Mathematical Methods and Models in Biosciences
June 15–20, 2025, Sofia, Bulgaria
https://biomath.math.bas.bg/biomath/index.php/bmcs

A multi-scale PBPK model for predicting mRNA-encoded therapeutic trafficking in mice

Elisa Pettinà[1,2], Chiara Rosati[1], Stefano Giampiccolo[2,3], Luca Marchetti[1,2]

[1]Department of Cellular, Computational and Integrative Biology (CIBIO), University of Trento, Italy
elisa.pettina@unitn.it
chiara.rosati@unitn.it
luca.marchetti@unitn.it

[2]Fondazione The Microsoft Research – University of Trento Centre for Computational and Systems Biology (COSBI), Rovereto, Italy
pettina@cosbi.eu
giampiccolo@cosbi.eu
marchetti@cosbi.eu

[3]Department of Information Engineering and Computer Science, University of Trento, Italy
stefano.giampiccolo@unitn.it

In the field of immunotherapy, mRNA-encoded monoclonal antibodies (mRNA-mAbs) have emerged as a promising treatment for several conditions – in particular, for cancer, infections and inflammatory diseases. Importantly, the successful use of mRNA-mAbs has been made possible by the development of efficient RNA delivery systems, such as Lipid Nanoparticles (LNPs), which protect mRNA from enzymatic degradation and enable targeted intracellular delivery.

Despite great achievements in this field, the mechanistic understanding underlying the metabolism of mRNA-LNP therapeutics remains poorly understood. To address this gap, we developed a ODE-based model that describes the principal events occurring after IV injection of mRNA-LNPs based on the most recent findings in literature, namely their adsorption in the liver, their clearance and subsequently their escape from the endosomes and translation. This mechanist layer is also equipped with a Physiologically Based Pharmacokinetic (PBPK) model, based on the work of Sepp et. al. (2019) [1], which describes the kinetics of mRNA-mAbs throughout 15 different organs and tissues.

To fit the unknown parameters in the model, we leveraged three preclinical studies in mice that report the concentration time-profile of mRNA-mAbs of

different sizes, all delivered with LNPs [2, 3, 4] and targeting cancer cells. Our multi-scale PBPK model accurately predicts the concentration-time profiles of both the mRNA-encoded therapeutics and the relative recombinant proteins. The model was also validated on unseen data presented in the reference literature [2, 3, 4], demonstrating high accuracy also in different dosing schedules and dosages.

Our model can predict mAbs disposition in remote tissues, which experimentally would require the sacrifice of the animal, and their kinetics in different animal models, including humans. Moreover, its inherent modularity enables the exploration of different routes of administration and tropisms of the mRNA-LNPs therapeutic of interest, offering a valid support to the development of these ground-breaking therapies.

Keywords: immunotherapy, mAbs, PBPK, ODE-based models

References

[1] A. Sepp, G. Meno-Tetang, A. Weber, A. Sanderson, O. Schon, A. Berges, Computer-assembled cross-species/cross-modalities two-pore physiologically based pharmacokinetic model for biologics in mice and rats, *Journal of Pharmacokinetics and Pharmacodynamics*, 46:339–359, 2019.

[2] L. Wu, W. Wang, J. Tian, C. Qi, Z, Cai, W. Yan, S. Xuan, A. Shang, Intravenous Delivery of RNA Encoding Anti-PD-1 Human Monoclonal Antibody for Treating Intestinal Cancer, *Journal of Cancer*, 13:579–588, 2022.

[3] C. Huang, X. Duan, J. Wang, Q. Tian, Y. Ren, K. Chen, Z. Zhang, Y. Li, Y. Feng, K. Zhong, Y. Wang, L. Zhou, G. Guo, X. Song, A. Tong, Lipid Nanoparticle Delivery System for mRNA Encoding B7H3-redirected Bispecific Antibody Displays Potent Antitumor Effects on Malignant Tumors, *Advanced Science*, 10:2205532, 2023.

[4] C. R. Stadler, U. Ellinghaus, L. Fischer, H. Bähr-Mahmud, M. Rao, C. Lindemann, A. Chaturvedi, C. Scharf, I. Biermann, B. Hebich, A. Malz, G. Beresin, G. Falck, A. Häcker, A. Houben, M. Erdeljan, K. Wolf, M. Kullmann, P. Chang, Ö. Türeci, U. Şahin, Preclinical efficacy and pharmacokinetics of an RNA-encoded T cell-engaging bispecific antibody targeting human claudin 6, *Science Translational Medicine*, 16:eadl2720, 2024.