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**.

OUTLINE

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

EXPERIMENTAL BACKGROUND

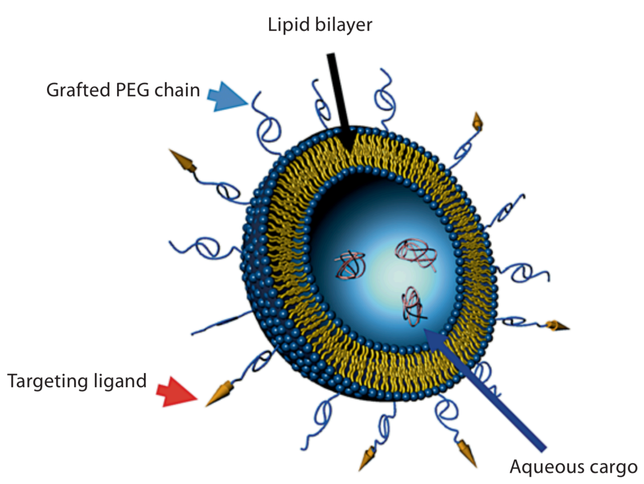
CANCER CELL LINES

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-

TREATMENTS

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



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

PRECLINICAL DATA

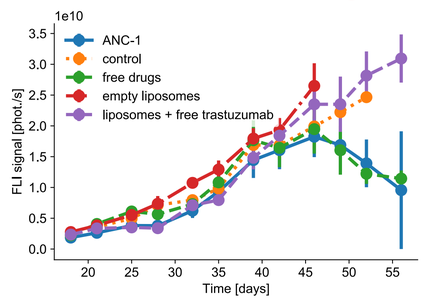
- In vitro: cell viability (2D assay).
- In vivo: tumor growth kinetics, biodistribution of liposomes (caliper, fluorescence and bioluminescence data).
- Ex vivo: drug penetration in the tumor tissue (MALDI imaging), vessels density in the tumor.

METHODS

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

$$R + \gamma C \underset{k_{-1}}{\overset{k_{+1}}{\rightleftarrows}} R_{\gamma C} \to E$$

- 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).

$$y_i^j = \underbrace{f(t_i^j, \boldsymbol{\theta}^j)}_{\text{structural model}} + \underbrace{\sigma\left(f(t_i^j, \boldsymbol{\theta}^j)\right)\varepsilon_i^j}_{\text{error model}}, \qquad \varepsilon_i^j \sim \mathcal{N}(0,1)$$

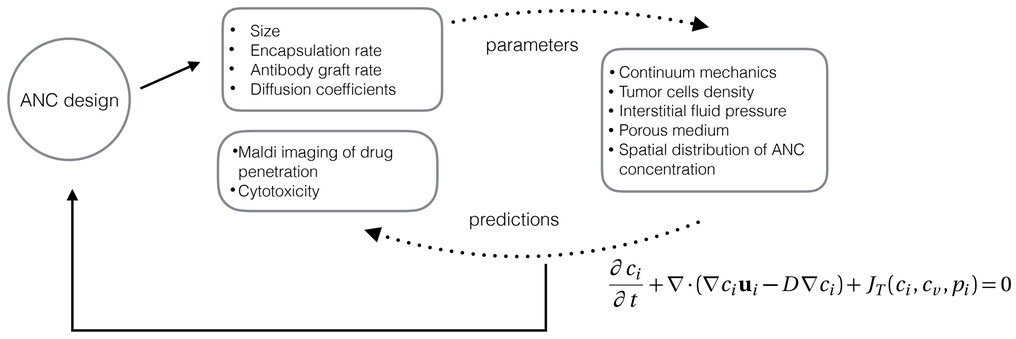
Nonlinear mixed effects modeling [2]:

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

Bayesian prediction:

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

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

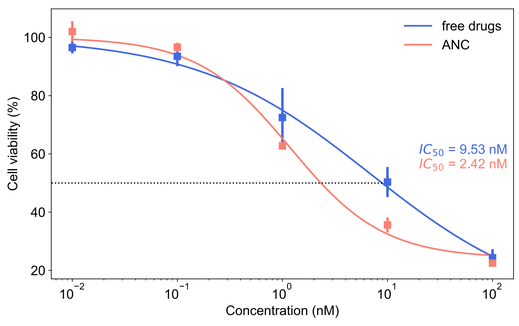


$$\frac{\partial c_i}{\partial t} + \nabla \cdot (\nabla c_i \mathbf{u}_i - D \nabla c_i) + J_T(c_i, c_v, p_i) = 0$$

PRELIMINARY RESULTS

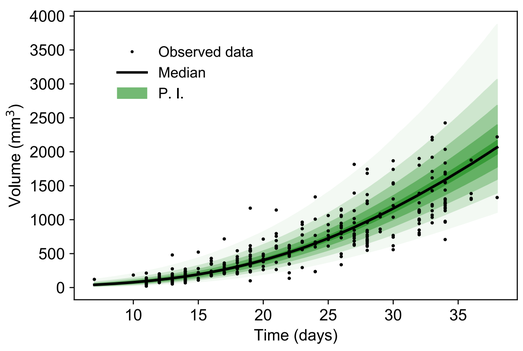
IN VITRO DATA ANALYSIS

- 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

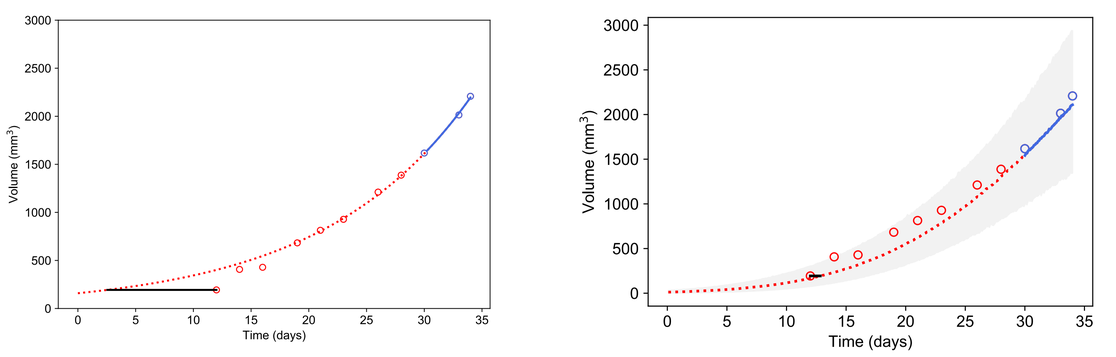


Nonlinear mixed effects modelling on the Gompertz model with the training set (33 individuals): prediction distribution. Data relative to MDA-MB-231.

NO PRIOR	exponential	gompertz
$\lvert t_1 - t_{1,\text{pred}}\rvert$, median	11	5.16
$\lvert t_1 - t_{1,\text{pred}}\rvert$, std	16.3	21.3

PRIOR	exponential	gompertz
$\lvert t_1 - t_{1,\text{pred}}\rvert$, median	2.57	1.9
$\lvert t_1 - t_{1,\text{pred}}\rvert$, std	2.97	2.47

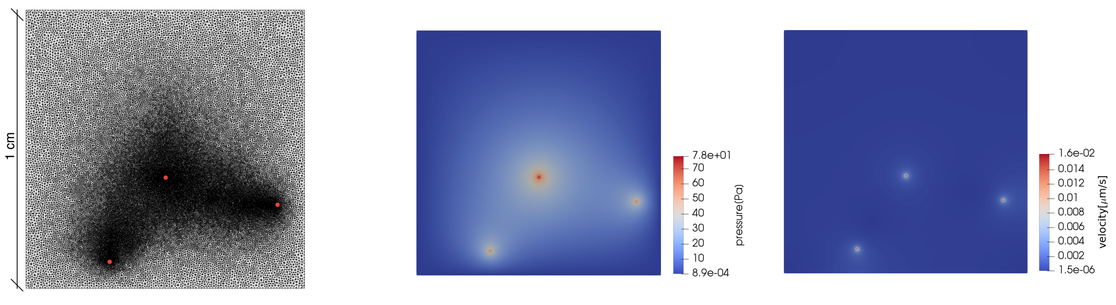
Results on the test set (33 individuals, data fit on the last 3 tumor growth points). The Gompertz model with a priori information has higher prediction power.



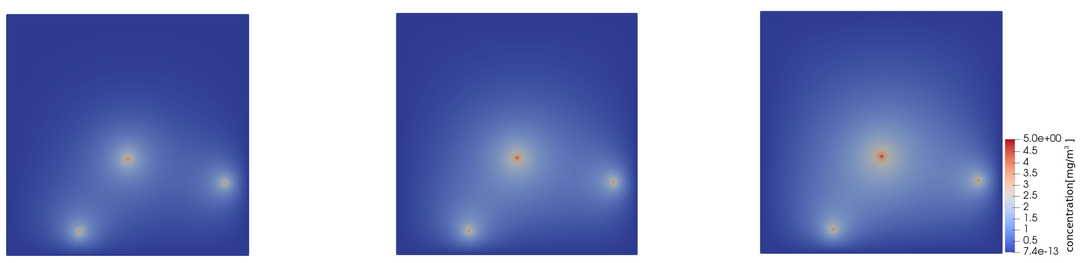
Backward prediction of the initiation time of an individual of the test set without a priori (left) and with a priori (right) using the Gompertz model. Data relative to MDA-MB-231.

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].



Domain with mesh, simulation of the interstitial fluid pressure and velocity, respectively.

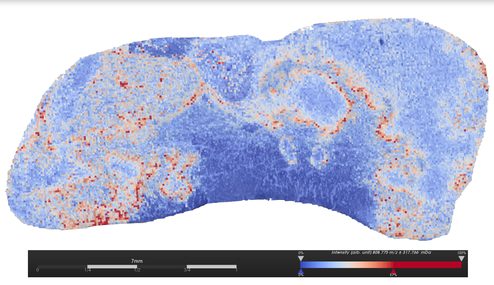


t = 6h t = 12h t = 48h

Simulation of drug concentration in the interstitium at three different times with continuous injection.

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).

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