Multiobjective Patient-Specific Estimation of a Coronary Circulation Model for Triple Vessel Disease

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Abstract— **Computational models can help understand the hemodynamics of the coronary circulation, which is of the upmost importance to help clinicians before, during and after a coronary artery bypass graft surgery. In this paper, we propose a multiobjective optimization method for parameter estimation of a computational model representing the coronary circulation on patients with a triple vessel disease. This estimation was not based on any assumption regarding the development of the collateral circulation, like in previous works. Indeed, the collateral development of a given patient is estimated through the model parameters. Parameter estimation was performed using clinical data from three patients, obtained before and during an off-pump coronary artery bypass graft surgery (CABG). Results showed a better performance when comparing the simulation with clinical data, since the total error estimation for three patients was reduced by $40 \pm 22\%$. Moreover, the proposed method provides new insight regarding the heterogeneous configuration of the alternative collateral vessels.**

I. INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of death worldwide. It is the result of the accumulation of plaque in the coronary arteries, which narrows the vessels that supply the heart with oxygen. As the disease progresses and arteries narrow further due to stenoses, coronary vessels fail to provide a sufficient blood supply to the myocardium, causing myocardial ischemia or infarction. Revascularization of the coronary circulation is critical for the patient outcome. Although some patients may develop an alternative source of blood supply from other coronary branches, through collateral vessels, limiting the impact of CAD, the recommended therapeutic action in the case of complete stenosis is based on coronary angioplasty or coronary artery bypass graft (CABG) surgery. Since these procedures are delicate and complex, all information that may help the surgeon to assess the particular hemodynamic situation of a given patient is useful.

Several computational models of the coronary circulation have been proposed in order to understand and predict the circulatory dynamics of the coronary tree [1]. One common approach is to use lumped-parameter Windkessel models, that represent blood flow and pressure dynamics through an electric-hydraulic analogy. Such approach is particularly useful because it presents a good compromise between computational cost and precision [2]. For the particular situation of patients with CAD, models have incorporated the effect of stenoses [3] and the dynamics of coronary grafts [4]. More recently, specific versions of these models have been developed for the representation of triple vessel disease [5], [6], which is a pathological situation where the right coronary artery is completely occluded and there are partial occlusions on the left coronary arteries.

One specificity of the model proposed by Maasrani et al. is the integration of the collateral circulation, a network of small-diameter vessels that provide an alternative source of oxygenated blood to perfuse areas affected by occlusions. Since these alternative vessels are difficult to assess directly [7], [8], the organization and function of collateral perfusion is still poorly understood and controversial [9]. The inclusion of collateral vessels in Maasrani's model assumes a uniform development of these vessels throughout the whole myocardium, presenting the same characteristics for all myocardial regions of each patient. However, clinical studies have shown that this assumption is difficult to sustain [7]. With the aim of improving this model, a first comprehensive sensitivity analysis and a parameter estimation method were proposed in [10]. We showed an uneven effect of collaterals on most major output variables of the model, depending on their position on the coronary tree, and preliminary results on a patient-specific parameter estimation method.

In this work, we present a new parameter identification approach that allows for the estimation of the uneven collateral development of a specific patient. This approach is based on the joint optimization of a set of objective functions, minimizing a distance between the data observed intra-operatively and the model simulation.

II. MATERIALS AND METHODS

A. Clinical Data

This paper uses a subset (patients 1, 2 and 3) of the clinical data published in [11], [6], which were obtained before and during an off-pump coronary artery bypass graft surgery (CABG). All data is from patients presenting triple vessel disease, as represented in fig. 1: chronic occlusion of the right coronary artery (RCA), and partial occlusion due to stenoses on the left main coronary artery (LMCA), left anterior descending artery (LAD) and left circumflex artery (LCx).

Pre-operative data consist of angiographic estimation of vessel diameter reduction caused by stenosis for LMCA,

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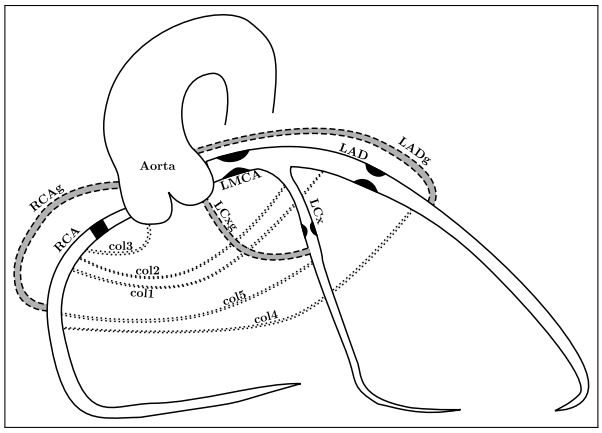


Fig. 1. Hemodynamic situation of the coronary circulation with triple vessel disease, after the revascularization with three coronary artery grafts. Grafts are represented with dashed lines, collaterals vessels with dotted lines.

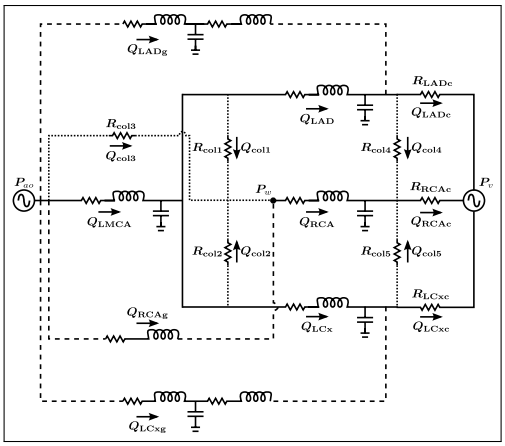


Fig. 2. Electrical representation of the coronary circulation model. Grafts are represented with dashed lines, collaterals with dotted lines.

LAD and LCx. Intra-operative data include blood pressure and blood flow measurements at specific sites of the coronary circulation, acquired during the revascularization procedure. All measurements are considered as the mean value after hemodynamic stabilization. Full details of this CABG surgery are available in [12]. During the intervention, the RCA is first revascularized with a saphenous vein graft (RCAg). At this point, the RCAg is clamped and the pressure after the RCA occlusion, or coronary wedge pressure (P_{w}), is measured (case 0G). Then, RCAg clamp is released in order to measure the flow across the RCAg graft (case 1G). After the LAD and LCx arteries are revascularized with internal mammary artery grafts (LADg and LCxg, respectively), P_{w} and the flow across LADg and LCxg are measured while clamping RCAg (case 2G). Finally, all graft flows are measured with all three grafts in place (case 3G).

B. Model Description

In this work, we used the coronary circulation model initially presented by Maasrani et al. [6]; a lumped-parameter model that represents blood flow dynamics with an electric circuit analogy [13], as shown in fig. 2. Coronary arteries are represented with an RLC circuit that accounts for blood flow through a resistive vessel, flow inertia and viscoelasticity of the vessel wall. The effect of inertia and vessel compliance can be neglected for small diameter vessels [2]; therefore, capillaries are represented with resistances. More information on the model can be found in [6], and detailed equations are presented in [3].

Collateral vessels are also included in the model as resistances that connect the occluded RCA with LAD before and after the stenosis (col1 and col4), with LCx before and after the stenosis (col2 and col5), and with the aorta (col3). However, each collateral vessel is represented by a the same parameter ($R_{\mathrm{col1}} = R_{\mathrm{col2}} = R_{\mathrm{col3}} = R_{\mathrm{col4}} = R_{\mathrm{col5}}$), implying a homogeneous development of all coronary collaterals.

In [10], we used the multiformalism modeling and simulation library (M2SL) [14] to extend our investigation of the coronary circulation model with an exhaustive parameter sensitivity analysis, focusing on the effects of the collateral resistances. The results of this study revealed two important conclusions: *(i)* capillary and collateral resistances were found to be the parameters that have the most significant effect on the outputs of the model, and *(ii)* collateral resistances showed different effects on graft flows and P_{w}, suggesting that the development of collaterals is not necessarily uniform, as expected from observations from clinical studies [7]. Also in [10], it was shown that it is possible to estimate patient-specific parameters without enforcing the equality of collateral parameters, but the optimization technique used to find these parameters could still be refined.

C. Parameter Identification

The objective of this investigation was to estimate patient-specific parameters without applying any constraint regarding collateral resistances. In order to obtain a model whose simulated values are as close as possible to real intra-operative data, the estimation was designed to jointly minimize the following functions:

$$f_V(\mathbf{p}) = \left| V^{\mathrm{O}} - V^{\mathrm{S}} \right|,$$
$$V \in \left\{ \begin{array}{ccc} P_{w,0G}, & Q_{\mathrm{RCAg},1G}, & P_{w,2G}, \\ Q_{\mathrm{LADg},2G}, & Q_{\mathrm{LCxg},2G}, & Q_{\mathrm{RCAg},3G}, \\ Q_{\mathrm{LADg},3G}, & Q_{\mathrm{LCxg},3G} & \end{array} \right\}, \quad (1)$$

where V^O denotes an observed variable during CABG, V^S denotes a simulated output variable, and $\mathbf{p}$ represents a set of parameter values of the model. These eight functions are not differentiable, so in order to optimize them, an evolutionary algorithm (EA) was used. In contrast to [10], the EA used in this case is a multiobjective evolutionary algorithm (MOEA).

EAs consist on a process of exploration and evaluation of individuals $\mathbf{p}$ in a population that is continuously modified for a number of generations. MOEAs use the same idea, but in this case the population estimates the pareto front of the objective functions: a region in the parameter space where the evaluation of each objective function is optimized as much as possible without penalizing another objective function. Among the variety of MOEAs available in the literature, this work uses the nondominated sorting-based multiobjective evolutionary algorithm (NSGA-II) [15]. The NSGA-II establishes an order of the individuals, (i.e. one solution dominates another one) when it can reduce at least

one objective function without increasing another one. The evolution of the population is elitist; the dominant individuals are selected for future generations. Finally, when two individuals do not dominate each other, they are compared according to a crowding factor in order to obtain a population that is diverse.

As the evolution progresses, the population might be composed only of nondominated individuals whose solutions are not useful. In order to avoid a population that suffers from this scenario, whenever the population contains more than 95% of nondominated individuals, the total error of each individual $\mathbf{p}$ is calculated:

$$\epsilon(\mathbf{p}) = \sum_{V} f_V(\mathbf{p}). \tag{2}$$

Then, the mean total error of the population $E[\epsilon]$ is calculated and a constraint is added to the evolutive process so that individuals with a total error lower than $E[\epsilon]$ are more likely to survive. More details on the handling of constraints during the evolutive process are presented in [15].

III. RESULTS

The multiobjective estimation was focused on the identification of the parameters $\mathbf{p} = [R_{\text{LADc}}, R_{\text{RCAc}}, R_{\text{LCxc}}, R_{\text{col1}}, R_{\text{col3}}, R_{\text{col4}}, R_{\text{col5}}]$, with $R_{\text{col1}} = R_{\text{col2}}$ These parameters were selected since [10] suggested an important sensitivity with respect to the variables in eq. (1). Parameter exploration was limited to physiologically relevant values. Capillary resistances were limited to a range between 27 to 525 mmHg s/mL; collateral resistances were limited from 104 to 2000 mmHg s/mL. These ranges were defined to enclose all possible estimated values in [6].

The MOEA was run with a population of 10000 individuals during 500 generations with a probability of 0.8 of crossover and 0.25 of mutation. After the evolutive process is finished, the best 1000 individuals, according to their total error (as defined in eq. (2)) were selected to generate the following tables: table I presents the mean value of each objective function and total error for this subset of the final population; table II shows the parameter values found in this study. Both tables include the obtained estimation error and parameter values published in [6], as a reference.

A. Performance of the estimation

The multiobjective optimization approach presented in this work shows a significant improvement with respect to previous identification approaches for most of the observed variables of the model. It is worth to note here that previous identifications since [5] have been limited to the analysis of clinical $Q_{\text{RCAg,3G}}$, $Q_{\text{LADg,3G}}$ and $Q_{\text{LCxg,3G}}$ to calculate analytically each capillary resistance. Then, a numerical optimization is performed to obtain the value of the common R_{col}, using $P_{\text{w,2G}}$ as a reference for error calculation. This method results in a estimation showing a low error associated with these four variables, but a significant error in all other cases and therefore, a significant total error for some patients.

The better performance obtained in our work can be explained by two main reasons: *(i)* the search space is not constrained to one dimension (R_{col}), but to a 7-dimensional space that has not been explored before, and *(ii)* the optimization is multiobjective, which will converge towards a minimum error for each function. Admittedly, some of the errors are higher for a few exceptions, particularly $Q_{\text{RCAg,3G}}$ for patient 2 and $Q_{\text{LCxg,2G}}$ for patients 2 and 3. However, it is very likely that the small loss in these functions entails a more significant improvement in the other functions, which is the purpose of multiobjective optimizations with pareto regions.

Even if the estimation error has been improved in this work, there is still a significant error on some of the variables. In particular, the flow Q_{RCAg} under the 1G case shows a very high error for patients 1 and 3. An analysis of the evolution of the population showed that some individuals may improve the error for the 1G case, but only while deteriorating the error of the graft flows of the 2G and 3G cases. Due to a slight difference on the total error, the population of patients 1 and 3 converged towards a better estimation of the 2G and 3G cases, and patient 2 converged towards a lower 1G error. This situation suggests that a unique set of parameter values for capillaries and collaterals that explains the dynamics of all graft configurations probably does not exist. A different set of parameters, depending of each case, implies the following interpretation: during the CABG, there are some physiological mechanisms that modify the resistance to the vessels of the coronary circulation. Indeed, clinical observations have shown that variations of coronary resistances can occur after revascularizations [16]. Considering that the 0G and 1G measurements are performed at different moments of the CABG procedure, separated by the time of revascularization of the left arteries, such variation of the model parameters seems plausible.

B. Analysis of estimated parameters

As shown in table II, the values estimated for capillary resistances are similar to those found by Maasrani et al. Considering that the evolutive algorithm constantly explores the parameter space, these results show that another capillary situation is unlikely to improve the estimation error. Given this similarity of the capillaries, the difference on the error in table I can only be accounted by the different collateral resistances, which highlights the improvement of the patient-specific estimation of this work.

The difference of collateral resistances suggests an heterogeneous development of the collateral vessels for each patient. For example, with the previous estimation of $R_{\text{col}} = 160$ mmHg s/mL, it was assumed that patient 1 presented a homogeneous, well developed collateral network. The results of this work show that this patient may have a very well developed collateral from LCx (R_{col5}) and from the aorta (R_{col3}), while a virtually non-existant connection between LAD and RCA. For this particular coronary circulation model, these new results allows us to better estimate the collateral development of a specific patient.

TABLE I

EVALUATION OF THE FINAL POPULATION AND MAASRANI'S PARAMETERS [6] (IN PARENTHESES). UNITS ARE (mmHg) FOR PRESSURE, (mL/min) FOR FLOWS.

Error function f_V	Patient 1	Patient 2	Patient 3
$V = P_{w,0G}$	0.7 (3.3)	0.0 (4.6)	0.2 (5.8)
$V = Q_{\text{RCAg},1G}$	41.1 (52.7)	0.0 (7.5)	49.0 (57.5)
$V = P_{w,2G}$	0.8 (0.3)	2.1 (0.0)	0.1 (0.2)
$V = Q_{\text{LADg},2G}$	0.5 (5.3)	0.0 (0.4)	0.0 (4.4)
$V = Q_{\text{LCxg},2G}$	0.0 (9.8)	13.2 (10.0)	4.6 (0.1)
$V = Q_{\text{RCAg},3G}$	0.7 (1.4)	4.4 (0.4)	0.1 (1.1)
$V = Q_{\text{LADg},3G}$	0.0 (1.4)	0.0 (0.3)	0.0 (0.8)
$V = Q_{\text{LCxg},3G}$	0.0 (0.5)	0.0 (0.1)	0.0 (0.7)
Total error (eq. (2))	43.8 (74.7)	19.7 (23.4)	53.9 (70.6)

TABLE II

MEAN AND STANDARD DEVIATION OF PARAMETER VALUES OF THE FINAL POPULATION AND MAASRANI'S PARAMETERS [6] (IN PARENTHESES), IN WHICH ALL R_{COL} ARE EQUAL.

Parameter	Patient 1	Patient 2	Patient 3
R_{LADc}	83.0 ± 0.0 (83.0)	172.3 ± 0.0 (174.6)	205.7 ± 0.0 (213)
R_{RCAc}	55.7 ± 0.3 (54.1)	108.0 ± 0.0 (96.9)	63.0 ± 0.1 (62.8)
R_{LCxc}	192.3 ± 0.1 (207.9)	211.6 ± 0.0 (210.9)	93.8 ± 0.0 (94.2)
R_{col1}	504.9 ±154.7 (160)	238.8 ± 0.3 (430)	1985.3 ± 17.0 (350)
R_{col3}	131.1 ± 67.3	1350.8 ± 16.5	100.2 ± 0.2
R_{col4}	1999.9 ± 0.3	498.1 ± 0.1	549.2 ± 0.6
R_{col5}	54.2 ± 0.1	1999.9 ± 0.1	1999.5 ± 0.5

Physiological deductions based on estimated values should be handled with care when there is a high variability of the parameters, which is the case for R_{col1} for patient 1. Due to the convergence of the optimization towards solutions that minimize eq. (2), this variability shows that modifications of R_{col1} have a weak effect on this total error. It is worth mentioning that this weak effect is only observed locally, i.e. around the values found for the other parameters. Therefore, it is not possible to deduce global sensitivity conclusions, which would contradict the results of [10], where it was found that collateral resistances have an important effect on P_{w} and all graft flows.

IV. CONCLUSION

In this work, we applied a multiobjective optimization method for parameter estimation of a coronary circulation model for triple vessel disease. The most original aspect of this work resides in the proposed parameter estimation method, which used all available pre- and intra-operative data, without imposing any constraint regarding the parameters of the collateral vessels. Results show a better performance than previous parameter estimations performed on this model by means of an analytic approach [5] or previous (mono-objective) evolutive algorithm optimization methods [10]. These results can provide important information of the collateral development for a specific patient and help the surgeon to optimize graft surgery. However, the estimation error is still significant for at least one of the observed variables, which may be due to regulation mechanisms occurring during the procedure. Further work will focus on the analysis of the collateral assessment using this estimation results, and exploring the possible evolution of the parameter values during revascularization.

REFERENCES

[1] S. L. Waters, J. Alastruey, D. A. Beard, P. H. Bovendeerd, P. F. Davies, G. Jayaraman, O. E. Jensen, J. Lee, K. H. Parker, A. S. Popel, T. W. Secomb, M. Siebes, S. J. Sherwin, R. J. Shipley, N. P. Smith, and F. N. van de Vosse, "Theoretical models for coronary vascular biomechanics: progress & challenges," *Prog Biophys Mol Biol*, vol. 104, no. 1-3, pp. 49–76, Jan 2011.

[2] M. Olufsen and A. Nadim, "On deriving lumped models for blood flow and pressure in the systemic arteries," *Math Biosci Eng*, vol. 1, no. 1, pp. 61–80, 2004.

[3] J. Z. Wang, B. Tie, W. Welkowitz, J. Kostis, and J. Semmlow, "Incremental network analogue model of the coronary artery," *Med Biol Eng Comput*, vol. 27, no. 4, pp. 416–422, Jul 1989.

[4] R. Pietrabissa, S. Mantero, T. Marotta, and L. Menicanti, "A lumped parameter model to evaluate the fluid dynamics of different coronary bypasses," *Medical Engineering & Physics*, vol. 18, no. 6, pp. 477–484, 9 1996.

[5] M. Maasrani, J. Verhoye, H. Corbineau, and A. Drochon, "Analog electrical model of the coronary circulation in case of multiple revascularizations," *Annals of Biomedical Engineering*, vol. 36, no. 7, pp. 1163–1174, April 2008.

[6] M. Maasrani, I. Abouliatim, M. Harmouche, J. Verhoye, H. Corbineau, and A. Drochon, "Patients specific simulations of coronary fluxes in case of three-vessel disease," *Journal of Biomedical Science and Engineering*, vol. 4, no. 1, pp. 34–45, 2011.

[7] G. S. Werner, M. Ferrari, S. Heinke, F. Kuethe, R. Surber, B. M. Richartz, and H. R. Figulla, "Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions," *Circulation*, vol. 107, no. 15, pp. 1972–1977, Apr 2003.

[8] C. Berry, K. Balachandran, P. L'Allier, J. Lespérance, R. Bonan, and K. Oldroyd, "Importance of collateral circulation in coronary heart disease," *European heart journal*, vol. 28, no. 3, pp. 278–291, 2007.

[9] W. Schaper, "Collateral circulation: past and present," *Basic Res Cardiol*, vol. 104, no. 1, pp. 5–21, Jan 2009.

[10] D. Ojeda, V. Le Rolle, A. Drochon, H. Corbineau, J.-P. Verhoye, and A. I. Hernández, "Sensitivity analysis and parameter estimation of a coronary circulation model for patients with triple-vessel disease," in *Proceedings of The Virtual Physiological Human 2012 (VPH2012)*, London, 2012.

[11] I. Abouliatim, M. Harmouche, A. Drochon, M. Maasrani, H. Corbineau, and J.-P. Verhoye, "Coronary flow in patients with three-vessel disease: Simulated hemodynamic variables in relation to angiographically assessed collaterality and history of myocardial infarction," *ISRN Vascular Medicine*, vol. 2011, pp. 1–10, 2011.

[12] H. Corbineau, J. P. Verhoye, T. Langanay, P. Ménestret, and A. Leguerrier, "Feasibility of the utilisation of the right internal thoracic artery in the transverse sinus in off pump coronary revascularisation: early angiographic results," *Eur J Cardiothorac Surg*, vol. 20, no. 5, pp. 918–922, Nov 2001.

[13] K. Sagawa, R. Lie, J. Schaefer, *et al.*, "Translation of Otto Frank's paper" die grundform des arteriellen pulses" zeitschrift fur biologie 37: 483-526 (1899)." *Journal of molecular and cellular cardiology*, vol. 22, no. 3, p. 253, 1990.

[14] A. I. Hernández, V. Le Rolle, A. Defontaine, and G. Carrault, "A multiformalism and multiresolution modelling environment: application to the cardiovascular system and its regulation," *Philos Transact A Math Phys Eng Sci*, vol. 367, no. 1908, pp. 4923–4940, Dec 2009, pTRSA.

[15] K. Deb, A. Pratap, S. Agarwal, and T. Meyarivan, "A fast and elitist multiobjective genetic algorithm: NSGA-II," *Evolutionary Computation, IEEE Transactions on*, vol. 6, no. 2, pp. 182–197, 2002.

[16] G. Werner, U. Emig, O. Mutschke, G. Schwarz, P. Bahrmann, and H. Figulla, "Regression of collateral function after recanalization of chronic total coronary occlusions," *Circulation*, vol. 108, no. 23, pp. 2877–2882, 2003.