

## Introduction

The fast development process, combined with the possibility to quickly update the target, designate mRNA vaccines as a formidable tool during pandemic. mRNA vaccines codify for the antigen protein that would trigger the immune system response to the pathogen associated to it. While the events occurring after the antigen presentation are expected to be similar to traditional vaccines, the interaction between the human innate immune cells and mRNA molecules appears to be fragmented amid the literature, making it difficult to formulate new hypotheses to be tested in clinical settings and ultimately improve this technology platform.

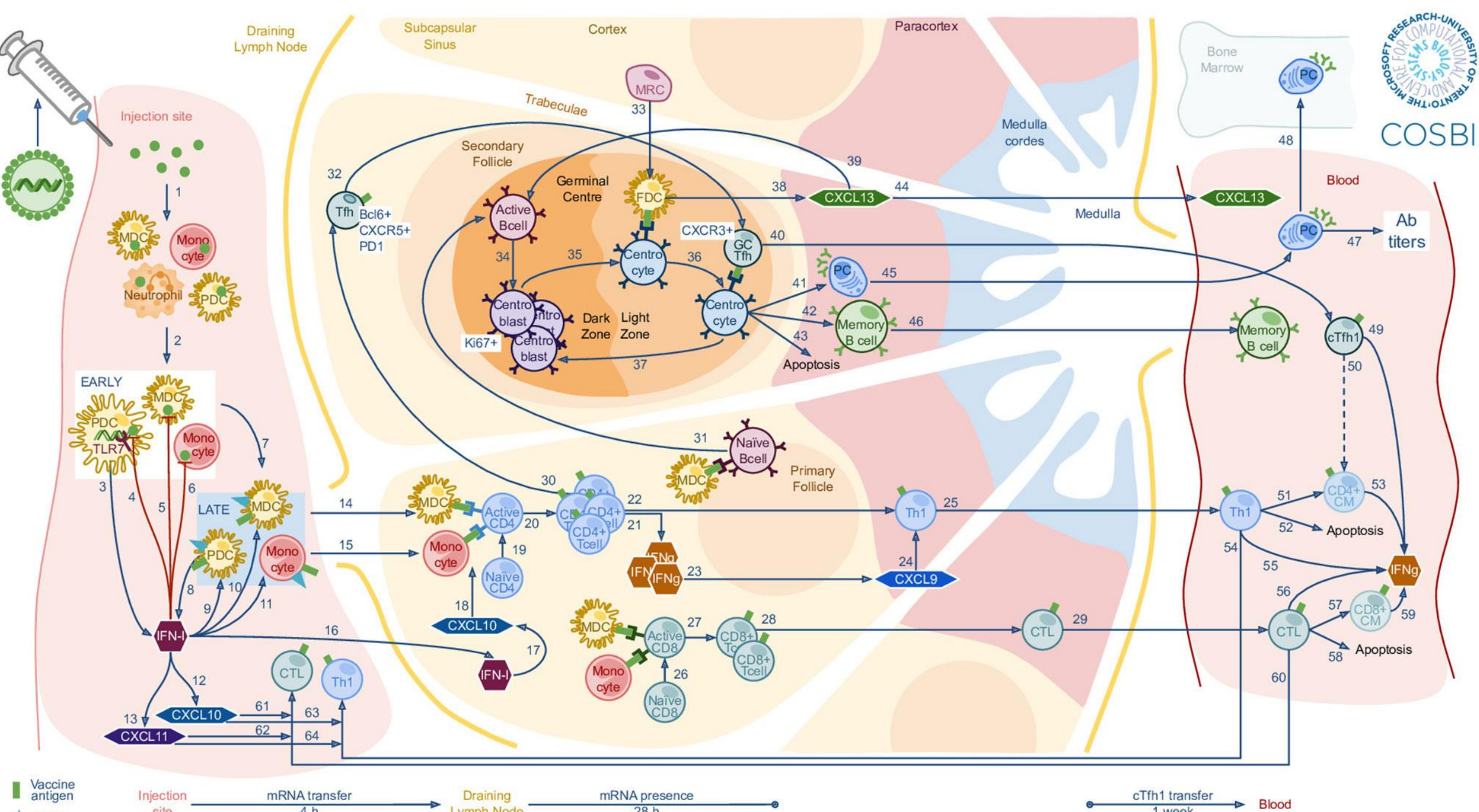


**Figure 1:** Mechanistic graphical model of the mRNA-based vaccine biological mechanism of action [1]. An interactive version of the model is available at <https://www.cosbi.eu/fx/9839203>

## Results

The retrieved information was merged into an interactive mechanistic graphical model [3] representing the biological processes including the published data (Figure 1). The information collected in the graphical model was then encoded into a QSP model [4] representing the whole immunogenic process (Figure 3).

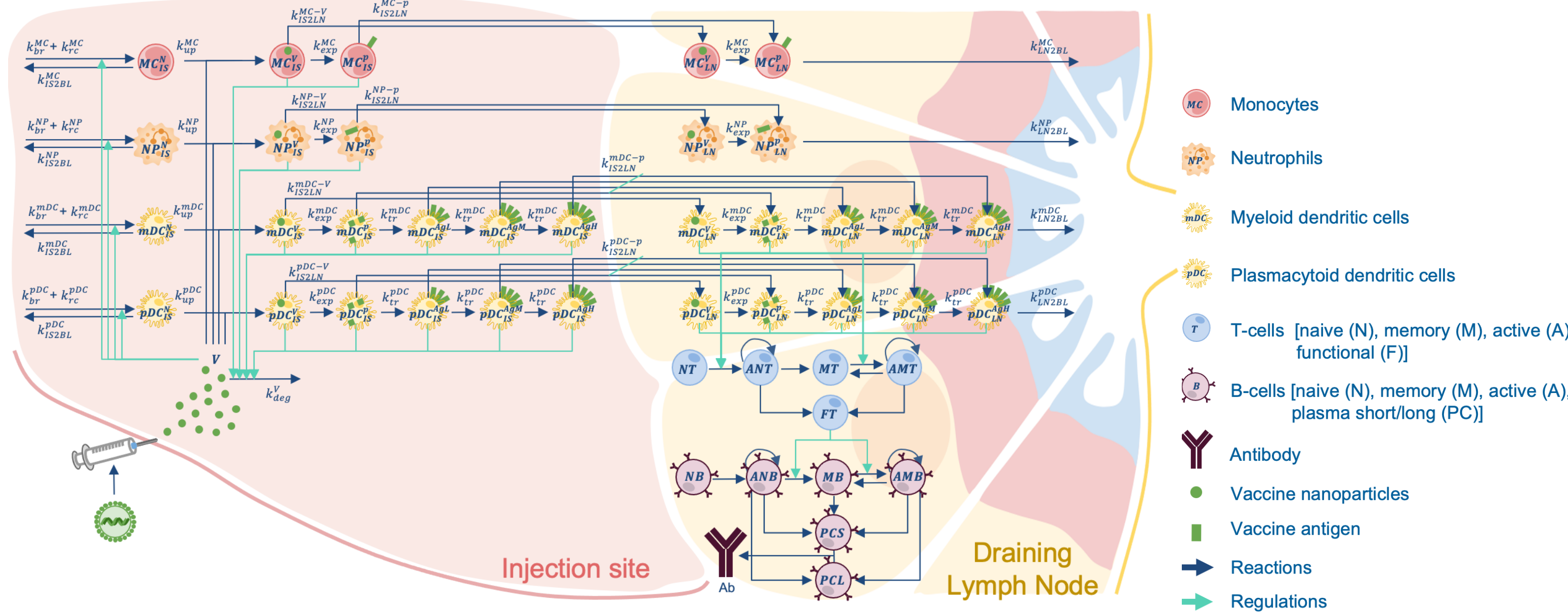


**Figure 3:** The mRNA vaccine model diagram [4].

The main **tuneable properties** of the vaccine were identified, and a sensitivity analysis carried out to show how such a model can help **prioritizing drug development strategies**.

**Table 1.** Sensitivity table on the model predicted antibody titer (Ab calculated 30 days after the injection). Cell colours highlight the sensitivity values from the lowest (grey) to the highest (dark blue).

| $S(Ab, \{p\})$ | $k_{tr}$ | $k_{up}$ | $k_{rc}$ | $k_{exp}$ |
|----------------|----------|----------|----------|-----------|
| $k_{tr}$       | 0.20     | 2.28     | 2.23     | 0.25      |
| $k_{up}$       | —        | 2.08     | 4.15     | 2.14      |
| $k_{rc}$       | —        | —        | 2.03     | 2.09      |
| $k_{exp}$      | —        | —        | —        | 0.05      |

Where:  $k_{tr}$  represents the rate of antigen accumulation on the membrane,  $k_{exp}$  identify the mRNA translation,  $k_{up}$  the rate of vaccine uptake by the cells and  $k_{rc}$  the immune system recruiting due to the presence of vaccine particles and adjuvants.

The model can be used to virtually explore the drug optimization landscape (Figure 4) and quantitatively address vaccine specifics (e.g., targets, mRNA properties, delivery systems etc.), playing a crucial role in accelerating *in silico* the development of mRNA-based products [5].

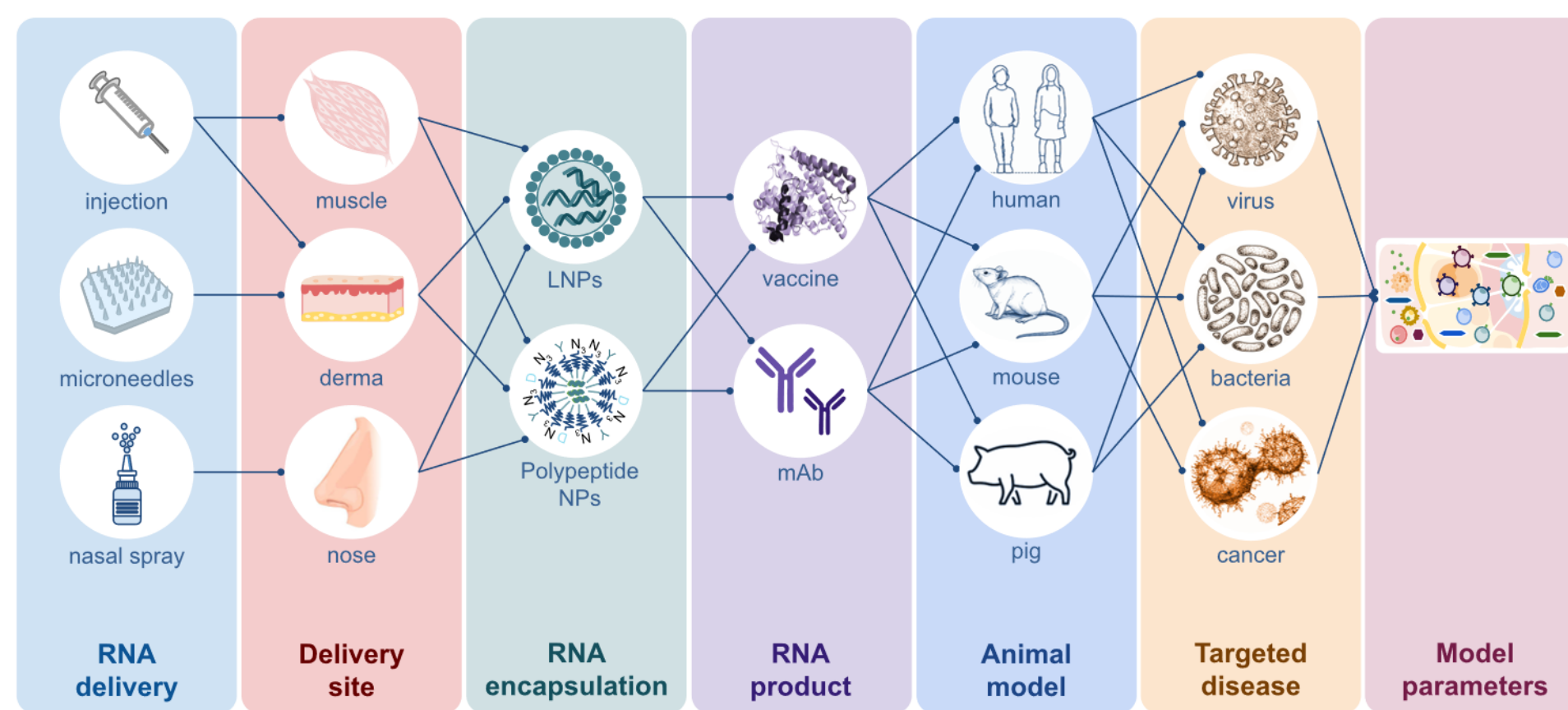


**Figure 4:** Different layers of complexity for defining the model.

In particular, upon proper calibration, the model can be used to inform clinical trials on dosage and scheduling of booster shots allowing for a knowledge-oriented drug design and development.

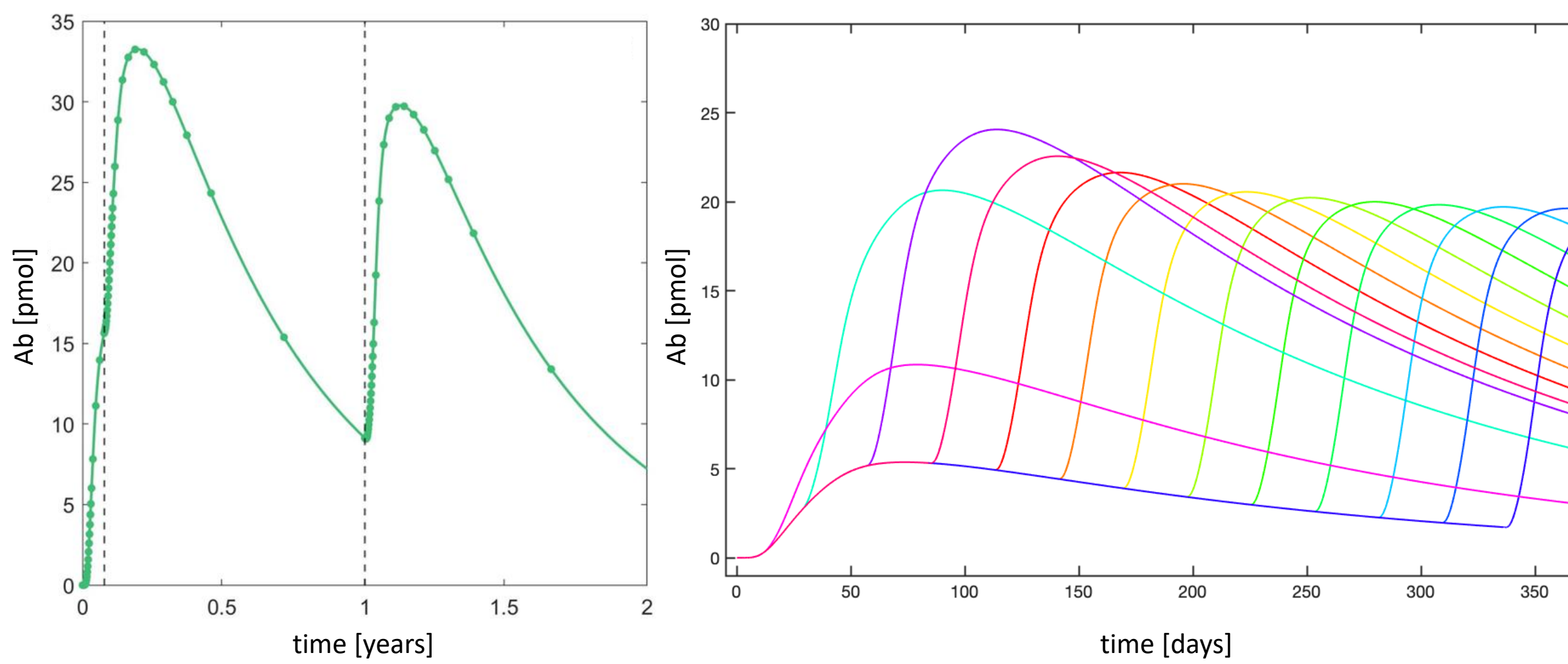


**Figure 5:** An example of model predicted three dose scheduling (left); second dose scheduling optimization (right).

## Conclusions

We presented an integrative systems biology pipeline applied to mRNA vaccines. The outcomes of the pipeline are:

- A graphical mechanistic model, which resumes the current state of the art knowledge about the mRNA vaccinations, designed to integrate specific data retrieved during the text mining process. The graphical model can ease stakeholders communication and internal sharing of data through an endearing user interface.
- A QSP model, which can be potentially used to test specific hypotheses on drug formulation, delivery, dosing and scheduling. *In silico* tools like this would be pivotal in drug development informing clinical trials design and reducing *in vitro-in vivo* disconnection.

## References

- Leonardelli et al. Front. Immunol. (2021) 12.
- Chen et al. CPT Pharmacometrics Syst. Pharmacol. (2014) 3 (133).
- Liang et al. Mol. Ther. (2017) 25.
- Selvaggio et al. CPT Pharmacometrics Syst. Pharmacol. (2021) 10 (12).
- The Wellcome Leap R3 project

## Aims

Propose an effective **systems biology pipeline** to **analyse** and **integrate** multi-source knowledge and **data**, with the goal of clarifying the intricate biological processes involved in the mechanism of action of **mRNA vaccines** and implement them in a **QSP model** able of simulating the induced immunogenicity at organism level, depending on different vaccine **doses**, **delivery** systems and **animal** species.

## Methods

An integrative systems biology approach, outlined in Figure 2, was applied to the mRNA vaccine topic. A Natural language processing (NLP) pipeline for automated knowledge extraction retrieved the evidences we used to build the mechanistic graphical model of Figure 1. The text mining effort combined with interactive representation capabilities results in a visual repository of data and knowledge that can be easily shared among the project stakeholders.

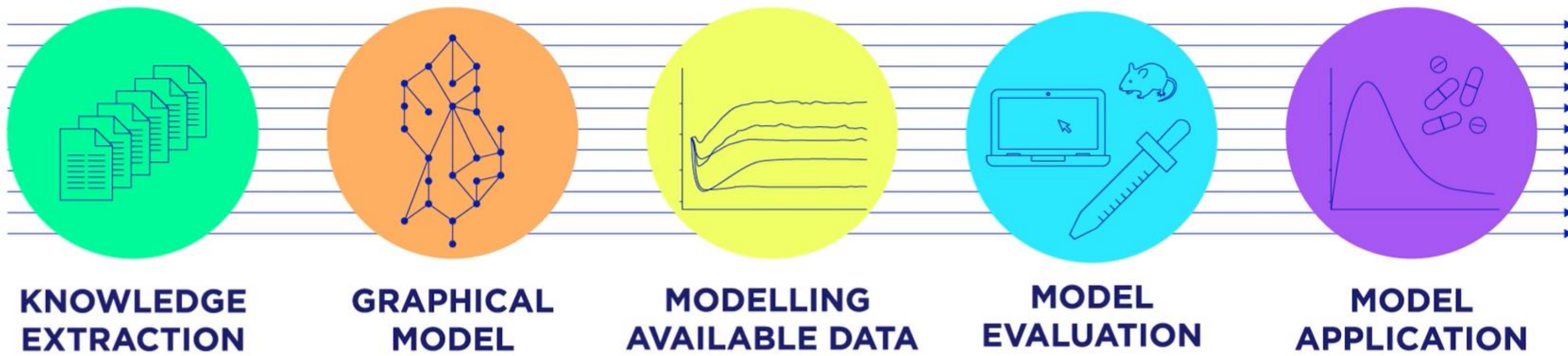


**Figure 2:** Integrative systems biology approach employed to develop the QSP model

The QSP model was implemented in MATLAB® as a set of ODEs and leverages on the work of Chen et al. 2014 [2], which was extended to represent in greater details the early events after injection according to the information retrieved during the text mining phase.

The vaccination early events as vehicle uptake, antigen expression and migration to the draining lymph node were then calibrated based upon experimental data from Liang et al. 2017 [3].