct and biologically reasonable simulation results are represented -- when Bayesian Calibration approaches cannot be used (because data distributions cannot be approximated). *CaliPro* refines parameter space by identifying all parameter sets that yield a pass run (shown as blue lines under model evaluation above) and narrows on this parameter space in an iterative manner. Using *CaliPro*, **We calibrate *HostSim* to experimental datasets at the host-scale, lung-scale, and granuloma-scale.**

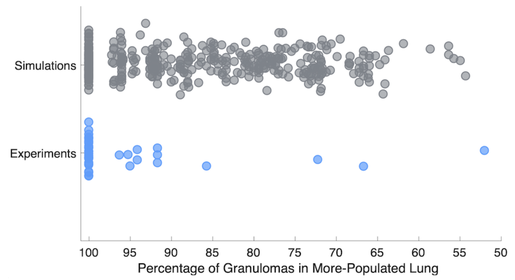
Calibrating our whole host simulations using *CaliPro*



Calibration to NHP granuloma-scale infection data including CFU per granuloma, macrophage and T-cell count per granuloma,**host-scale infection data** – various T cell phenotypes in blood – are not shown. Additional *HostSim* outcomes that were calibrated to **lung-scale** data include the granuloma count, location of granulomas, and distribution of Mtb barcodes lung granulomas (not shown) [3].

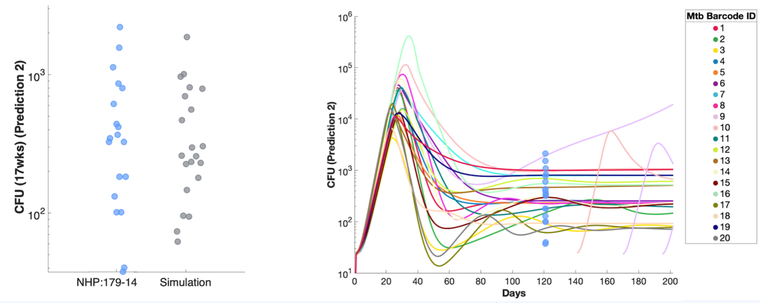


Validation by separate NHP infection dataset. The number of granulomas within in the more-populated lung of each NHP (shown as blue dots) was used as a validation dataset [1].
NHP whose percentage was closer to 50% suggests a monkey that had widespread dissemination across both lungs.



Predicting and preventing dissemination events

1. Matching individual infection dynamics across time



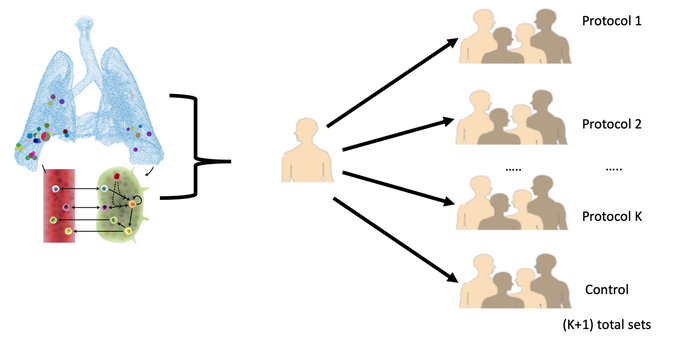
2. Predicting the dissemination event rate

- 0.04 dissemination events per month per granuloma
- Local dissemination events occur twice as frequently as widespread dissemination via airways

3. Mechanisms associated with lower dissemination

Parameter Description	Main Take-Away
Multi-functional CD8+ T cells	• A higher magnitude of multi-functional CD8+ T cells could be a target for vaccination and other therapies against TB.
Extracellular bacteria killed by macrophages	
decay rate of IL-10 cytokine	
TNF based recruitment of primed CD4+ T cells	
rate of differentiation from primed to Th1 CD4+ T cells	• Increasing the ability of macrophages to kill bacteria can prevent dissemination.

Using our whole host simulations in *virtual clinical trials*



Future Work – Virtual Clinical Trials: Each *HostSim* simulation represents a single virtual individual who has been infected with Mtb.

- Control group includes 500 infected individuals, without vaccination. Spectrum of disease states.
- Each protocol is a different "vaccine" that engenders a different level of Mtb-specific memory T-cells in the blood.
- **In a virtual clinical trial, the control group is re-simulated for each protocol.**

References and Funding

1. Wessler T & Joslyn LR, et al. "A computational model tracks whole-lung *Mycobacterium tuberculosis* infection and predicts factors that inhibit dissemination". Online at https://www.biorxiv.org/content/10.1101/713701v1 -- PloS Comp Bio
2. Joslyn LR et al. "Integrating non-human primate, human, and mathematical studies to determine the influence of BCG timing on H56 vaccine outcomes. 2018 Frontiers in Microbiology.
3. Martin et al. "Barcoding *Mtb* reveals in vivo infection dynamics in the macaque model of tuberculosis". 2017 mBio

This research was supported by R01AI123093 awarded to DEK and JLF; R01HL110811 awarded to DEK, JLF, and JLL; and UO1HL131072 awarded to DEK, JLF, and JLL.