

Integrating an agent-based immune model with PBPK/PKPD to simulate antitubercular treatment in humans

A. Ravoni¹, E. Mastrostefano¹, D. Moretti¹, E. Onofri¹, P. Tieri¹, F. Castiglione^{1,5}, A. Dokoumetzidis^{2,3}, E. Karakitsios¹, S. D'Agate^{1,4}, U. Villani^{1,4}, O. Della Pasqua^{1,4}

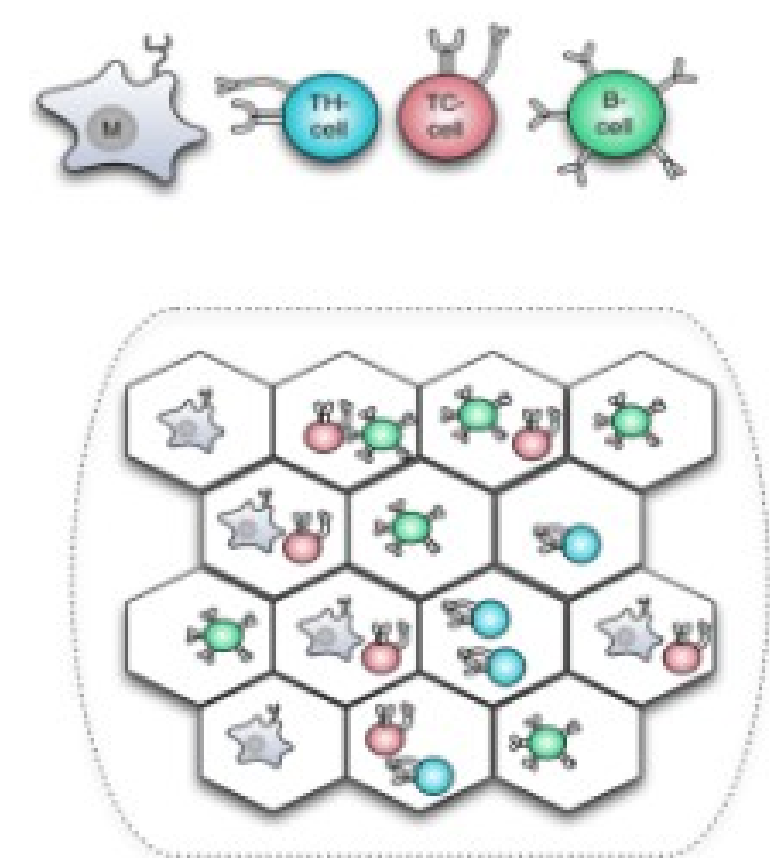
1. Istituto per le Applicazioni del Calcolo (IAC), CNR National Research Council of Italy, Rome, Italy
2. Department of Pharmacy, University of Athens, Athens, Greece
3. Pharma-Informatics Unit, Athena Research Center, Marousi, Greece
4. Clinical Pharmacology and Therapeutics Group, University College London, London, UK
5. Medicine Department, Pulmonary Systems Medicine, University of Florida, 100225, Gainesville, FL 32610, USA

Abstract

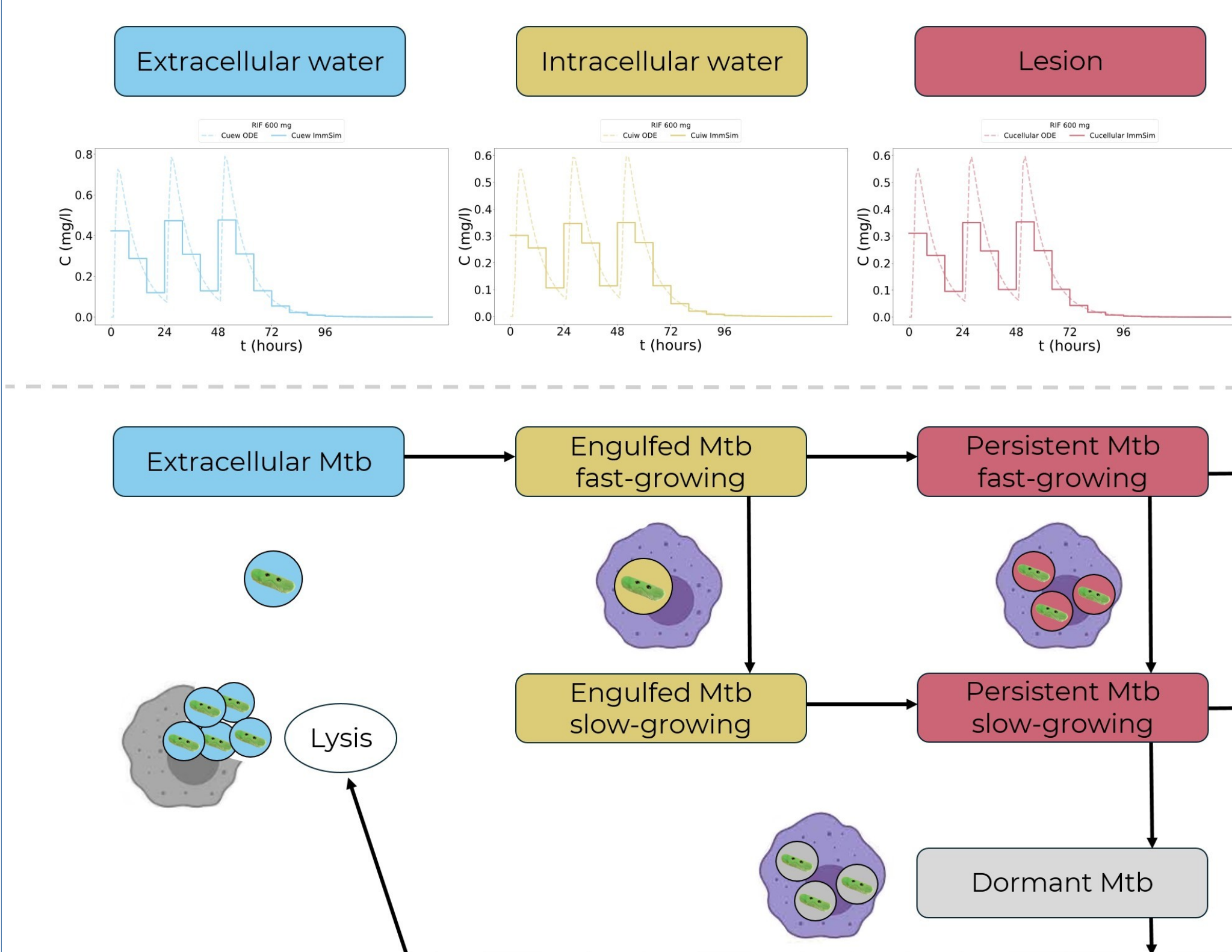
The role of the **immune system** (IS) in managing **Mycobacterium tuberculosis** (Mtb) during antitubercular drug treatment is difficult to characterize. To address this, we introduce a **multiscale in silico framework** that integrates an agent-based model (ABM) of the immune response [1], a physiologically based pharmacokinetic (PBPK) model of drug distribution in the lung [2], and a pharmacokinetic-pharmacodynamic (PKPD) model capturing drug-induced bacterial killing [3]. We calibrate the integrated model using **real clinical data** and simulate the effect of rifampicin (RIF) monotherapy on a population of virtual patients. Our results indicate that the pharmacological treatment is essential to counter the infection and enhance the IS, although outcome depends on the balance between latency and reactivation.

The model

The ABM C-ImmSim [1] reproduces both innate and adaptive immune responses by simulating molecule-mediated interactions and changes of state of immune cells and pathogens



A population of individuals can be simulated, each with a unique IS and event history



RIF concentrations from the PBPK model are mapped to corresponding Mtb states

In vitro PKPD estimate is used to calculate a death probability for Mtb that depends on drug concentration and cell state

$$E(c) = E_{MAX} c^H / (EC_{50}^H + c^H)$$

$$P(c) = 1 - \exp[-E(c)\Delta t]$$

Calibration

Parameters α , β , γ control RIF effect:

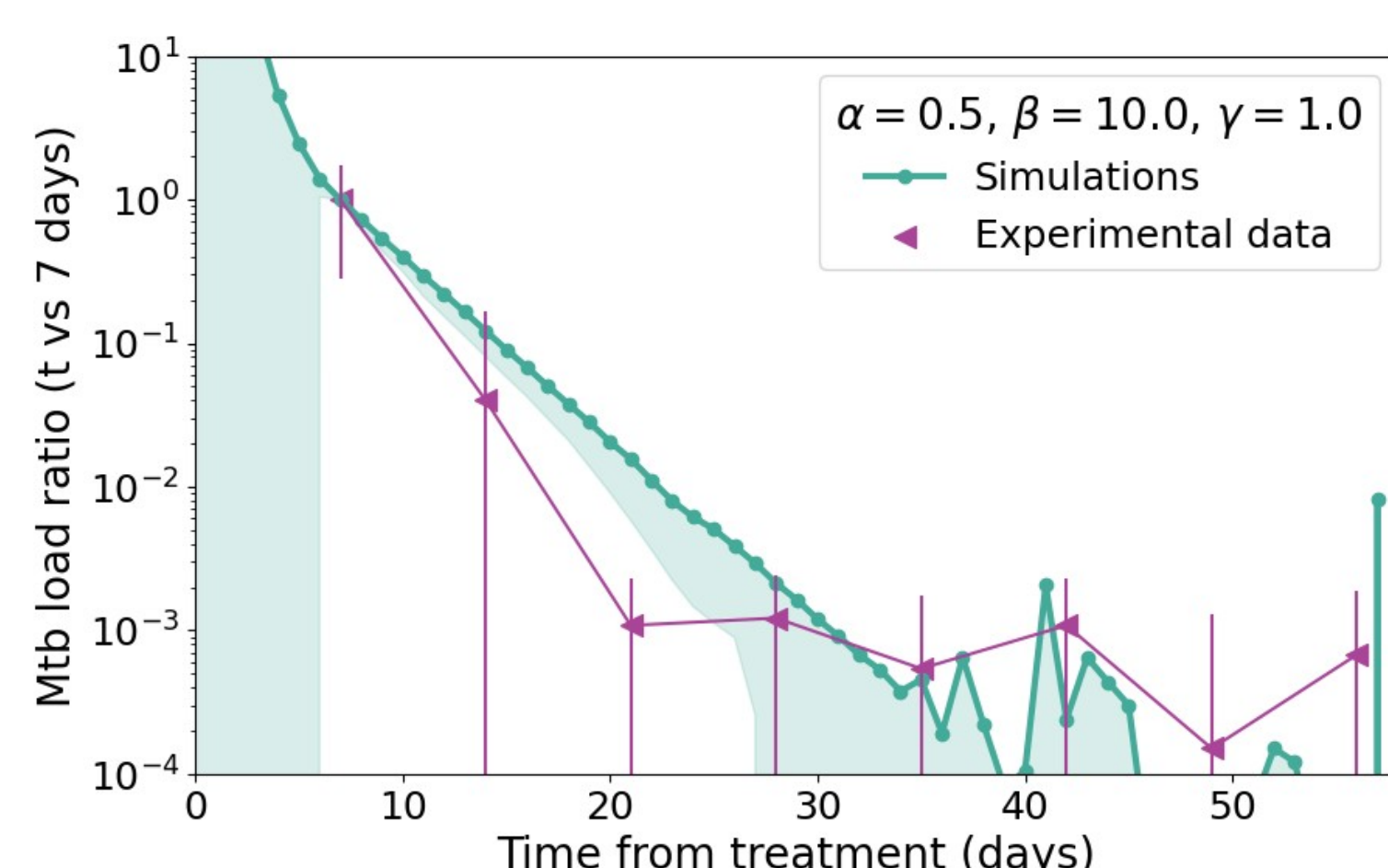
$$E(c,i) = \alpha E(c,f) + (1-\alpha)E(c,s)$$

$$E(c,e) = \gamma E_{MAX}(e) c^{H(e)} / [EC_{50}(e)^{H(e)} + c^{H(e)}]$$

$$E(c,f) = \gamma \{ \beta / [\alpha(\beta-1)+1] \} E_{MAX}(i) c^{H(i)} / [EC_{50}(i)^{H(i)} + c^{H(i)}]$$

$$E(c,s) = \gamma \{ 1 / [\alpha(\beta-1)+1] \} E_{MAX}(i) c^{H(i)} / [EC_{50}(i)^{H(i)} + c^{H(i)}]$$

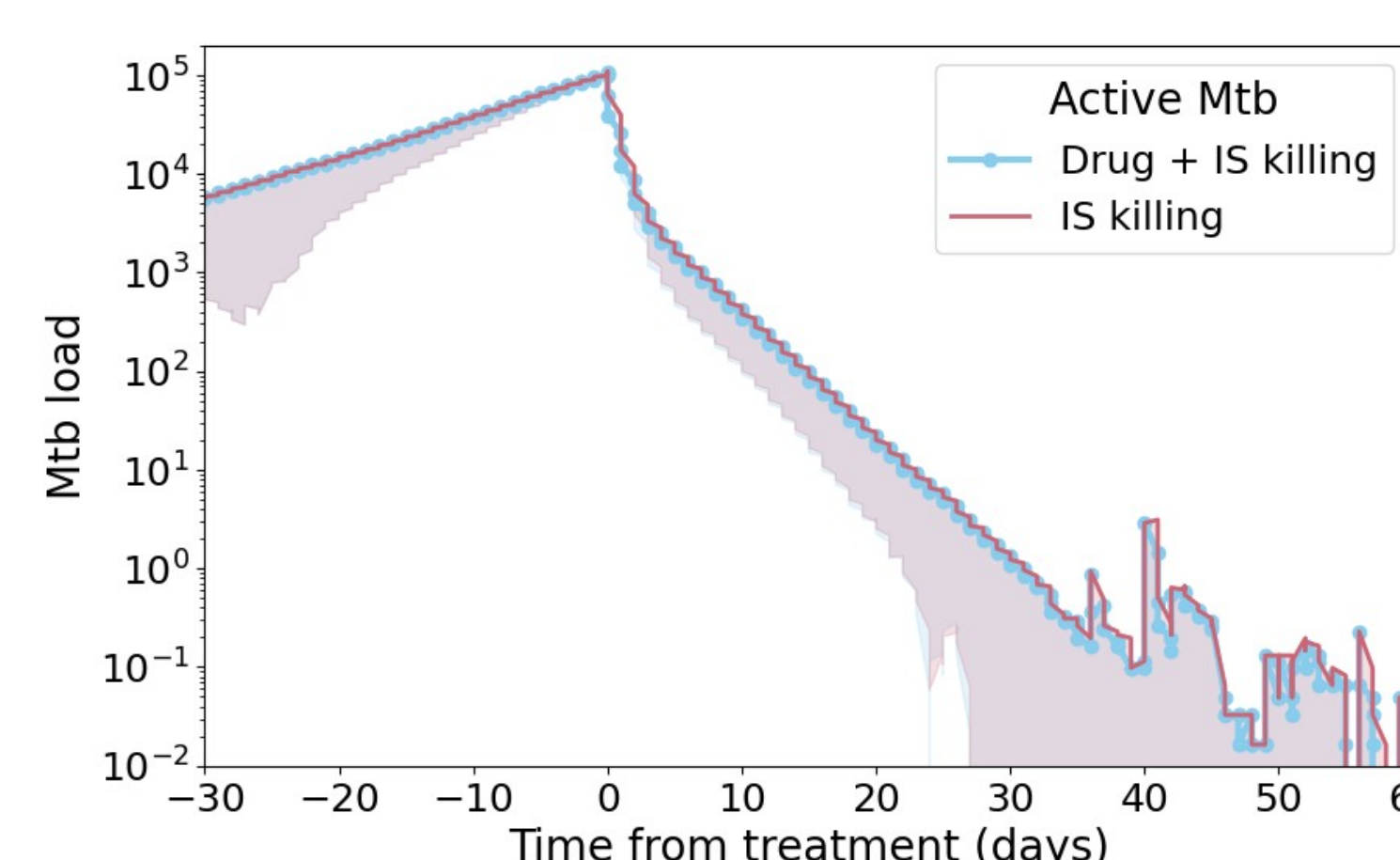
The model is calibrated on clinical data [4,5]



Results

Mtb clearance is observed in early stage of treatment

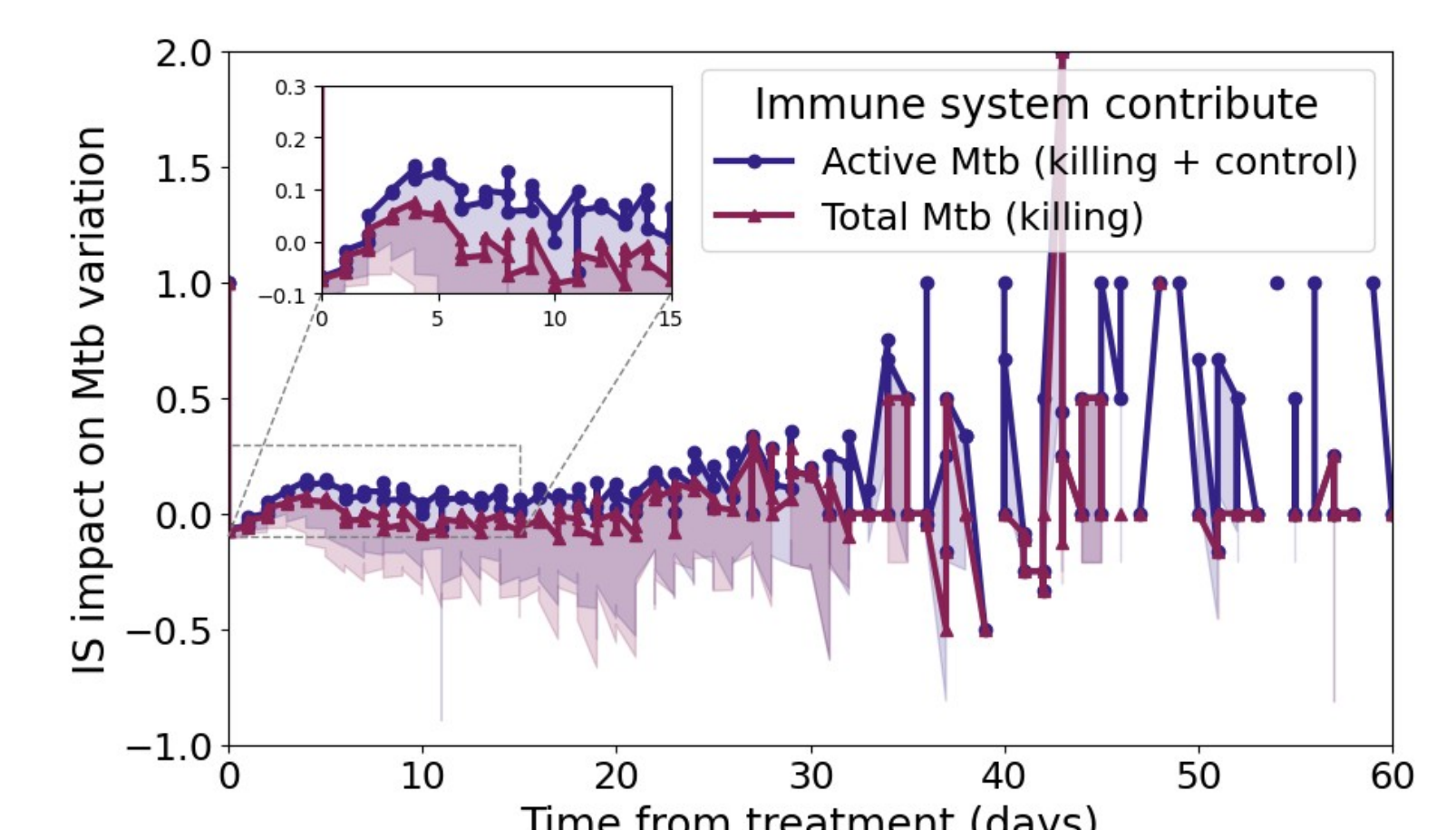
Pharmacological treatment enhance the IS activity



Relapse after treatment: 21% in simulations vs 20% in clinical data [4]

15% of Mtb deaths in the first 10 days are immune-mediated

Treatment outcome depends on balance between latency and reactivation



Bibliography

- [1] Bernaschi, M. and Castiglione, F. Design and implementation of an immune system simulator. *Comput. Biol. Med.* 2001.
- [2] Karakitsios, E. and Dokoumetzidis, A. Extrapolation of lung pharmacokinetics of antitubercular drugs from preclinical species to humans using pbpk modelling. *J. Antimicrob. Chemother.* 2024.
- [3] Muliaditan, M. and Della Pasqua, O. Evaluation of pharmacokinetic-pharmacodynamic relationships and selection of drug combinations for tuberculosis. *Br. J. Clin. Pharmacol.* 2020.
- [4] Gyselen, A. Rifampicin in retreatment and original treatment cases of pulmonary tuberculosis. *Proc. R. Soc. Med.* 1970.
- [5] Okada, Y. The examination of tubercle bacilli in sputum. *Tohoku J. Exp. Med.* 1949.

Acknowledgement

This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 853989. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA and Global Alliance for TB Drug Development non profit organisation, Bill & Melinda Gates Foundation and University of Dundee.

Email: a.ravoni@iac.cnr.it