AI-based Modeling of Nanotheranostic Photo- or Thermo-active Drug Release using Dynamic MRI and Optical Imaging

3 year PhD position

Keywords: Artificial Intelligence (AI), Machine learning (ML), Nanotheranostics, Kinetic bioditribution, Biomaging, Quantitative image processing, Bioimaging engineering

1. General Context

One of the targeted objectives of personalized medicine, with examples in conventional chemotherapy, or when fighting inflammatory diseases, controlled drug delivery to the lesion gives hopes to limit severe side effects of the therapy. In this purpose, nanotheranostic strategy [1,2,3], developing chemical multifunctional therapeutic systems equipped with imaging abilities associated with drugs allows to visualize drugs biodistribution, map drug delivery and monitor the therapeutic responses in vivo. Magnetic Resonance Imaging (MRI) and optical imaging are adapted to provide microscopic and macroscopic information with a dynamic dimension in time to follow the physio pathological stages in vivo.

Among the medical imaging methods, MRI is a powerful imaging method used in clinics, with 3D and contrast advantages at the macroscopic in vivo scale. Optical imaging is a complementary modality which allows mapping the biodistribution of fluorescent probes at the microscopic, cellular level as well as at the macroscopic whole body scale. The kinetic biodistribution in time of the imaging probes provided by this theranostic strategy as well as the evolution of the image will benefit from quantitative computing developments using AI to provide accurate diagnosis and efficiency.

The pharmacokinetic theory has been developed over decades based on the physiology and kinetics of reactions [4]. Explicit, mathematical models allow pharmacokinetic data to be reduced to parameter values, providing insight, and understanding of ADME processes (Absorption, distribution, metabolism, and excretion) and predicting the outcome of different dosing scenarios. However, explicit modeling is difficult due to the lack of precise knowledge of many hidden parameters such as inter-individual, inter-organ and inter-drug differences and the predicting the outcome remains hazardous. Machine learning (ML) tools are expected to provide solutions to these difficulties [5]. However, it becomes evident that even though data-driven ML techniques allow to overcome the difficulties of explicit mathematical modeling they bring other drawbacks, related to data readiness and availability.

2. Objectives

Using quantitative, experimental data obtained by MRI and optics bioimaging, *in vitro* and *in vivo*, the final objective is to model and optimize the efficiency of nanotheranostic administration of photoactivable formulations of antitumoral drugs, against cancer.

MRI and optics images (3D+time data) will be recorded and analyzed to monitor the therapy and its efficiency. We will study the kinetic biodistribution of the drug in the tumor and in the whole body, to record pharmacodynamic activity and quantify the impact on the tumoral pathological areas in a dynamic manner. The objective of this PhD is to develop an IA model to optimize pharmacokinetic processes to obtain the desired drug release.

3. Methods

Data acquisition

For studying pharmacokinetics of therapeutical formulation, sequences of MRI images will be recorded and processed. The sensitivity of detection of contrast agent will be optimized using quantitative

acquisition methods (T1, T2, T2*, Susceptibility SWI weighting images [6]). These techniques are developed and implemented in preclinics and clinics to enhance the MRI contrast to improve the diagnosis of pathological biological areas. Moreover, the susceptibility is possibly different in different organs and tissues or due to the presence of MR contrast agents. We will extract spatial maps of the concentration and weight the signal with the local magnetic susceptibility by QSM Quantitative Susceptibility Methods [7].
In addition, processing integrative methods to provide the kinetic biodistribution information of the imaging probes will be developed.

Data Analysis and Modeling
New ML techniques appeared recently as a tradeoff between explicit modeling on one side, and purely data-driven methods at the other, allowing to use some knowledge together to fit a more reliable, and more physics-based model to available, observed data. The *physics-informed machine learning* [8] appeared as a new field of ML and steadily gains in popularity. It allows informing an ML model with underlying physics and requires less data to train. Other recent works illustrate how to use physics-informed ML to solve inverse problems [9].
For more complex phenomena, where no underpinning physics is known, yet another type of ML appeared that allows automated discovery of hidden, state variables from high-dimensional data [10]. Early works show how it allows to identify a stable, canonical physical model only from video recordings in time, without any knowledge of the governing physic laws.

Sets of kinetic multiparametric data will be recorded and processed to optimizing the efficacy of the therapy :

- Assessing the impact of the therapy using optical microscopy data of the subcellular internalization
- Controlling the drug administration in the tumoral zone (using MRI and/or optical modalities)
- MRI contrasts pre and post theranostic agents' injection in 3D images,
- AI based prediction of the therapeutical outcome

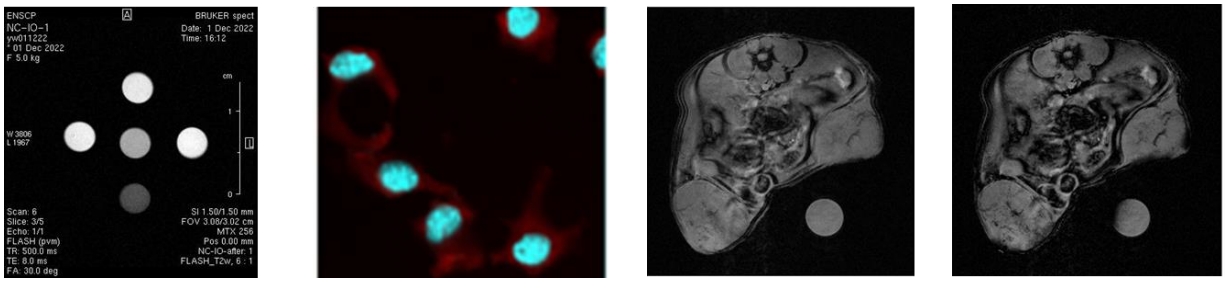

Figure : MRI- images of contrast agents and in vitro/in vivo micro images, IA imaging process

4. Expected Results

In the end we expect the AI based data analysis to better control the nanotheranostic drug administration and optimize the therapeutic outcome in various administration scenarii. We aim at providing a reliable tool for preclinical fundamental studies to make advances in the knowledge of these pathologies and evaluate new drugs and offer better diagnostic and follow-up to the patients.

Funding and partnership: This PhD will be submitted for funding by the PSL University. As part of academic collaboration with Chimie ParisTech, the PhD candidate will have the opportunity to work with teams at Chimie ParisTech (responsible for the development of the nanotheranostic formulations and the imaging).

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Application conditions: finished M2 programme with excellent academic records, expertise in image analysis, excellent AI coding skills (python, tensorflow/pytorch).

Application procedure: a prospective candidate should send his curriculum, academic track, motivation letter, two reference letters to petr.dokladal@minesparis.psl.eu

References:

1. Thébault CJ, …, Doan BT. Theranostic MRI liposomes for magnetic targeting and ultrasound triggered release of the antivascular CA4P. J Control Release. 2020 322, 137. DOI: 10.1016/j.jconrel.2020.03.003
2. Ha, Phuong Thu, et al. "Properties and bioeffects of magneto–near infrared nanoparticles on cancer diagnosis and treatment." New Journal of Chemistry 44.40 (2020). https://doi.org/10.1039/D0NJ02848G
3. Do HD, Couillaud BM, Doan BT, Corvis Y, Mignet N. Advances on non-invasive physically triggered nucleic acid delivery from nanocarriers. Adv Drug Deliv Rev. 2019;138:3-17. doi: 10.1016/j.addr.2018.10.006.
4. Gabrielsson J. *et al*, Early integration of pharmacokinetic and dynamic reasoning is essential for optimal development of lead compounds: strategic considerations, Drug Discov. Today 14 (2009), https://doi.org/10.1016/j.drudis.2008.12.011.
5. Ota. R., Yamashita F., Application of machine learning techniques to the analysis and prediction of drug pharmacokinetics, Journal of Controlled Release, Vol. 352, (2022) https://doi.org/10.1016/j.jconrel.2022.11.014.
6. Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng Y-CN. Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. AJNR Am J Neuroradiol 2009; 30:19-30. DOI: 10.3174/ajnr.A1400
7. Haacke EM, Xu Y, Cheng Y-C, Reichenbach JR. Susceptibility weighted imaging (SWI). Magn Reson Med 2004; 52:612-618, DOI: https://doi.org/10.1002/mrm.20198
8. Karniadakis, *et al.* Physics-informed machine learning. *Nat Rev Phys* **3**, 422–440 (2021). https://doi.org/10.1038/s42254-021-00314-5
9. Raissi M., *et al*, Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving nonlinear partial differential equations, Journal of Computational Physics, Volume 378, 2019, https://doi.org/10.1016/j.jcp.2018.10.045.
10. Chen, *et al.* Automated discovery of fundamental variables hidden in experimental data. *Nat Comput Sci* **2**, 433–442 (2022). https://doi.org/10.1038/s43588-022-00281-6