From In Silico to In Vivo: a Multiscale PBPK Model for Model-Informed Drug Development (MIDD) of mRNA-LNP-Delivered Monoclonal Antibodies

Elisa Pettinà[1,2], Elio Campanile[2,3], Stefano Giampiccolo[2,4], Luca Marchetti[1,2]

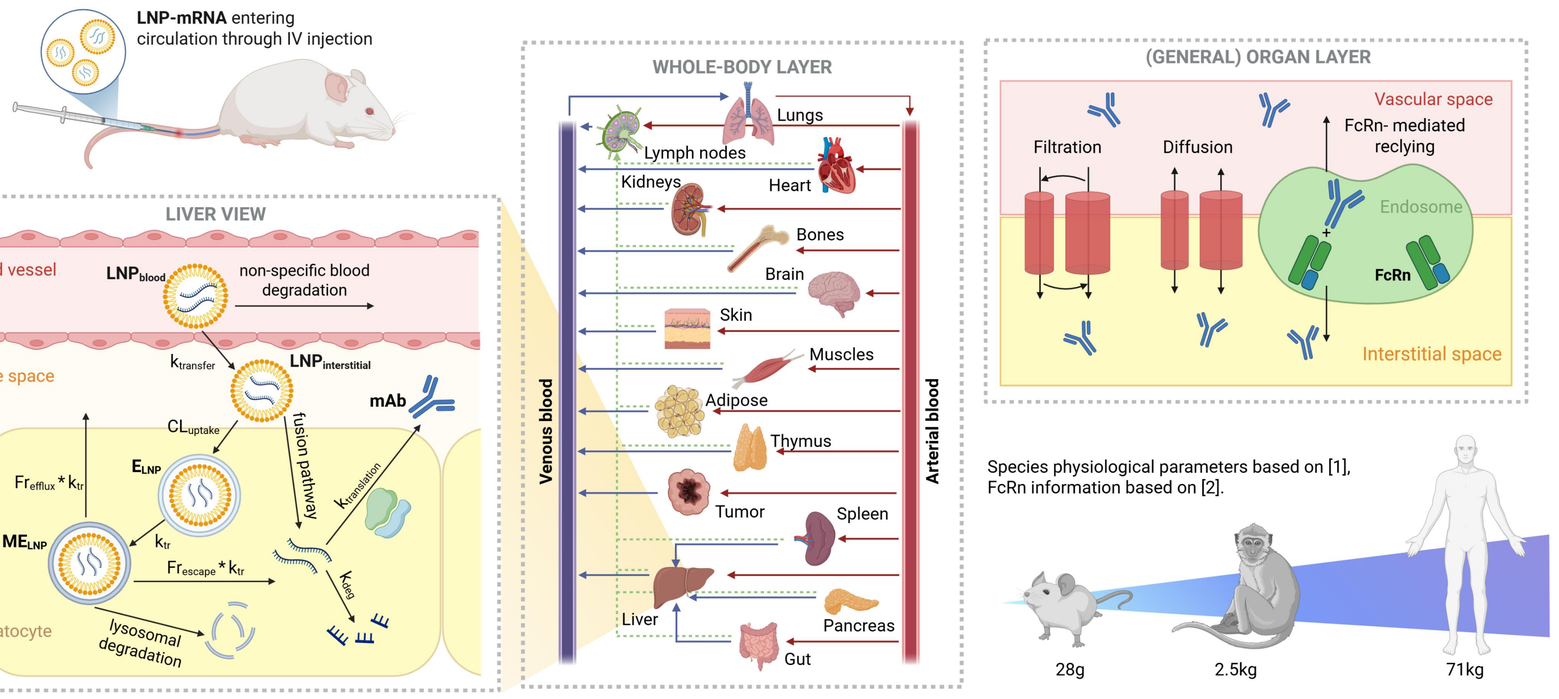
[1]University of Trento, Department of Cellular, Computational and Integrative Biology (CIBIO), Italy
[2]Fondazione The Microsoft Research – University of Trento Centre for Computational and Systems Biology (COSBI), Italy
[3]University of Trento, Department of Mathematics, Italy
[4]University of Trento, Department of Information Engineering and Computer Science, Italy

elisa.pettina@unitn.it , luca.marchetti@unitn.it

Motivation

Recent advances in mRNA technology and its delivery have enabled the use of mRNA-encoded proteins to treat a wide range of diseases, from infectious conditions to cancer.

We introduce a Physiologically Based Pharmacokinetic (PBPK) model that can predict the absorption, distribution, metabolism and excretion (ADME) of mRNA-LNP encoded monoclonal antibodies (mAbs). This modelling paradigm acquired a central role in the newest Model-Informed Drug Development (MIDD) guidelines released by the European Medicines Agency, as it provides quantitative *in silico* measurements to accelerate drug development and inform decision-making in clinical settings, saving time and resources.



The Model

This ODE-model is composed by two layers: the whole-body representation and the singular organs modules. The PBPK, extended from [3], is composed by 14 organs, which are connected by the blood and lymphatic compartment. The organ layer is equipped with the "two pore hypothesis equations", that hydrodynamically model the tissue uptake of mAbs, and the FcRn recycling, which proved to be fundamental to have a precise ADME description. Moreover, the liver is equipped with an additional set of equations to describe, at a molecular level, the main metabolic steps following the IV injection of mRNA-LNP: the accumulation in the Disse space of the liver, the uptake by hepatocytes and the mRNA escape from the endosomes [4,5].

Fig. 1: Our PBPK model comprises 14 compartments representing organs connected by the circulatory and lymphatic systems. The liver is where mRNA translation occurs, while the whole-body structure describes the PK of the therapeutics in the different organs.

Validation: Various Dosages in Mice and NHP

The validation was carried out for the three products using other PK profiles on multiple doses presented in the reference papers [6,7,8]. For RiboMab02.1, the presence of datapoints also for cynomolgus monkeys allowed for validation in this species. The model was validated using the same parametrization that proved successful in mice (Fig. 9, dashed lines), which was refined based on literature findings [9] to better capture the different physiology of the species.

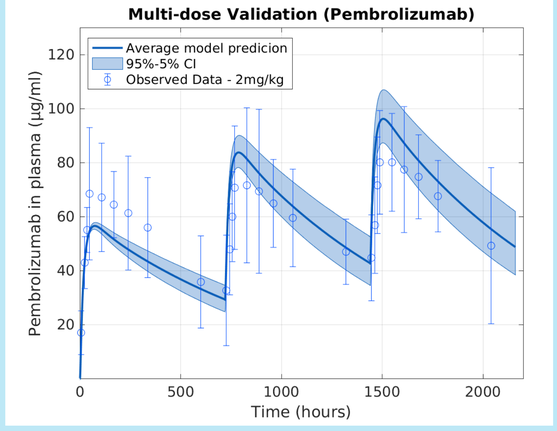


Fig. 6: PBPK model validation on Pembrolizumab data

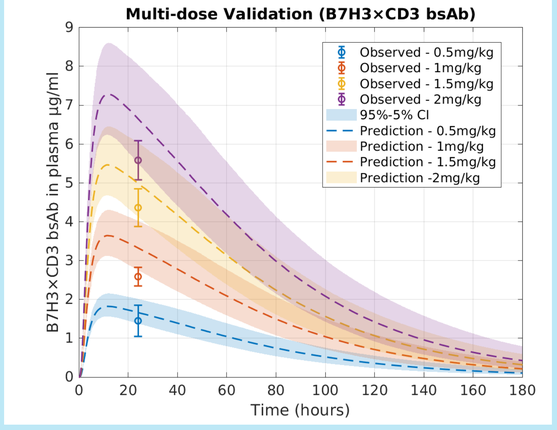


Fig. 7: PBPK model validation on onB7H3×CD3 bsAb data

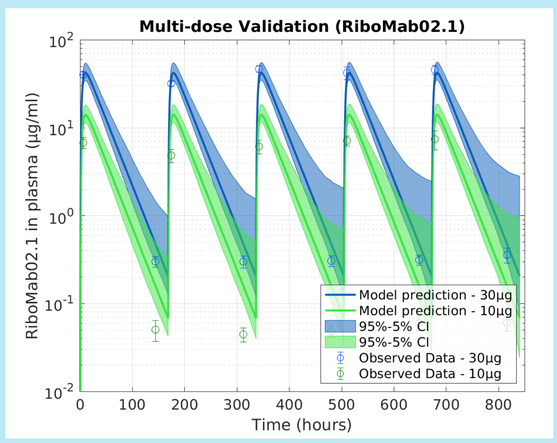


Fig. 8: PBPK model validation on RiboMab02.1 data

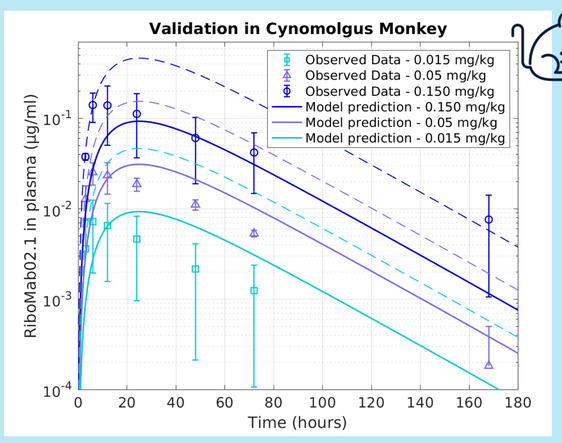


Fig. 9: PBPK model validation on RiboMab02.1 data

Training: Recombinant and mRNA-encoded mAbs

The PBPK model was calibrated on three mRNA-encoded antibodies of different sizes and properties: 1) the RiboMab02.1 therapeutic, encoding a bispecific T-cell engager of 100kDa and with no Fc region [6] (Fig. 3), 2) Pembrolizumab, a commercial anti-PD-1 mAb, subjected to the FcRn-mediated recycling and with a mass of 140 kDa [7] (Fig. 4), and 3) a B7H3×CD3 bispecific T-cell engager, weighing 55kDa [8] (Fig. 5).

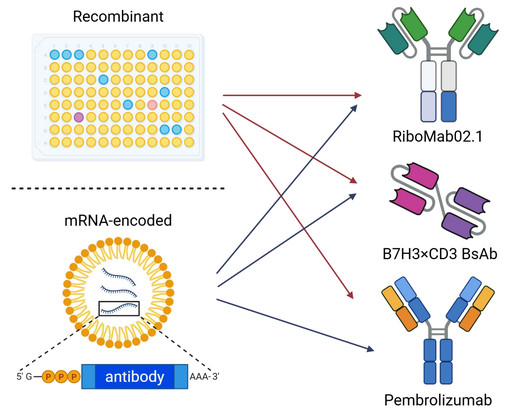


Fig. 2: Both the recombinant and mRNA data are used

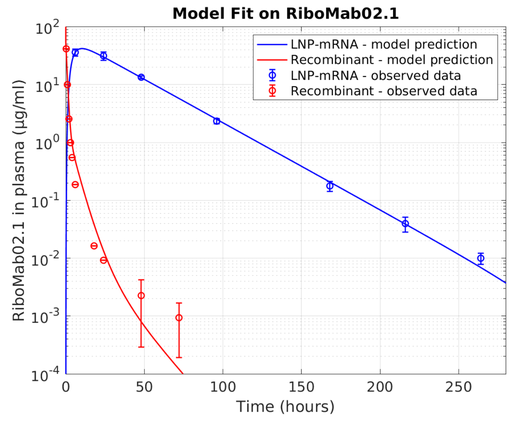


Fig. 3: PBPK model calibration on RiboMab02.1 data

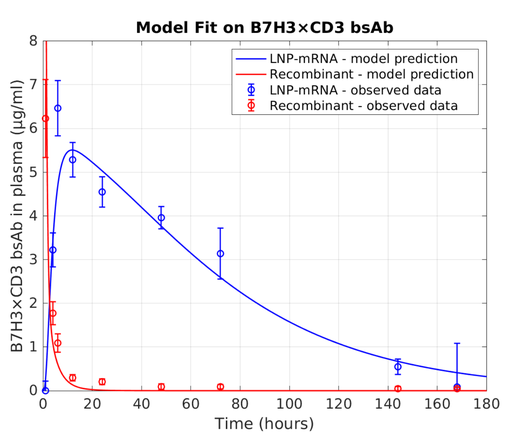


Fig. 5: PBPK model calibration onB7H3×CD3 bsAb data

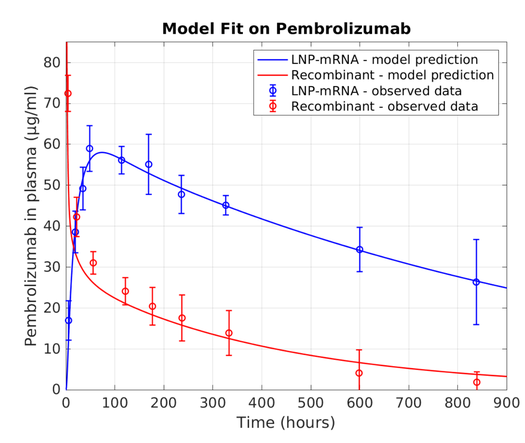


Fig. 4: PBPK model calibration on Pembrolizumab data

Representative Applications

The validated model can be used to test different dosing and schedule scenarios, to infer the concentration of the antibody in tissues that are difficult to test (Fig. 10), or track the metabolism of mRNA-LNP, giving a quantitative understanding to imaging data (Fig 11).

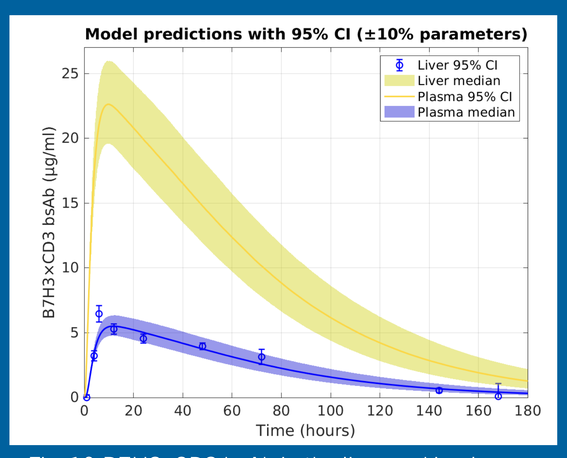


Fig. 10:B7H3×CD3 bsAb in the liver and in plasma

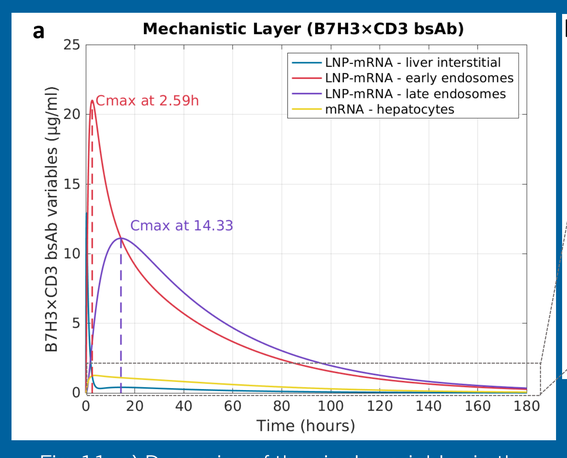


Fig. 11: a) Dynamics of the single variables in the mechanistic layer

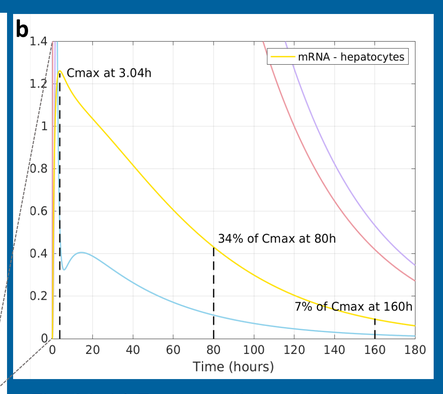


Fig. 11: b) Focus on the mRNA dynamic in the hepatocytes, following LNP fusion and endosomal escape

Future Perspectives

- **Full customization**: The PBPK framework can be further adapted to account for delivery routes (intravenous, muscular, dermal, via aerosol), antibody size, FcRn affinity, and tissue tropism.
- **Translational perspective**: Efforts will be directed toward confirming the applicability of the PBPK framework in humans, with the goal of establishing it as a reliable instrument for informing dosing and scheduling decisions.
- **Extended applications**: Thanks to the precise mechanistic layer, the model will be investigated for its ability to represent diverse LNP formulations and mRNA designs (e.g., circular or self-amplifying).

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