



A stable loosely-coupled scheme for cardiac electro-fluid-structure interaction

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ABSTRACT

We present a loosely coupled scheme for the numerical simulation of the cardiac electro-fluid-structure interaction problem, whose solution is typically computationally intensive due to the need to suitably treat the coupling of the different submodels. Our scheme relies on a segregated treatment of the subproblems, in particular on an explicit Robin-Neumann algorithm for the fluid-structure interaction, aiming at reducing the computational burden of numerical simulations. The results, both in an ideal and a realistic cardiac setting, show that the proposed scheme is stable at the regimes typical of cardiac simulations. From a comparison with a scheme with implicit fluid-structure interaction, it emerges that, while conservation properties are not fully preserved, computational times significantly benefit from the explicit scheme. Overall, the explicit discretization represents a good trade-off between accuracy and cost, and is a valuable alternative to implicit schemes for fast large-scale simulations.

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1. Introduction

Mathematical and numerical modeling of the cardiac function can provide meaningful insight into physiology, as well as assist in the development of personalized treatment [60,83,95,96,122]. Several computational models of the human heart function have been proposed, often focusing on specific features of its function: electrophysiology [5,21,37,59,91,103,119,121], electromechanics [8,9,13,34,46,51,54,63,77,90,92,100,107,112,113,120], hemodynamics [18,31,72,116,118,134–136], fluid-structure interaction [19,20,30,74,85,132] and myocardial perfusion [33,39,40,69,88,135].

Usually, the remaining features are neglected or surrogated by means of simplified models. While this approach can provide meaningful results in physiological [51,72,100,136] as well as pathological scenarios [93,107], the heart function is characterized by the coordinated interplay of different physical processes, each affecting every other in multiple ways [95]. Therefore, models featuring fully coupled and three-dimensional representations of electrophysiology, active and passive mechanics and fluid dynamics have the potential of providing a very accurate description of the physics of the heart [53,

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66,109,114,126,127]. Models of this kind have been employed e.g. in computational studies on ventricular assist devices [14] and for in-silico clinical trials on digital cohorts of bundle branch block patients [125]. However, this comes at a high price in terms of model complexity and computational cost. For this reason, electro-fluid-structure models for the cardiac function are seldom considered in the literature. In particular, modeling the fluid-structure interaction (FSI) effects between the cardiac muscle and the blood dynamics is computationally challenging [20,30,43,48,65,85,132]. This is due in part to the anisotropy and non-linearity of the constitutive laws of muscular tissue, but also to the so-called added-mass effect [29,50]: since fluid and structure have similar densities, numerical methods must be carefully designed to avoid time instability while keeping under control computational costs. These issues become even more pressing since, in the cardiac context, the FSI model is driven by the active muscular contraction, in turn triggered by electrical excitation, adding to its overall complexity and computational burden.

In this framework, explicit yet stable FSI schemes are very attractive [15,16,23,25–27,49,56,57,62,78,110,111]. We focus in particular on loosely coupled Robin-Neumann (RN) type schemes, as discussed in [56,57]. Here, RN indicates the kind of interface conditions that are alternatively enforced at the interface between the fluid and the structure. Analysis and numerical experiments for such schemes have been performed in both idealized and realistic vascular cases, considering a linear, isotropic and passive material for the structure [56,57], highlighting their stability for suitable ranges of the interface Robin parameter and of the time step.

The aim of this paper is to introduce, for the first time, a complete loosely coupled segregated scheme for the cardiac electro-fluid-structure interaction (EFSI) problem. To this aim, we combine, in a modular framework, a loosely coupled scheme used so far to couple electrophysiology and FSI [22] with the explicit RN scheme proposed in [56,57] for FSI. We assess the effectiveness of the proposed scheme in a cardiac context, where the structure is characterized by a non-linear constitutive law, anisotropy and active contraction driven by electrophysiology. Moreover, we consider all the four cardiac phases (systolic and diastolic phases, together with the two isovolumic phases). We compare the complete loosely coupled scheme for EFSI against an explicit-implicit scheme where fluid and structure are strongly coupled in a monolithic fashion. We also consider a hybrid scheme, in which a small number of RN iterations is performed. We compare the schemes in terms of both accuracy and computational efficiency. Numerical results indicate that the complete loosely coupled scheme is stable in time and allows for significant computational savings. We also highlight a good accuracy of the explicit algorithm when compared to the explicit-implicit one, except for a mass loss during the isovolumic phases, so that overall the latter allows to strike a compromise between accuracy and computational efficiency. Finally, our conclusions are supported by a numerical experiment performed for a realistic ventricular model.

The rest of the paper is structured as follows. In Section 2 we introduce the cardiac EFSI problem. In Section 3 we detail the numerical methods used, with reference in particular to the complete loosely coupled scheme, and in Section 4 we present numerical results and a comparison between the schemes under consideration. Finally, in Section 5 we draw some conclusive remarks.

2. Mathematical modeling of cardiac electrophysiology-fluid-structure interaction

Let us denote by $t \in [0, T]$ the independent time variable. We consider a time-dependent domain $\Omega(t) \subset \mathbb{R}^3$ representing a human left ventricle [20]. The domain is split into the fluid part $\Omega_f(t)$, representing the volume occupied by the blood inside the chamber, and a solid part $\Omega_s(t)$, corresponding to the volume occupied by the cardiac muscle, such that $\overline{\Omega(t)} = \overline{\Omega_f(t)} \cup \overline{\Omega_s(t)}$ and $\Omega_f(t) \cap \Omega_s(t) = \emptyset$. The two domains share an interface $\Sigma(t) = \partial\Omega_f(t) \cap \partial\Omega_s(t)$. We denote by $\mathbf{n}(t)$ the unit vector normal to $\partial\Omega(t)$, outgoing from $\Omega(t)$, and to $\Sigma(t)$, outgoing from $\Omega_f(t)$. To keep the notation light, we shall henceforth drop the explicit dependence on time of the sets defined so far, e.g. we will denote $\Omega(t)$, at the time-continuous level, simply by Ω .

We denote by $\Gamma_{f,b}$ and $\Gamma_{s,b}$ the portion of boundary corresponding to the ventricular base on the fluid and structure domains, respectively. Moreover, we denote by $\Gamma_{s,epi}$ the epicardial surface (i.e. the outer wall), while Σ corresponds to the endocardial surfaces on fluid and solid domains. There holds $\Gamma_{f,endo} = \Gamma_{s,endo} = \Sigma$. Finally, we denote by Γ_{MV} and Γ_{AV} two regions, possibly intersecting (see Section 2.8 for further details), of the fluid domain boundary representing the mitral and aortic valve orifices. The domain is represented in Fig. 1a.

To track the motion of the domains, we introduce three fixed *reference configurations* $\widehat{\Omega}$, $\widehat{\Omega}_f$, $\widehat{\Omega}_s$. We similarly denote with a hat the reference configuration for any of the previously defined boundary portions. The displacement of the time-dependent domains is expressed by the maps

$$\begin{aligned} \mathcal{L}_s : \widehat{\Omega}_s \times (0, T) &\rightarrow \Omega_s & \Omega_s(t) &= \{\mathbf{x} = \mathcal{L}_s(\widehat{\mathbf{x}}, t), \widehat{\mathbf{x}} \in \widehat{\Omega}_s\}, \\ \mathcal{L}_f : \widehat{\Omega}_f \times (0, T) &\rightarrow \Omega_f & \Omega_f(t) &= \{\mathbf{x} = \mathcal{L}_f(\widehat{\mathbf{x}}, t), \widehat{\mathbf{x}} \in \widehat{\Omega}_f\}. \end{aligned}$$

The precise definitions of \mathcal{L}_s and \mathcal{L}_f are provided in the following sections.

The unknowns of our model are the following functions:

$$\begin{aligned} v : \widehat{\Omega}_s \times (0, T) &\rightarrow \mathbb{R} && \text{transmembrane potential,} \\ \mathbf{w} : \widehat{\Omega}_s \times (0, T) &\rightarrow \mathbb{R}^{N_{\text{ion}}^w} && \text{gating variables,} \end{aligned}$$

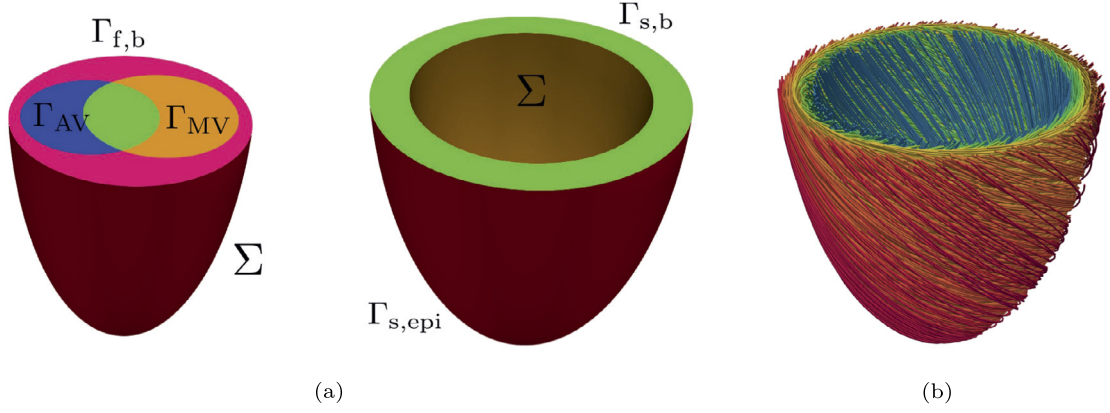


Fig. 1. (a) Computational domain Ω_f (left) and Ω_s (right) of the idealized ventricle. Colors and labels denote the different portions of the boundary. (b) Streamline representation of the fiber field \mathbf{f}_0 . Color is used to distinguish endocardium, myocardium and epicardium. (For interpretation of the figure(s), the reader is referred to the web version of this article.)

$$\begin{aligned}
 \mathbf{z} : \widehat{\Omega}_s \times (0, T) &\rightarrow \mathbb{R}^{N_{\text{ion}}^z} && \text{ionic concentrations,} \\
 \mathbf{s} : \widehat{\Omega}_s \times (0, T) &\rightarrow \mathbb{R}^{N_{\text{act}}} && \text{activation state variables,} \\
 \mathbf{d} : \widehat{\Omega}_s \times (0, T) &\rightarrow \mathbb{R}^3 && \text{solid displacement,} \\
 \mathbf{d}_{\text{ALE}} : \widehat{\Omega}_f \times (0, T) &\rightarrow \mathbb{R}^3 && \text{fluid domain displacement,} \\
 \mathbf{u} : \Omega_f \times (0, T) &\rightarrow \mathbb{R}^3 && \text{fluid velocity,} \\
 p : \Omega_f \times (0, T) &\rightarrow \mathbb{R} && \text{fluid pressure,}
 \end{aligned}$$

with $N_{\text{ion}}^w = 12$, $N_{\text{ion}}^z = 6$ and $N_{\text{act}} = 2$, according to the chosen ionic and force generation models (see Sections 2.2 and 2.3).

2.1. Fiber generation

The cardiac tissue is characterized by the presence of fibers, that influence both its electrical and mechanical behavior [44,58,91,102]. We account for their presence by defining at every point of $\widehat{\Omega}_s$ an orthonormal basis $\{\mathbf{f}_0, \mathbf{s}_0, \mathbf{n}_0\}$, representing the local directions of fibers, of fiber sheetlets and normal to fiber sheetlets, respectively. The basis is generated at every point by means of the algorithm presented in [104], as a preprocessing step. We refer the interested reader to [91] for a detailed review of fiber generation methods for the whole heart. Fig. 1b reports the generated fiber field on the idealized ventricle.

2.2. Electrophysiology

Electrophysiology models the evolution of the *transmembrane potential*, i.e. the difference of potential v between the intra- and extra-cellular spaces, as well as the evolution of ionic concentrations and ionic channels that determine the electrical excitation of cardiac cells [32]. To this end, we use the monodomain equation, coupled with the ionic model by Ten Tusscher and Panfilov [115]:

$$\left\{ \begin{aligned}
 \frac{\partial v}{\partial t} - \nabla \cdot (\Sigma_m \nabla v) + I_{\text{ion}}(v, \mathbf{w}, \mathbf{z}) &= I_{\text{app}}(\widehat{\mathbf{x}}, t) && \text{in } \widehat{\Omega}_s \times (0, T), \\
 \frac{\partial \mathbf{w}}{\partial t} &= \mathbf{F}_{\text{ion}}^w(v, \mathbf{w}) && \text{in } \widehat{\Omega}_s \times (0, T), \\
 \frac{\partial \mathbf{z}}{\partial t} &= \mathbf{F}_{\text{ion}}^z(v, \mathbf{w}, \mathbf{z}) && \text{in } \widehat{\Omega}_s \times (0, T), \\
 \Sigma_m \nabla v \cdot \mathbf{n} &= 0 && \text{on } \partial \widehat{\Omega}_s \times (0, T), \\
 v &= v_0 && \text{in } \widehat{\Omega}_s \times \{0\}, \\
 \mathbf{w} &= \mathbf{w}_0 && \text{in } \widehat{\Omega}_s \times \{0\}, \\
 \mathbf{z} &= \mathbf{z}_0 && \text{in } \widehat{\Omega}_s \times \{0\}.
 \end{aligned} \right. \tag{1}$$

In the above system, the first equation is the monodomain model, whereas the second and third equations express the ionic model in a compact form. We refer the interested reader to [115] for the precise definition of \mathbf{F}_{ion}^w , \mathbf{F}_{ion}^z and I_{ion} , as well as for the definitions of the components of \mathbf{w} and \mathbf{z} . We point out that the vector \mathbf{z} includes the intracellular concentration of calcium ions $[Ca^{2+}]_i$, that is relevant to the force generation model.

The tensor Σ_m expresses the anisotropic conduction properties of the myocardium. It is computed in terms of the fiber field as

$$\Sigma_m = \sigma_m^f(\mathbf{f}_0 \otimes \mathbf{f}_0) + \sigma_m^s(\mathbf{s}_0 \otimes \mathbf{s}_0) + \sigma_m^n(\mathbf{n}_0 \otimes \mathbf{n}_0),$$

where σ_m^f , σ_m^s and σ_m^n are conductivities in the fiber, sheetlet and normal directions, respectively [91].

Finally, the I_{app} term in the monodomain equation models the ventricular stimulation by the Purkinje network in a simplified way, by applying a stimulus at three distinct locations on the endocardial wall [91,100].

We remark that we are neglecting the so-called geometry-mediated mechano-electric feedback effects [108], that account for the fact that the electrical activation propagates in a moving domain. While relevant in pathological conditions, such effects have limited impact on simulations in sinus rhythm [108]. Nonetheless, the generalization of the proposed loosely coupled EFSI scheme to a model including mechano-electric feedback is straightforward.

Initial conditions v_0 , \mathbf{w}_0 and \mathbf{z}_0 are obtained by running a single-cell electrophysiology simulation until a periodic limit cycle is reached, as detailed in [100].

2.3. Force generation

The state of contraction of cardiac cells is expressed at every point in $\widehat{\Omega}_s$ by the state vector \mathbf{s} . Its evolution is modeled by the ODE model proposed in [98]. Since the model features a very large number of variables, we use its reduced-order counterpart discussed in [99]. The reduced model can be expressed as a system of ODEs defined at each point in $\widehat{\Omega}_s$:

$$\begin{cases} \frac{\partial \mathbf{s}}{\partial t} = \mathbf{F}_{act}(\mathbf{s}, [Ca^{2+}]_i, \mathbf{d}) & \text{in } \widehat{\Omega}_s \times (0, T), \\ \mathbf{s} = \mathbf{s}_0 & \text{in } \widehat{\Omega}_s \times \{0\}. \end{cases} \quad (2)$$

The generated active tension is then computed as a function of the contraction state as

$$T_{act}(\mathbf{s}) = T_{act,max}G(\mathbf{s})$$

with $G(\mathbf{s}) \in [0, 1]$ and $T_{act,max}$ the maximum generated contraction. We refer the interested reader to [98,99] for the precise definition of \mathbf{F}_{act} and G . We remark that \mathbf{F}_{act} depends on \mathbf{d} accounting for the positive correlation between the stretch in the fiber direction and the generated force, coherently with the well-known Frank-Starling mechanism [73,75,87].

2.4. Solid mechanics

We define the map \mathcal{L}_s as

$$\mathcal{L}_s(\widehat{\mathbf{x}}, t) = \widehat{\mathbf{x}} + \mathbf{d}(\widehat{\mathbf{x}}, t),$$

where \mathbf{d} is the displacement field of the muscle, which is obtained as the solution of the elastodynamics equation in Lagrangian formulation [86]:

$$\begin{cases} \rho_s \frac{\partial^2 \mathbf{d}}{\partial t^2} - \nabla \cdot \mathbf{P}_s(\mathbf{d}, \mathbf{s}) = \mathbf{0} & \text{in } \widehat{\Omega}_s \times (0, T), & (a) \\ \mathbf{d} = \mathbf{0} & \text{on } \widehat{\Gamma}_{s,b} \times (0, T), & (b) \\ \mathbf{P}_s(\mathbf{d}, \mathbf{s})\mathbf{n} = -(\mathbf{n} \otimes \mathbf{n}) \left(K_{\perp}^{epi} \mathbf{d} + C_{\perp}^{epi} \frac{\partial \mathbf{d}}{\partial t} \right) - (I - \mathbf{n} \otimes \mathbf{n}) \left(K_{\parallel}^{epi} \mathbf{d} + C_{\parallel}^{epi} \frac{\partial \mathbf{d}}{\partial t} \right) & \text{on } \widehat{\Gamma}_{s,epi} \times (0, T), & (c) \\ \mathbf{d} = \mathbf{d}_0 & \text{in } \widehat{\Omega}_s \times \{0\}, & (d) \\ \frac{\partial \mathbf{d}}{\partial t} = \mathbf{0} & \text{in } \widehat{\Omega}_s \times \{0\}. & (e) \end{cases} \quad (3)$$

In the above, P_s is the first Piola-Kirchhoff stress tensor, that accounts for both active and passive mechanical properties in the active stress framework [4]. It is decomposed additively as

$$P_s(\mathbf{d}, \mathbf{s}) = P_{pas}(\mathbf{d}) + P_{act}(\mathbf{d}, \mathbf{s})$$

into the passive contribution $P_{\text{pas}}(\mathbf{d})$ and active contribution $P_{\text{act}}(\mathbf{d}, \mathbf{s})$. On the epicardial boundary $\widehat{\Gamma}_{\text{s,epi}}$, we impose visco-elastic Robin boundary conditions that mimic the mechanical effect of the pericardium and the organs surrounding the heart [90,113]. K_{\perp}^{epi} and $K_{\parallel}^{\text{epi}}$ represent elastic stiffness coefficients in the normal and tangent direction to the boundary, respectively, while C_{\perp}^{epi} and $C_{\parallel}^{\text{epi}}$ are normal and tangent viscosity coefficients.

The passive stress tensor is defined in the hyperelastic framework as the derivative of a strain energy functional \mathcal{W} :

$$P_{\text{pas}}(\mathbf{d}) = \frac{\partial \mathcal{W}}{\partial F},$$

where $F = I + \nabla \mathbf{d}$. We use the Guccione constitutive law for ventricular tissue [61,100,120] with a penalization term for near-incompressibility. The constitutive law is non-linear and features anisotropy determined by the fiber field. See Appendix A for more details.

The active contribution to the stress tensor is defined as [100]

$$P_{\text{act}}(\mathbf{d}, \mathbf{s}) = T_{\text{act}}(\mathbf{s}) \frac{F \mathbf{f}_0 \otimes \mathbf{f}_0}{\sqrt{I_{4f}}},$$

where $I_{4f} = F \mathbf{f}_0 \cdot F \mathbf{f}_0$ measures the stretch along the fiber direction. We remark that P_{act} acts only in the direction of the fibers.

To find the initial displacement \mathbf{d}_0 , we solve a quasi-static solid mechanics problem imposing a homogeneous endocardial pressure p_0 on $\widehat{\Gamma}_{\text{s,epi}}$ [100].

The condition (3c) is a generalized visco-elastic Robin boundary condition that mimics the presence of the pericardial sac, a fluid-filled cavity that provides mechanical support, lubrication and protection from infections to the heart [90,100,113].

Finally, we remark that the use of a homogeneous Dirichlet condition on the ventricular base is not consistent with physiology, and more sophisticated conditions should be applied [92,100]. However, since our focus is on the numerical method for the FSI problem, we use a homogeneous Dirichlet condition for simplicity.

2.5. Fluid domain displacement

We model the motion of the fluid domain in the Arbitrary Lagrangian-Eulerian (ALE) framework [41,42,68,84]. The displacements involved in ventricular simulations are large but regular enough to allow the ALE method to be effectively employed [31,72,134,136]. We remark that, if valve leaflets were included in the model, the ALE approach would not be robust enough to account for their displacement, and alternative approaches such as the immersed boundary method would be better suited [81,123,127].

We introduce a fluid domain displacement field $\mathbf{d}_{\text{ALE}} : \widehat{\Omega}_f \rightarrow \mathbb{R}^3$ and define the mapping \mathcal{L}_f as

$$\mathcal{L}_f(\widehat{\mathbf{x}}, t) = \widehat{\mathbf{x}} + \mathbf{d}_{\text{ALE}}(\widehat{\mathbf{x}}, t).$$

The displacement \mathbf{d}_{ALE} is obtained by arbitrarily extending to $\widehat{\Omega}_f$ the solid displacement on the interface, $\mathbf{d}|_{\widehat{\Sigma}}$. We do so by means of a harmonic lifting operator:

$$\begin{cases} -\Delta \mathbf{d}_{\text{ALE}} = \mathbf{0} & \text{in } \widehat{\Omega}_f \times (0, T), \\ \mathbf{d}_{\text{ALE}} = \mathbf{d} & \text{on } \widehat{\Sigma} \times (0, T), \\ \mathbf{d}_{\text{ALE}} = \mathbf{0} & \text{on } (\widehat{\Gamma}_{\text{f,b}} \cup \widehat{\Gamma}_{\text{AV}} \cup \widehat{\Gamma}_{\text{MV}}) \times (0, T). \end{cases} \quad (4)$$

We define the ALE velocity \mathbf{u}_{ALE} as the time derivative of the ALE displacement, pushed forward to the current configuration:

$$\mathbf{u}_{\text{ALE}}(\mathbf{x}, t) = \frac{\partial \mathbf{d}_{\text{ALE}}}{\partial t}(\mathcal{L}_f^{-1}(\mathbf{x}, t), t).$$

2.6. Fluid dynamics

We model the blood as an incompressible Newtonian fluid through Navier-Stokes equations in the ALE framework [41, 68,94]:

$$\begin{cases} \rho_f \frac{\partial \mathbf{u}}{\partial t} + \rho_f ((\mathbf{u} - \mathbf{u}_{\text{ALE}}) \cdot \nabla) \mathbf{u} - \nabla \cdot \sigma_f(\mathbf{u}, p) = \mathbf{0} & \text{in } \Omega_f \times (0, T), \\ \nabla \cdot \mathbf{u} = 0 & \text{in } \Omega_f \times (0, T), \\ \mathbf{u} = \mathbf{0} & \text{in } \Omega_f \times \{0\}, \\ \mathbf{u} = \mathbf{0} & \text{on } \Gamma_{\text{f,b}}, \end{cases} \quad (5)$$

where ρ_f is the fluid density,

$$\begin{aligned} \sigma_f(\mathbf{u}, p) &= 2\mu\varepsilon(\mathbf{u}) - pI, \\ \varepsilon(\mathbf{u}) &= \frac{1}{2}(\nabla\mathbf{u} + \nabla\mathbf{u}^T), \end{aligned}$$

and μ is the dynamic viscosity of the blood. Suitable boundary conditions are imposed on Γ_{MV} and Γ_{AV} to model the opening and closing of the mitral and aortic valve, respectively, as detailed in Section 2.8.

2.7. Fluid-structure interaction

Besides the *geometric coupling* expressed by (4), fluid and solid are coupled at the interface by imposing the continuity of velocity (*kinematic coupling*) and of stresses (*dynamic coupling*), expressing a no-slip condition and Newton's third law, respectively [17]:

$$\begin{cases} \mathbf{u} = \frac{\partial \mathbf{d}}{\partial t} & \text{on } \Sigma \times (0, T), \\ \sigma_f(\mathbf{u}, p)\mathbf{n} = \sigma_s(\mathbf{d}, \mathbf{s})\mathbf{n} & \text{on } \Sigma \times (0, T), \end{cases} \quad (6)$$

where $\sigma_s(\mathbf{d}, \mathbf{s})$ is the Cauchy stress tensor of the structure, related to $P(\mathbf{d}, \mathbf{s})$ by

$$J\sigma_s(\mathbf{d}, \mathbf{s}) = FP_s(\mathbf{d}, \mathbf{s})^T.$$

By taking a linear combination, the interface conditions (6) can be equivalently rewritten as follows [11,56]:

$$\begin{cases} \alpha\mathbf{u} + \sigma_f(\mathbf{u}, p)\mathbf{n} = \alpha\frac{\partial \mathbf{d}}{\partial t} + \sigma_s(\mathbf{d}, \mathbf{s})\mathbf{n} & \text{on } \Sigma \times (0, T), \\ \sigma_f(\mathbf{u}, p)\mathbf{n} = \sigma_s(\mathbf{d}, \mathbf{s})\mathbf{n} & \text{on } \Sigma \times (0, T), \end{cases} \quad (7)$$

with $\alpha > 0$ a suitable Robin coefficient.

2.8. Modeling of the four heartbeat phases

Cardiac valves open and close passively to prevent reverse flow, and determine four distinct phases of the heartbeat [73,75,87]. Focusing on the left heart, the phases are as follows:

1. isovolumetric contraction: both the mitral and aortic valves are closed, and the ventricle starts to contract. This leads to a rapid increase in ventricular pressure, without any variation in ventricular volume. As soon as the ventricular pressure becomes larger than the pressure in the aorta, the aortic valve opens;
2. ejection: blood is ejected from the ventricle into the aorta, leading to a decrease in ventricular volume. The mitral valve is closed, and the aortic valve is open. As soon as the flow through the aortic valve becomes null or negative, it closes;
3. isovolumetric relaxation: both valves are again closed, and the ventricle starts relaxing. Ventricular pressure reduces, while ventricular volume stays constant. When the ventricular pressure becomes smaller than the atrial pressure, the mitral valve opens;
4. filling phase: the mitral valve is open and the aortic valve is closed. Blood flows from the atrium into the ventricle, whose volume increases. When the flow through the mitral valve becomes null or negative, it closes.

Isovolumetric contraction and ejection form the systolic phase, during which the ventricle contracts, whereas isovolumetric relaxation and filling form the diastolic phase. In order to model a full heartbeat, all of these phases must be captured adequately. We point out that isovolumetric phases pose significant modeling challenges for standalone computational fluid dynamics simulations [31,118,133], since they would lead to a fully Dirichlet problem on the ventricular chamber. For this kind of problem, ventricular pressure would not be uniquely defined, and the prescribed boundary displacement would be required to be compatible with fluid incompressibility. On the contrary, FSI models such as the proposed one can deal with isovolumetric phases naturally, thanks to the fact that the FSI interface conditions include a stress condition on the fluid solid interface, and the boundary displacement is an unknown of the problem, determined in accordance with fluid incompressibility [22].

We use switching boundary conditions on Γ_{MV} and Γ_{AV} to model opening and closing of the mitral and aortic valve, as done in [20]. No-slip conditions $\mathbf{u} = \mathbf{0}$ are used for closed valves, the open mitral valve is modeled through a Neumann boundary condition, $\sigma(\mathbf{u}, p)\mathbf{n} = -p_{MV}\mathbf{n}$, and the open aortic valve is modeled through a resistance boundary condition,

$$\sigma_f(\mathbf{u}, p)\mathbf{n} = -\left(p_{AV}^0 + R_{AV} \int_{\Gamma_{AV}} \mathbf{u} \cdot \mathbf{n}\right)\mathbf{n}.$$

The choice of a resistance condition on the aortic valve allows to account for the typical evolution in time of the aortic pressure [80], at the same time preventing spurious reflections of pressure waves [70,97,124]. Conversely, atrial pressure can be approximated as constant in time.

Valves are instantaneously switched from closed to open when the pressure upstream becomes larger than that downstream. Conversely, they are switched from open to close when the flowrate through them becomes null or reversed (i.e. when there is outflow through the mitral orifice or inflow through the aortic orifice). Thus, the opening and closure of valves is regulated by the numerical simulation and not prescribed a priori.

Notice that the mitral valve orifice Γ_{MV} and the aortic one Γ_{AV} present an overlapping region (see Fig. 1a), since due to the movement of the heart the effective open orifice regions share a common part. On such region of intersection, we impose a no-slip condition when both valves are closed. When instead either of the two valves is open, we impose the corresponding open-valve condition on $\Gamma_{AV} \cap \Gamma_{MV}$. The opening and closing conditions of the valves prevent them from being both open at the same time.

3. Numerical discretization

Due to the large size of the problem, as well as its multiphysics and multiscale nature, the efficient numerical solution of the fully coupled electrophysiology–fluid–structure interaction (EFSI) system is a challenging task. One possible approach is based on a fully monolithic solver [53], where the coupled problem is discretized at each time step into a single large non-linear system. While very robust and stable, this approach requires the development of a dedicated solver and the use of suitable non-linear and linear solvers and preconditioners. Instead, one can choose to solve separately the different subproblems. This can be done maintaining a strong coupling between the problems, by means of subiterations [24,109], resulting in an implicit partitioned approach. However, iterative schemes of this kind might suffer from convergence issues, and can quickly become more computationally expensive than their monolithic counterpart [20].

In this context, we propose a fully loosely coupled scheme in which all problems are solved only once per time step, and coupling terms are treated in an explicit fashion. This segregated approach, while possibly requiring the time step parameter to be sufficiently fine to guarantee stability, has the potential of being very computationally efficient. Moreover, the proposed method is inherently modular, and allows to flexibly choose spatial and temporal discretizations for the different equations.

While this approach is very common for electromechanics simulations [9,36,51,92,100], the FSI coupling is usually treated in a strongly coupled way [65,85,109,129,132]. Indeed, when the fluid and solid have comparable densities, as in biological applications, the so-called added-mass effect [29] may lead to stability issues when a loosely coupled scheme is considered. Nonetheless, some loosely coupled FSI schemes have been investigated in the cardiovascular modeling literature [15,23,25–27,49,56,57,78,110,111]. In particular, in [56,57] the authors investigated the stability properties of loosely coupled fluid structure interaction schemes based on Robin interface conditions, showing that for suitable choices of the Robin coefficients one may obtain a stable method. For the coupling of fluid and structure in our EFSI problem, we rely on a particular case of the Robin-based schemes, the loosely coupled Robin-Neumann (RN) scheme [25,49,56,57].

We introduce a partition of the time domain $(0, T)$ into equally spaced sub-intervals (t^n, t^{n+1}) , and denote by $\Delta t = t^{n+1} - t^n$ the width of each sub-interval. We denote with a superscript n over any solution variable the time-discrete approximation of that solution variable at time t^n (e.g. $\mathbf{u}^n \approx \mathbf{u}(t^n)$). We use finite differences for the time discretization of the subproblems. In the remainder of this section, we detail the proposed loosely coupled EFSI time discretization scheme (denoted with the abbreviation EFS₁), as well as an explicit-implicit (E₁FS_∞) scheme in which the fluid-solid coupling is treated implicitly and monolithically [20,64,71,101,130,132], still maintaining explicit the coupling with the electrophysiology problem. We also present a scheme based on performing 2 fluid-structure subiterations (E₁FS₂). The E₁FS_∞ scheme will be used as a reference for comparing numerical results. The considered schemes and the corresponding abbreviations are summarized in Table 1.

We remark that the new schemes discussed below are based on a loosely coupling (one or two iterations for time step) among electrophysiology, fluid and structure solvers. The same overall loosely-coupled structure can be seamlessly adapted to alternative methods to solve FSI, both strongly and loosely coupled, depending on the needs of the application under consideration or to improve the order of accuracy. Similarly, alternative approaches can be considered for the solution of the electrophysiology subproblem [82,112].

3.1. Fully loosely coupled EFSI scheme (EFS₁)

We detail in what follows the steps composing at each time step the fully loosely coupled FSI scheme (EFS₁). Given the solution up to time step t^n , in order to compute the solution at time t^{n+1} :

1. Solve the electrophysiology model (1) with the following implicit-explicit (IMEX) scheme [100]:

Table 1

Summary of the abbreviations used to indicate the considered EFSI schemes. All schemes considered treat electrophysiology, force generation and fluid domain displacement in an explicit way.

Abbreviation	Electromechanical coupling	Geometric coupling	FSI coupling
EFS ₁	explicit	explicit	explicit RN
E ₁ FS _∞	explicit	explicit	implicit
E ₁ FS ₂	explicit	explicit	2 RN iterations

(a) Solve the non-linear ionic model equations:

$$\begin{cases} \frac{\mathbf{w}^{n+1} - \mathbf{w}^n}{\Delta t} = \mathbf{F}_{\text{ion}}^{\mathbf{w}}(v^n, \mathbf{w}^{n+1}) & \text{in } \widehat{\Omega}_s, \\ \frac{\mathbf{z}^{n+1} - \mathbf{z}^n}{\Delta t} = \mathbf{F}_{\text{ion}}^{\mathbf{z}}(v^n, \mathbf{w}^n, \mathbf{z}^n) & \text{in } \widehat{\Omega}_s; \end{cases} \quad (8)$$

We remark that an implicit discretization is used for gating variables \mathbf{w} , whereas an explicit one is used for ionic concentrations \mathbf{z} ;

(b) Solve the monodomain equation to compute v^{n+1} :

$$\begin{cases} \frac{v^{n+1} - v^n}{\Delta t} - \nabla \cdot (\Sigma_m \nabla v^{n+1}) + I_{\text{ion}}(v^n, \mathbf{w}^{n+1}, \mathbf{z}^{n+1}) = I_{\text{app}}^{n+1} & \text{in } \widehat{\Omega}_s, \\ \Sigma_m \nabla v^{n+1} \cdot \mathbf{n} = 0 & \text{on } \partial \widehat{\Omega}_s; \end{cases} \quad (9)$$

2. Solve the time discretization of the force generation model (2):

$$\frac{\mathbf{s}^{n+1} - \mathbf{s}^n}{\Delta t} = \mathbf{F}_{\text{act}}(\mathbf{s}^n, [\text{Ca}^{2+}]_i^{n+1}, \mathbf{d}^n) \quad \text{in } \widehat{\Omega}_s; \quad (10)$$

3. Update the fluid domain solving (4):

$$\begin{cases} -\Delta \mathbf{d}_{\text{ALE}}^{n+1} = \mathbf{0} & \text{in } \widehat{\Omega}_f, \\ \mathbf{d}_{\text{ALE}}^{n+1} = \mathbf{d}^n & \text{on } \widehat{\Sigma}, \\ \mathbf{d}_{\text{ALE}}^{n+1} = \mathbf{0} & \text{on } \widehat{\Gamma}_{f,b}; \end{cases} \quad (11)$$

then set $\mathbf{u}_{\text{ALE}}^{n+1} = \frac{\mathbf{d}_{\text{ALE}}^{n+1} - \mathbf{d}_{\text{ALE}}^n}{\Delta t}$ and compute the fluid domain at time t^{n+1} as $\Omega_f^{n+1} = \mathcal{L}_f(\widehat{\Omega}_f, t^{n+1})$;

4. Solve the time discretization of Navier-Stokes equations (5) to compute \mathbf{u}^{n+1} and p^{n+1} , with Robin boundary conditions on the fluid-solid interface:

$$\begin{cases} \rho_f \frac{\mathbf{u}^{n+1} - \mathbf{u}^n}{\Delta t} + \rho_f \left((\mathbf{u}^n - \mathbf{u}_{\text{ALE}}^{n+1}) \cdot \nabla \right) \mathbf{u}^{n+1} - \nabla \cdot \sigma_f(\mathbf{u}^{n+1}, p^{n+1}) = \mathbf{0} & \text{in } \Omega_f^{n+1}, \\ \nabla \cdot \mathbf{u}^{n+1} = 0 & \text{in } \Omega_f^{n+1}, \\ \mathbf{u}^{n+1} = \mathbf{0} & \text{on } \Gamma_{f,b}^{n+1}, \\ \alpha \mathbf{u}^{n+1} + \sigma_f(\mathbf{u}^{n+1}, p^{n+1}) \mathbf{n}^{n+1} = \alpha \frac{\mathbf{d}^n - \mathbf{d}^{n-1}}{\Delta t} + \sigma_s(\mathbf{d}^n, \mathbf{s}^{n+1}) \mathbf{n}^n & \text{on } \Sigma^{n+1}, \end{cases} \quad (12)$$

endowed with suitable boundary conditions on Γ_{MV}^{n+1} and Γ_{AV}^{n+1} as described in Section 2.6. We remark that interface conditions are computed using the solid displacement from previous time step, and that the advection term is treated in a semi-implicit way [94], so that the resulting problem is linear;

5. Solve the time discretization of the elastodynamics equation (3) to compute \mathbf{d}^{n+1} , with Neumann boundary conditions on the fluid-solid interface:

$$\begin{cases} \rho_s \frac{\mathbf{d}^{n+1} - 2\mathbf{d}^n + \mathbf{d}^{n-1}}{\Delta t^2} - \nabla \cdot P_s(\mathbf{d}^{n+1}, \mathbf{s}^{n+1}) = \mathbf{0} & \text{in } \widehat{\Omega}_s, \\ \mathbf{d}^{n+1} = \mathbf{0} & \text{on } \widehat{\Gamma}_{s,b}, \\ P_s(\mathbf{d}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} = -(\mathbf{n} \otimes \mathbf{n}) \left(K_{\perp}^{\text{epi}} \mathbf{d}^{n+1} + C_{\perp}^{\text{epi}} \frac{\mathbf{d}^{n+1} - \mathbf{d}^n}{\Delta t} \right) & \\ \quad - (I - \mathbf{n} \otimes \mathbf{n}) \left(K_{\parallel}^{\text{epi}} \mathbf{d}^{n+1} + C_{\parallel}^{\text{epi}} \frac{\mathbf{d}^{n+1} - \mathbf{d}^n}{\Delta t} \right) & \text{on } \widehat{\Gamma}_s^{\text{epi}}, \\ \sigma_s(\mathbf{d}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} = \sigma_f(\mathbf{u}^{n+1}, p^{n+1}) \mathbf{n} & \text{on } \Sigma^{n+1}. \end{cases} \quad (13)$$

We point out that this problem is non-linear, due to the non-linearity of the constitutive law.

3.2. Explicit-implicit EFSI scheme (E_1FS_∞)

The explicit-implicit (E_1FS_∞) scheme is based on treating explicitly the coupling of electrophysiology, force generation and mechanics, as well as the geometric FSI coupling, while treating the kinematic and dynamic FSI coupling in an implicit way. Given the solution up to time step t^n , in order to compute the solution at t^{n+1} , we repeat steps 1–3 as in the EFS₁ scheme (Section 3.1), replacing steps 4 and 5 with

4. Solve the time discretization of the FSI problem

$$\left\{ \begin{array}{ll} \rho_f \frac{\mathbf{u}^{n+1} - \mathbf{u}^n}{\Delta t} + \rho_f \left((\mathbf{u}^n - \mathbf{u}_{ALE}^{n+1}) \cdot \nabla \right) \mathbf{u}^{n+1} - \nabla \cdot \sigma_f(\mathbf{u}^{n+1}, p^{n+1}) = \mathbf{0} & \text{in } \Omega_f^{n+1}, \\ \nabla \cdot \mathbf{u}^{n+1} = 0 & \text{in } \Omega_f^{n+1}, \\ \mathbf{u}^{n+1} = \mathbf{0} & \text{on } \Gamma_{f,b}^{n+1}, \\ \mathbf{u}^{n+1} = \frac{\mathbf{d}^{n+1} - \mathbf{d}^n}{\Delta t} & \text{on } \Sigma^{n+1}, \\ \sigma_s(\mathbf{d}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} = \sigma_f(\mathbf{u}^{n+1}, p^{n+1}) \mathbf{n} & \text{on } \Sigma^{n+1}, \\ \rho_s \frac{\mathbf{d}^{n+1} - 2\mathbf{d}^n + \mathbf{d}^{n-1}}{\Delta t^2} - \nabla \cdot P_s(\mathbf{d}^{n+1}, \mathbf{s}^{n+1}) = \mathbf{0} & \text{in } \widehat{\Omega}_s, \\ \mathbf{d}^{n+1} = \mathbf{0} & \text{on } \widehat{\Gamma}_{s,b}, \\ P_s(\mathbf{d}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} = -(\mathbf{n} \otimes \mathbf{n}) \left(K_\perp^{\text{epi}} \mathbf{d}^{n+1} + C_\perp^{\text{epi}} \frac{\mathbf{d}^{n+1} - \mathbf{d}^n}{\Delta t} \right) & \\ \quad - (I - \mathbf{n} \otimes \mathbf{n}) \left(K_\parallel^{\text{epi}} \mathbf{d}^{n+1} + C_\parallel^{\text{epi}} \frac{\mathbf{d}^{n+1} - \mathbf{d}^n}{\Delta t} \right) & \text{on } \widehat{\Gamma}_s^{\text{epi}}, \end{array} \right. \quad (14)$$

endowed with suitable boundary conditions on Γ_{AV}^{n+1} and Γ_{MV}^{n+1} . The time-discrete problem (14) is non-linear due to the non-linearity of the solid constitutive law.

We point out that both kinematic and dynamics FSI interface conditions are now treated implicitly. We will refer to this scheme as E_1FS_∞ for short.

3.3. Explicit-hybrid EFSI scheme (E_1FS_2)

A hybrid approach between the EFS₁ and the E_1FS_∞ schemes is obtained by introducing RN [11,12,52] subiterations with parameter α at each time step between fluid and structure problems, and performing 2 of such iterations. The steps 1–3 are the same as in the EFS₁ scheme (Section 3.1). Then, in place of the steps 4 and 5,

4. Setting $\mathbf{u}_0^{n+1} = \mathbf{u}^n$, $p_0^{n+1} = p^n$, $\mathbf{d}_0^{n+1} = \mathbf{d}^n$, iterate for $k = 0, 1$:

(a) Solve the time discretization of the Navier-Stokes equations to compute $\mathbf{u}_{(k+1)}^{n+1}$ and $p_{(k+1)}^{n+1}$ by using structural displacement at previous iteration to prescribe Robin boundary conditions on the fluid-solid interface:

$$\left\{ \begin{array}{ll} \rho_f \frac{\mathbf{u}_{(k+1)}^{n+1} - \mathbf{u}^n}{\Delta t} + \rho_f \left((\mathbf{u}^n - \mathbf{u}_{ALE}^{n+1}) \cdot \nabla \right) \mathbf{u}_{(k+1)}^{n+1} - \nabla \cdot \sigma_f(\mathbf{u}_{(k+1)}^{n+1}, p_{(k+1)}^{n+1}) = \mathbf{0} & \text{in } \Omega_f^{n+1}, \\ \nabla \cdot \mathbf{u}_{(k+1)}^{n+1} = 0 & \text{in } \Omega_f^{n+1}, \\ \mathbf{u}_{(k+1)}^{n+1} = \mathbf{0} & \text{on } \Gamma_{f,b}^{n+1}, \\ \alpha \mathbf{u}_{(k+1)}^{n+1} + \sigma_f(\mathbf{u}_{(k+1)}^{n+1}, p_{(k+1)}^{n+1}) \mathbf{n} = \alpha \frac{\mathbf{d}_{(k)}^{n+1} - \mathbf{d}^{n-1}}{\Delta t} + \sigma_s(\mathbf{d}_{(k)}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} & \text{on } \Sigma^{n+1}; \end{array} \right.$$

(b) Solve the time discretization of the elastodynamics equations to compute $\mathbf{d}_{(k+1)}^{n+1}$, using newly computed fluid velocity and pressure to provide Neumann conditions on the fluid-solid interface:

$$\left\{ \begin{array}{ll} \rho_s \frac{\mathbf{d}_{(k+1)}^{n+1} - 2\mathbf{d}^n + \mathbf{d}^{n-1}}{\Delta t^2} - \nabla \cdot P_s(\mathbf{d}_{(k+1)}^{n+1}, \mathbf{s}^{n+1}) = \mathbf{0} & \text{in } \widehat{\Omega}_s, \\ \mathbf{d}_{(k+1)}^{n+1} = \mathbf{0} & \text{on } \widehat{\Gamma}_{s,b}, \\ P_s(\mathbf{d}_{(k+1)}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} = -(\mathbf{n} \otimes \mathbf{n}) \left(K_{\perp}^{\text{epi}} \mathbf{d}_{(k+1)}^{n+1} + C_{\perp}^{\text{epi}} \frac{\mathbf{d}_{(k+1)}^{n+1} - \mathbf{d}^n}{\Delta t} \right) \\ \quad - (I - \mathbf{n} \otimes \mathbf{n}) \left(K_{\parallel}^{\text{epi}} \mathbf{d}_{(k+1)}^{n+1} + C_{\parallel}^{\text{epi}} \frac{\mathbf{d}_{(k+1)}^{n+1} - \mathbf{d}^n}{\Delta t} \right) & \text{on } \widehat{\Gamma}_s^{\text{epi}}, \\ \sigma_s(\mathbf{d}_{(k+1)}^{n+1}, \mathbf{s}^{n+1}) \mathbf{n} = \sigma_f(\mathbf{u}_{(k+1)}^{n+1}, p_{(k+1)}^{n+1}) \mathbf{n} & \text{on } \Sigma^{n+1}. \end{array} \right.$$

Then, set $\mathbf{u}^{n+1} = \mathbf{u}_{(2)}^{n+1}$, $p^{n+1} = p_{(2)}^{n+1}$ and $\mathbf{d}^{n+1} = \mathbf{d}_{(2)}^{n+1}$.

We refer to this scheme as *explicit-hybrid*, due to the fact that the iterative algorithm is arbitrarily truncated at 2 iterations, instead of checking for convergence, resulting in a hybrid approach between the explicit and implicit discretizations.

3.4. Space discretization, non-linear and linear solvers

The discretized-in-time problems introduced above are discretized using finite elements [67,94]. Depending on the test case and on the subproblem, we consider tetrahedral or hexahedral elements, and either linear or quadratic finite elements. Independently of the scheme presented in the above sections, fluid and solid meshes are conforming at the interface Σ , and we stabilize the discretized Navier-Stokes equations using the SUPG-PSPG stabilization [117]. Moreover, the ionic model (8) and force generation model (10) are solved independently at each vertex of the computational mesh. For the ionic model, in particular, we adopt the *ionic current interpolation* (ICI) approach [76,89]. The linear systems arising from the discretization of the monodomain equation (9) and of the fluid domain displacement problem (11) are solved by means of the conjugate gradient (CG) method [94,105], with an algebraic multigrid (AMG) preconditioner [131].

Specifically to the EFS₁ and E₁FS₂ schemes, the non-linear system arising from the solid mechanics discretization (13) is first linearized by means of Newton’s method, and the resulting linear system is solved with GMRES [105], preconditioned using AMG. The block linear system arising from the discretization of Navier-Stokes equations (12) is solved with GMRES with the SIMPLE preconditioner [38], which in turn falls back onto AMG for the approximation of velocity and pressure diagonal blocks.

Instead, referring to the E₁FS_∞ scheme, for the solution of the FSI problem (14), we use a monolithic solver as presented in [20], in which both fluid and solid equations are assembled in a single non-linear system. The latter is linearized with Newton’s method and then solved with GMRES, using a block-lower triangular preconditioner that falls back onto SIMPLE and AMG for the fluid and structure submatrices.

4. Numerical results

Numerical methods were implemented in `lifex` [1–3,79], a C++ high-performance computing library tailored at cardiac applications and based on the finite element core `deal.II` [6,7,35]. In the following sections we report the results of numerical simulations using all the schemes presented in Section 3, considering an idealized left ventricle described as a prolate ellipsoid (Fig. 1a) and a realistic left ventricle model [137]. We report in Table 2 the discretization parameters of the meshes under consideration. We compare the solutions obtained with the different schemes as well as their computational efficiency.

The values used for model parameters are reported in Appendix B. Unless otherwise specified, simulations were run in parallel on 20 cores with CPUs Xeon E5-2640v4@2.4 GHz, using the computational resources available at MOX, Mathematics Department, Politecnico di Milano.

4.1. Solution indicators

One of the aims of the comparison among the schemes is to assess the loss of mass they feature, in particular during isovolumetric phases. To quantify this effect, we introduce two indices, the *isovolumetric loss indices* (ILI), representing the relative variation of blood volume during isovolumetric phases:

$$ILI_C = \left| \frac{V_{C,i} - V_{C,f}}{\max\{V_{C,i}, V_{C,f}\}} \right| \quad ILI_R = \left| \frac{V_{R,i} - V_{R,f}}{\max\{V_{R,i}, V_{R,f}\}} \right|,$$

wherein $V_{C,i}$ and $V_{C,f}$ are the volumes at the beginning and end of isovolumetric contraction, and $V_{R,i}$ and $V_{R,f}$ are the volumes at the beginning and end of isovolumetric relaxation. Optimal values for these two indices are $ILI_C = ILI_R = 0$, while positive values indicate that blood mass is not exactly preserved during the isovolumetric phases.

Table 2

Type of elements (hexahedra or tetrahedra), number of elements, number of nodes and average element diameter h for the meshes considered on the prolate ellipsoid geometry (\mathcal{M}_1 , \mathcal{M}_1^{EP} , \mathcal{M}_2 and \mathcal{M}_3) and for the realistic ventricle mesh (\mathcal{M}_R), for both the fluid and the structure domain.

Mesh	Type	Fluid			Structure		
		# elem.	# nodes	h [mm]	# elem.	# nodes	h [mm]
\mathcal{M}_1	hex	4684	5927	6.1	6612	8789	5.2
\mathcal{M}_1^{EP}	hex	-	-	-	52 896	60 459	2.6
\mathcal{M}_2	hex	13 780	16 669	4.0	22 396	28 117	3.3
\mathcal{M}_3	hex	32 628	38 429	3.0	51 364	62 589	2.5
\mathcal{M}_R	tet	140 644	157 369	1.8	73 860	89 314	2.2

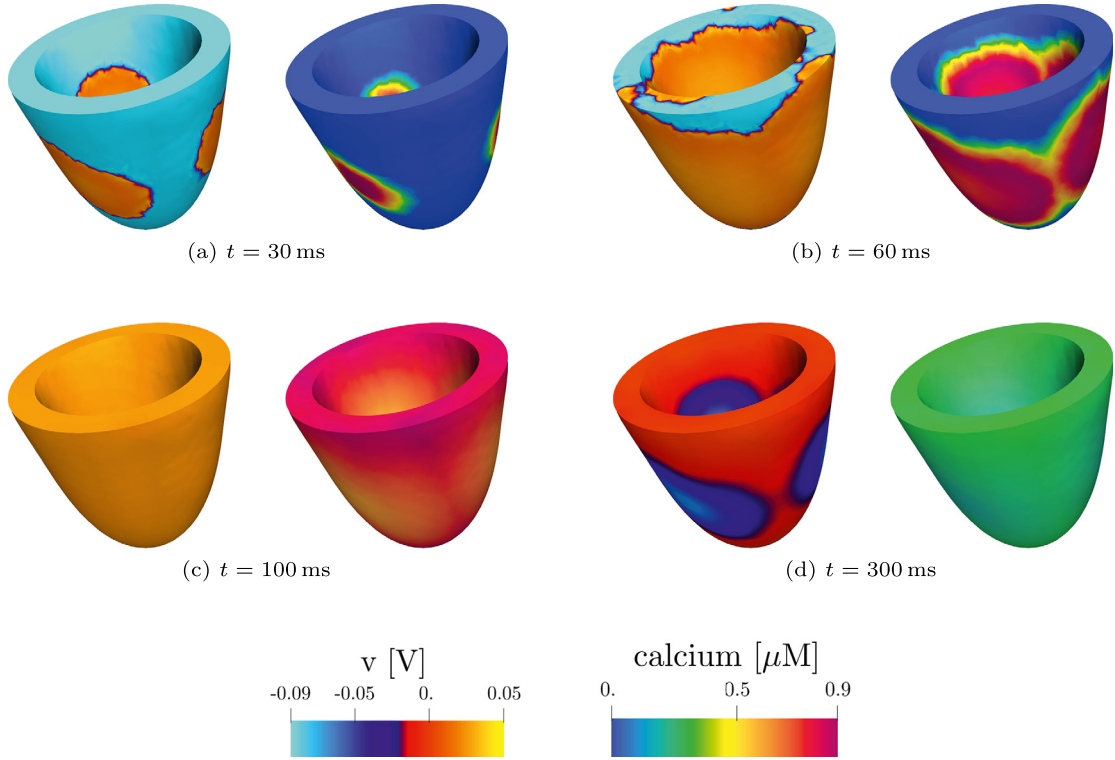


Fig. 2. Test A. Transmembrane potential v (left) and intracellular calcium concentration $[Ca^{2+}]_i$ (right) at several instants during the simulation, computed using the EFS₁ with $\Delta t = 0.2$ ms.

We also take into account the *ejection fraction* EF and *peak systolic pressure* p_{\max} , defined as

$$EF = \frac{EDV - ESV}{EDV} \quad p_{\max} = \max_{t \in (0, T)} \bar{p}(t),$$

where $\bar{p}(t)$ is the ventricular average pressure at time t , and EDV and ESV are the end-diastolic and end-systolic volumes, i.e.

$$EDV = \max_{t \in (0, T)} V(t) \quad ESV = \min_{t \in (0, T)} V(t),$$

where $V(t)$ is the ventricular volume. Both EF and p_{\max} have significant clinical relevance [73,75,87].

4.2. Test A: on the stability of the loosely coupled scheme

The explicit treatment of FSI coupling with RN interface conditions was shown to be conditionally stable [57] in idealized settings. More precisely, there exists $\delta > 0$, possibly depending on the domain size, the material properties, the mesh size

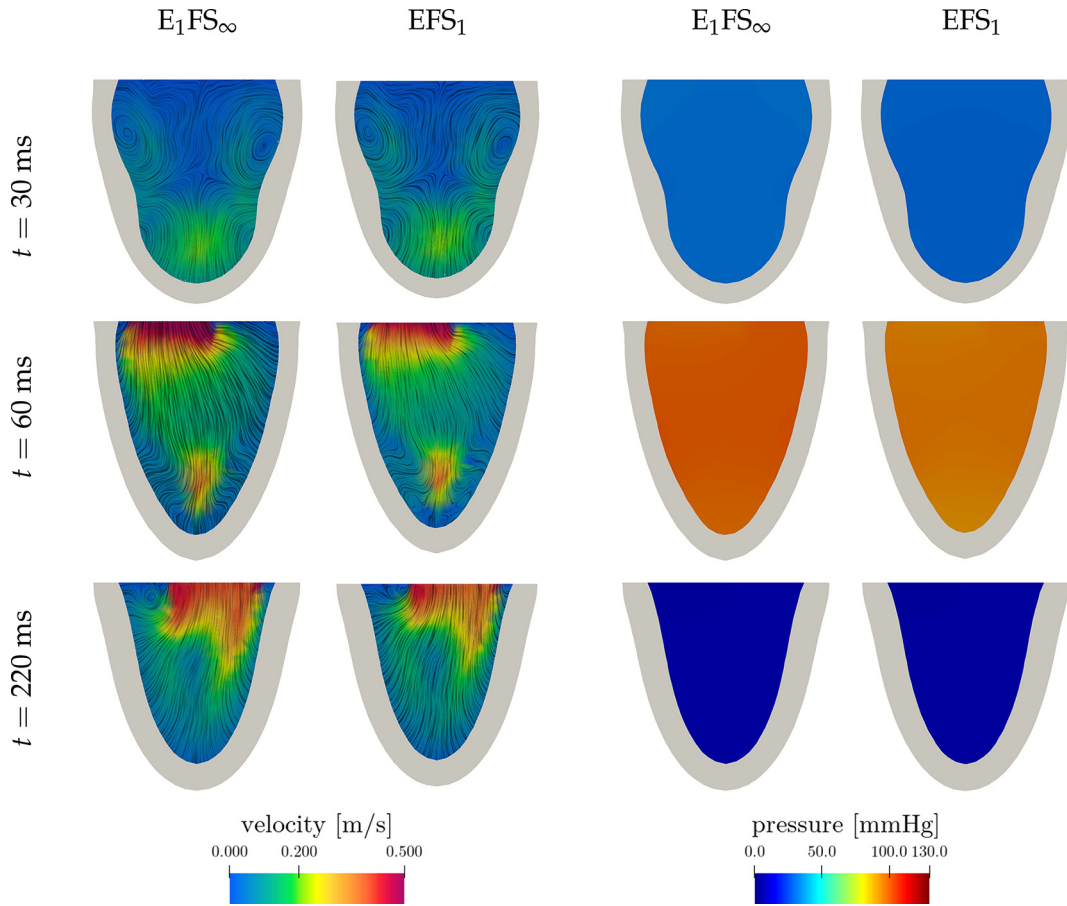


Fig. 3. Test A. Fluid velocity magnitude $|\mathbf{u}|$ (left) and pressure p (right) at three time instants computed with the E_1FS_∞ and EFS_1 schemes. The velocity is overlaid with a surface line integral convolution rendering of the velocity field [28]. From top to bottom, the snapshots correspond are taken during the isovolumetric contraction, ejection, and filling phases, respectively.

h and α , such that the scheme is stable if $0 < \Delta t < \delta$. Precisely, as shown in [57], δ satisfies the conditions $\delta < C_1 h$ and $\delta < C_2 \alpha^{-1}$, with C_1 and C_2 constants depending on the domain and material properties of the problem.

In order to verify numerically whether the regime and the discretization settings typical of cardiac modeling fall within the stability range, we perform tests on the idealized left ventricular geometry depicted in Fig. 1a over a whole heartbeat, including all four phases. We consider the mesh \mathcal{M}_1 (see Table 2), composed of hexahedral elements. The electrophysiology problem (9) is solved on a finer mesh \mathcal{M}_1^{EP} , nested into \mathcal{M}_1 and with half its mesh size, to better capture the sharp propagating activation front [100,106], and displacement and calcium are interpolated between the two meshes. For all subproblems, we consider trilinear finite elements. We set $\Delta t = 0.2$ ms, and choose $\alpha = 5000$ kg/(m² · s).

A guideline for the choice of α in relation to the problem parameters (both physical and numerical) can be found in [55–57], wherein the optimized Schwarz method is applied in a geometrically idealized setting with a linear constitutive law. Since the material law for the present tests is non-linear and anisotropic, the results obtained in [55–57] only served as an initial indication, and we manually fine-tuned the value of α (see also Section 4.3.1 for a discussion of the effect of α on the accuracy). A more formal investigation of the models used in this work will be the subject of future works.

We report in Figs. 2 and 3 the solution at several time instants, computed using the EFS_1 scheme. In the latter figure, the solution obtained with the E_1FS_∞ scheme is also reported. The corresponding ventricular volume and pressure over time can be found in Fig. 4a. We can appreciate how in this setting the EFS_1 scheme, despite being explicit, yields results that are stable in time and in qualitative agreement with those obtained with the E_1FS_∞ scheme.

In agreement with [56,57], we found the stability of the EFS_1 scheme to depend on the choice of α . Indeed, as $\alpha \rightarrow \infty$, interface conditions (7) tend to Dirichlet-Neumann (DN) interface conditions (6), which are known to lead to unstable loosely coupled schemes in the hemodynamic regime [29]. As a consequence, we can expect the EFS_1 method to become unstable for values of α not small enough. Our numerical experiments indicate that, in this setting, the EFS_1 scheme is stable for all $\alpha < 6750$ kg/(m² · s), in qualitative accordance with [56].

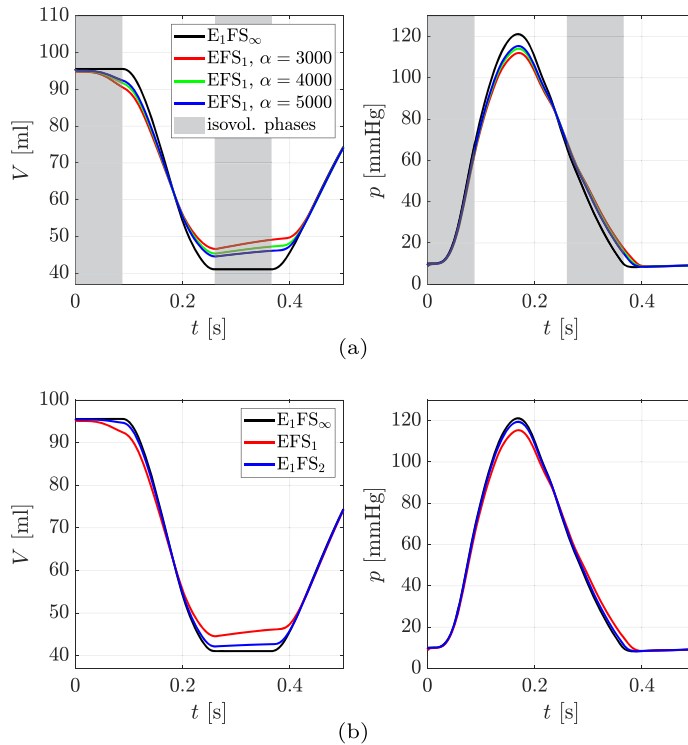


Fig. 4. (a) Test B1. Time evolution of ventricular volume (left) and average pressure (right) with the E_1FS_∞ and EFS_1 schemes, with different values of the Robin coefficient α . Gray areas identify the isovolumetric phases. (b) Test B3. Ventricular volume (left) and average pressure (right) for the E_1FS_∞ , E_1FS_2 and EFS_1 schemes. For the last two schemes we use $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

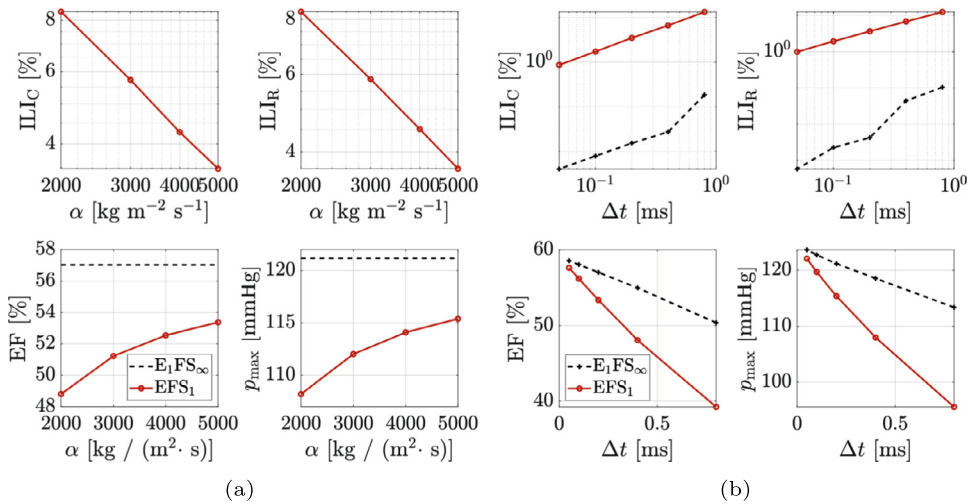


Fig. 5. (a) Test B1. Isovolumetric loss indices, ejection fraction, and peak systolic pressure as a function of the Robin coefficient α . Where present, the dashed lines represent the values obtained with the explicit-implicit scheme. (b) Test B2. Isovolumetric loss indices, ejection fraction, and peak systolic pressure as a function of Δt , for the E_1FS_∞ (black) and EFS_1 (red) schemes, with $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

4.3. Test B: on the accuracy of the loosely coupled scheme

In the following sections, we consider the same setting as in Test A (Section 4.2), and assess the accuracy of the EFS_1 scheme, depending on the choice of the Robin coefficient α and of the time discretization step Δt .

4.3.1. Test B1: on the influence of the Robin coefficient α on the accuracy

We start by comparing the results of the EFS_1 scheme against those of the E_1FS_∞ scheme, varying the Robin coefficient α in the range of stability experienced in Test A (i.e. $\alpha < 6750 \text{ kg}/(\text{m}^2 \cdot \text{s})$). The choice of the parameter α influences

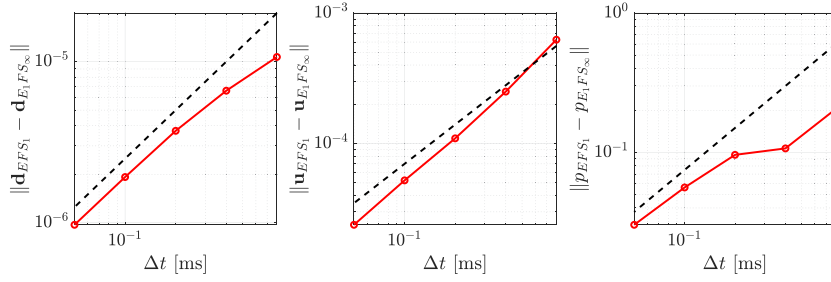


Fig. 6. Norm of the difference between the solutions (from left to right, displacement, velocity and pressure) of the EFS₁ and E₁FS_∞ schemes, with varying Δt . The dashed black lines are parallel to $f(\Delta t) = \Delta t$, and are used as a reference for the convergence order. The differences are computed at the final simulation time $T = 0.5$ s.

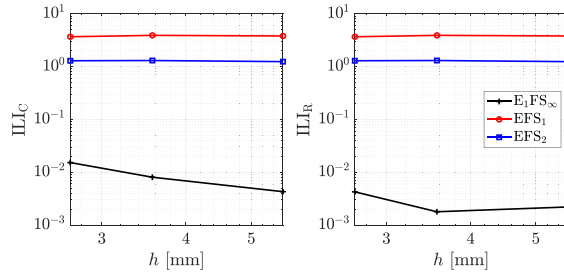


Fig. 7. Isovolumetric loss indices for the E₁FS_∞, EFS₁ and E₁FS₂ methods, varying the mesh size h . All the tests were run using $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$ and $\Delta t = 0.2$ ms.

the accuracy of the method. Indeed, as $\alpha \rightarrow 0$, interface conditions (7) reduce to two Neumann-type conditions, and no kinematic coupling is present anymore, hindering the accuracy of the scheme.

In Fig. 4a we report the time evolution of ventricular volumes and pressures for the E₁FS_∞ scheme and for different values of α in the EFS₁ scheme. From these results, we can observe a general qualitative agreement between EFS₁ and E₁FS_∞ solutions. However, unlike the latter, the EFS₁ solutions feature a loss of mass and, consequently, volume variations during the isovolumetric phase. This leads to a slower ejection and filling, as well as a lower peak pressure. This behavior increases for decreasing values of α .

Similar conclusions can be drawn by looking at the plots in Fig. 5a, where the value of the considered indicators obtained by the EFS₁ scheme has been plotted against the Robin coefficient α . Although the mismatch reduces as α increases, even with the highest value of α the two results present differences of 6.3% in ejection fraction and 4.7% in peak systolic pressure.

4.3.2. Test B2: on the influence of Δt and the mesh size on the accuracy

We expect the mismatch between the E₁FS_∞ and EFS₁ schemes to reduce as Δt is reduced. To this end, considering $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$, we perform several simulations reducing the time step of both the schemes. The resulting indicators are reported in Fig. 5b. As expected, we observe that as $\Delta t \rightarrow 0$ there is increasing agreement between the solutions computed by the two schemes in terms of EF and p_{\max} . For both schemes the isovolumetric loss indices ILL_C and ILL_R tend to zero as $\Delta t \rightarrow 0$, with similar rates. However, the ones obtained with the E₁FS_∞ scheme are in any case smaller than those of the EFS₁ one.

We report in Fig. 6 the norm of the difference between the solutions computed with the EFS₁ and E₁FS_∞ schemes, with varying Δt , evaluated at the final time $T = 0.5$ s. We observe that the mismatch tends to zero as $\Delta t \rightarrow 0$, with order 1. Therefore, we conclude that the segregation of the fluid and solid solver introduces a splitting error which is at most of order 1, the same order of the time discretization used for the individual subproblems. We remark that higher-order time discretization schemes may require to enhance the EFS₁ scheme to preserve the time convergence order.

Furthermore, we consider three differently refined meshes (see Table 2) and assess the corresponding accuracy by comparing the ILL indicators of the E₁FS_∞ and EFS₁ schemes as the mesh size h varies. For all the tests, we set $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$ and $\Delta t = 0.2$ ms. The results are reported in Fig. 7: we observe only minor variations with h in the ILL indices. Most importantly, the relative ordering of the ILL indices is independent of h , indicating that our considerations are valid independently of the mesh size.

The results presented in this section also highlight how the chosen value of α remains effective under significant variations of both Δt and h .

Table 3

Test B3. Isovolumetric loss indices, ejection fraction and peak systolic pressure for three simulations, using the E_1FS_∞ , EFS_1 and E_1FS_2 schemes. For the last two schemes, we set $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

Scheme	ILI _C [%]	ILI _R [%]	EF [%]	p_{\max} [mmHg]
E_1FS_∞	0.02	0.00	57.0	121.2
EFS_1	3.48	3.66	53.4	115.4
E_1FS_2	0.96	1.29	55.9	119.5

Table 4

Test B4. Ejection fraction and peak systolic pressure in the ejection phase test, for the E_1FS_∞ and EFS_1 schemes. For comparison, we report the same quantities computed in the full heartbeat test (Test A) with the EFS_1 scheme. In both cases, we set $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

Scheme	EF [%]	p_{\max} [mmHg]
E_1FS_∞	57.0	121.2
EFS_1	54.4	119.6
EFS_1 (full heartbeat)	53.4	115.4

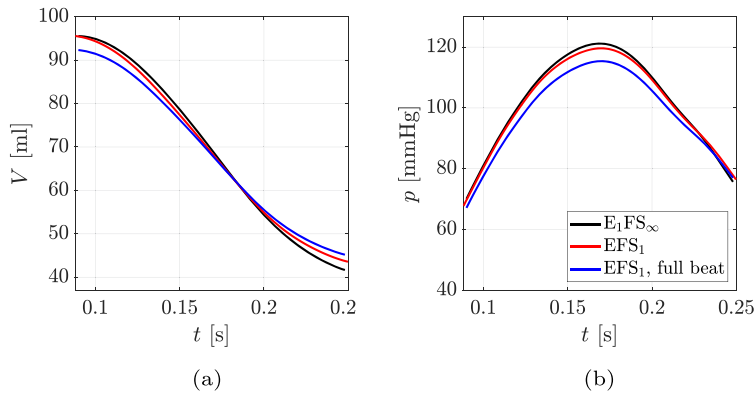


Fig. 8. Test B4. Ventricular volume (a) and average pressure (b) in the ejection phase test, computed with the E_1FS_∞ and EFS_1 schemes. For comparison, we report in blue the volume and pressure corresponding to the full heartbeat test (Test B1) with the EFS_1 scheme. For loosely coupled schemes we set $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

4.3.3. Test B3: on the influence of multiple Robin-Neumann subiterations on the accuracy

We run a simulation using the scheme E_1FS_2 , with $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$ and $\Delta t = 0.2 \text{ ms}$, and compare the results against the corresponding ones obtained with the E_1FS_∞ and EFS_1 schemes in terms of the evolutions of ventricular volume and pressure. The results obtained are reported in Fig. 4b, while in Table 3 we report the values of the ILI, EF and p_{\max} indicators for the three schemes. We observe that doing two RN iterations can significantly improve the agreement with the explicit-implicit scheme. In particular, the isovolumetric phases are captured more accurately, as indicated by the ILI indices.

Furthermore, in Fig. 7, we compare the ILI indices for the E_1FS_2 scheme with those of the E_1FS_∞ and EFS_1 schemes with varying mesh size h , showing how the previous considerations hold independently of the mesh refinement.

4.3.4. Test B4: on the accuracy during the ejection phase

Previous sections show that the EFS_1 scheme introduces an error in capturing volume conservation during isovolumetric phases. This has an impact on the evolution of pressure during those phases, that in turn influences the solution during ejection and filling.

To understand to what extent the mismatch between E_1FS_∞ and EFS_1 schemes is determined by isovolumetric phases, we simulate only the ejection phase, by providing as initial condition the solution of the E_1FS_∞ scheme from test A (Section 4.2) at time $t_0 = 88 \text{ ms}$ (corresponding to the end of isovolumetric contraction). We compare EF and p_{\max} obtained with the E_1FS_∞ and EFS_1 schemes. Results for these indicators are reported in Table 4. We observe that, while both ejection fraction and peak pressure are smaller in the EFS_1 case than they are in the E_1FS_∞ case, the reduction is less significant than what is observed in a full heartbeat explicit simulation. Similar conclusions are drawn by comparing the pressure and volume over time, as reported in Fig. 8: in the ejection-only simulation, there is better agreement between the E_1FS_∞ and the EFS_1 schemes.

Overall, this result indicates that the mismatch between the two schemes could be particularly relevant during the isovolumetric phases. Therefore, it can be of interest to explore adaptive methods that adjust e.g. the number of RN subiterations depending on the simulated heartbeat phase.

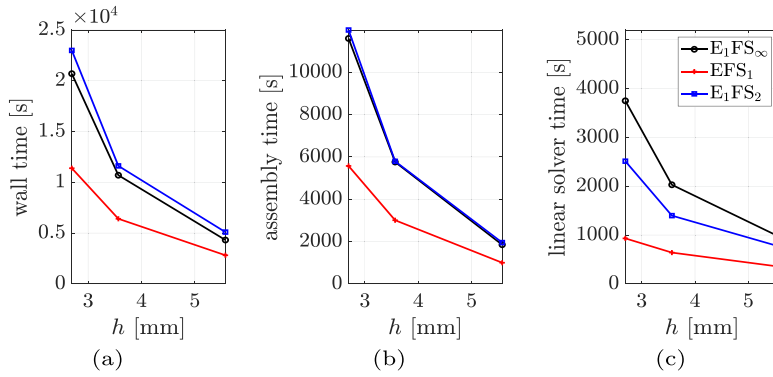


Fig. 9. Test C. Total wall time (a), wall time spent to assemble the fluid and structure systems (b) and to solve them (c) against average mesh size h of the three considered meshes (Table 2). E_1FS_{∞} , EFS_1 and E_1FS_2 schemes. For the last two schemes, we set $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

4.4. Test C: computational efficiency

The chief advantage of a loosely coupled scheme is its computational efficiency if compared to a method where the couplings are treated implicitly. To verify this, we perform numerical simulations of the E_1FS_{∞} , EFS_1 and E_1FS_2 schemes with three differently refined meshes, detailed in Table 2. We compare the total wall time, the portion of wall time devoted to the assembly of fluid and structure systems, as well as the wall time spent in the solution of the fluid, structure or FSI systems. We do not consider in detail computational times associated to electrophysiology, force generation and fluid domain displacement, since the considered schemes are identical in those steps. These simulations ran in parallel using 44 cores with Intel Xeon Platinum 8160@2.1 GHz processors.

Results are reported in Fig. 9. From these results, we can appreciate how the EFS_1 scheme leads to a very significant reduction in computational time with respect to the E_1FS_{∞} one. This reduction becomes more significant as the mesh is refined: the total wall time for the simulation on the finest mesh \mathcal{M}_3 using the EFS_1 scheme is approximately 45 % less than the corresponding simulation using the E_1FS_{∞} scheme. In particular, the cost associated to both the assembly and the solution of the linear systems for the FSI problem is much smaller in the EFS_1 scheme than it is in the E_1FS_{∞} . Overall, the EFS_1 scheme allows for a significant saving in computational time with respect to the E_1FS_{∞} one.

Conversely, the E_1FS_2 requires a computational time similar to that of the E_1FS_{∞} scheme. While the two require almost identical computational times in the assembly phase, the E_1FS_2 scheme spends less time than the E_1FS_{∞} one during the linear solver phase, consistently with the fact that the former entails solving smaller linear systems than the latter. This advantage might become more significant when increasing the number of parallel cores, due to the generally less-than-ideal scalability properties of linear solvers and preconditioners. A more in-depth performance analysis of the E_1FS_2 scheme will be the subject of future studies.

4.5. Test D: the case of a realistic human ventricle

We present a test case in a more realistic setting to showcase the effectiveness of the proposed scheme. We consider the left ventricle from the heart model provided by Zygote Media Group [137], represented in Fig. 10. We processed the geometry using the meshing algorithms presented in [47] using the software VMTK [128].

The model includes ventricular inflow and outflow tracts. Those portions are not formed of muscular tissue, as the bulk of the ventricle is [73]. To account for this, we introduce two subdomains into $\hat{\Omega}_s$, denoted by $\hat{\Omega}_{LV}$ and $\hat{\Omega}_{ring}$ (see Fig. 10c), representing the left ventricle and the valvular rings, respectively, and employ a neo-Hookean constitutive law in $\hat{\Omega}_{ring}$ (while keeping the Guccione constitutive law in $\hat{\Omega}_{LV}$). We also set $T_{act,max} = 0$ in $\hat{\Omega}_{ring}$.

For the discretization, we use tetrahedral elements for fluid and solid domains. The mechanics and fluid dynamics equations are discretized with linear finite elements. To deal with the higher accuracy requirements of electrophysiology, we use quadratic finite elements to discretize Equation (9). This is an alternative approach to the one used in previous sections, based on nested mesh refinement. We set $\Delta t = 0.2 \text{ ms}$. The test ran on 48 cores from the CINECA GALILEO100 supercomputer.¹

We report in Fig. 11 some snapshots of the electrophysiology solution for this test case, while in Fig. 12 we report a comparison of domain deformation and fluid dynamics variables with the E_1FS_{∞} solution. From these results we observe the stability of the proposed loosely coupled scheme and the qualitative agreement of the solution with the E_1FS_{∞} one.

In Fig. 13 we show the ventricular volume and pressure over time for the two schemes, whereas in Table 5 we report the computed indicators. We observe again that the EFS_1 scheme introduces an error in capturing the isovolumetric phases,

¹ Technical specifications: <https://wiki.u-gov.it/confluence/display/SCAIUS/UG3.3%3A+GALILEO100+UserGuide>.

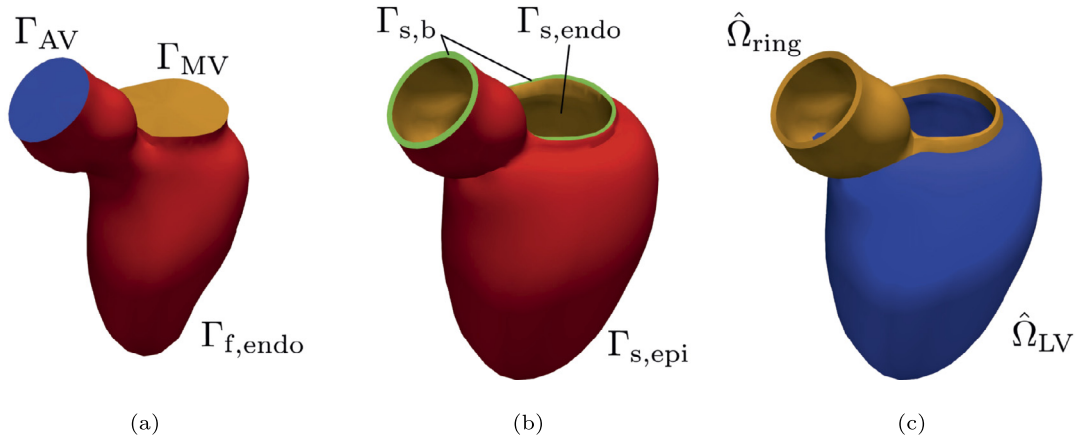


Fig. 10. Test D. Computational domain Ω_f (a) and Ω_s (b, c) of the realistic ventricle. Colors and labels denote the different portions of the boundary in (a) and (b), and denote the two subdomains in (c).

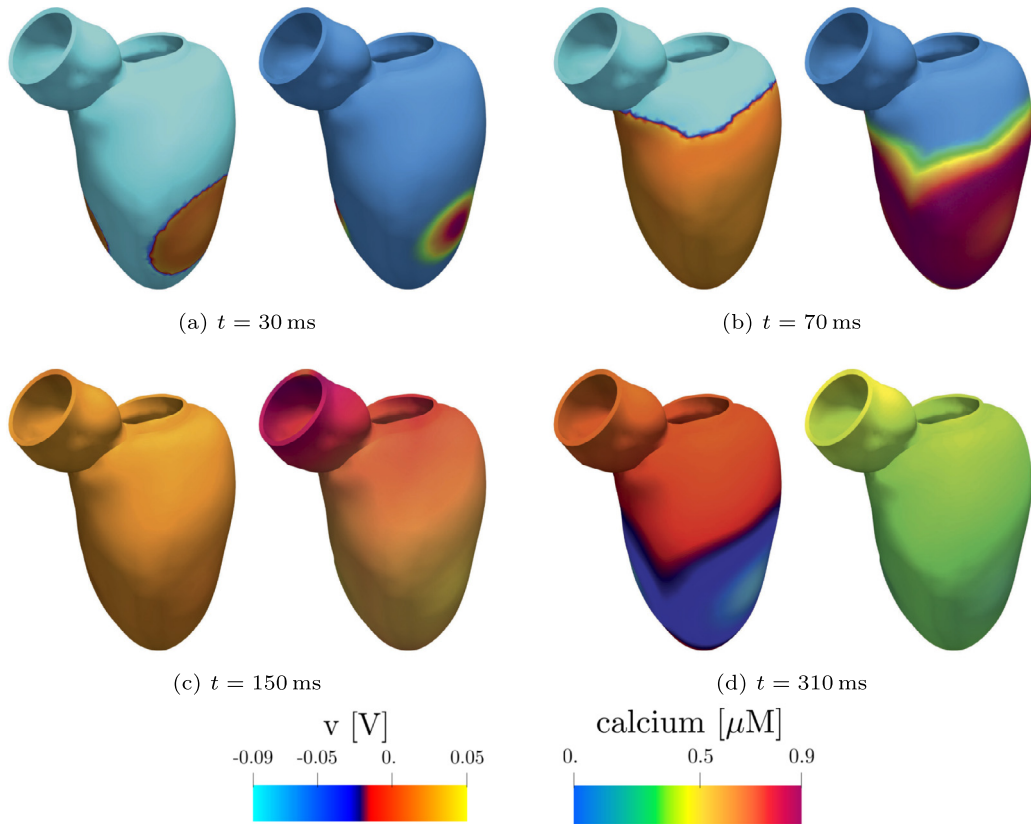


Fig. 11. Test D. Transmembrane potential v (left) and intracellular calcium concentration $[Ca^{2+}]_i$ (right) at several instants during the simulation of the realistic ventricle, computed using the EFS₁ scheme.

Table 5
 Test D. Isovolumetric loss indicators, ejection fraction and peak systolic pressure for the realistic test case, using the E₁FS_∞ and EFS₁ schemes, with $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

Scheme	ILL _C [%]	ILL _R [%]	EF [%]	p_{\max} [mmHg]
E ₁ FS _∞	0.04	0.00	55.8	148.9
EFS ₁	2.76	3.60	55.5	136.2

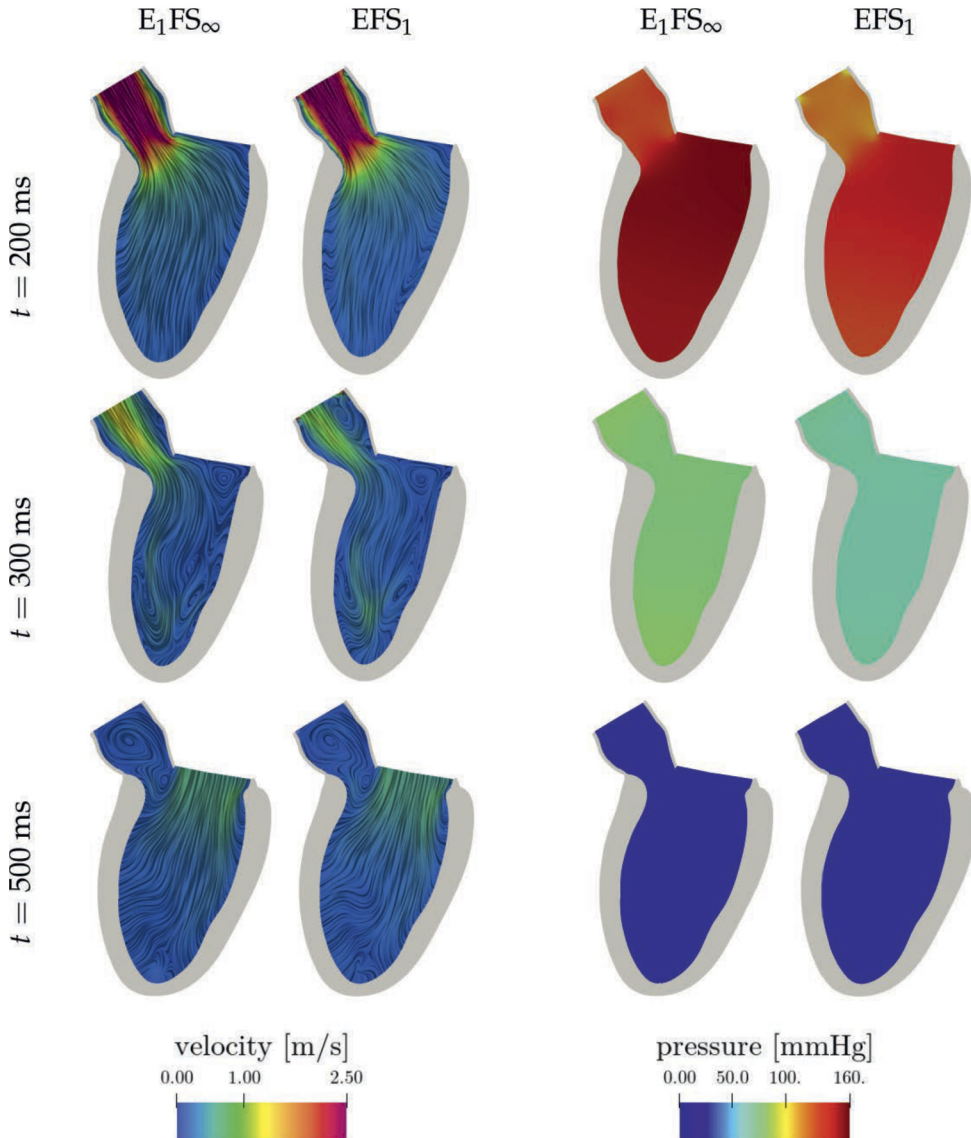


Fig. 12. Test D. Fluid velocity magnitude $|\mathbf{u}|$ (left) and pressure p (right) at three instants during the simulation of the realistic ventricle, computed using the E_1FS_∞ and EFS_1 schemes. The velocity magnitude is overlaid with a surface line integral convolution rendering of the flow field [28].

and this leads to a mismatch with the E_1FS_∞ scheme in terms of peak systolic pressure, while the ejection fraction is well captured.

5. Conclusions

We propose a loosely coupled scheme (EFS_1) in the context of cardiac simulations, for the coupling of electrophysiology, active and passive tissue mechanics, and hemodynamics, where the subproblems are solved only once per time step and a Robin interface condition is considered for the fluid subproblem. We compare its performance with two other schemes where electrophysiology is treated explicitly, one with strong FSI coupling (E_1FS_∞) and one where 2 FSI iterations are performed (E_1FS_2). The main findings of our work (valid for both an idealized and a realistic geometry) are:

1. the EFS_1 scheme is stable in the physiological regime, provided that the Robin interface parameter α is small enough;
2. EFS_1 introduces a further error, besides the time discretization, due to the lack of synchrony between the FSI interface conditions. This error is mostly relevant during the isovolumetric phases, although it vanishes for decreasing values of the time step Δt ;
3. EFS_1 is about 45% faster than E_1FS_∞ , with the computational saving becoming more relevant as the mesh is refined.

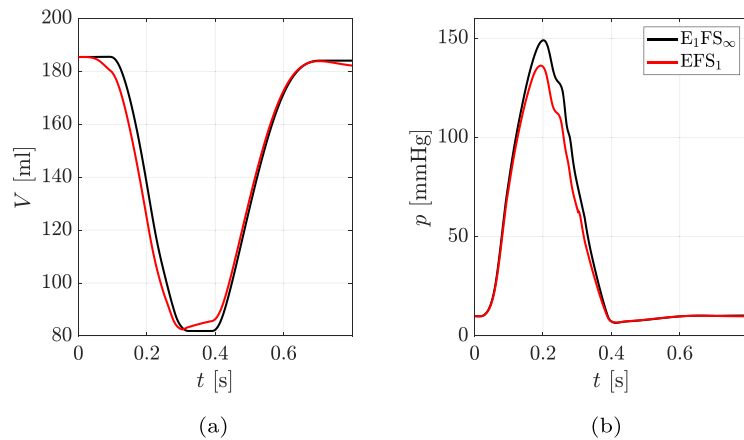


Fig. 13. Test D. Ventricular volume (a) and average pressure (b) in the realistic test for the E_1FS_∞ and EFS_1 schemes, with $\alpha = 5000 \text{ kg}/(\text{m}^2 \cdot \text{s})$.

In conclusion, we propose the EFS_1 scheme as an effective algorithm for the solution of the cardiac EFSI problem, in particular when one is focused on the ejection or filling phases or when a modular approach (i.e. the use of separate codes for the subproblems) is needed. In the latter case, we also propose the use of the E_1FS_2 scheme as a competitive approach for the isovolumetric phases, i.e. when one is interested in the whole heartbeat. A more in-depth analysis of the E_1FS_2 scheme, and the development of a scheme that adaptively switches between the EFS_1 and E_1FS_2 schemes during the heartbeat, are the subject of ongoing studies. While we have shown that the proposed loosely coupled scheme can achieve stability and efficiency in both idealized and realistic settings, further investigations are in order to determine optimal values for the Robin coefficient α when realistic geometries and constitutive laws are considered.

The computational framework for EFSI simulations discussed in this paper provides an efficient, flexible and modular platform for combining methods for the solution of each of the subproblems involved. The modularity, in particular, was demonstrated by considering different approaches to the solution of the FSI subproblem. Future studies will take into consideration alternative loosely-coupled strategies for FSI, aiming at a higher order of accuracy and possibly improved stability properties.

CRedit authorship contribution statement

Michele Bucelli: Conceptualization, methodology, software, numerical simulation, writing - original draft. **Martin Geraint Gabriel:** conceptualization, methodology, numerical simulation, writing - review and editing. **Alfio Quarteroni:** conceptualization, supervision, funding acquisition, writing - review and editing. **Giacomo Gigante:** conceptualization, methodology, formal analysis, writing - review and editing. **Christian Vergara:** conceptualization, methodology, supervision, formal analysis, writing - review and editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Solid mechanics constitutive laws

Given the solid displacement \mathbf{d} and the associated deformation gradient $F = I + \nabla \mathbf{d}$, the strain energy function associated to the Guccione constitutive law is computed as [61,120]

$$\mathcal{W}_G(\mathbf{d}) = \frac{c_G}{2} (\exp(Q) - 1) + \frac{\kappa_G}{2} (J - 1) \log(J),$$

where

$$Q = \sum_{i,j \in \{f,s,n\}} a_{i,j} (E\mathbf{j} \cdot \mathbf{i})^2,$$

$$E = \frac{1}{2} (F^T F - I),$$

$$J = \det F.$$

In the above equations, c_G , κ_G and $a_{i,j}$ are positive parameters.

We consider for Test C (Section 4.5) a neo-Hookean material, whose strain energy function is defined as [86]

$$\mathcal{W}_{NH}(\mathbf{d}) = \frac{\mu_{NH}}{2} \left(J^{-\frac{2}{3}} F : F - 3 \right) + \frac{\kappa_{NH}}{4} \left((J - 1)^2 + \log^2(J) \right).$$

Coefficients μ_{NH} and κ_{NH} are positive parameters.

Appendix B. Model parameters

Table B.6 reports value of physical parameters used in our model for the prolate ellipsoid test cases (Tests A and B). The parameters used for the realistic ventricle (Test C) are reported in Table B.7. For brevity, we only report those parameters whose values are different from the corresponding ones in Tests A and B. For all the test cases, the electrical conductivities were tuned so that, with the mesh resolution considered, the conduction velocities are equal to 0.6 m/s, 0.4 m/s and 0.2 m/s along fibers, sheets and cross-fibers, respectively [10,34,45,91], so that the activation times are consistent with physiology.

Table B.6
Model parameters used in the prolate ellipsoid test cases (Tests A, B and C).

	Parameter	Value	Unit
Electroph.	σ_m^f	1.68	m ² /s
	σ_m^s	0.769	m ² /s
	σ_m^n	0.248	m ² /s
Force gen.	$T_{act,max}$	500	kPa
Mechanics	ρ_s	1	g/cm ³
	K_{\perp}^{epi}	10	kPa/m
	K_{\parallel}^{epi}	20	kPa/m
	C_{\perp}^{epi}	20	kPa·s/m
	C_{\parallel}^{epi}	2	kPa·s/m
Guccione	c_G	0.88	kPa
	a_{ff}	8	
	a_{ss}	6	
	a_{nn}	3	
	a_{fs}	12	
	a_{fn}	3	
	a_{sn}	3	
	κ_G	50	kPa
Fluid	ρ_f	1.06	g/cm ³
	μ	3.5	Pa·s
	p_{MV}^0	1333	Pa
	p_{AV}^0	9000	Pa
	R_{AV}	1.3	kg/(s·m ⁴)

Table B.7

Test D. Model parameters used in the realistic ventricle test case. For brevity, we only report parameters whose values are different from the corresponding ones in Tests A, B and C. The latter can be found in Table B.6.

	Parameter	Value	Unit
Electroph.	σ_m^f	2	m^2/s
	σ_m^s	1.05	m^2/s
	σ_m^h	0.55	m^2/s
Mechanics	K_{\perp}^{epi}	200	kPa/m
	$K_{\parallel}^{\text{epi}}$	20	kPa/m
	C_{\perp}^{epi}	20	kPa-s/m
	$C_{\parallel}^{\text{epi}}$	2	kPa-s/m
Neo-Hooke	μ_{NH}	5000	kPa
	κ_{NH}	5000	kPa
Fluid	R_{AV}	1	$\text{kg}/(\text{s}\cdot\text{m}^4)$

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