M2 internship

Data-based modeling of pharmacological effects in a biomechanical model of the cardiovascular system Application in critical care monitoring

Inria-Saclay M3DISIM team & Lariboisière Hospital

Keywords

Neural network, data-driven and physics-based modeling hybrid methods, pharmacology, clinical application, real medical data, time series

Context

In operating rooms and intensive care units, patients are placed under anesthesia, which alters the state of their cardiovascular systems. To counter dangerous drifts, medical doctors have at their disposal drugs that modify the property of some components of the cardiovascular system (size of the arterial lumen, heart contraction force, heart rate, ...). These modifications result in variations in the patient's hemodynamic state - i.e. blood pressure and blow flow. With the choice of the drug and by adjusting the drug dose, the doctors aim at driving the patient's hemodynamic state to the target pressure and flow levels.

In the current practice, the amount of drug administered is based on general rules, experience and a reactive trial-and-error process.

To improve their practice and the patients care, anesthesiologists and intensivists seek to transition from a reactive to a proactive approach in which they could better personalize the therapeutic strategy for each patient. In particular, they want to be able to predict the amount of drug that should be administered over time to reach the target hemodynamic state.

Numerical models of the cardiovascular systems can help solve this need expressed by medical doctors. Indeed, models that can link, in a predictive and quantitative manner, a drug dose to a variation of the hemodynamics state can, in reverse, be used to adjust the drug dose to the desired end effect.

Cardiovascular models have long been developed and some versions of them are adapted to the description of patients under anesthesia [1]. However, the pharmacological inputs are largely missing in the models.

Objectives

The main objective of this internship is to develop a so-called *pharmaco-dynamic* model capturing the link between the concentration of a drug in the blood and the evolution of relevant cardiovascular parameters. More precisely, we will focus on the effect of noradrenaline on the heart contractility and the peripheral arterial resistance. Noradrenaline is one of the most commonly used drugs worldwide to manage blood pressure during anesthesia.

This approach is original in that it does not aim to link the drug dose to the hemodynamic state but instead follow-up the physiology and link the drug dose to the parameter of the cardiovascular system on which it directly acts. The description of the hemodynamic state from the cardiovascular parameters is then performed with biophysical models whose validity is now well established [1]. This has the advantage to produce more interpretable results, which is of primary importance in medical applications.

The dynamics of the relation between the drug dose and the cardiovascular parameters occurs at a slow timescale compared to the fast timescale of the heartbeat. The pharmaco-dynamic model (slow timescale) will be sought as a nonlinear map built with a neural network. The particularity of this neural network is that it aims to learn a dynamical equation describing the cardiovascular parameters evolution and that it contains patient specific inputs allowing a personalization of the dynamics. These patients specific inputs are determined from the patient's data with data assimilation techniques based on the fast timescale biophysical models. Leveraging the separation of timescales between the heartbeat and the effect of drugs on the cardiovascular system, this approach mixes physics-based modeling for the fast timescale and data-driven modeling for the slow timescale dynamics. It has already proven its validity on synthetic data [2].

The dynamic neural network model will be trained on a real patients database containing: high-frequency recordings of the hemodynamic state and coarse time sampling recordings of the drug concentration in the blood (in particular during periods of drug administration). The cardiovascular parameters will be estimated from the high-fidelity recordings through data assimilation techniques and used along the low-fidelity recordings to train the neural network.

An efficient implementation of the biophysical models and associated data assimilation methods is already available.

The work will consist in:

- building the software environment for the training and use of the neural network based on existing libraries;
- setting up the pipeline to train the neural network with real data using the existing and newly developed codes;
- optimizing the method to deliver performance improvements.

Data:

- The data necessary to accomplish the work have already been collected as part of a research protocol led by Dr. Jona Joachim, anesthesiologist at Lariboisière Hospital. Dr. Jona Joachim will be an advisor for the current project.
- Clearances for the use of the data in the present project have been obtained.

Candidate Profile:

- The candidate must have a solid background in mathematics. Some experience with object-oriented programming is also expected. Knowledge about neural networks and their implementation would be appreciated.

Work environment:

The internship will take place in the M3DISIM team, a joint team between Inria and École Polytechnique, in the Inria Saclay building located on the campus of École Polytechnique, in collaboration with the anesthesiology department of Lariboisière Hospital (AP-HP, Paris 10). The internship duration is 6 months.

Contacts / Applications:

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Bibliography:

[1] A. Le Gall et al., “Monitoring of cardiovascular physiology augmented by a patient-specific biomechanical model during general anesthesia. A proof of concept study,” PLoS ONE, vol. 15, no. 5, p. e0232830, 2020.

[2] F. Regazzoni, D. Chapelle, and P. Moireau, “Combining data assimilation and machine learning to build data-driven models for unknown long time dynamics—Applications in cardiovascular modeling,” International Journal for Numerical Methods in Biomedical Engineering, vol. 37, no. 7, p. e3471, 2021.