

Research Proposal

In this section you must present your proposal, developing the following aspects: a) Theoretical-conceptual and state-of-the-art developments that underpin the proposal, b) Objectives and hypotheses or research questions, c) Methodology, d) Work Plan or Gantt chart and e) Scientific or technological novelty.

Remember that:

-You must strictly comply with what is established in the Guidelines of the 2023 Postdoctoral Fondecyt Competition.

-All text, paragraphs or textual phrases from a bibliographic reference, whether by other authors or their own, must be duly identified in the text and in the list of references.

This file must contain a maximum of **10 pages** (use letter size format, Verdana font size 10 or similar).

Is the proposal part of an ongoing proposal of the sponsoring researcher? Check the appropriate alternative:

YES

NO

1. Fundaments and state-of-the-art

Modern medicine has been challenged by the growth and development of computers. One of the most important goals of the healthcare industry these days is the personalization of the diagnosis. The majority of the healthcare companies have been targeting the concept of **the digital twin** in their agenda, and for that, they mean the feasibility of extracting all the essential data from one subject in order to create a model which can be treated as a new patient, opening the possibilities for a complete status monitoring and, which is more attractive, the testing of solutions remotely. The word model here is the key factor since all the complexity of this idea depends on it.

In blood flows, the personalization of spatially distributed (i.e., 3D) models is crucial in performing predictive patient-specific simulations. Such a step relies on the formulation and numerical solution of Inverse Problems using medical images for measuring both anatomy and function of the vasculature. However, since full-scale hemodynamics simulations are not feasible by a large number of degrees of freedom, reduced-order modelling techniques have become a possible alternative for realistic modelling of the blood flow

In that line, lumped parameter models can efficiently deliver realistic boundary conditions, accounting for the effects of the omitted parts of the vascular system at the cost of coupling the primary model, based typically on Navier-Stokes equations (NS), with a 0D compartment. The most common alternative here is the so-called **three-element Windkessel** model, which couples the flow rate and the average pressure introducing some parameters related to the resistance of the flow through that boundary and the elastic ability of store energy during the beginning of the cardiac cycle. In this context, the personalization typically relies on estimating those 0D model parameters at each outlet boundary of the 3D model from velocity (and eventually pressure) data. This inverse problem is usually solved using variational or sequential methods. [cites]

The gold standard for distributed blood flow velocity measurements in the clinical context is the 2D Phase-Contrast Magnetic Resonance Imaging (**PC-MRI**) [cites]. This technique allows the computation of the blood flow through and specific plane and usually involves short scan times. However, 2D PC-MRI presents important artifacts: noise and velocity aliasing. When personalizing the models with such data, not taking into account these artifacts, can lead to essential inaccuracies in the blood flow model personalization.

Time-resolved 3D flow magnetic resonance imaging, also referred to as **4D Flow MRI**, has shown in the last years increasing potential in assessing cardiovascular diseases since it offers complete coverage of the region of interest [cites] and multiple options for visualization and quantification [cites]. Moreover, it allows for the computation of several hemodynamic parameters, which can be used as new biomarkers [cites]. However, high-quality 4D flow in subjects involves long time scans (>20 minutes) even with coarse spatio-temporal resolutions making it challenging for everyday clinical use.

Machine learning is the capacity of computers to learn from data. In particular, deep learning uses artificial Neural Networks (NNs) to extract and represent knowledge from training data. Nowadays, NNs obtain state-of-the-art performance in most areas of knowledge. Nevertheless, neural architectures do not know the physical principles behind processes, such as energy and momentum conservation, and cannot assure that the solutions do not violate these principles. For that reason, in recent years, Physics-Informed Neuronal Networks (PINNs) have attracted enormous interest of the scientific community.

Recent hemodynamic applications of the PINNs have shown great potential in estimating velocity and pressure fields on cardiovascular problems. Even though for forward simulations, the existing CFD algorithms perform better than PINNs, for situations where the physics is unknown and partial measurements are available (namely inverse problems), PINNs have shown outperformed any existing method so far [cites].

Kissas et al. applied the PINNs methodology to one-dimensional cardiovascular problems. They found good agreement between the PINNs estimations and 2D PC-MRI observations, capable of reconstructing pressure values and Windkessel parameters for their simplified model [cite]. However, they encountered difficulties in the use of real data since typical PC-MRI has relatively coarse resolution and possesses a significant level of noise. Gao et al. used the PINNs in order to increase the resolution of low-quality measurements [cite]. They presented a decoupled architecture capable of avoiding the use of high-resolution data for the training stage, leading to the state variables being trained only by NS equations. However, this work was only based on 2D flows with relatively simple geometries and using the stationary form of the NS equations.

These works motivate the use of PINNs for the development of faster inverse problems on cardiovascular applications and the development of robust architectures for the use of clinical data.

2. Objectives of this project

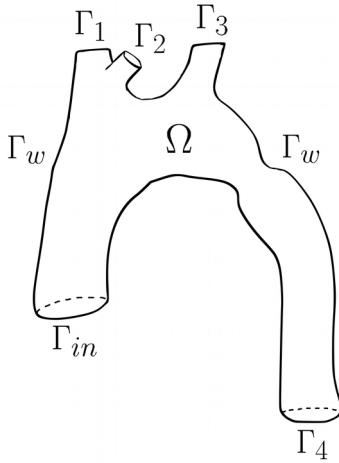
The main goals of this project are:

1. The implementation of a PINNs, trained on NS equations, capable of predict a high resolution 3D blood velocity field on the aorta, from low resolution 2D PC-MRI images.
2. The use of PINNs for extracting physical parameters from velocity measurements. The parameters to be considered are: a) the Windkessel loads on the aorta outlets, b) the wall shear-stress field and c) the pressure field.
3. To perform a validation the PINNs results against a **Reduced-Order Unscented Kalman Filter** (ROUKF) approach, which is considered the state-of-the-art for solving sequential inverse problem on cardiovascular applications.
4. To develop a **Transferable Learning** methodology on the PINNs capable of shorten the learning for assimilating new medical data. Also robustness against noise and other artifacts are meant to be developed for deal with such data.
5. Explore the clinical applicability of the PINNs on surgical decisions-making on the cardiovascular system.

3. Methodology

3.1 The fluid model

Synthetic velocity data will be generated using CFD simulations on realistic aortic geometries. We first simulate the blood flow through the aorta as a Newtonian incompressible fluid governed by the Navier-Stokes equations as:



$$\begin{cases} \rho \frac{\partial \mathbf{u}}{\partial t} + \rho(\mathbf{u} \cdot \nabla) \mathbf{u} - \mu \Delta \mathbf{u} + \nabla p = 0 & \text{in } \Omega \times [0, T] \\ \nabla \cdot \mathbf{u} = 0 & \text{in } \Omega \times [0, T] \\ \mathbf{u} = \mathbf{u}_{inlet} & \text{on } \Gamma_{in} \times [0, T] \\ \mathbf{u} = \mathbf{0} & \text{on } \Gamma_w \times [0, T] \\ \mu \frac{\partial \mathbf{u}}{\partial n} - p \mathbf{n} = -P_\ell(t) \mathbf{n} & \text{on } \Gamma_\ell \times [0, T], \quad \ell = 1, \dots, K, \end{cases}$$

Problem 1: left: aortic geometry in consideration. (right) incompressible Navier-Stokes equations

Where \mathbf{u} is the 3D velocity field defined on the aortic volume Ω , p is the pressure field, u_{inlet} is a Dirichlet boundary condition at the inlet and ρ , μ are the density and dynamic viscosity of the fluid respectively. Moreover, the pressure at every outlet of the system comes from the coupling with a three-element Windkessel boundary conditions as:

$$\begin{cases} P_\ell = R_{p,\ell} Q_\ell + \pi_\ell \\ Q_\ell = \int_{\Gamma_\ell} \mathbf{u} \cdot \mathbf{n} \\ C_{d,\ell} \frac{d\pi_\ell}{dt} + \frac{\pi_\ell}{R_{d,\ell}} = Q_\ell. \end{cases}$$

Where C_d is the compliance and R_p and R_d represent the proximal and distal resistance of the vasculature. The values P_l and π_l are called the proximal and distal pressure respectively.

The model explained before can be seen as the state-of-the-art in 3D computational hemodynamics modelling, and it has been used in several works [cites]. Different numerical strategies can be used to solve this problem. In this work, I will use a **finite element method** developed during my PhD thesis to solve this forward coupled problem. This method has shown great versatility in complex geometries based on monolithic or fractional step schemes.

3.2 The Physics-Informed Neuronal Network scheme

The basic scheme of a Physics-Informed Neuronal Network (PINN) is depicted in Figure 1.

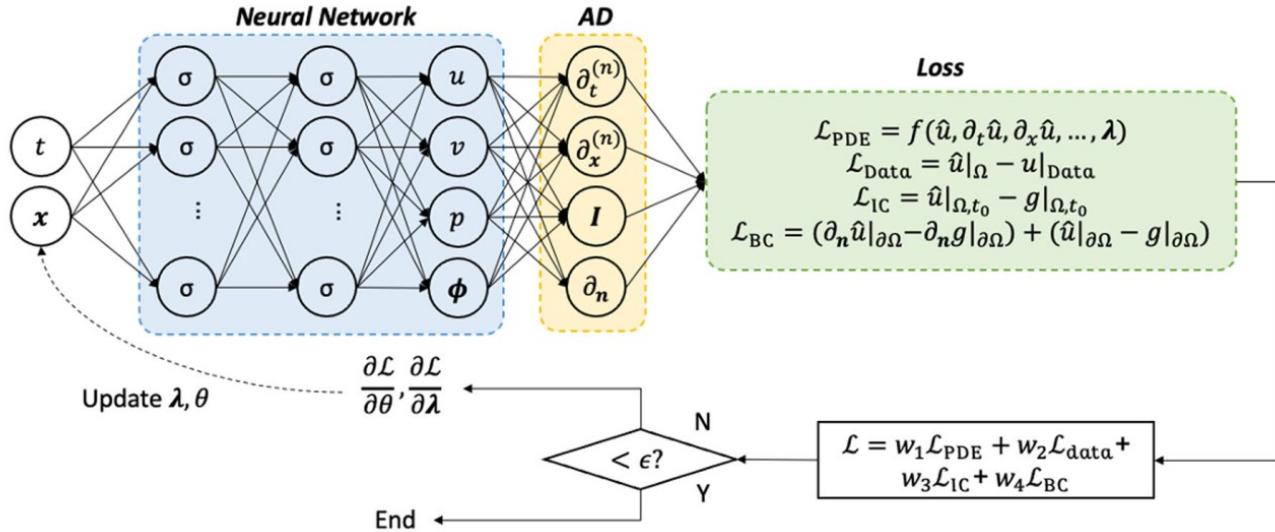


Figure 1: General Neuronal-Network scheme with a physical-informed learning process. Figure taken from [cite].

The main goal of the PINNs is to approximate the solution of a PDE (partial differential equation) taking the coordinate and time (\mathbf{x}, t) as input variables. In this case the PDE is written in the form: $f = 0$. These values enter the multiple layer network as:

$$\begin{aligned} \mathbf{z}^0 &= (\mathbf{x}, t), \\ \mathbf{z}^k &= \sigma(\mathbf{W}^k \mathbf{z}^{k-1} + \mathbf{b}^k), \quad 1 \leq k \leq L-1, \\ \mathbf{z}^L &= \mathbf{W}^L \mathbf{z}^{L-1} + \mathbf{b}^L, \quad k = L, \end{aligned}$$

Where the maximum number of layers is denoted by L . \mathbf{W}^k and \mathbf{b}^k denote the weight matrix and bias vector of the k -th layer. All these layer parameters are captured in θ . σ is a non-linear activation function. In this way, the solution of the equation will be the result of the last layer ($k=L$): $u \approx z^L$. As a consequence, the solving procedure is converted into an optimization problem in which the parameters of the PINNs (weights and biases) are obtained minimizing the so-called **loss function** (\mathcal{L}), which in this case is composed by (green rectangle of Figure 1): a PDE contribution, a data (if any) contribution and an initial condition and a boundary condition contribution. The main advantage of this type of method is the fact that the networks parameters θ and the PDE parameters λ can be learned simultaneously. In other words, the same scheme can be used for solving both: forward and inverse problems, making the PINNs capabilities of assimilating data, faster than any other CFD solver [cites]. Also, the **automatic-differentiation** method (yellow rectangle of Figure 1) can compute the derivatives in an explicit fashion, avoiding any discretization error on it.

3.3 Parameter estimation on hemodynamics

In this work, a PINNs will be implemented using the equations explained in Section 3.1 as part of the \mathcal{L}_{pde} term. Different types of network parameters and optimizers are also meant to be explored. This methodology will be used for solving the forward and inverse parameter reconstruction problems.

The **Reduced-Order Unscented Kalman Filter** approach (ROUKF) is considered the state-of-the-art for sequential parameter estimation on cardiovascular applications [cites]. I have implemented this method during my PhD thesis and it will be used for reconstruction (on the synthetic data experiments) and estimation (on the real data applications) of the Windkessel parameters, in order to validate the performance of the PINNs on the same tasks.

Once the numerical experiments with synthetic data allow us to test the PINNs, experiments with real data will be performed. For that purpose, PC-MRI images on a 1.5 T Philips MRI scanner acquisitions will be performed on 3-5 healthy volunteers, targeting the flow through different planes at the aorta artery. Anatomical images are also needed in order to validate against the ROUKF, where typically a good-enough resolution mesh is used for the computations.

For the data process and mesh generations, in-home codes developed during my PhD thesis will be used. Additionally, 4D Flow acquisitions are also planned in order to investigate its trainable value on the PINNs methodology.

The main experiments planned for the PINNs are summarized in the next points:

- Training the PINNs with synthetic data, the reconstruction of the whole velocity field will be performed using the 2D PC-MRI images. This process is also known as image **super-resolution**, since the output will have the same resolution than the anatomical image (usually x10 - x20 times the resolution of a normal PC-MRI image). Also **denoising** and the use of aliased velocity measurements will be explored.
- Training another PINNs with only the PC-MRI images and the hemodynamic model, the same procedure will be attempted. One of the measured planes is used for validation of the PINNs results against it. This experiment is repeated separately on every volunteer. **Transferable Learning** techniques are explored in order to shorten the training stage on every new data set.
- Another PINN will be implemented in order to infer physical parameters from the low or high resolution images. These are: The wall-shear stress, which can be obtained directly from the velocity measurements and the Windkessel parameters. For the latter, a Windkessel calibration similar to the one presented here [cite] will be implemented.
- Pressure fields reconstruction using the PINNs methodology is tested. Validation against other classical methods such as: Bernoulli's formula, PPE, STE, WARP and vWARP is done. One of the main advantages presented by the PINNs is the no need of mesh for solving this problem, which in most of the cases introduces further errors in the reconstructed results [cite david] and long post-process times.

4. Scientific and technology novelty

The main reason why CFD is not taken into account in clinical-decision making on hemodynamic studies is the need for long post-process times even when high-performance computer machines are available. To solve this bottleneck, faster and more robust inverse problems strategies have to be designed.

PINNs parameter reconstructions have been reported around 1000 times faster than classical approaches [cites]. This speed-up, in comparison with other methods, is mainly supported by a long offline training stage, in which the parameters of the network are optimized. Then, the network is capable of using the accumulated past information for making new estimations. This highly motivates the use of PINNs in a future clinical environment for the following possible tasks:

1. **3D blood flow reconstruction from fast 2D MRI images**

To the best of my knowledge, this is the first time that a PINNs methodology will be designed for being trained with a time-dependent NS equation in a 3D complex geometry.

This project is intended to use 2D and 3D PC-MRI images, where typically the 2D images are easy to obtain than the 3D.

The impact of this project will be that a comprehensive study can be done using both the PINNs and a sequential inverse problem to reconstruct the velocity field from 2D images. Then, a validation against the 3D measurements is planned. Also, this workflow offers more possibilities to explore since the learning and the validation can also be done with only 3D measurements. Focusing on the PINNs performance, transferable learning strategies will be used to leverage the data for multiple patients. So after one patient is used for training, the PINNs do not have to learn from scratch for a new patient.

2. **Fast parameter extraction from MRI images**

Another significant potential impact on the clinical world is the fast reconstruction of the pressure fields. **Aortic coarctation** is a narrowing of the proximal descending aorta, accounting for 5-8% of all heart congenital diseases. The peak-to-peak pressure difference across the coarctation is the most important hemodynamic parameter for clinical decisions. This value is obtained typically with a very invasive procedure of catheterization.

Many works are devoted on obtaining the pressure field from MRI images, enforcing the known physics (namely Navier-Stokes) in order to reconstruct the pressure from the velocity. However, all these works need first to define from the images an accurate segmentation and mesh among other data preparation processes, making the clinical applicability of such method not so straightforward for clinicians. However, the PINNs learning method requires no mesh, leveraging previous assimilated data for fast parameter reconstruction.

3. **Super-resolution and denoising on MRI images**

A common problem with clinical data is noise on the velocity measurements (typically up to 15% of the max. velocity), and also other artifacts. This highly contaminates the inverse problem results, making the personalization of the models even more difficult. During my PhD thesis, I worked on a robust algorithm for sequential inverse problems to avoid artifacts on PC-MRI, especially noise and aliasing.

Super-resolution is a classical Machine Learning application commonly used in image processing [cite]. In this methodology, a mapping from a low-resolution image to a high-resolution image is learned. Similar methods have been applied to 4D Flow MRI images in cardiovascular hemodynamics. Recently, PINNs have shown promising results in this task. By incorporating NS equations, super-resolution and denoising have been achieved [cite].

The novelty of this project is also to incorporate the use of aliased measurements. In this approach, the loss function accounting for the measurements can be modified in order to include the aliasing directly, as I did in my PhD thesis in a Kalman filtering context [cite]. This will allow the use of lower

velocity encoding parameters, which will directly enhance the noise level of the image. Afterward, a PINNs super-resolution method is expected to perform much better than it was reported.

5. Work Plan

Activity	Year 1				Year 2				Year 3			
	1	2	3	4	1	2	3	4	1	2	3	4
Literature review	X											
Implementation of the PINN	X	X	X	X								
Synthetic data experiments												
• Simulated data generation		X	X									
• Validation against classic method			X	X	X							
Real data experiments												
• PC-MRI acquisitions and data process						X				X		
PINN Super-Resolutions experiments		X	X	X		X	X	X		X	X	
PINN parameter reconstructions		X	X	X		X	X			X	X	
Clinical application development									X	X	X	X
Manuscript preparation					X				X			X