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Executive Summary of the Thesis

Optimization study of cardiac resynchronization therapy by means of a calibrated electro-mechanics computational model

Laurea Magistrale in Biomedical Engineering - Ingegneria Biomedica

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1. Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for heart failure patients, that aims at restoring the correct pumping action of the heart [1]. In particular, CRT systems are composed by three elements: the pulse generator, that sends electrical stimuli to the ventricles, the right ventricular lead, placed at the apex of the right ventricle (RV), and the left ventricular lead, positioned through the epicardial coronary vein (ECV) on the epicardium of the left ventricle (LV). CRT is mostly indicated in patients with left bundle branch block, a conduction disorder that leads to an impaired contraction. By sending electrical stimuli to the ventricles, CRT allows to resynchronize the heart contraction: acutely, the therapy instantly increases the cardiac output, while in some months CRT induces long-term effects, in a process called reverse remodeling. The latter changes the heart structure, improving both systolic and diastolic functions. Among patients selected for CRT, 30% do not respond to the therapy [1]: reasons besides CRT failure are still unknown and under investigation.
In this context, this work aims at investigating how CRT outcomes could be improved, by means of a computational electro-mechanics (EM) model of the LV. In particular, we will analyse four patients (called P2, P3, P8 and P11) who underwent CRT in Ospedale S. Maria del Carmine in Rovereto, developing for each patient a personalized EM model, calibrated with available clinical data. We will then simulate virtual CRT in every patient, investigating the effects of the positioning of the left and right electrodes and of the setting of the ventriculoventricular (VV) delay, which is the time interval between the right and left stimuli. As far as we know, this is the first work that investigates the effect of the right electrode position on CRT: indeed, neither clinical nor computational studies have been performed before. For this reason, there has been a growing interest in understanding how the right electrode positioning can affect CRT outcomes.

2. Integration of clinical data

We here summarize the clinical data included in our work:

- LV geometries and fibrotic regions (only for P8 and P11) reconstructed from magnetic

resonance imaging (MRI) in the work of [3];
- Measures of the end systolic volume (ESV) and of the end diastolic volume (EDV). They are the volume of blood remaining in the LV after the contraction and after the ventricular filling, respectively. These volumes were measured with MRI in Ospedale S. Maria del Carmine;
- Measures of the systolic pressure (SP) and diastolic pressure (DP), obtained from the use of a sphygmomanometer. SP is the maximum pressure reached by arterial blood during systole, while DP is the minimum pressure reached by arterial blood during diastole;
- Measures of activation times (ATs) recorded at the LV ECV and at the RV septum (available only for P2 and P3), through the electro-anatomic mapping procedure;
- ECVs reconstructed in [3] from the electro-anatomic mapping procedure;
- Cardiac frequency.

We point out that all the clinical data listed above were recorded before CRT was implanted.

3. Mathematical and numerical methods

To simulate CRT, we used the EM model developed in [4], described in Figure 1. Electrophysiology is modeled by the Eikonal problem and by the reaction problem. In particular, the Eikonal model allows to compute LV ATs, needed by the the reaction model to retrieve intracellular calcium concentration. The latter allows to couple the electrophyisiology model to the mechanics model. The reaction problem is solved once and for all offline, thus reducing the computational cost. With respect to the model described in [4], in this work we used as ionic model the Tor-ORd model [5], that allows to accurately model intracellular calcium dynamics at different heart rates: in this way, we can include in our model patient-specific cardiac frequencies.
Once calcium concentration is computed, it is used to couple the electrical and mechanical models. The latter is composed by the mechanical activation model, the mechanics model and the circulation model. The mechanical activation model is a biophysically detailed model, that allows to precisely describe the behaviour of proteins involved in the cardiac contraction and relaxation cycle, computing the generated active tension. The latter constitutes the coupling element with the mechanics model, which is described by finite elasticity equations. Lastly, the mechanics model is coupled with a 0D circulation model, i.e. the two element Windkssel model. It is coupled with the mechanics model by means of a constraint on the LV pressures and volumes.

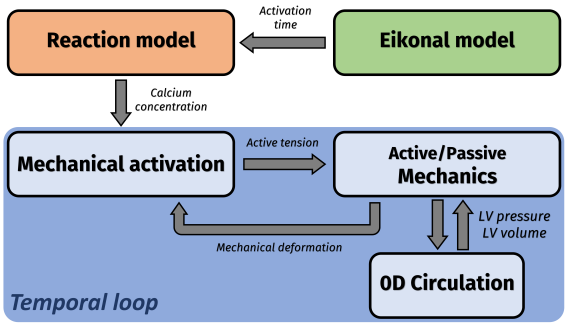

Figure 1: General structure of the EM model used in this work. Taken from [4].

The EM model previously described is numerically solved with a segregated method, based on a loosely-coupled strategy for the couplings between mechanics and active force model and between mechanics and the circulation model [4]. Regarding time discretization, the reaction problem and the mechanics problem are solved by means of the backward Euler scheme, while the active force generation model is discretized with a forward Euler scheme. Eventually, space discretization is implemented through the finite element method (FEM) of order 1 on hexahedral meshes. To solve the final linear system arising from the FEM, the GMRES method was used, preconditioned with the AMG preconditioner.
Regarding the meshes used in this work, we point out that the Eikonal model has to be solved on a finer mesh (characteristic mesh size $h \simeq 0.8-1\ mm$) with respect to the active force generation model and to the mechanics model ($h \simeq 3-4\ mm$) [3, 4]. In this way, we can ensure the convergence of the Eikonal problem. The coarser mesh is generated with the `vmtk` software, while the finer mesh is obtained by uniformly refining the coarser one until the correct h is reached. Meshes of P2 and P8 were generated by [3], while P3 and P11 are generated in this work.
All the EM simulations are performed on `lifex`,

a high performance C++ finite element library, mainly focused on cardiac applications, developed in the MOX department in Politecnico di Milano (`https://lifex.gitlab.io`).

4. Calibration procedure

To simulate CRT, we first model the pre-operative condition, fitting the EM model to available clinical data. In particular, we perform an electrical and a mechanical calibration.

Electrical calibration

The first phase of the electrical calibration procedure consists in generating the cardiac fibers, by means of the Bayer-Trayanova algorithm, a rule based method that allows to assign cardiac fibers orientation. The second phase consists in estimating the parameters of the Eikonal model in order to reproduce ATs measured at ECVs. We keep on adjusting the Eikonal parameters until we have a small discrepancy (error $< 10\%$) between computed and measured ATs. To calibrate the Eikonal model, we need also to prescribe an input datum for the problem: when available (in P2 and P3), this datum corresponds to ATs measured at the septum. Otherwise (in P8 and P11), three arbitrary points are selected at the septum and given as input datum to the Eikonal model. In case of fibrosis (P8 and P11), we simulate different degree of fibrosis in terms of dampened electrical conduction in correspondence of scarred regions and we choose the configuration that best matches the electrical measures taken at the ECV. In Figure 2, we show the result of the electrical calibration in P2: as we can see, there is a good correspondence between simulated and measured ATs. This is valid also for P3, P8 and P11: indeed, the calculated relative error is always less than 10%.

Mechanical calibration

The main purpose of the mechanical calibration is reproducing pressure-volume (PV) tracings clinically recorded. In particular, we want to calibrate our model in order to fit measures of the ESV, the EDV, the SP and the DP. In our work, the maximum LV pressure P_{max} corresponds to the SP, while the aortic valve pressure opening p_{AVO} corresponds to the DP.

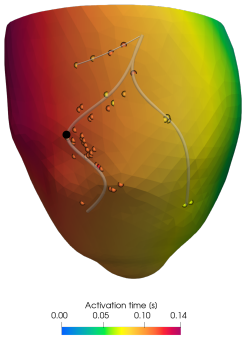

Figure 2: Results of the electrical calibration in P2. On the anterior view of the LV of P2, computed ATs are shown together with measured ATs (colored dots). The black dot is the computed LEAS. Reconstructed ECV are colored in grey.

Firstly, we set the heartbeat period in the TorORd ionic model, to match the patient cardiac frequency. Then, we impose that simulated EDV and p_{AVO} are equal to their clinical measures: in this way, we have to calibrate the model to match only ESV and P_{max}. To reach this goal, we calibrate the total peripheral resistance R and the contractility a_{XB}, two parameters belonging to the Windkessel model and to the mechanical activation model, respectively.
The mechanical calibration requires to run the EM model (simulation time: $5 \sim 8$ hours) every time a parameter is changed, thus it can become a very long procedure. To speed-up the calibration procedure, we introduce a novel approach that exploits the 0D cardiac emulator developed by [2]. The emulator is a surrogate cardiac model, built on the basis of some PV loop samples obtained from the 3D EM model. The emulator is defined by three functions: the end-systolic PV relationship $\mathcal{P}_{ES}$, that represents the maximum pressure achievable by the ventricle at a given volume, the end-diastolic PV relationship $\mathcal{P}_{ED}$, that represents the passive properties of the LV and the activation kinetics φ_{act}. The latter is a time-dependent function that ideally is equal to zero at the end of diastole, while it is equal to one at the end of systole.
To exploit the 0D emulator, we run two EM simulations that differ only from the parameter a_{XB}: in this way, we can build two 0D emulators, fitting $\mathcal{P}_{ES}$, $\mathcal{P}_{ED}$ and φ_{act} to the PV loop obtained from the 3D simulations. Then,

we build a parametric emulator, interpolating between the two previously created. The parametric emulator is used to calibrate our model: in particular, we can modify R and a_{XB}, evaluating their effects on the cardiac emulator built, with a very low computational cost. Once we have estimated R and a_{XB} from the emulator, we run few simulations to precisely adjust the parameters. In this way, we can greatly reduce the number of simulations needed to calibrate the model. We report in Table 1 the results of the mechanical calibration. We also calculate the ejection fraction EF, defined as $EF = \frac{SV}{EDV}$, where SV is the stroke volume, the volume of blood pushed out from the ventricle. As we can notice from Table 1, we are able to reproduce the pre-operative scenario with a high degree of accuracy.

		ESV $[mL]$	**EF** [%]	$\boldsymbol{P_{max}}$ $[mmHg]$
P2	*Clinical*	419	15.2	110
	Simulated	419	15.1	110
P3	*Clinical*	238	32.0	140
	Simulated	238	31.9	140
P8	*Clinical*	143	33.3	130
	Simulated	143	33.2	130
P11	*Clinical*	173	24.8	110
	Simulated	173	25.0	110

Table 1: Comparison between simulated and clinically measured data. ESV and P_{max} are rounded to the nearest integer.

5. Virtual cardiac resynchronization therapy

As we have previously mentioned, the calibrated pre-operative scenario is used to simulate CRT. Indeed, we point out that in our work we only simulate acute post-CRT scenarios, excluding long term effects. For this reason, we hypothesize that the electrical and mechanical properties of the heart do not change just after the CRT implant. In this way, the calibration performed for the pre-operative scenario is considered to be still valid for the simulation of CRT. Indeed, CRT induces significant effects on the cardiac muscle only some months after the implant: therefore, we can reasonably assume that cardiac properties do not significantly change just after CRT implant.
To simulate CRT, we will position the left electrode in the LEAS along the ECV, the standard location of the left electrode in clinical practice. The LEAS will be determined by the simulation (see Figure 2), since in in [6] it was proved that the EM model can accurately predict the LEAS location. We will also simulate other left electrode locations along the ECV. Regarding the right electrode position, in clinics it is commonly placed at the apex of the RV: since the RV is not included in our model, we will position it on the septal side of the LV, near the apex.
To evaluate CRT outcomes, we take in consideration standard indices used in clinics: the SV, the EF, the dP/dt_{max} and the stroke work (SW). The dP/dt_{max} is the maximum rate of ventricular pressure, an index of myocardium contractility. The SW is defined as the work done by the ventricle to eject blood. CRT is considered to be effective if it can be noticed an increase with respect to the pre-operative condition in the computed indices values.

6. Study of the left electrode positioning

We now analyse how the left electrode positioning affects CRT outcomes. For each patient, we simulate different left electrode locations along reconstructed ECVs, keeping the right electrode fixed at the apex. The VV delay is set to zero. The principal results are summarized as follows:

- In all the patients analysed, virtual CRT increases P_{max} (see Figure 3): probably, the therapy restores a more coordinated contraction, that results in an increased SV. Since resistances do not change with respect to the pre-operative scenario, P_{max} has to rise, so that a greater quantity of blood can be pushed out;
- Among the patients analysed, P8 is the only one who does not show any significant improvements from CRT. Fibrotic regions in P8 may be the most impacting factor on CRT outcomes: indeed, in regions detected with fibrosis conduction velocities are reduced with respect to healthy tissue. This could result in an asynchronous contraction, explaining why CRT fails. Also P11 is fibrotic: however, we point out that P11 is modeled with a lower degree of fibrosis, i.e. conduction velocities are less reduced with respect to P8. This could explain why P11 seems to benefit from CRT;

- The index dP/dt_{max} seems highly influenced by fibrotic regions: indeed, in both P8 and P11 this index does not increase significantly with respect to the pre-operative scenario (maximum increase: +2.01% in P8, +1.46% in P11). The presence of scarred regions may decrease the rate of ventricular pressure, because of an impaired contraction resulting from reduced conduction velocities;
- CRT at LEAS improves all the considered indices in P2 (see Figure 3), P3 and P11. In P8, the LEAS is within the scarred region: this can explain why stimulating at LEAS does not bring any benefits.

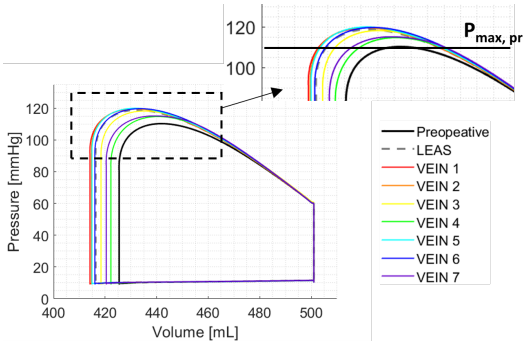

Figure 3: Computed PV loop in P2, at different points of stimulation. We zoom the PV loop to show the increase in P_{max} with respect to the pre-operative condition ($P_{max,pr}$).

In conclusion, stimulating at the LEAS would seem to be a good choice to best optimize CRT. Even though other points of stimulation achieve the maximum indices values, we are not able to give general indications to correctly position the left electrode. Indeed, dP/dt_{max} and the group of indices SV, EF and SW are not maximized in the same LV region: therefore, aiming at the LEAS seems to us the best way to improve the therapy outcomes. The only exception regards the case in which the LEAS is within a scarred region: in this context, the left electrode should be placed in a healthy region, if accessible.
In Figure 4, we compare the LV contraction before and after CRT. As we can see, before CRT the contraction is asynchronous (see the black arrows): the LV lateral wall moves down, while the septal wall moves up. With CRT, both walls move in a more coordinated way: they first moves towards the LV outside and then to the LV inside.

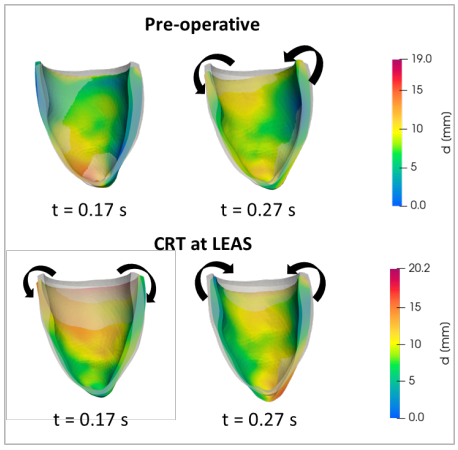

Figure 4: Comparison between displacements d in the pre-operative scenario and with CRT at LEAS in P2, during the cardiac cycle. The LV is shown from the anterior truncated view. The LV volume at the beginning of the cardiac cycle is colored in grey. Black arrows indicate the uncoordinated and coordinated contraction for the pre-operative scenario and for CRT, respectively.

7. Study of the ventriculoventricular delay

We now study the effect of the VV delay on CRT. We perform virtual CRT simulations at LEAS in P2, P3 and P11. For P8, we choose a different point of stimulation along the ECVs in the non-fibrotic region, since in the previous section we proved that LEAS is not a suitable point for CRT (only in P8). In our work, we consider the VV delay positive if the right stimulus anticipates the left one, and viceversa. We simulate delays within the range [-30, +30] ms: these are common values used in clinical practice.
Regarding SV, EF and SW, no significant changes are recorded with respect to the case in which the VV delay is set to zero. Only with a delay of +30 ms and -30 ms, their values are slightly decreased, probably because in this way the contraction results slightly asynchronous. The most interesting result of this analysis is related to dP/dt_{max}: indeed, this index seems to be highly dependent on the delay. As we can notice from Figure 5, higher delays correspond to higher dP/dt_{max}. Only in P11 this index does not increase: this is probably related to the fact that in P11 the LEAS is within the fibrotic regions. Differently from P8, in P11 all the possible left electrode stimulation points

fall within the scarred region: therefore, we cannot position the left electrode on a healthy region. The correlation between dP/dt_{max} and the VV delay should be deeply investigated: a possible way to study this trend could be simulating a wider range of delays, e.g. [-60, +60] ms, in order to understand how dP/dt_{max} evolves.
In this context, we propose to set the delay to +15 ms: in our work, this is the best compromise to obtain improved values of all the indices considered.

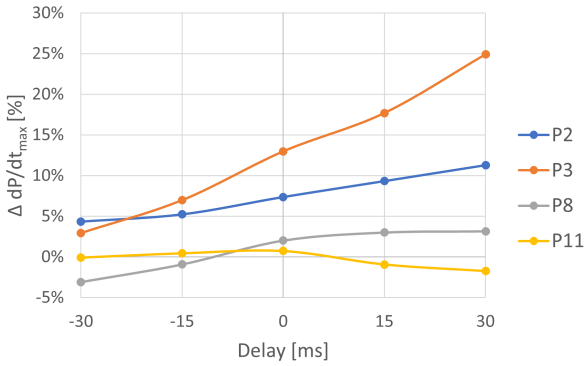

Figure 5: Relative variation of dP/dt_{max} with respect to the pre-operative condition at different VV delays, for P2, P3, P8 and P11.

8. Study of the right electrode positioning

In this section, we study how CRT outcomes are influenced by the right electrode position. The right electrode is placed in some points along the LV septum, while the left electrode is positioned in the LEAS in all patients. In this way, the only change with respect to standard CRT (i.e. left electrode at LEAS, right electrode at the apex) is the right electrode location. While dP/dt_{max} does not benefit from different right electrode locations, SV, EF and SW are significantly improved (see Table 2, we reported only SW values): indeed, it seems that placing the right electrode at the same height of the left one results in more synchronized contraction. This is probably related to a more symmetric electrical activation, as we can notice in Figure 6, where we report a comparison between ATs with standard CRT and with the best scenario obtained changing the right electrode position.
In this work, we propose to take in consideration to move the right electrode on the septum, such that it is vertically aligned with the left electrode. This could be realistically performed in clinical practice, exploiting the electro-anatomic mapping, performed every time CRT is implanted.

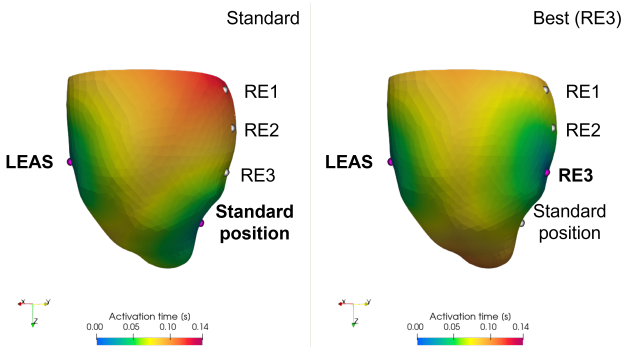

Figure 6: ATs with standard CRT (left) and with CRT performed at the best right electrode position (right) in P2.

	Δ $(SW_{standard})$ [%]	Δ (SW_{best}) [%]
P2	+19.41	+33.44
P3	+14.84	+22.30
P8	-1.56	+11.34
P11	+15.60	+19.60

Table 2: Comparison between relative variations of SW with respect to the pre-operative scenario, with standard CRT and with CRT performed at the best right electrode location.

9. Conclusions

In this work, we have successfully managed to investigate how CRT outcomes could be improved. The most interesting result of this work regards the effects of the right electrode position, that were never studied before. This work has obviously some limits. First of all, we only simulated acute post-CRT scenario, evaluating CRT outcomes with some clinical indices: further investigations should be performed to understand which are the best indices to be taken in consideration for the post-acute scenario. Moreover, it is still not clear the correlation between short and long term effects of CRT. Secondly, we modeled CRT using calibrated parameters of the pre-operative scenario, thus excluding changes in cardiac properties just after CRT implant. Lastly, our work analysed a small number of patients: therefore, we cannot extend our results to a more general clinical scenario.

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