Reduced order modelling for direct and inverse problems in haemodynamics

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Abstract

In this chapter we propose a review of reduced-order models (ROMs) to speed-up direct and inverse problems in the context of haemodynamics. In particular, we highlight three different ways of building them and comment upon the numerous contributions and methodological advancements in this field.

1 Introduction.

This chapter aims at proposing a review of reduced-order modelling (ROM) methods applied to the context of haemodynamics. The cardiovascular system plays a key role in ensuring all the tissues of the human body receive the necessary molecules to maintain their regular daily activity. It is an extraordinarily complex system, characterised by the interaction of numerous phenomena at different scales. Consider that the larger arteries have a diameter of the order of the centimetre, the capillaries of 5 to 10 micro-metres (the size of a red blood cell being typically 7 micro-metres). The vessel diameter spanning more than three orders of magnitude, this fact alone hints that a model accounting simultaneously for all the phenomena involved is currently out of reach. The physical description of part of the circulation has to be tailored on the application targeted. As the circulation plays a central role in human life, numerous applications in medicine and biomedical engineering are related to it, ranging from diagnosis to therapy, surgery planning and device optimisation. In every application, the goal consists in, or can be reached by, estimating several quantities of interest (QoIs). These can take the form of predictions, either inferences or forecasts, or can help in devising a systematic interaction with the system under scrutiny. The estimation of the QoIs has to be performed by exploiting the information conveyed by a set of observations of the system. The pair observations-QoIs characterise every application and the methodological tools need to be defined and developed based on the nature of this pair. The problems related to realistic and clinical applications are such that the estimation of QoIs involves often a heavy computational burden. ROMs are a viable tool to perform the estimation with an affordable computational cost.

This review is organised as follows. In the next section, we propose a synthetic background pointing towards some references in the literature which propose a comprehensive overview of the contributions in computational haemodynamics. In particular, we recall the equations which are used to describe haemodynamics at a macroscopic scale, the QoIs which are related to realistic applications and the observations which are usually available in order to estimate them. We then divide the Reduced-Order models in three classes, based on the differences in the methodology used to derive them: physics-based, projection-based and data-driven based ROMs.

In every section we present, first, some methodological aspects (investigated not only in haemodynamics, even if related to issues raised also in this field) some contributions for the reduction of direct and inverse problems. The list of contributions cited, especially when pointing to some general methodological aspects, is far from being exhaustive. We try to be as complete as possible for references related to haemodynamics.

2 Background

A review on the physical principle governing the haemodynamics is presented in (Secomb, 2016). The reology of blood and its description are covered in (Baskurt et al., 2007). A comprehensive description of the mathematical models and methods to describe the cardiovascular system is provided in (Formaggia et al., 2010) and the citations therein. The blood flow in large arteries is well described by the incompressible Navier-Stokes equations ((Formaggia et al., 2010)) for a Newtonian fluid. An abundant literature on non-Newtonian models taking into account the blood rheology is available. One of the first studies is (Perktold et al., 1989), in which the authors considered the simulation of a non-Newtonian fluid in an idealised arterial bifurcation. The influence of the non-Newtonian behaviour of the blood in large arteries is studied in (Gijsen et al., 1999; Mandal, 2005). In (Johnston et al., 2006) a non-Newtonian fluid model (of power law type) is compared to a Newtonian one in 3D simulations of coronary flows. When considering the micro-circulation (arterioles), non-Newtonian effects such as Farhaeus and Farhaeus-Lindqvist become relevant (Azelvandre and Oiknine, 1977; Pries et al., 1992; Sriram et al., 2014).

The different scales involved as well as the different physical phenomena to be represented are so diverse that we do not describe here all the models introduced so far in the literature. We just recall the equations which are used to describe haemodynamics at a macroscopic level (especially in the heart and large arteries), since they are the ones which are used more often in applications. This depends on the fact that most of the observations of the system, in realistic (clinical) applications take place at macroscopic level (think for instance to pressure measurement or medical imaging).

Let $d \in \mathbb{N}^*$ be the domain dimension (typically $d = 2, 3$), let $\Omega_f \subset \mathbb{R}^d$ be an open bounded domain, the fluid domain, let $\varrho_f, \mu_f \in \mathbb{R}^+$ be the fluid density and the dynamic viscosity, respectively. Let $u_f : \Omega_f \to \mathbb{R}^d$ be the vector valued velocity field, $p : \Omega_f \to \mathbb{R}$ be the pressure. It holds:

$$\begin{aligned} \varrho_f \left(\partial_t u_f + u_f \cdot \nabla u_f\right) &= -\nabla p + \mu_f \Delta u_f, \\ \nabla \cdot u_f &= 0. \end{aligned} \tag{1}$$

This model has to be completed by imposing initial and boundary conditions. These latter deserve particular attention in haemodynamics. Consider, for instance, a blood vessel. At the inlet and at the outlet we need to specify either the velocity or a condition on the fluid stress (*e.g.* a pressure). To be more realistic, we often make use of Windkessel models (Alastruey et al., 2011) which account for the vasculature we are not describing and to which the blood vessel is connected. At the lateral boundary of the vessel we need to describe the coupling between the blood flow and the vessel wall. This coupling consists in imposing kinematic and mechanical equilibrium at the interface between the fluid and the solid. The mechanics of the wall is described by means of the elasticity equations. Let $\varrho_s \in \mathbb{R}^+$ be the structure density, let $\Omega_s \subset \mathbb{R}^d$ be the structure domain, its reference configuration. Let $u_s : \Omega_s \to \mathbb{R}^d$ be the structure displacement field. Let $\mathcal{P}(u_s)$ denote the first Piola-Kirchhoff stress tensor. It holds:

$$\varrho_s \partial_t^2 u_s = \nabla \cdot \mathcal{P}(u_s). \tag{2}$$

For the structure, as well, we need to specify some initial and boundary conditions. In particular, it is critical to mimic the tissue surrounding the portion of circulation we are modelling. Several models were proposed in the literature to describe the constitutive laws of arterial walls. We refer to (Holzapfel et al., 2000; Holzapfel and Ogden, 2010).

We now briefly discuss the Quantities of Interest which appear more frequently in the applications.

1. Pressure and pressure drop. Pulse Wave Velocity measurements are used as an indirect indicator of arterial stiffening in hypertension. Pressure drop is one of the main indicators to assess the severity of stenoses and vessel blockages. Estimating pressure and pressure drops non-invasively is a particularly challenging and important task (the reader is referred to (Hatle et al., 1978, 1979, 1980; Mates et al., 1978; Funamoto and Hayase, 2013)).

2. Wall shear stress. It is the tangential part of the stress exerted by the blood on the wall, it is known as one of the most relevant indicators to study aneurysms, plaque formation and a number of other diseases ((Gibson et al., 1993; Shojima et al., 2004; Reneman et al., 2006)).

3. Vorticity. The curl of the velocity is monitored in particular in the heart cavity, where a natural vorticity field is directly related to the mechanical efficiency. For instance,

when considering valves replacement, it is important for the artificial valve not to cause an unnatural vorticity field and induce potentially haemolysis and loss of efficiency. Examples are provided in (Abe et al., 2013; Pedrizzetti et al., 2014; Mehregan et al., 2014; Hirtler et al., 2016).

4. Mechanical stress inside the wall: this is related to the estimation of the risk of rupture and to the estimation of pressure waves intensity and speed (for instance in cases of hypertension, (Yang et al., 2018; Liu et al., 2018)).

In order to estimate the above described quantities, several kind of measurements are available. We briefly describe here few common examples. Doppler ultrasound measurements can be modelled as the application of a set of linear forms on the velocity field: in the 1-D modality, in every voxel $\{\Omega_j\}_{1\leq j\leq N_v}$ we measure the fluid velocity in the direction of the ultrasound beam $b \in \mathbb{R}^d$:

$$\ell_j = \frac{1}{|\Omega_j|}\int_{\Omega_j} u_f \cdot b \; dx, \; j = 1, \ldots, N_v. \tag{3}$$

A richer modality is represented by 4D-flow MRI, which makes it possible to have an estimation of the velocity field in voxels. A first model of this measurement reads:

$$\ell_j = \frac{1}{|\Omega_j|}\int_{\Omega_j} u_f \; dx, \; j = 1, \ldots, N_v. \tag{4}$$

Medical imaging (especially MRI) makes it possible to have an estimation of displacements and tissue velocity. These are measurements concerning the structural mechanics of the wall. They can be related to the Lagrangian displacement and the velocity fields of the structure.

Other kind of measurements can be used, to estimate flow or pressure in a specific location of the vascular tree. Pressure catheters, for instance, make it possible to have an invasive estimation of the pressure in one or more locations. Every measurement is affected by noise, hence providing a partial and imperfect observation of the system state. Dealing with noise is a crucial step in order to properly exploit the information the measurements convey about the state. Every modality has its own noise structure, which needs to be modelled (think for instance at clutter for Doppler ultrasound). In this chapter, for sake of brevity, we do not detail the different ways noise can be filtered, we just mention here that models and ROMs can be used as an effective way to filter the measurements noise in some contexts.

Given the observations listed above, we can remark that the observation of the system reduces often to the application of linear forms to the system state. Given the size of the vasculature and the constraint of observing the system in a non-invasive way, we have that the observations available are often scarce, making the data assimilation problems a challenging and cumbersome task. Furthermore, since the system is described by coupled parametric PDEs, the computational cost of data assimilation is very large, sometimes prohibitive considering the time constraint of clinical applications. The introduction of reduced order models aims at palliating to these issues by speeding up the estimation of the dynamics of the system or the data assimilation problem directly and in some cases by implicitly regularising ill-posed inverse problems.

3 Physics reduction based ROMs.

Given a certain physical regime of interest, it is sometimes possible to simplify the governing equations and obtain a system whose solution can be computed with a significantly lower computational cost. In this review we use the expression physics reduction based ROMs. This is a way of proceeding which has been classically used in many branches of mathematical physics to gain some insight about the behaviour of a system in various parametric regimes. When applied to the context of haemodynamics, these simplified descriptions were introduce in order to:

(P1) Provide a representation of the global circulation.

(P2) Modelling the heart function.

(P3) Modelling the micro-circulation.

(P4) Simplify fluid-structure interaction problems.

3.1 Direct problems.

In several applications we are interested in simulating the global circulation (P1), or, at least, a large portion of the vasculature. The system state reduces in this case to:

1. Pressure and flow in time, in $N \in \mathbb{N}^*$ point locations of the body $\{Q_i(t), P_i(t)\}_{1\leq i\leq N}$. This is described by 0–D models or lumped parameters models. They can often be represented by an electrical analogy (in which the pressure plays the role of the voltage and the flow of the current). A global model is henceforth a circuit approximating the behaviour of a large portion of the vasculature.

2. Pressure and flow in time, along the blood vessels, on a network $Q(x,t), P(x,t)$. This is described by 1–D models, which are sets of hyperbolic 1d-1d PDEs in a subcritical regime. Let $A(x,t)$ be the cross-sectional area of the blood vessel at axial coordinate x and time t. An example of the equations obtained in one segment of the vasculature

reads:

$$\partial_t A + \partial_x(Q) = 0, \tag{5}$$

$$\partial_t Q + \partial_x \left(\frac{Q^2}{A}\right) + \frac{A}{\varrho_f}\partial_x P + \mathcal{D}(Q, A) = 0, \tag{6}$$

$$P = P_0 + \beta \left(\frac{A^{1/2}}{A_0^{1/2}} - 1\right). \tag{7}$$

The term $\mathcal{D}(Q, A)$ accounts for the viscous dissipation of the fluid and $\beta > 0$ is the coefficient accounting for the blood vessel elasticity (which can be related to Young modulus and wall thickness in simple geometries).

These models can be derived from Navier-Stokes equations Eq.(1) and elastic equations Eq.(2) under some geometrical assumptions and by taking an average with respect to the blood vessel section, for 1–D models, and also length in the case of 0–D models. By proceeding in this way the number of degrees of freedom used to represent the system state is substantially reduced, resulting in a gain in computational speed. As a consequence of the reduction of the number of degrees of freedom per unit length of blood vessel, we can represent a portion of the vasculature that would be unaffordable if a full 3–D model was used. What we lose is the possibility of representing 3–D features of the blood flow. Numerous works were proposed in the literature on the definition of such models and their validation. Among them (we propose a non-exhaustive list), we cite: (Olufsen and Nadim, 2003; Moore et al., 2005; Alastruey et al., 2008; Reymond et al., 2009; Alastruey et al., 2011; Kroon et al., 2012; Blanco et al., 2014). These models can be used as stand-alone models, or as a boundary condition for 3–D models, as detailed in (Blanco et al., 2007; Formaggia et al., 2007). In (Lyras and Lee, 2021) and the references cited therein, the authors derive a reduced-model for pressure drop across a stenosis based on a simplification of the Navier-Stokes equations. In order to approximate the 3-D features of the flows, the work in (Mansilla Alvarez et al., 2017) introduce pipe elements: in these, the 3D flows is estimated in generic cross-section pipes: in the longitudinal direction 1-D reduced models are used while in the transversal direction a polynomial spectral discretisation is introduced. This method has been used to efficiently perform Uncertainty Quantification on systemic networks in (Guzzetti et al., 2020).

The heart functions (P2) has been simulated through physical based models in (Moulton et al., 2017; Hong et al., 2019). These consists in simplifying the 3–D equations accounting for the elastic deformation of the heart (a particularisation of Eq.(2)); the resulting model can be considered as a lumped parameter model.

The problem of representing the micro-circulation (P3) deals with the ability to describe oxygen delivery inside a tissue, the auto-regulation phenomena and the complex rheology of the blood at the micro-scale. In (Pries and Secomb, 2003; Arciero and Secomb, 2012) some lumped parameters models accounting for the rheology and the vessels contraction are presented. The works (Wang et al., 2019; Balachandran Nair et al., 2021) deal with reduced-order models for the mechanics of red blood cells and in (Perdikaris et al., 2016) several contributions to account for the multi-scale aspects of blood flows are presented.

In (Gashi et al., 2019) the authors propose a study on the estimation of the Fractional Flow Reserve in parametrised coronary arteries geometries and compare several reduction methods in estimating this quantity.

In several works in the literature, a physics reduction has been applied to fluid-structure interaction (P3). The main idea consists in seeing the structure as a special boundary condition for the fluid problem. The gain in computational speed comes from the fact that, instead of solving two coupled problems (often written in different coordinates, the fluid in Eulerian and the solid in Lagrangian) we solve one problem with modified boundary conditions. What we loose is the possibility of describing the mechanical stress in the structure in a precise way. This has been proposed and analysed in (Figueroa et al., 2006; Nobile and Vergara, 2008; Colciago et al., 2014; Pironneau, 2014; Chacon-Rebollo et al., 2014). In (Aletti et al., 2016) a modification of the method proposed in (Nobile and Vergara, 2008) is presented, in which we added a set of fibres to mimic the presence of smooth muscle cells. This makes it possible to describe arteriole mechanics and to simulate the phenomenon of autoregulation.

3.2 Inverse problems.

The reduction in computational cost has been exploited in several works in order to perform Data Assimilation. In particular, a description of the global circulation (P1) is particularly well suited for all the applications in which the data come in form of point measurements (of pressure or flow), at several locations of the vasculature. A paradigmatic example is the estimation of the arterial wall stiffeness given the measurements of the Pulse Wave Velocity (PWV). This is, in itself, an indirect measurement obtained, usually, by measuring the pressure in two locations of the arterial tree, in time (Saito et al., 2011). In (Martin et al., 2005) a variational method is proposed in order to identify the parameters of 1D-models. Given the nature of the measurements, a set of time signals (well resolved in time, scarce in space), a sequential estimation appears as a natural candidate to solve efficiently the data assimilation problem. This has been investigated in (Lombardi, 2014; Caiazzo et al., 2017; Lal et al., 2017a,b; Müller et al., 2018). In (Lucor and Le Maître, 2018) a bayesian approach is proposed, in order to account in a natural way for the uncertainty. More global models (mixing eventually 0D and 1D models) were used to sequentially estimate state and parameters in (Pant et al., 2016, 2017; Audebert and Vignon-Clementel, 2018; Vignon-Clementel and Pant, 2019). An estimation in a multi-scale context is proposed in (Pant et al., 2014).

In (Laleg et al., 2007), the authors consider a further approximation of the 1D-1D hyperbolic system defining 1D models and show that, in some regimes, the flow behaves as an integrable system (of Korteweg-de Vries type). Henceforth, we can identify the system state by using the Inverse Scattering Transform: given a pressure signal in time, measured in a point, we can estimate the scattering coefficients and these can be used to estimate the pressure in different locations.

A Data Assimilation application concerning the estimation of the cardiac mechanics (P2) by using a reduced model and a Gaussian Process regression is discussed in (Di Achille et al., 2018).

4 Projection-based ROMs.

Projection-based ROM are one of the most classical strategies of model reduction. The problem solution is decomposed into two phases: an *offline* phase in which a database of instances of the Full-Order model (FOM, high-fidelity numerical simulations) is computed varying the parameters in order to simulate meaningful scenarios of the system. The database is used in order to learn a possibly low dimensional representation of the system state. The classical choice consists in determining a low dimensional linear subspace. In the *online* phase the learned underlying structure is exploited in order to speed-up the computations. We give here a brief account of the method in the case in which a linear subspace is used and perform the reduction of a linear equation, in the form of a parsimonious discretisation. Let $\Omega \subset \mathbb{R}^d$ be the space domain, let $t \in [0, T]$ be the time variable. Let the state be $u(x,t) : \Omega \times [0,T] \to \mathbb{R}$. Let $\langle u, v \rangle = \int_\Omega uv \, dx$ denote the classical $L^2(\Omega)$ scalar product. Let $\mathcal{A}$ be, for instance, a generic linear elliptic differential operator, the equation governing the system evolution be:

$$\begin{aligned} \partial_t u &= \mathcal{A}u, \text{ in } \Omega, \\ u &= 0, \text{ on } \partial\Omega, \\ u(x,0) &= u_0. \end{aligned} \tag{8}$$

A classical discretisation of this system would use $\mathcal{N}$ degrees of freedom (think, for instance to finite differences, volume or elements discretisations). Let a linear subspace of $L^2(\Omega)$ (other choices can be made according to different variational and functional settings) be spanned by the orthonormal basis $\{\varphi_i(x)\}_{1 \le i \le n}$, with $n \ll \mathcal{N}$. This has been computed by making use of a set of solution snapshots, at different times (and eventually parameters). Let the solution u be approximated as follows:

$$u(x,t) \approx \sum_{j=1}^{n} a_j(t) \varphi_j(x). \tag{9}$$

The fact that the boundary conditions are homogeneous and that the basis has been computed by using the snapshots of the solution guarantees that the boundary conditions will be automatically respected. A classical choice consists in using a Galerkin method to find the solution representation $a_j(t)$:

$$\sum_{j=1}^{n} \dot{a}_j \langle \phi_j, \phi_i \rangle = \langle \mathcal{A}\varphi_i, \varphi_j \rangle.$$

Let $A_{ij} = \langle \mathcal{A}\varphi_i, \varphi_j \rangle$ be the representation of the differential operator on the basis $\{\varphi_i(x)\}_{1 \le i \le n}$. It holds:

$$\dot{a}_i = \sum_{j=1}^{n} A_{ij} a_j,$$
$$a_i(0) = \langle u_0, \varphi_i \rangle,$$

which is a small dimensional linear ordinary differential system of equations to be solved. Here we have chosen to present the equations in this abstract way for sake of brevity. Numerous studies in the literature propose other formulations (starting from the FOM), leading essentially to the same result.

In haemodynamics, the clear advantage is that we can devise methods able to represent the 3–D structures of the flows as well as the coupling with the structure. Some critical methodological issues need to be discussed. We briefly report here the ones which are of the utmost relevance for direct and inverse problems in haemodynamics.

Reduced-basis methods have been developed for Navier-Stokes equations in several contributions, among which we cite (Veroy and Patera, 2005; Burkardt et al., 2006; Quarteroni and Rozza, 2007; Manzoni, 2014). The projection-based reduced-order models require a stabilisation, which is discussed for instance in (Bergmann et al., 2009; Balajewicz and Dowell, 2012; Kean and Schneier, 2020; Ali et al., 2020).

The non-linearities appearing in the governing equations (1) and (2) need to be addressed. The problem is the following: consider a residual in which a non-linear non-polynomial term appears, say, for instance $\sin(u)$. In a Galerkin formulation, this term would lead to $\langle \sin(\sum_{j=1}^{n} a_j \varphi_j), \varphi_i \rangle$, which would need an expensive quadrature (with order $\mathcal{N}$ operations) to be evaluated online, deteriorating the speed-up. The key observation is the following: roughly speaking, collocation commutes with the non-linearities: $\sin(u)|_{x=x_0} = \sin(u|_{x_0})$. This observation, when introducing a modal approximation of the solution (and eventually matrices when dealing with Jacobians), leads to: empirical interpolation EIM (Barrault et al., 2004) (a generalised version is presented in (Maday and Mula, 2013)), DEIM (Chaturantabut and Sorensen, 2010), and, also Q-DEIM (Drmac and Gugercin, 2016) and M-DEIM (Negri et al., 2015; Bonomi et al., 2017). Hyper-reduction (Ryckelynck, 2009) and Petrov-Galerkin formulations (Carlberg et al., 2011) have been introduced to circumvent the difficulties related to non-linear terms and to come up with efficient projection based methods.

In several systems, due to intrinsic limitations, using a linear subspace may lead to poor performances. This phenomenon can be rigorously quantified by the Kolmogorov widths, which may decay slowly, especially when advection dominated sets of solutions are considered. Several methods were introduced in the literature to propose more effective strategies and this is, *per se*, an active field of research. Local bases were proposed in (Amsallem et al., 2012; Maday and Stamm, 2013), and used in cardiac electro-physiology in (Pagani et al., 2018). Basis refinement was proposed in (Carlberg, 2015). In (Cheng et al., 2013; Musharbash and Nobile, 2018) methods are proposed in order to dynamically evolve the subspace used to performed the reduction, in such a way that, for every time, the dimension of the subspace needed to well approximate the solutions is small. Another way to make the basis evolve is proposed in (Gerbeau and Lombardi, 2014), in which the idea of Lax pairs is adapted to the context of dynamical bases. Recently, non-linear model reduction based on deep-learning methods have been proposed and are currently under scrutiny to provide a more efficient representation of the solution sets. We review these works in the next section (as some of them may be considered as data-driven methods).

A crucial question for haemodynamics is related to the variability of the domain geometry: indeed, every individual has its own anatomy, and although the portion of vasculature considered has the same topology for everyone, there is a significant geometrical variability. This means that, in principle, we should construct a database for every individual: this could jeopardise the advantages of the approach as the computational cost of the offline phase would become very large. In their standard version, projection based ROMs are quite well suited for all the applications in which we follow the evolution of a pathology in a given patient and we need to assess the QoIs related to the haemodynamics repeatedly in the same geometrical configuration. They are less appealing for screening-type of applications, in which we need to estimate some quantities for different patients (with different vasculature geometry). Several works in the literature tried to overcome this issue. Most of them introduce a mapping of the domain into a reference configuration and write (and reduce) the equations in this latter. In (Rozza et al., 2013) the authors investigate how the reduced basis method applied to the Stokes problem can be adapted in parametrised geometries, and how the inf-sup stability condition is impacted. In (Dal Santo and Manzoni, 2019) a model reduction for Navier Stokes equations in parametrised geometries is proposed, which makes use of an hyper-reduction method to deal with the non-linearities. In (Guibert et al., 2014) a method is proposed to deal with non-parametrised geometries, as the ones which are available through medical imaging. A reference geometry is defined by building an atlas, an average (in a sense specified in the paper) of a set of available geometries. The database of simulation and the reduced basis are built in the reference geometry and then mapped to the actual geometric configuration. A similar approach, in the spirit, is proposed in (Galarce et al., 2022). In this work we first introduce a notion of distance between sets of solutions in different geometries. This is because, albeit the fact that two geometries are close, the sets of solutions in these domains might be quite different (think for instance to separated flows past obstacles). A framework is proposed in which sets of modes in different reference configurations can be mapped into a new non-parametric geometry and used to perform model reduction.

4.1 Direct problems.

In haemodynamics, projection-based ROMs have been used to perform efficiently 3-D simulations of blood flows in arteries. In (Ballarin et al., 2016) the authors use a Proper-Orthogonal-Decomposition basis to reduce the simulation of coronary arteries flows in presence of a bypass. The method is patient specific and the authors present a complete pipeline to parametrise the geometry of the coronaries based on imaging data of the patient. The computational speed-up obtained is of more than two orders of magnitude. A comparison between the full-order simulations and the reduced-order models is presented in terms of representation of QoIs, showing a good agreement. In (Ballarin et al., 2017), a projection-based reduced-order method is proposed in order to account for the fluid-structure interaction phenomena in arterial flows. In (Tezzele et al., 2018) the method of active subspaces is combined with a reduced-basis method to simulate blood flow in a carotid bifurcation. The database of full order model solutions is built by varying the parameters in the active subspace (instead of considering point instances in the whole parametric space).

4.2 Inverse problems.

Several strategies were proposed in the literature in order to speed-up inverse problems. The first one is based on the optimisation formulation of inverse problems (4D-VAR). This formulation and several applications in computational haemodynamics are discussed in (D'Elia et al., 2012). The first idea to speed-up such a formulation consists in replacing the repeated evaluation of the FOM by the cheaper evaluation of the ROM. Otherwise stated, we make use of a 4D-VAR formulation in which the system state evolution is governed by the ROM. The key advantage is that the repeated evaluation of the ROM are much faster than the FOM. Roughly speaking, if, typically one needs between 10^2 and 10^3 iterations to solve the optimisation problem, with a speed-up of that order of magnitude, the cost of the inverse problem would be comparable to one single direct problem simulation of the FOM. This strategy has been fully analysed in (Kaercher et al., 2018). Data Assimilation in a variational formulation is used in (Zainib et al., 2021), in which a patient specific framework is proposed to investigate coronary flows.

Another set of works deal with sequential data assimilation approaches. In these, an observer is introduced, which progressively minimises the discrepancy between the model observations and the actual measurements. This approach is discussed, for instance, in (Bertoglio et al., 2012). In (Pagani et al., 2017) the authors propose to use a reduced basis method coupled with an Ensemble Kalman Filter in order to perform data assimilation. It has been tested in this work in the context of the electro-physiology. Recently, in (Habibi et al., 2021), the authors perform state estimation in haemodynamics by using a Kalman filter. In this, the FOM is replaced by a reduced order model obtained by Dynamical Mode Decomposition.

A different line of research consists in casting data assimilation as an optimal recovery problem. We focus in particular on the problem of state estimation. Let the unknown state be an element $u \in \mathcal{V}$, where $\mathcal{V}$ is a Hilbert space. Let $w \in \mathbb{R}^m$ be the set of $m \in \mathbb{N}^*$ measurements, assumed to be a set of linear forms $\{\ell_i\}_{1\leq i\leq m}$ applied to the state. A small dimensional linear subspace $V_n \subset \mathcal{V}$, $n \leq m$ has been determined, so that some of its elements may be close to the actual system states. Let $\mathcal{P}_n$ be its projector. The state estimation reads as follows:

$$u_* = \arg\inf_{u\in\mathcal{K}} \|u - \mathcal{P}_n u\|^2_{\mathcal{V}}, \tag{10}$$
$$\mathcal{K} = \{u \in \mathcal{V} \ \text{ such that : } \ \ell_\mathrm{i}(\mathrm{u}) = \mathrm{w_i}, \ 1 \leq \mathrm{i} \leq \mathrm{m}\}.$$

The linear optimal recovery can be summarised as follows: among all the elements of the space such that, when observed, we get the measurements values, we chose the one which is the closest to the linear subspace V_n. This is at the basis of the Parametrised Background Data Weak (PBDW) method. This has been proposed, extended and analysed in (Maday et al., 2015; Gong et al., 2019; Binev et al., 2017; Cohen et al., 2020). Its adaptation to the context of haemodynamics has been discussed in (Galarce et al., 2021a,b). In these works we compared the performances of optimal recovery for different ways of constructing the reduced space V_n and for several QoIs. In particular, instead of using a single linear subspace V_n, we proposed a method to build a piece-wise affine reduced representation. This proved to be key in order to get good reconstruction performances in semi-realistic 3D test cases. The advantage of optimal recovery is the following: we can perform state estimation without performing parameter estimation. This is due to the fact that the parametric model is just accounted for by means of a reduced space (or set of spaces, or subsets of a Hilbert space). The main drawback, as far as haemodynamics is concerned, is that the classical optimal recovery makes it possible to perform a static estimation. Henceforth, when estimating the state at different times, every estimation is independent, whereas in the natural phenomenon the states are related. Taking properly into account this aspect would make it possible to improve the accuracy of the estimation even further.

5 Data-Driven based ROMs.

We conclude this review by presenting contributions in which the reduced-order model is not set up based on a parsimonious discretisation of the PDE model. Instead, the goal is to exploit either a database of real data or of FOM simulations (or both) to define a surrogate model. Let $\Theta \subseteq \mathbb{R}^p$ be the parameter set and $\{y^{(i)}\}_{1\leq i\leq N} \in \mathbb{R}^m$ be a set of instances of the system observations. It is assumed here that the variability of the observations, beside the inevitable measurement noise, is solely due to the variation of these parameters. The instances might be obtained through experiments, by numerical simulation, or both. The hybrid approach taken by data-driven based ROMs consists in finding a mapping $\phi : \Theta \to \mathbb{R}^m$ linking the system parameters to the observations. Once the mapping has been learned by exploiting the available instances it can be used either to perform direct problems in a fast way, or to estimate parameters given new system measurements. Numerous methods are available to estimate the mapping ϕ: linear mappings (least squares, partial least squares), kernel based methods, neural networks. Several works are currently aiming at introducing physics and integrate it to this approach to palliate to the eventual scarcity of data.

5.1 Direct problems.

Recently, in (Arzani and Dawson, 2021), several data-driven reduced-order methods are reviewed and applied to cardio-vascular flows. The methods discussed includes POD (standard and robust), Dyanamic Mode Decomposition, filtering methods, machine learning based ROMs. In (Girfoglio et al., 2021), the authors discuss a non-intrusive framework to perform model reduction. A database of FOM simulation is computed and a POD basis extracted. Instead of projecting the equations on the basis and derive a projection-based ROM the authors propose to use an RBF based interpolation in order to determine the coefficients representing the solution on the basis for new instances. In (Liang et al., 2020) an artificial neural network is used in order to build a surrogate model of the steady flow inside an aorta geometry. In this proof of concept, the authors trained the network by using the aorta geometry and tried to predict the flow. The training was performed by building a database of simulations. In (Koeppl et al., 2018) a database of 1-D reduced models on a systemic network is build and a surrogate model based on kernel methods is proposed in order to perform a real time simulation of the global circulation. In (Fresca and Manzoni, 2021) a method based on deep learning is proposed to speed up the approximation of blood flow. In this work, the authors perform, first, a POD basis extraction, whose goal is to reduce the training phase cost. Then, the map between the parameters and the coefficients representing the solution on the POD basis is learned and reduced by means of autoencoders. The method proved to efficiently speed-up 3-D flow simulations. In (Buoso et al., 2021) a Physics-Informed Neural Network is set up in the context of cardiac-mechanics. In this work, the author propose a data driven method in which the network training minimises as well a cost function related to the problem physics. A numerical experiment illustrates the properties of the method in this application.

5.2 Inverse problems.

In purely data-driven approaches, the goal is to learn the link between the QoIs and the observations by exploiting a dataset in which we know the pairs QoIs-observations for a sufficiently large number of cases. This learning task can be performed in an agnostic way, *i.e.* without any a priori assumption on how the system works. Recent efforts in the litterature try to introduce some a priori knowledge in order to improve the prediction performances.

A first example of application of a data-driven approach in haemodynamics was proposed in (Akay et al., 1994), in which a diastolic heart sound recording is used to predict coronary artery disease. The authors used a wavelet analysis coupled with an artificial neural network to build a predictive tool. Another example was described in (Smith et al., 1996), in which the authors used ANN to detect anomalies in Doppler Ultrasound waveforms. A similar application on neonatal abnormal waveform detection was discussed in (Seker et al., 2001) and to the prediction of hypotension episodes in (Rocha et al., 2010). In (Kara and Dirgenali, 2007) wavelets, principal component analysis and artificial neural networks are used to predict atherosclerosis condition. In (Spencer et al., 1997) data-driven methods are used in pattern recognition: short term memory layers and self-organising articficial neural networks are proposed in order to correctly detect haemodynamic patterns for Intensive Care Units patients and identify potential dangers. In (Al-Abed et al., 2019) oxygen saturation signals and photoplethysmography are used to predict the temporal blood flow velocity in obstructive sleep apnoea studies by means of neural networks.

In (Vallée et al., 2019), artificial neural networks were used in the prediction of coronary heart disease based on Pulse Wave Velocity and other clinical parameters. Recently, several works proposed methods in order to exploit medical imaging data in order to predict tissue properties and mechanical quantities. In (Ayala et al., 2019) a deep learning strategy is proposed in order to monitor live, the in vivo haemodynamics by exploiting multi-image resolution. In (Gao et al., 2020) a tree-structured recurrent neural network is set up in order to estimate the fractional flow reserve in coronaries given CT images. In (Kissas et al., 2020) a Physics Informed Neural Network (PINN) is defined, in order to predict pressure waveforms given data coming from 4d-flow MRI. In this contribution a 1D model on a network is used as a model in the PINN. This is a contribution in which the reduced model is a network which is not purely data driven, but in which an *a priori* knowledge is introduced, in this case, a reduce model of circulation. In (Zhou et al., 2021) a deep learning method is proposed (making also use of Transfert Learning) in order to perform parameter estimation given scarce measurements on a systemic arterial network. We observe here that parameters which are not directly observable are inherently related to an *a priori* physical knowledge and description of the system. So, even if the model is just used in a training stage (in which a database of solutions has been computed) this is a way of introducing some *a priori* knowledge.

6 Conclusion.

Many contributions were proposed in the literature to provide a reduced-order description of some aspects of the haemodynamics. Given the complexity of the system under investigation, ROMs are necessary to build a bridge between the mathematical modelling and the applications. The complexity is such that we cannot devise, at present, a unique and universal strategy, but we need to define ROMs tailored to the specific problems we face.

In this review we have divided the ROMs in three different classes. We stress that this subdivision is merely intended to highlight certain methodological aspects and to better describe them. In realistic applications, several strategies could be envisioned which do not fit precisely into this subdivision, but take advantage of several aspects of the different approaches to reach a specific goal.

Several open problems and promising research directions are currently under development. For what concerns methodology, two main topics are under investigation. First, the use of non-linear model reduction (through compositional approximations) seems to open interesting perspective for fast simulation of flows and haemodynamics. The dichotomy between equation based and data-driven based is a crucial point, and many works are trying to propose trade-offs between these two different visions, in order to exploit, at best, all the sources of information about the system behaviour. A second topic is related to the geometry and to the possibility of developing methods which make it possible to estimate in a fast and automatic way haemodynamics in different geometrical configurations, for different patients, by minimising human and computer time.

All these methodological investigations can contribute to significantly improve numerous realistic applications, for which more and more data (and of higher quality) are available.

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