



# Improving the efficacy of anti-cancer nanoparticles with data-driven mathematical modeling

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# Improving the efficacy of anti-cancer nanoparticles with data-driven mathematical modeling

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## MOTIVATIONS & OBJECTIVES

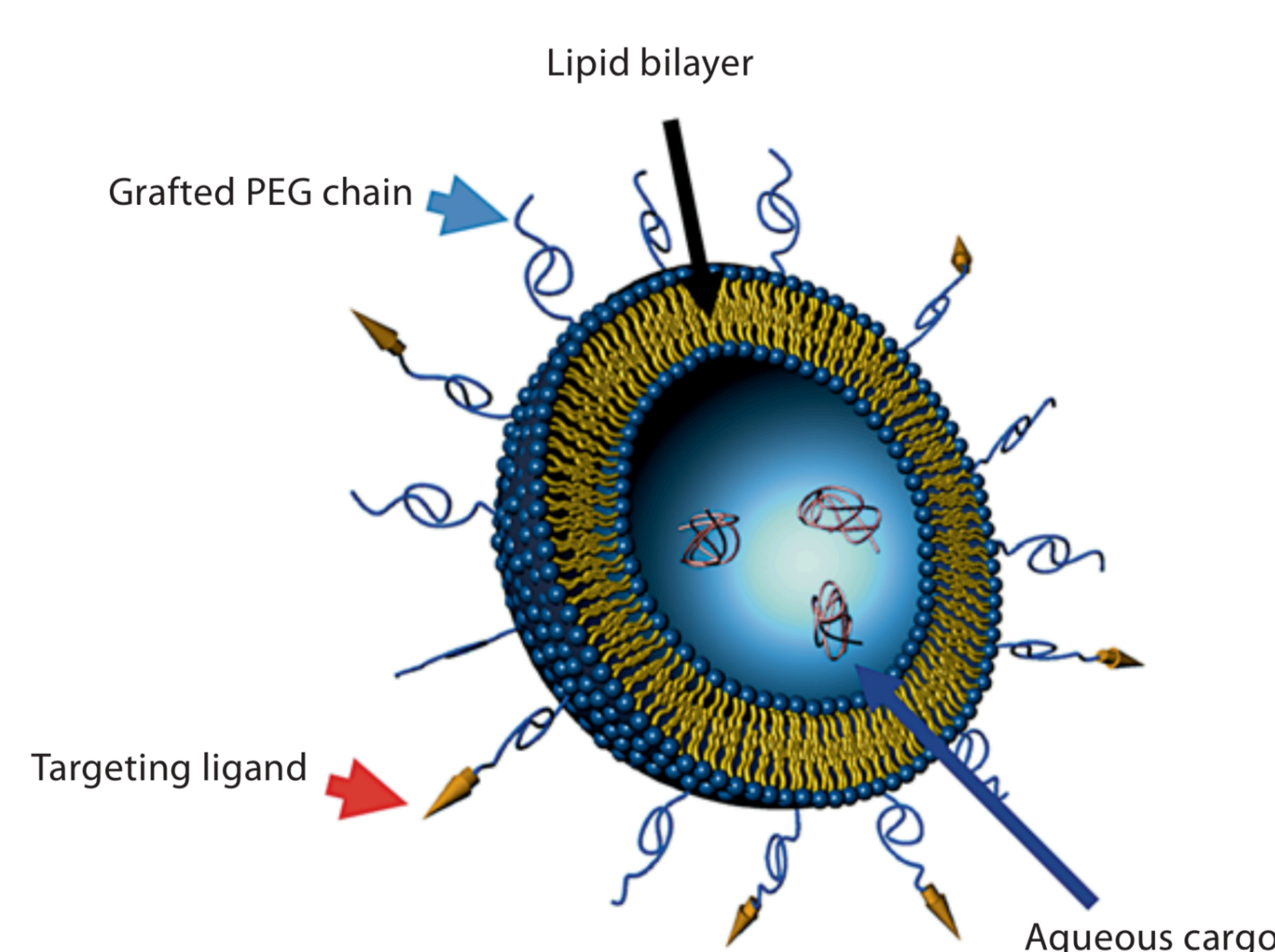
- Nanoparticles conjugated with cancer cell specific antibodies are being developed in order to improve drug delivery to the tumor and to spare healthy tissues. These nanoparticles are called **antibody-nanoconjugates (ANCs)**.
- The goal of this project is to develop mathematical and numerical tools to **optimize the design** of ANCs and to **improve their biodistribution**.

## EXPERIMENTAL BACKGROUND

### CANCER CELL LINES

We consider breast cancer cell lines, with different levels of expression of the Her2 receptor.

Cell line	Immunoprofile
SKBR3	Her2++
MDA-MB-453	Her2+
MDA-MB-231	Her2-



ANC structure, [Moghimi et al. (2012)]

### TREATMENTS

- Free drugs:** docetaxel + trastuzumab
- ANC:** liposomes with encapsulated docetaxel and engrafted trastuzumab on the surface [1].

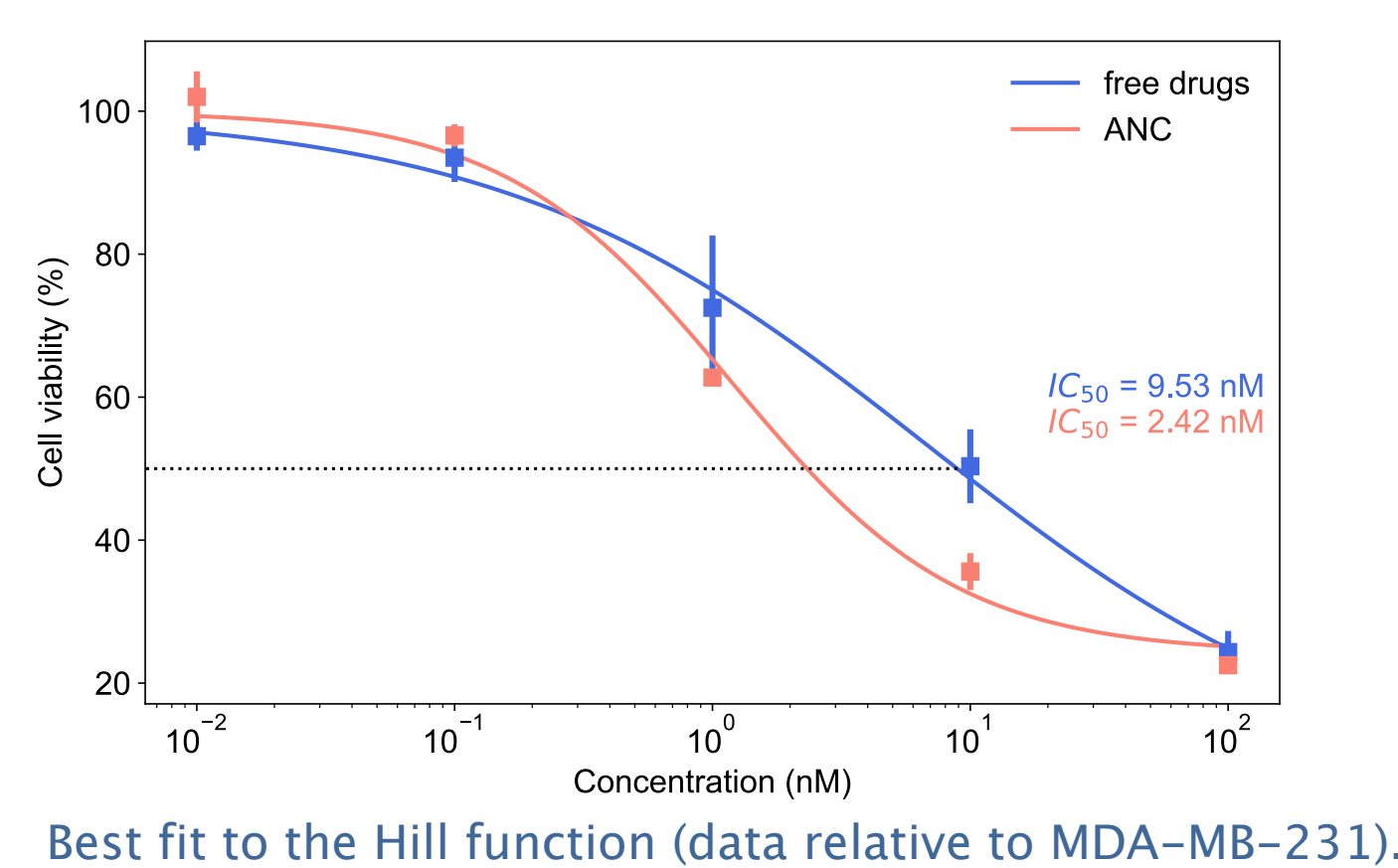
### PRECLINICAL DATA

- In vitro:** cell viability (2D assay).
- In vivo:** tumor growth kinetics, biodistribution of liposomes (caliper, fluorescence and bioluminescence data).
- Ex vivo:** drug penetration in the tumor tissue (MALDI imaging), vessels density in the tumor.

## PRELIMINARY RESULTS

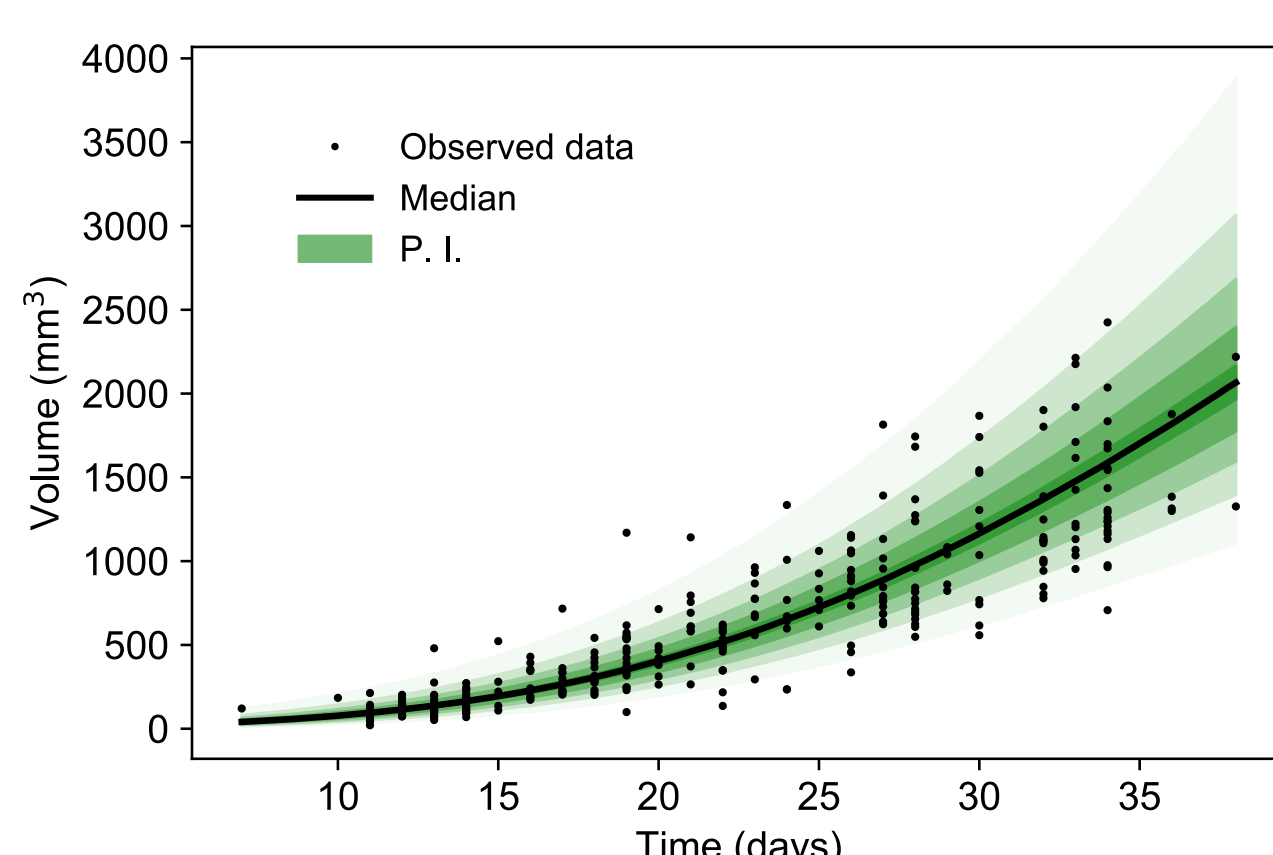
### IN VITRO DATA ANALYSIS

- Classical Hill model described well the effect of the nanoparticles on cell culture.
- ANC had **equal or higher efficacy** than free drugs

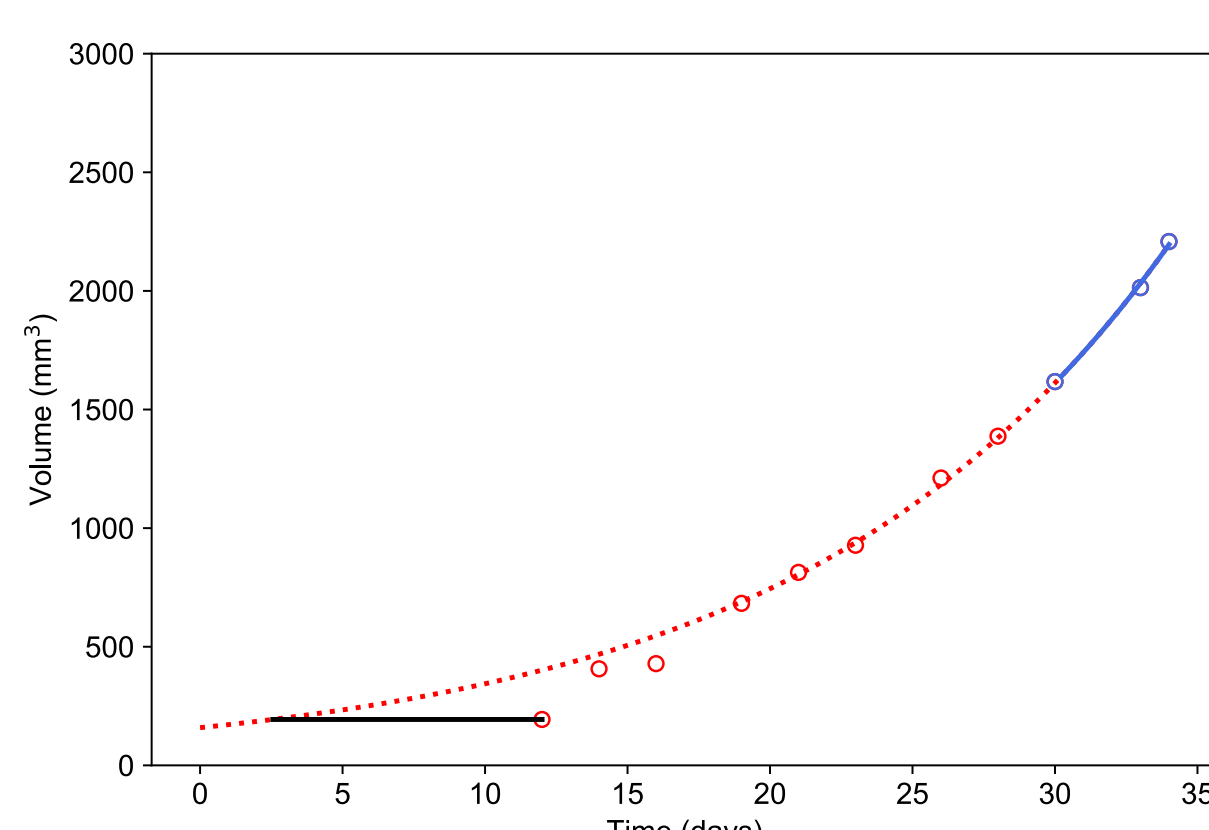


Best fit to the Hill function (data relative to MDA-MB-231).

### TUMOR GROWTH AND BACKWARD PREDICTION OF THE INITIATION TIME



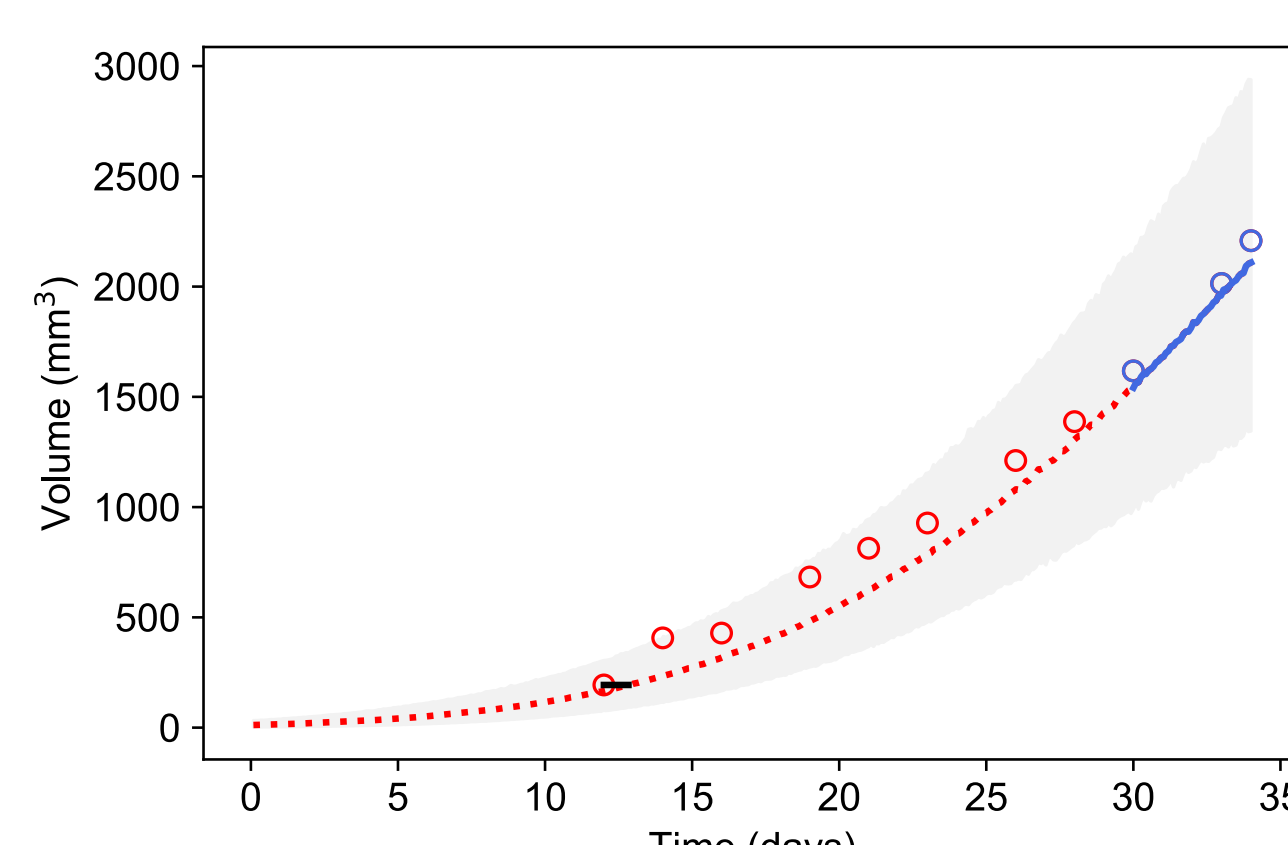
Nonlinear mixed effects modelling on the Gompertz model with the training set (33 individuals): prediction distribution. Data relative to MDA-MB-231.



Backward prediction of the initiation time of an individual of the test set without a priori (left) and with a priori (right) using the Gompertz model. Data relative to MDA-MB-231.

NO PRIOR	exponential	gompertz
$ t_1 - t_{1,pred} $ , median	11	5.16
$ t_1 - t_{1,pred} $ , std	16.3	21.3
PRIOR	exponential	gompertz
$ t_1 - t_{1,pred} $ , median	2.57	1.9
$ t_1 - t_{1,pred} $ , std	2.97	2.47

Results on the test set (33 individuals, data fit on the last 3 tumor growth points). The Gompertz model with a priori information has higher prediction power.

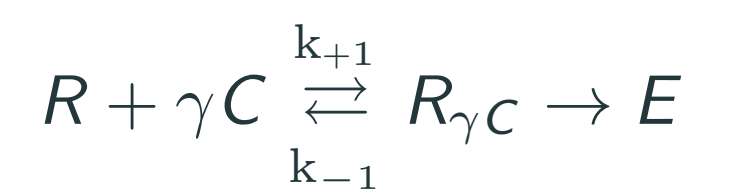


## OUTLINE

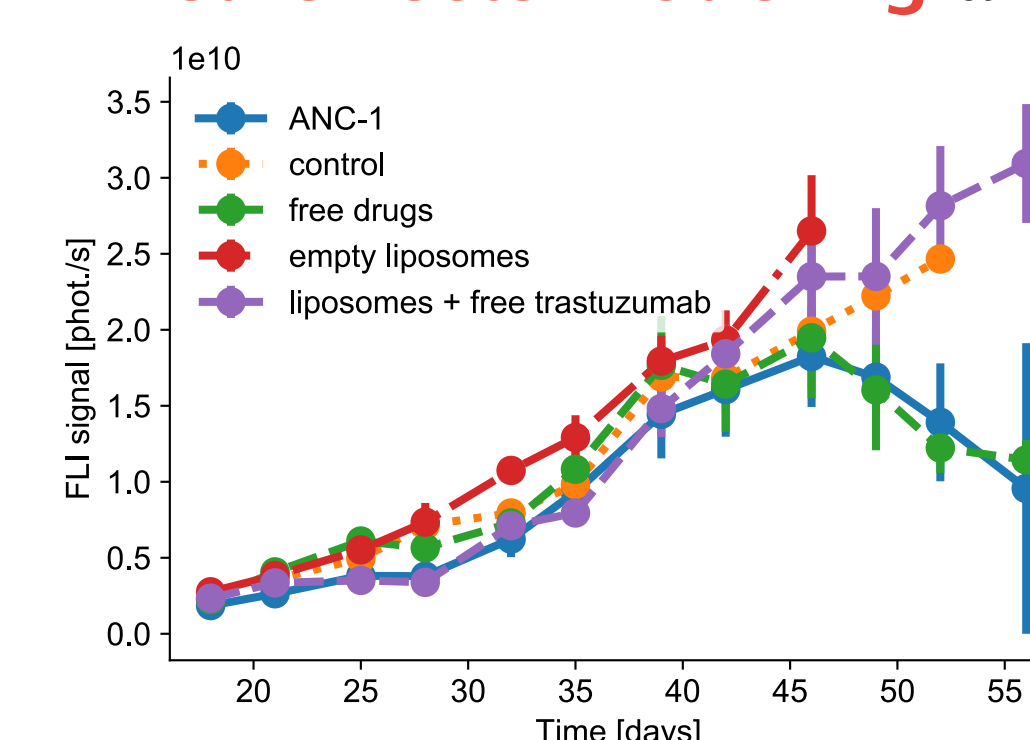
- PK/PD modeling: **dose regimen optimization**.
- Development of a computational model describing the transport of nanoparticles in tumors: **ANC design**.

## METHODS

- Characterization of the biochemical behaviour of the nanoparticles: in vitro data fit to the Hill function and IC50 determination.



- Individual tumor growth prediction and treatment response: **nonlinear mixed effects modeling** and **bayesian inference** of in vivo data.



Mean trend of tumor growth relative to different treatment groups (MDA-MB-231 cell line).

$$y_i^j = \underbrace{f(t_i^j, \theta^j)}_{\text{structural model}} + \underbrace{\sigma(f(t_i^j, \theta^j)) \epsilon_i^j}_{\text{error model}}, \quad \epsilon_i^j \sim \mathcal{N}(0, 1)$$

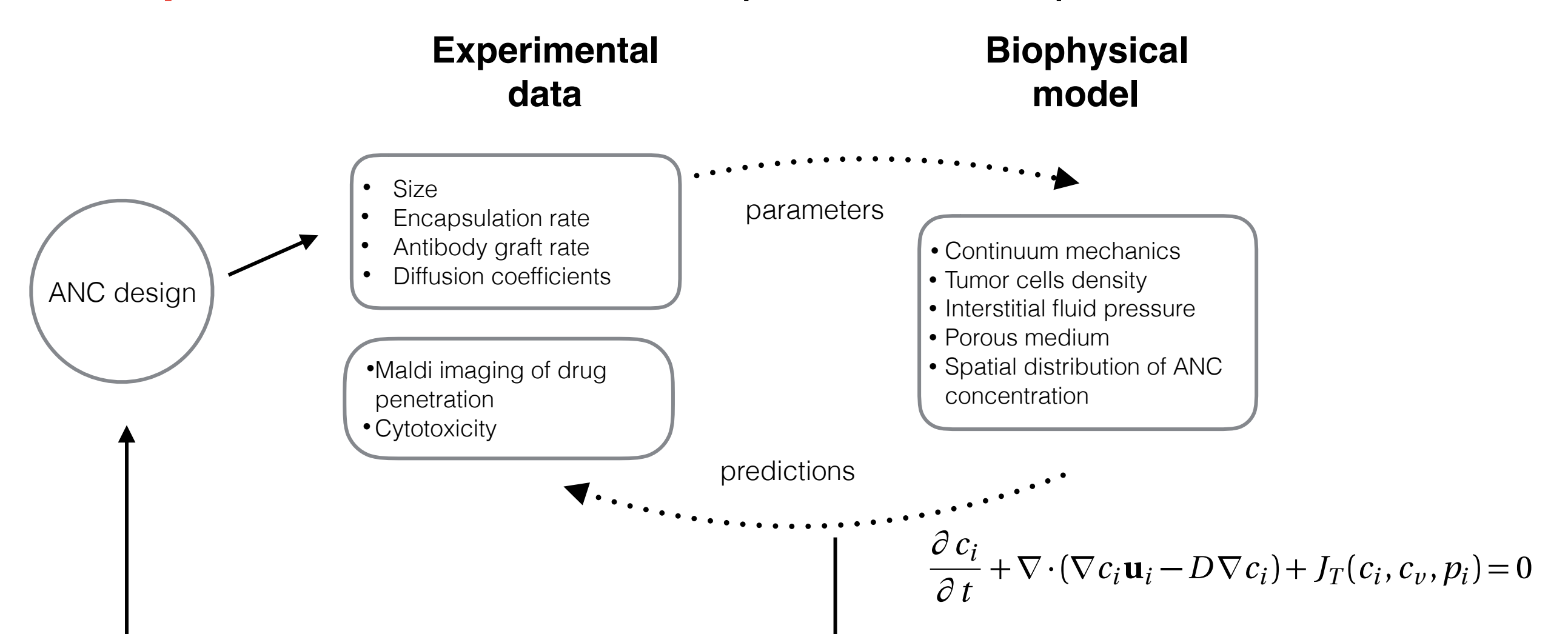
Nonlinear mixed effects modeling [2]:

$$\theta^1, \dots, \theta^N \sim \mathcal{LN}(\mu_\theta, \omega_\theta)$$

Bayesian prediction:

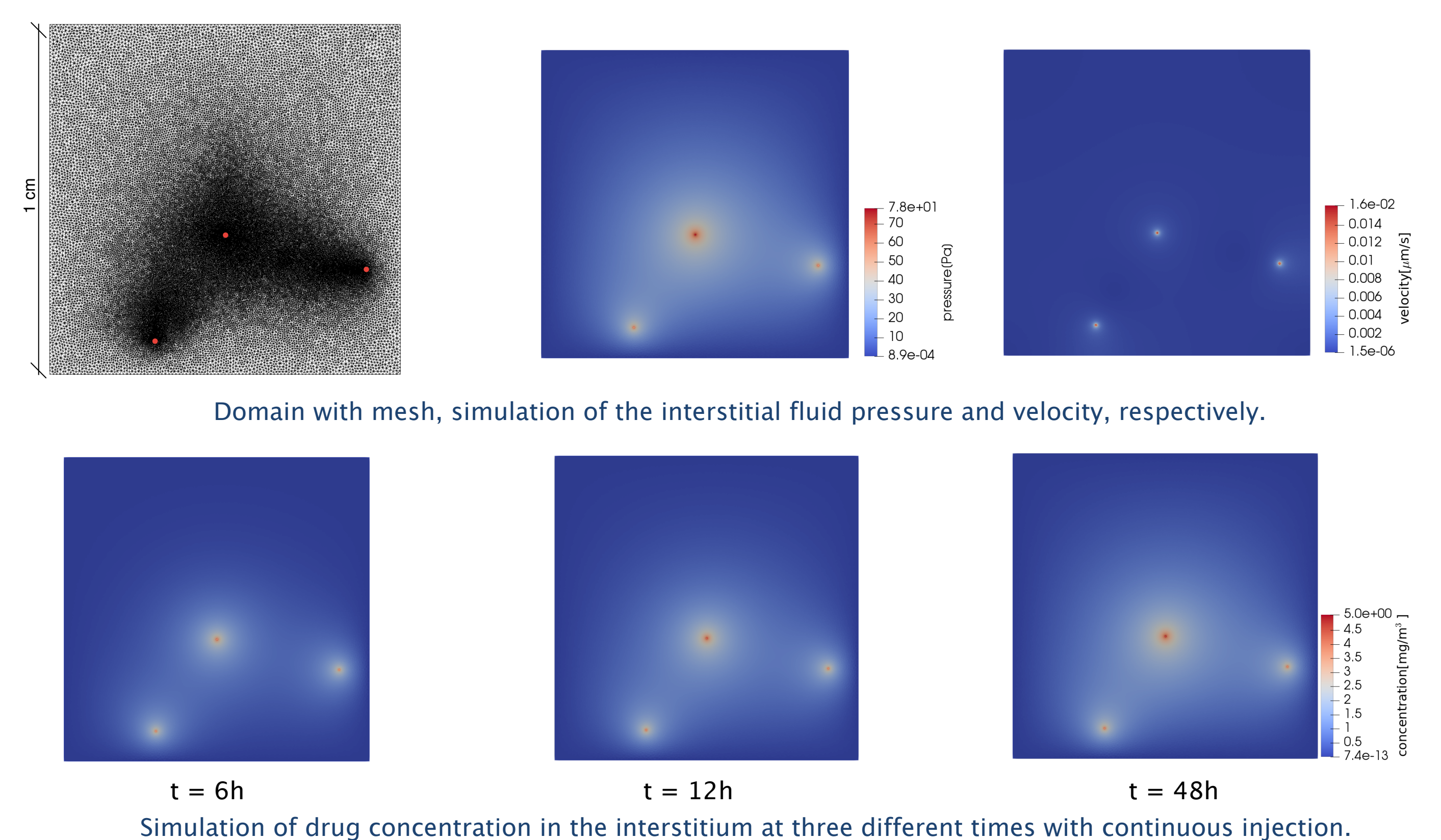
$$\hat{\theta}_{\text{MAP}} = \arg \max \mathbb{P}(\theta | y), \quad \mathbb{P}(\theta | y) = \frac{\mathbb{P}(\theta) \mathbb{P}(y | \theta)}{\mathbb{P}(y)}$$

- Spatial computational model** of nanoparticles transport in tumor tissue.



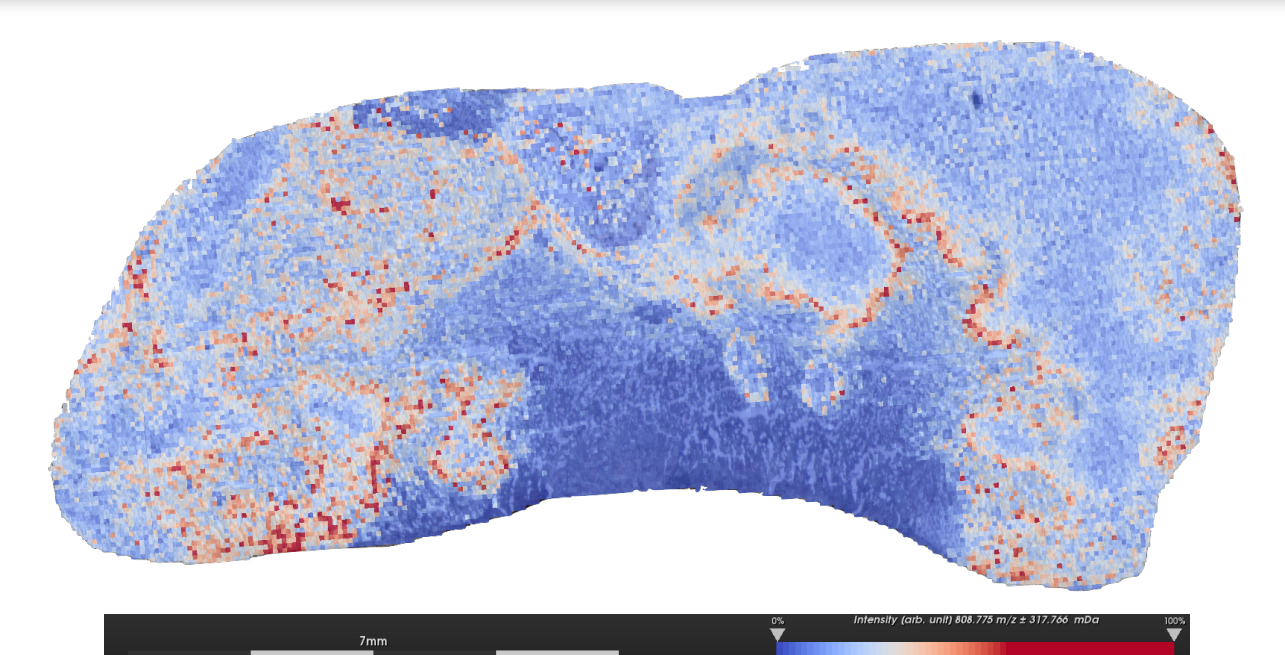
### QUALITATIVE RESULTS OF THE SPATIAL MATHEMATICAL MODEL OF NANOPARTICLES TRANSPORT IN TUMOR TISSUE

- Determinants of drug transport in tumor tissue: vascular transport, transvascular transport, interstitial transport, cellular uptake and metabolism [3].



## FUTURE PERSPECTIVES

- Pharmacokinetics** modeling of the biodistribution of nanoparticles in the tumor and in the body.
- Comparative **pharmacodynamics** modeling of the in vivo drugs efficacy.
- Spatial model calibration** with experimental data.



Nanoparticles distribution in the tumor tissue (MALDI image).