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Critical Path to TB Drug Regimens

Gap identification as a critical step to enable integrated clinical trial simulation platforms

Application to TB

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Tuberculosis is a big disease which needs a smart drug development approach

- Major cause of morbidity and mortality
  - 2011: 8.7 million new cases of TB and 1.4 million deaths
    - 13% co-infected with HIV
  - Number of multidrug-resistant TB cases increasing
- Infection via lung with Mycobacterium tuberculosis (Mtb)
  - Usually limited to lung (*pulmonary TB*)
    - *Extrapulmonary TB*: lymph nodes, bone, CNS
  - Interaction of host immune system and pathogen results in different disease outcome (*clearance, latency, active disease*)
    - Aggregates of immune cells and pathogens called granulomas form in lung
    - Sources of long term infection
- Understanding dynamics between Mtb and immune system essential for drug development

CPTR aims to develop an *in silico* Clinical Trial Simulation (CTS) Platform for TB

- Evaluation of novel combination drug regimens
  - Minimize the risk of resistance development
  - Simpler regimens
  - Shorter regimens
- Exploration of alternative clinical trial designs
  - Determine trial duration and measurement times
  - Aid in dose selection
  - Investigate the impact of inclusion criteria or disease severity
  - Increase probability of successful trial

A gap analysis is the first step towards a CTS platform

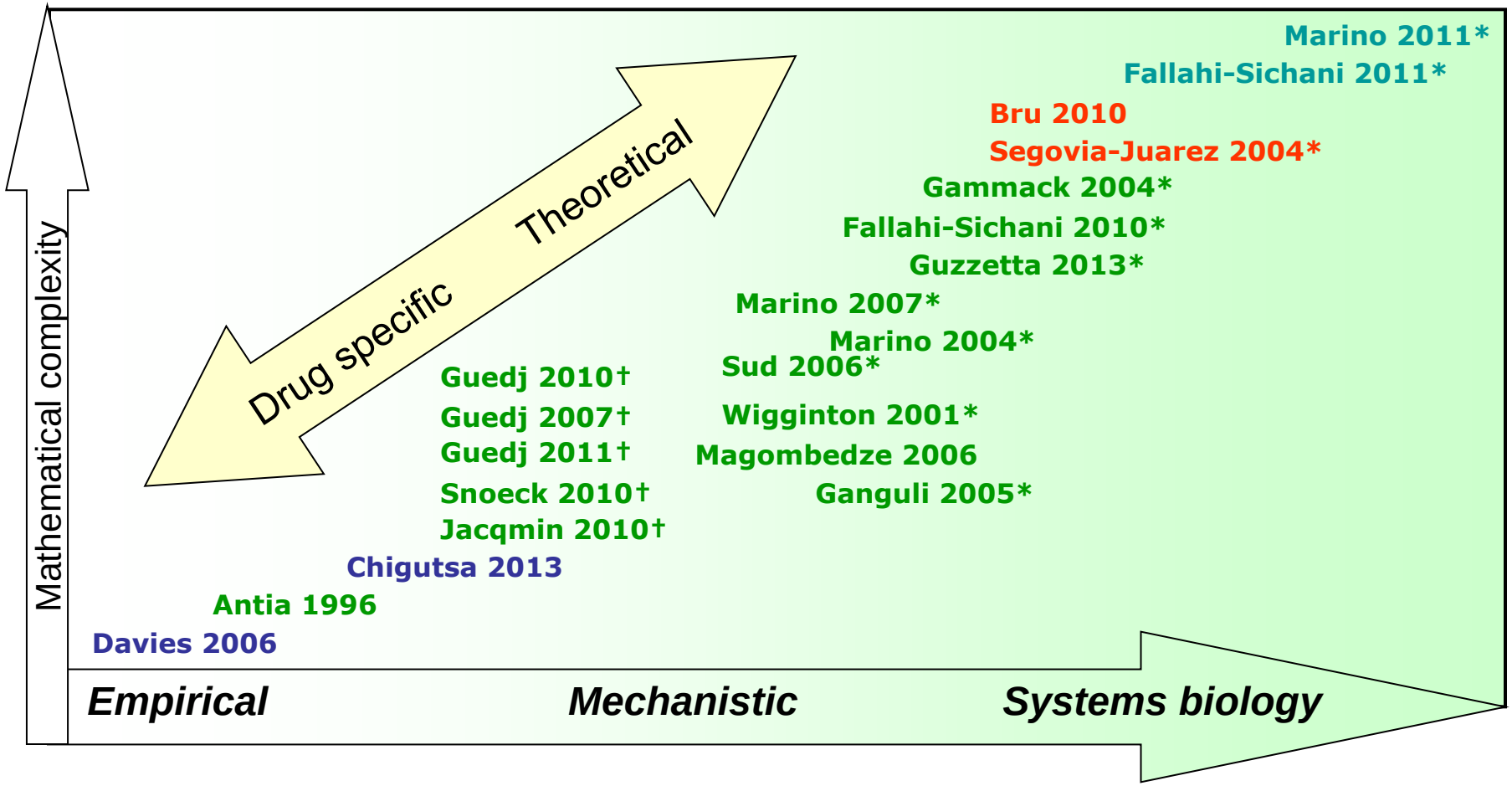
- Review
  - Assess utility of currently published models to inform CTS platform & identify data/model gaps
  - Question Based review from 22 preselected papers
- Investigate
  - Investigate most promising papers that can function as a base for simulation model
- Recommend
  - Recommend strategies for further model development to support CTS

Question-based review (QBR)
Map of results

Green= meets criteria; *Yellow*= partially meets criteria; *Red*= does not meet criteria; *Grey*= unclear

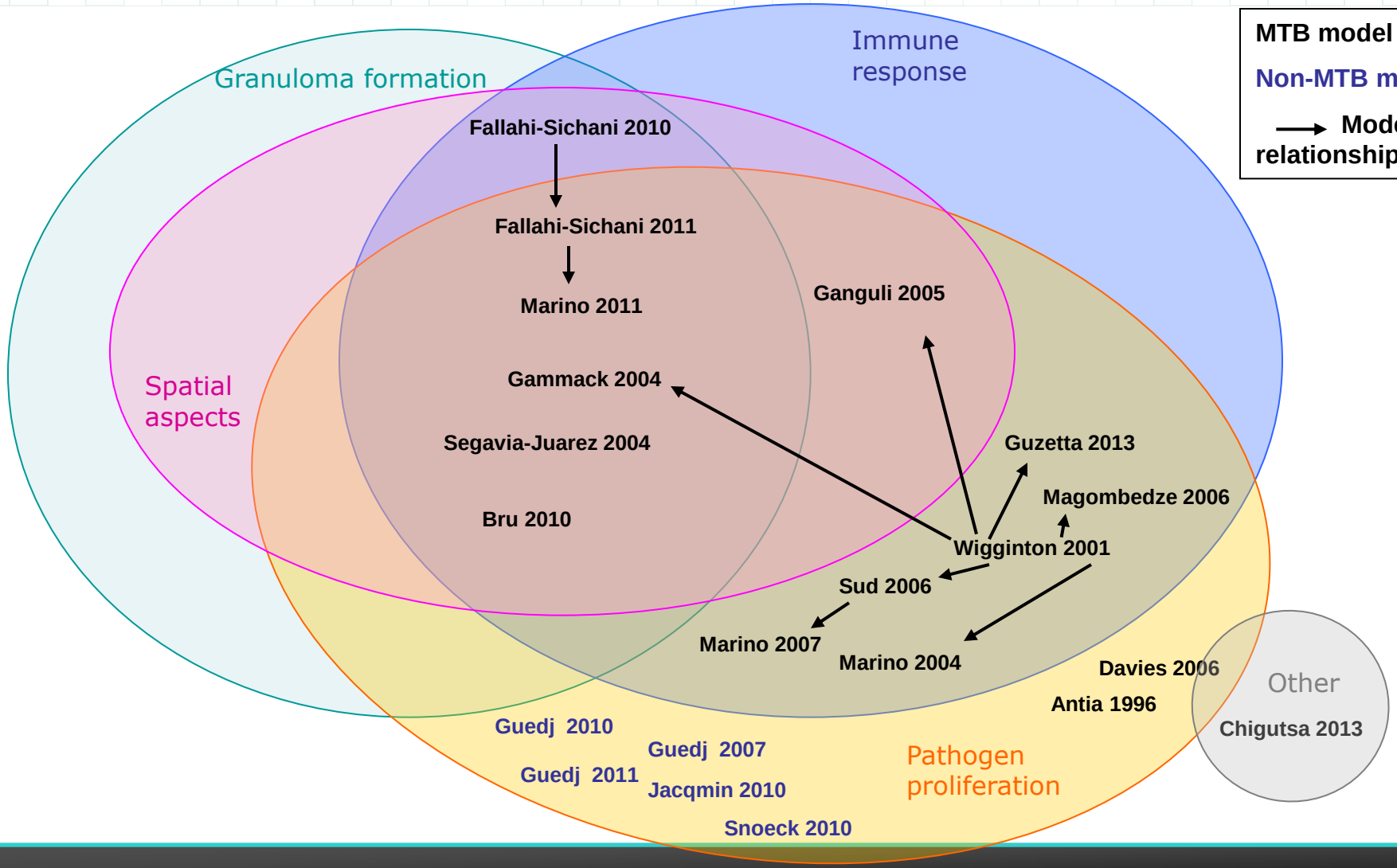
Model features		Model number																					
	Question	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
MOA	Does the model include mechanism of action (MOA)?																						
	Is the model empirical, based on an PK/PD model, or mechanistically based?																						
	Can a change in MOA be implemented?																						
Combination therapy	Can combination therapy be studied? (quantitative/qualitative)																						
	Are combination parameters for synergy/antagonist included?																						
TB strain and study population	Is it known which TB strain was studied and what drug susceptibility of the strain is (DS, MDR, XDR)?																						
	Is anything known of the patient population that was studied?																						
PK	Is anything known of the pharmacokinetics of the compounds studied?																						
	Are plasma population PK terms included?																						
	Interaction in PK expected for combination therapy?																						
	Are lung lesion PK compartments included?																						
Disease progression	Does the model give insight in disease progression?																						
	Does the model characterize the time course of key PD measures (i.e., TTP & CFU)?																						
	Is the inter & intra patient variability characterized for key PD measures?																						
	Is the correlation between key PD measures characterized?																						
	Does the model include full disease progression (latent-active-death)?																						
Data	How were model parameters informed / data pedigree?																						
	Were parameters estimated based on human data, in vivo animal data, or in vitro data?																						
	What additional data would be needed to inform the respective models?																						
	What is the level of information required to allow the model to be predictive?																						
	What is the data source and could the data be available to C-Path for further modeling work?																						
Dropout	Is dropout in TB clinical trials characterized and covariate dependent? (yes/no)																						
Superior model	Is it possible to identify a model that is superior to other models in terms of the criteria above? (yes/no)																						

TB Models were organized by type



* Group Marino/Kirschner †Non-MTB models *Hybrid models* *ODE models* *Agent-based models* *Other*

Venn diagram model similarity



System biology model implementation Marino & Kirschner 2004

ELSEVIER

Journal of Theoretical Biology 227 (2004) 463–486

www.elsevier.com/locate/jtbi

The human immune response to *Mycobacterium tuberculosis* in lung and lymph node

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Abstract

A key issue for the study of tuberculosis is to understand why individuals infected with *Mycobacterium tuberculosis* (*Mtb*) experience different clinical outcomes. To better understand the dynamics of *Mtb* infection and immunity, we have previously developed a temporal mathematical model that qualitatively and quantitatively characterizes the cellular and cytokine control network during infection. In this work we extend that model to a two compartmental model to capture the important processes of cellular activation and priming that occur between the lung and the nearest draining lymph node. We are able to reproduce typical disease progression scenarios including primary infection, latency or clearance. Then we use the model to predict key processes determining these different disease trajectories (i.e. identify bifurcation parameters), suggesting directions for further basic science study and potential new treatment strategies.

Keywords: Human; *M. tuberculosis*; Lung and lymph nodes; Model; Dendritic cells

Physiological modeling space ('2 compartments')

Model purpose

Analyse biology of disease trajectories in ***untreated*** patients

- primary TB
- latency
- clearance (adaptive immunity)

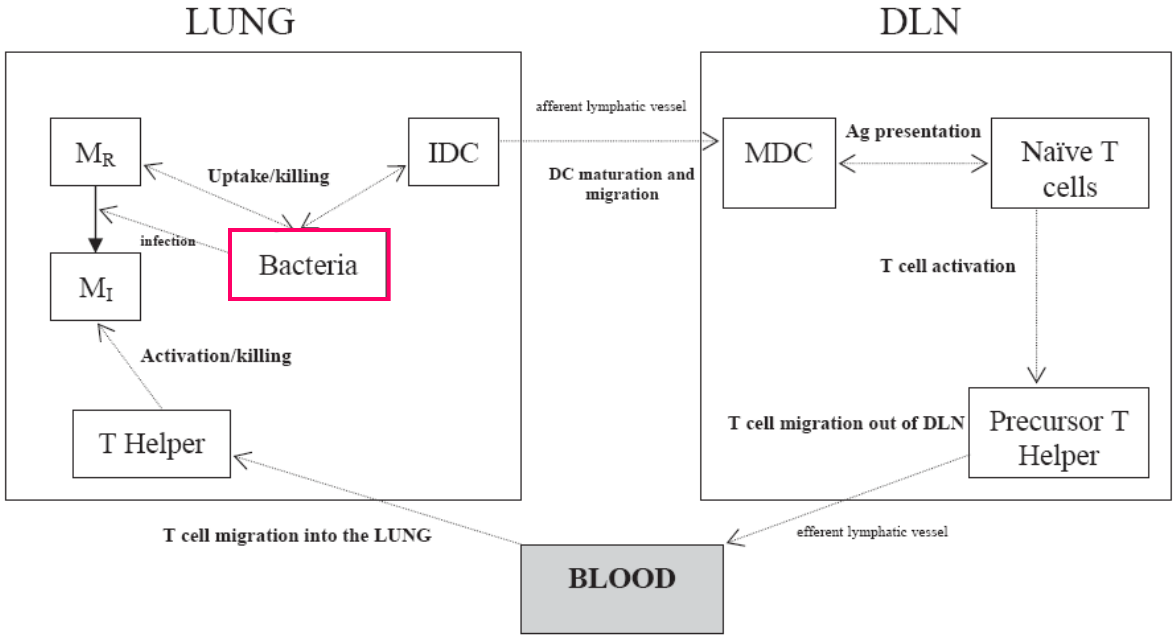


Fig. 1. Scheme representing uptake, trafficking and presentation in *M. tuberculosis* infection.

Model structure & complexity

- Complexity
  - 17 ODE's (representing dependent biological variables)
  - 77 parameters
- Bacterial growth separated in two 'subpopulations'
  - Extracellular
  - Intracellular (internalized by macrophages & immature DC's)

Bacterial growth

Bacteria killing (by M_A and M_R)

Number of bacteria released after macrophage apoptosis

$$\frac{dB_E}{dt} = \alpha_{20}B_E - k_{15}M_A B_E - k_{18}M_R B_E + k_{14}N_1 M_I \left(\frac{\frac{T_1}{M_I}}{\frac{T_1}{M_I}+c_4}\right) \quad (1.11)$$

$$+k_{17}NM_I\left(\frac{B_I^m}{B_I^m+(NM_I)^m}\right) - k_2\left(\frac{N}{2}\right)M_R\left(\frac{B_E}{B_E+c_9}\right) - \delta_{12}B_E\ IDC$$

From B_I to B_E (M_I-bursting)

From B_E to B_I (M_R-chronically infected)

IDC bacteria uptake

"Conservative" B_I growth

From B_I to B_E (M_I-bursting)

$$\frac{dB_I}{dt} = \alpha_{19}B_I\left(1-\frac{B_I^m}{B_I^m+(NM_I)^m}\right) - k_{17}NM_I\left(\frac{B_I^m}{B_I^m+(NM_I)^m}\right) \quad (1.12)$$

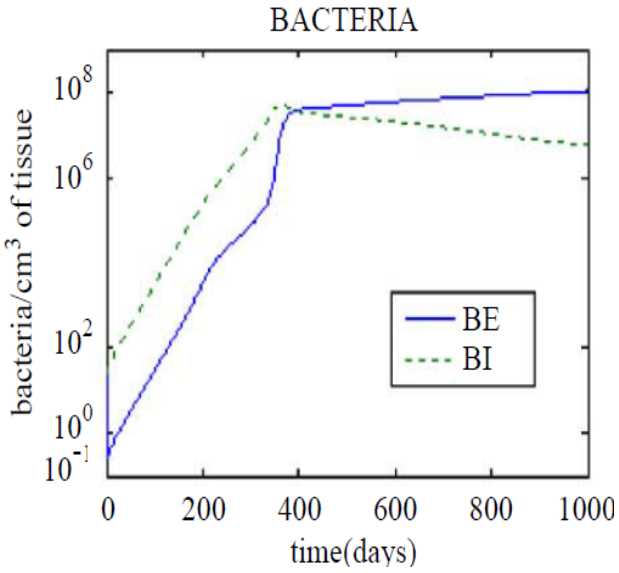
$$+k_2\left(\frac{N}{2}\right)M_R\left(\frac{B_E}{B_E+c_9}\right) - k_{14}N_1M_I\left(\frac{\frac{T_1}{M_I}}{\frac{T_1}{M_I}+c_4}\right)$$

T-cell mediated killing

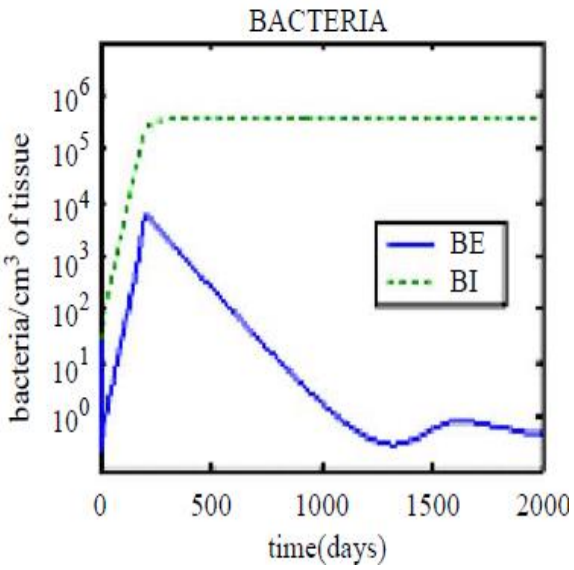
Marino model is theoretical framework that allows the description of primary infection or latent infection at bacterial level

Model simulation on bacterial level:

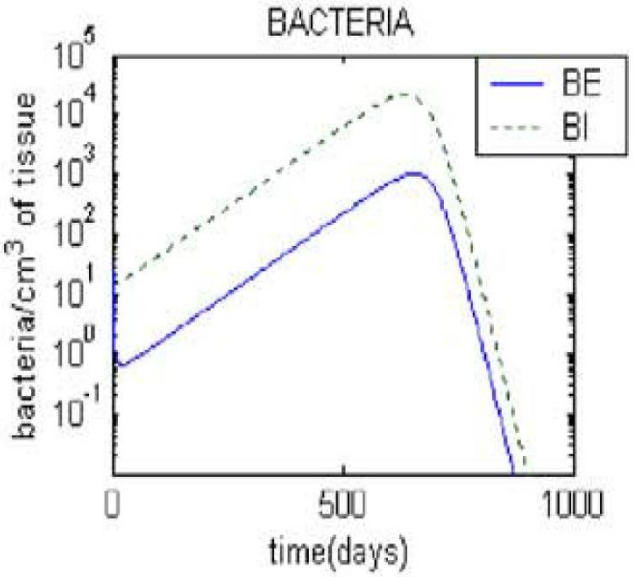
Primary infection



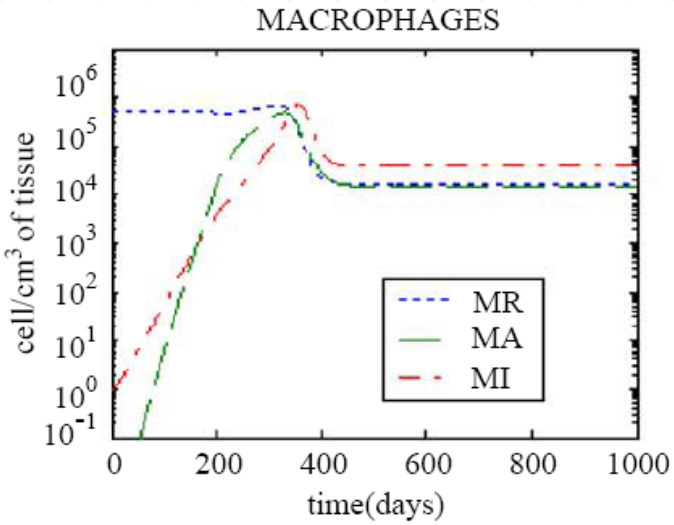
Latency



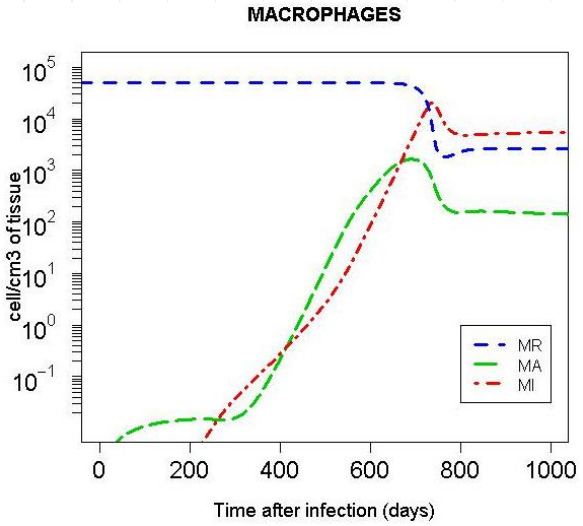
Clearance



There are many difficulties replicating the model. Here: Macrophage response has similar shape Disagreement effector T cell response

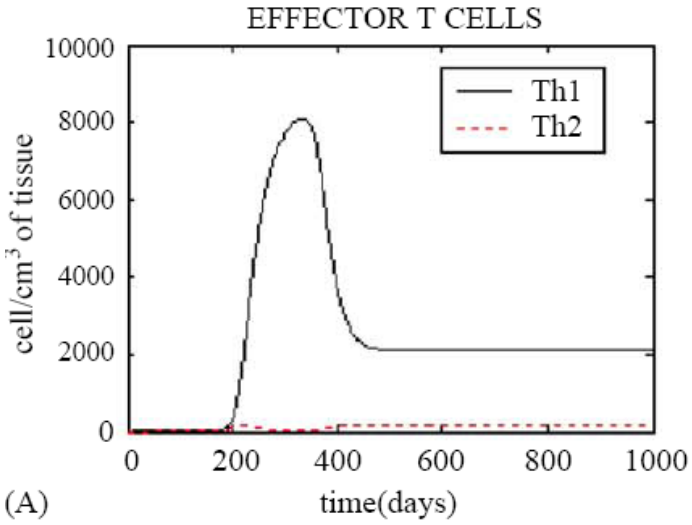


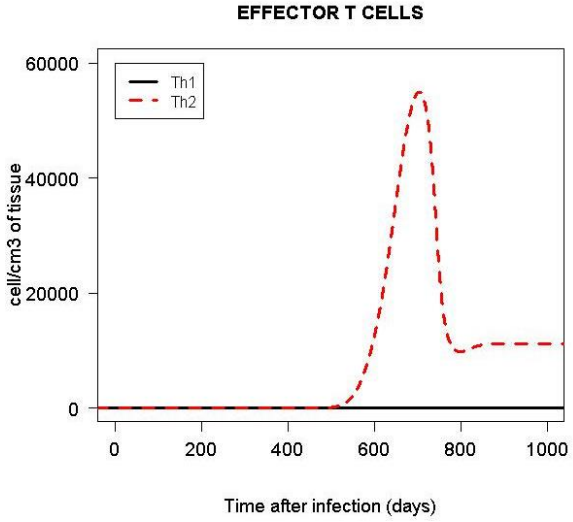
Marino



Replication

MR: resident macrophages
MA: activated macrophages
MI: infected macrophages





Model replication Marino: There is value and there are challenges

- Marino model must be seen as hypothesis generating, rather than supplying absolute numbers
- Observed differences paper and replication
  - May have various causes
    - Steady state condition assumptions
    - One parameter value undocumented in paper
    - High number of model parameters & related DE terms
      → probability of typographic error in paper ↑

⇒Debugging process time consuming and fear inducing!

General proliferation model implementation Jacqmin et al. 2010

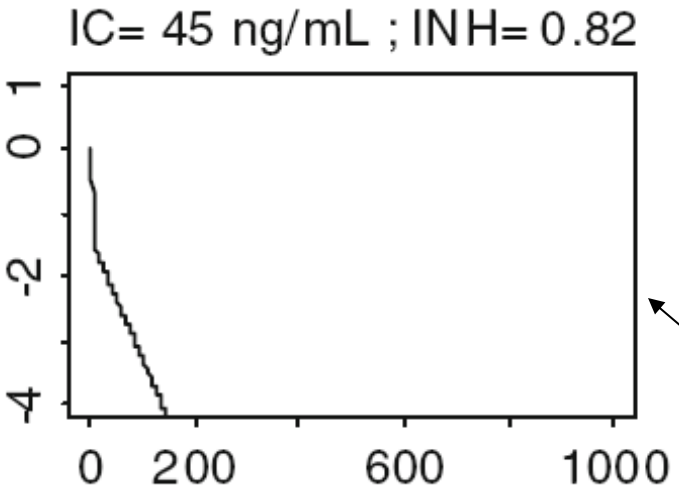
J Pharmacokinet Pharmacodyn (2010) 37:157–177
DOI 10.1007/s10928-010-9151-7

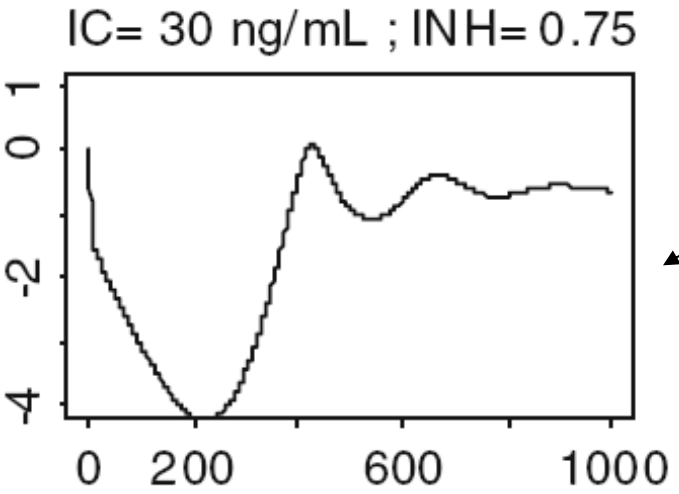
Basic PK/PD principles of drug effects in circular/ proliferative systems for disease modelling

Philippe Jacqmin · Lynn McFadyen · Janet R. Wade

it is shown that scenarios that have the same steady state ECC whatever the dose, dosage schedule or PK parameters have also the same average R_0 in the presence of the inhibitor (i.e. $R_{0\text{-INH}}$) and therefore lead to the same outcome. This allows predicting equivalent active doses and dosing schedules in circular and proliferative systems when the IC_{50} and pharmacokinetic characteristics of the drugs are known. The results from the simulations performed demonstrate that, for a given system (defined by its RMIC), treatment success depends mainly on the pharmacokinetic characteristics of the drug and the dosing schedule.

Replication of pathogen drop resulting from drug treatment for two disease trajectories

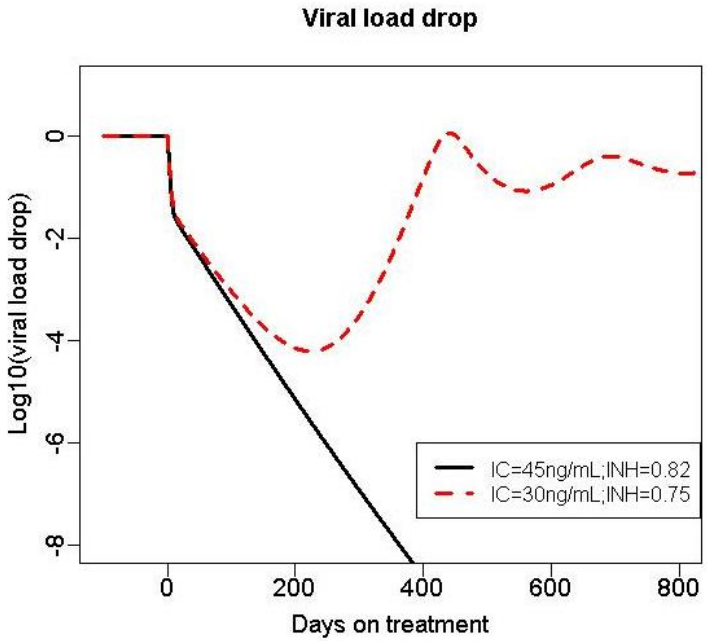




Replication

Used parameter values from paper and one from a related paper by same authors

Calculated steady state values, as these were not provided



HIV Connection: Simulation of active & latent infected cell populations for two disease trajectories

- Model for HIV possibly relevant for TB if dependent variables are remapped to TB physiology

  - Active & latent infected cells in HIV ~ intra- & extracellular Mtb load
  - Marino $\Rightarrow$ different TB disease trajectories (clearance vs. Latency) characterised by contrast in intra- & extracellular Mtb loads
  - In system biology models relationship between intra- & extracellular bacteria is more complex
  - Jacqmin $\Rightarrow$ infectious proliferation model relationship between latent and active pathogen loads is very simple, but can explain & describe (two) different disease trajectories for HIV

HIV *vs.* TB disease trajectories
(models have different purposes and parameterisation)

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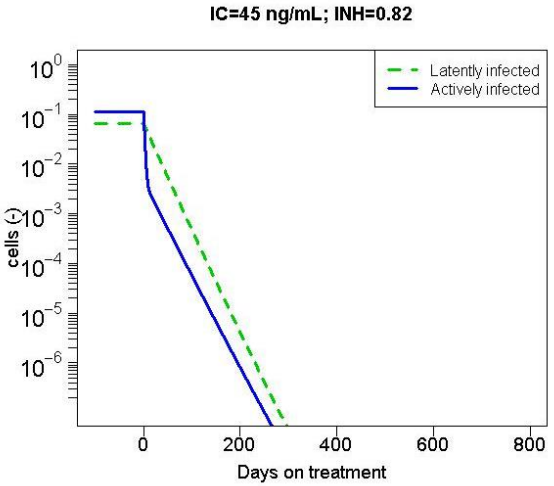
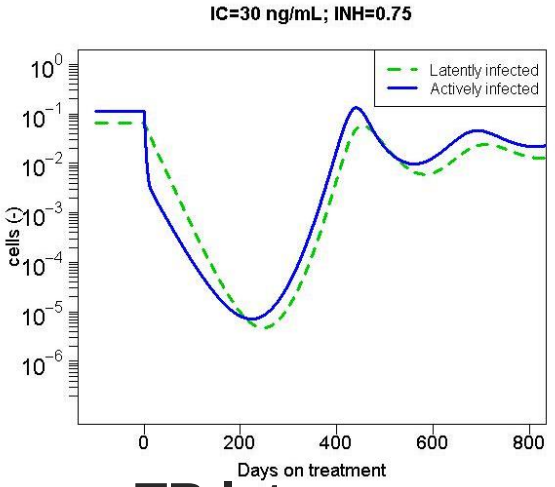
HIV treatment succes



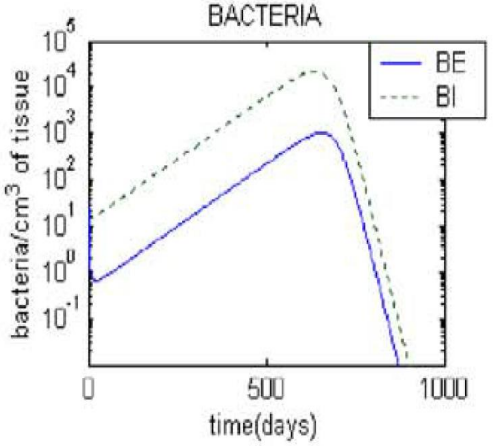
HIV treatment failure



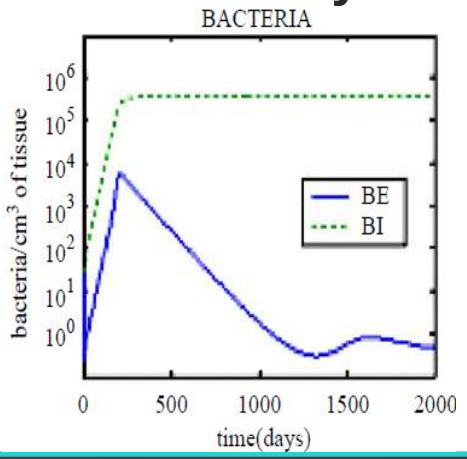
Drug Treatment

Immune response (primary infection)

TB clearance



TB latency



Leverage of existing proliferation model for TB

- Lessons learned from general proliferation model:
  - Presence of active and latent pathogen compartments results in ability to describe various relevant clinical disease trajectories
  - Structure between active and latent compartments does not necessarily require complexity for this purpose

- Can this model be physiologically remapped, refined to TB?
  - Also requires time-related parameters to be rescaled
  - May have implications for the data (that need to be) collected

☞ General infectious proliferation model may capture TB disease progression in a more simple manner than a full biology systems model

Useful biomarkers play a useful role: Is pathogen load enough?

- Currently only one common clinical biomarker *(CFU sputum count)* can be related to a model variable *(bacterial load)* *(Time to positivity, TTP, is a marker for the same)*

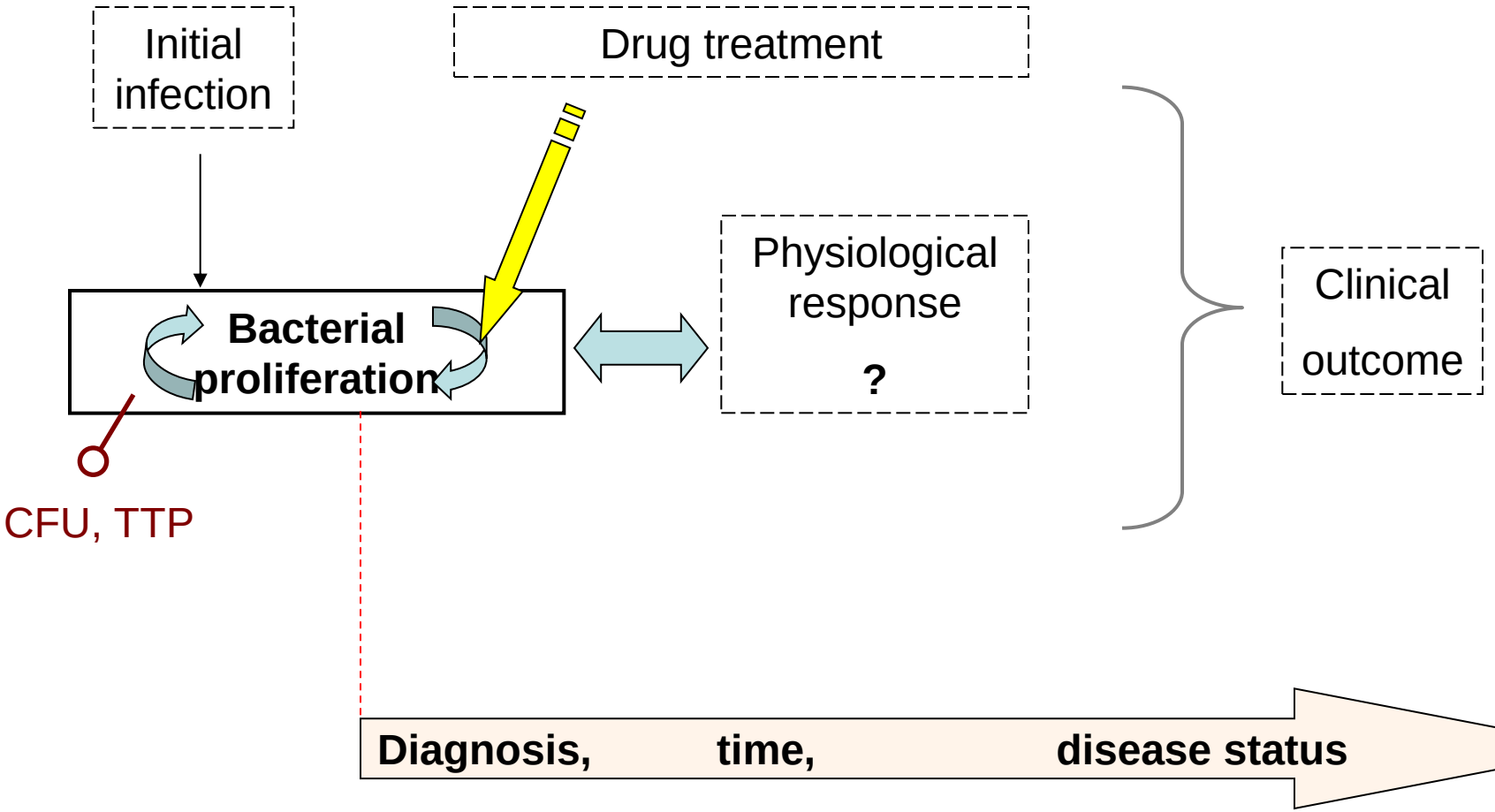
- CFU data alone appear not informative enough to characterize all clinically relevant disease trajectories for CTS

- Accuracy and precision of model parameter values not clear
  No sensitivity analysis or parameter correlation available.

→*Are there any additional clinical biomarker(s) to guide model selection & development process ?*

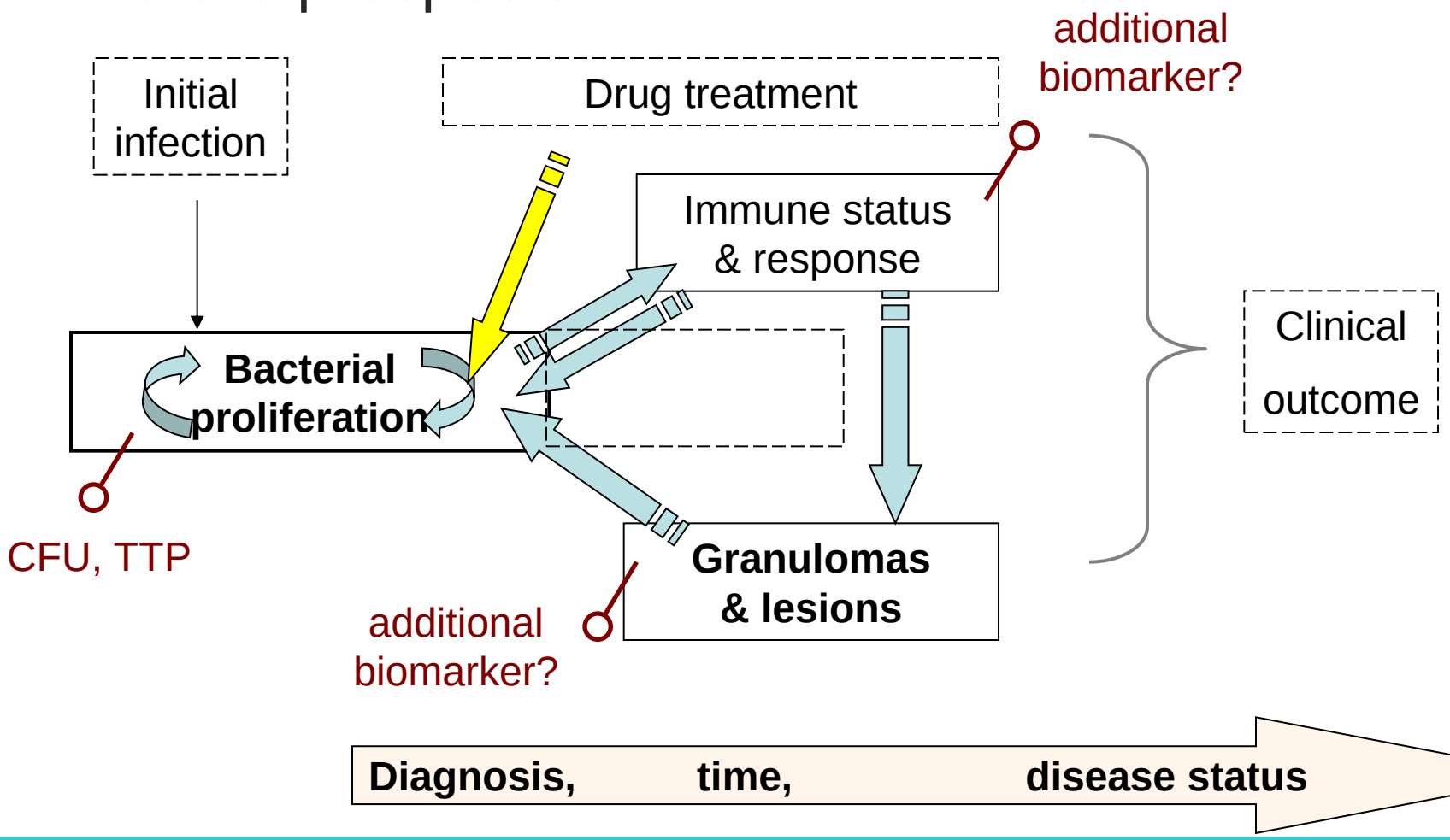
It appears there is a structural gap in the prediction of clinical outcome based on CFU/TTP alone

- Current status



Which may be filled by the addition of appropriate marker describing important parts of the disease process

- Future prospects



Recommendation based on current state of experience

Currently available systems biology models have no clinical connection. To arrive at clinically relevant PK-PD models for TB:

1. Consider appropriate parts of the system biology models and simplifying them by 'lumping' states

2. Consider options for remapping and rescaling of ‘General infectious proliferation model’ to Mtb
   - Including influence of pop. PK-PD variability on outcome

3. Connect to multiple clinical biomarkers, responding on various time scales to inform model
   - Review databases for available clinical trial data
   - Optimize designs of upcoming trials
   - Model-based quantitative validation of clinical biomarkers
   - Predictive simulation of different disease trajectories (‘bifurcation’)
   - Use clinical results to determine population distribution of parameters