Sensitivity Analysis and Parameter Estimation of a Coronary Circulation Model for Patients with Triple Vessel Disease

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Triple vessel disease, which refers to the obstruction (stenosis) of three coronary arteries, requires in most of the cases a coronary bypass graft surgery (CABG). The integrative modelling of the normal and pathological coronary circulation can help to understand and predict the physiopathological consequences of this surgery. An appropriate model of the coronary circulation should integrate interacting sub-systems with heterogeneous physical and time scales [1]. The integration of the collateral circulation is particularly important in pathological cases, since these vessels can reestablish an appropriate perfusion when the main arteries are partially or completely occluded [2]. This point is one of the major difficulties of the coronary modelling approach since the understanding of collateral circulation is still limited [3].

This work is focused on the analysis of a model of the hemodynamics of the coronary system. The lumped-parameter model of the coronary circulation analyzed in this paper was initially presented by [4] and adapted by [5, 6]. It is based on a well-known hydraulic/electric analogy (Figure 1). It specializes in the coronary circulation of patients that present a total occlusion of the right coronary artery (RCA) and partial stenoses of the left main coronary (LMCA), left anterior descending (LAD), and left circumflex artery (LCx). This model has been reimplemented in M2SL, a multi-formalism modelling and simulation library allowing an easy integration with sensitivity analysis and parameter identification methods [7].

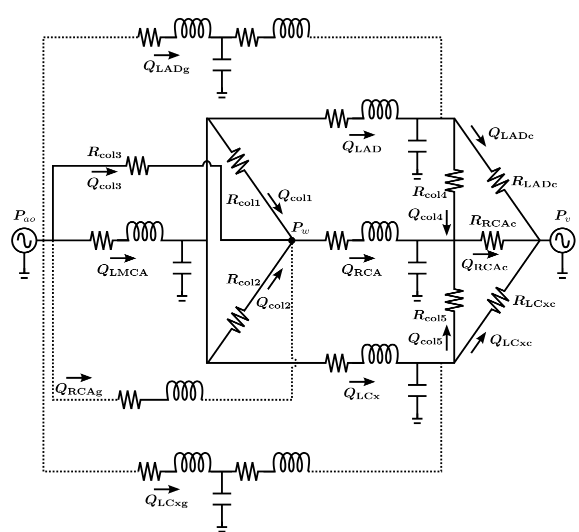

Figure 1: Electrical equivalent model of the coronary circulation. The left main coronary artery (LMCA), left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) are represented as RLC lumped-parameter elements. Left coronary grafts (LADg, LCxg) and right coronary grafts (RCAg) are represented in a similar fashion, while capillaries (LADc, RCAc, LCxc) and collaterals ($Rcol_{1,2,3,4,5}$) are represented by resistances.

Due to the difficulty of the assessment of collaterals and capillaries [8], efforts towards patient-specific parameter values have been limited. Following the pioneering works of [9, 4], Maasrani et al. recently proposed an analytical procedure for the estimation of capillary resistances, based on the assumption that all collateral vessels have an equal resistive effect. In this work, a comprehensive sensitivity analysis of a coronary circulation model is performed in order to: i) study the impact of the assumption of the equality of collateral resistances on the simulated coronary flows and ii) improve the patient-specific parameter estimation phase.

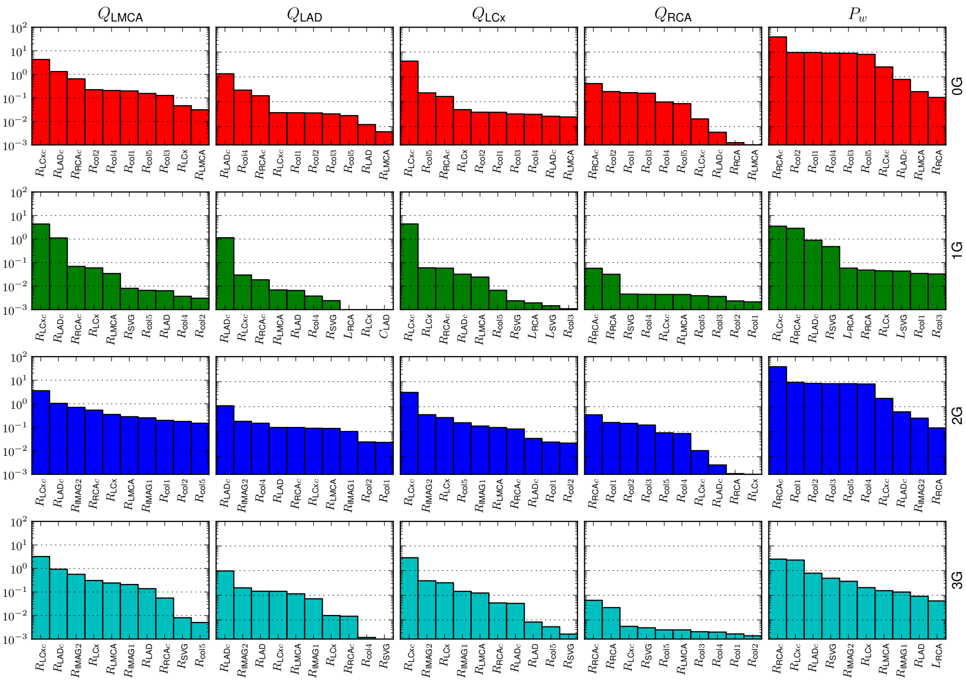

Figure 2: Sensitivity results of the ten most important parameters over the mean of arterial flows and over the pressure distal to the RCA occlusion. The sensitivities of each model outputs are organized by columns: left main coronary (Q_{LMCA}), left anterior descending (Q_{LAD}), left circumflex (Q_{LCx}), right coronary artery (Q_{RCA}), and coronary wedge pressure (P_w). Each graft configuration (0G, 1G, 2G and 3G) is represented in a different row.

In spite of the relative simplicity of the model, the effect of pulsatile dynamics and the strong interaction between all elements of the model hinders the analysis of its parameters. Therefore, we studied the effect of all parameters using the screening method of Morris since it also provides information on nonlinearities and interactions between parameters [10]. This method consists in evaluating several random parameter perturbations for a given output of the model. In each case, parameter *elementary effects* are calculated. The mean μ_{ee} and standard deviation σ_{ee} of the elementary effects for each parameter are thus obtained. Finally, the global sensitivity of a parameter is calculated as $\sqrt{\mu_{ee}^2+\sigma_{ee}^2}$. This sensitivity analysis was performed for different therapeutic configurations: when no graft has been placed (configuration 0G), when only the right graft is in place (1G), when only the left grafts are in place (2G), and when all grafts are in place (3G), and for the main outputs of the model.

An additional objective of this work was the estimation of model parameter values that reproduce the clinical data of a patient under a CABG procedure. The following data are available for five patients: (1) coronary wedge pressure, P_w^o (for cases 0G and 2G); (2) mean flow through the right graft, $Q^o_{\mathrm{RCA}g}$ (for cases 1G and 3G); and (3) mean flow through left grafts, $Q^o_{\mathrm{LAD}g}$ and $Q^o_{\mathrm{LCx}g}$ (for cases 2G and 3G). Results from the sensitivity analysis will guide the selection of the parameter vector P to be estimated. The simplex multidimensional optimization method was used for parameter estimation [11]. The objective function is defined as the absolute difference between all the available intra-operative data and the outputs of the model for a given P. For each evaluation, this function requires the simulation of the four graft scenarios. In order to evaluate the reproducibility of the optimal parameter vector P^*, 30 realizations of the whole parameter estimation process were performed with different random P as initial conditions.

Figure 2 shows the sensitivity analysis results for cases 0G, 1G, 2G and 3G on the main outputs of the model: the arterial flows and the mean blood pressure distal to the RCA occlusion (P_w). Other were graft scenarios and output variables were also considered, but these results are not included in this work. This results show that the most sensitive parameters are the capillary and collateral vessel resistances. Briefly, for all graft scenarios, the total input flow of the coronary system (Q_{LMCA}) is mainly affected by the resistance of capillaries and collaterals. Sensitivity results obtained for Q_{LAD} and Q_{LCx} show similar profiles, presenting a higher sensitivity to collateral resistances than Qlmca. Results also show that the right circulation (Q_{RCA} and P_w) is the most sensitive to collateral resistances. When taking into account different graft scenarios, the cases in which the right graft is in place (1G and 3G) present a lower collateral sensitivity compared to the cases in which this graft is not present (0G and 2G). This is specially the case for Q_{RCA} and P_w. Moreover, an important result is the uneven effect of the collateral vessels on each arterial flow. For example, LAD and LCx flows show a greater effect from their corresponding distal collateral (R_{col4} and R_{col5}, respectively), while RCA flow exhibits the opposite behaviour: proximal collaterals $R_{\mathrm{col1,2,3}}$ have a more significant effect than distal ones. These results agree with medical observations that identify the capillaries as a crucial regulator of blood flow [12] and acknowledge the importance of collaterals for occluded coronary arteries [2]. Contrary to previous identifications of this coronary model, the sensitivity analysis results suggest that the parameter estimation should be done without supposing an equality of the collateral resistances.

Parameter estimation results are synthesized on Tables 1a and 1b. Values are presented as the mean $\pm$ standard deviation computed over the 30 realizations of the parameter estimation phase. The comparison between simulated data and clinical measurements (Table 1b) show small differences for most variables, yet some simulated graft flows are still significantly different from real patient data, in particular $Q^{\mathrm{3G}}_{\mathrm{RCA}g}$ and $Q^{\mathrm{2G}}_{\mathrm{LCx}g}$. These differences may be explained by the fact that only one P^* is estimated for all graft scenarios. Although this approach maximizes observability, it may induce errors related to the non-stationary physiological conditions during surgery. The estimated parameter values (Table 1a) show a low standard deviation for the capillary resistances and a high standard deviation for collateral resistances. Interestingly, the mean results do not coincide with the values published by [5, 6]. Further investigation is needed to determine whether these differences are due to the non equality of the collateral resistances or from the existence of local minima. These results are encouraging even though the optimization method and target function still needs to be refined.

To the authors' knowledge, this work is the first exhaustive parameter sensitivity analysis of a coronary circulation model for patients with triple-vessel disease. Results underlined the important relative effects of capillaries and collateral vessels on the coronary blood flow, under different therapeutic configurations. Moreover, the analysis provided evidence that the supposition of the equality of collaterals has an important and uneven consequence on the coronary flows, particularly on the right part of the circulation. Lastly, the most important parameters of the model were estimated using all the observable flows of a CABG procedure. The identification provided an estimation of the collateral and capillary situation of several patients. Yet, better results should be obtained by increasing the observability of the system, including both complementary pre-operative and intra-operative data. Current work is directed towards the acquisition of these new data and the improvement of the estimation method.

Parameter	Patient 1	2	3	4
R_{col1}	640±335	686±354	582±341	669±255
R_{col2}	626±316	634±328	610±360	616±307
R_{col3}	709±311	604±314	603±240	554±242
R_{col4}	701±269	663±318	709±333	681±234
R_{col5}	698±370	684±331	678±272	812±301
$R_{\text{LAD}c}$	40±1	143±53	116±15	34±31
$R_{\text{RCA}c}$	131±24	113±16	110±39	232±74
$R_{\text{LCx}c}$	116±39	125±41	45±1	52±5

(a) Mean and standard deviation of all parameter values found by the parameter estimation method.

Variable	Patient 1	2	3	4
$P_w^{0\text{G,o}}$	35	49	40	43
$P_w^{0\text{G,s}}$	28.4±4.6	43.6±4.6	35.3±2.4	40.7±2.7
$Q_{\text{RCA}g}^{1\text{G,o}}$	35	45	28	11
$Q_{\text{RCA}g}^{1\text{G,s}}$	38.0±7.0	44.5±4.7	54.1±14.5	28.1±5.2
$Q_{\text{LAD}g}^{2\text{G,o}}$	34	23	22	59
$Q_{\text{LAD}g}^{2\text{G,s}}$	33.1±3.9	18.0±4.0	21.1±1.9	53.7±8.6
$Q_{\text{LCx}g}^{2\text{G,o}}$	27	32	48	40
$Q_{\text{LCx}g}^{2\text{G,s}}$	12.4±2.7	20.0±4.8	46.7±1.1	28.7±8.4
$P_w^{2\text{G,o}}$	31	49	40	42
$P_w^{2\text{G,s}}$	29.0±3.8	46.3±5.3	42.7±3.4	46.4±2.2
$Q_{\text{LAD}g}^{3\text{G,o}}$	40	21	19	57
$Q_{\text{LAD}g}^{3\text{G,s}}$	39.7±4.8	16.3±4.3	18.1±1.7	57.5±9.4
$Q_{\text{LCx}g}^{3\text{G,o}}$	14	19	45	30
$Q_{\text{LCx}g}^{3\text{G,s}}$	13.9±3.2	18.2±5.1	45.6±0.9	30.2±9.5
$Q_{\text{RCA}g}^{3\text{G,o}}$	66	45	74	26
$Q_{\text{RCA}g}^{3\text{G,s}}$	28.9±5.6	41.5±4.9	45.2±13.1	19.0±4.5

(b) Comparison of observed clinical measurements (^{o}) and simulated data (^{s}).

Table 1: Parameter estimation results and evaluation with real patient data previously published in [5, 6]. Units for coronary wedge pressure (P_w) are mmHg, for coronary graft flows mL/min, and for resistances mmHg s/mL.

References

[1] Waters SL, Alastruey J, Beard DA, Bovendeerd PH, Davies PF, Jayaraman G, et al. Theoretical models for coronary vascular biomechanics: progress & challenges. Prog Biophys Mol Biol. 2011 Jan;104(1-3):49–76. doi:10.1016/j.pbiomolbio.2010.10.001.

[2] Koerselman J, van der Graaf Y, de Jaegere PP, Grobbee DE. Coronary collaterals: an important and underexposed aspect of coronary artery disease. Circulation. 2003 May;107(19):2507–2511. doi:10.1161/01.CIR.0000065118.99409.5F.

[3] Loukas M, Bilinsky S, Bilinsky E, Matusz P, Petru M, Anderson RH. The clinical anatomy of the coronary collateral circulation. Clin Anat. 2009 Jan;22(1):146–60. doi:10.1002/ca.20743.

[4] Pietrabissa R, Mantero S, Marotta T, Menicanti L. A lumped parameter model to evaluate the fluid dynamics of different coronary bypasses. Medical Engineering & Physics. 1996 9;18(6):477–484.

[5] Maasrani M, Verhoye JP, Corbineau H, Drochon A. Analog electrical model of the coronary circulation in case of multiple revascularizations. Annals of Biomedical Engineering. 2008 April;36(7):1163–1174.

[6] Maasrani M, Abouliatim I, Harmouche M, Verhoye JP, Corbineau H, Drochon A. Patients specific simulations of coronary fluxes in case of three-vessel disease. Journal of Biomedical Science and Engineering. 2011;4(1):34–45.

[7] Hernández AI, Le Rolle V, Ojeda D, Baconnier P, Fontecave-Jallon J, Guillaud F, et al. Integration of detailed modules in a core model of body fluid homeostasis and blood pressure regulation. Progress in Biophysics and Molecular Biology. 2011;107:169–182. doi:10.1016/j.pbiomolbio.2011.06.008.

[8] Werner GS, Ferrari M, Heinke S, Kuethe F, Surber R, Richartz BM, et al. Angiographic assessment of collateral connections in comparison with invasively determined collateral function in chronic coronary occlusions. Circulation. 2003 Apr;107(15):1972–1977. doi:10.1161/01.CIR.0000061953.72662.3A.

[9] Wang JZ, Tie B, Welkowitz W, Kostis J, Semmlow J. Incremental network analogue model of the coronary artery. Med Biol Eng Comput. 1989 Jul;27(4):416–422.
[10] Morris MD. Factorial sampling plans for preliminary computational experiments. Technometrics. 1991 May;33(2):161–174.
[11] Nelder JA, Mead R. A simplex method for function minimization. The computer journal. 1965;7(4):308.
[12] Jayaweera AR, Wei K, Coggins M, Bin JP, Goodman C, Kaul S. Role of capillaries in determining CBF reserve: new insights using myocardial contrast echocardiography. Am J Physiol. 1999 Dec;277(6 Pt 2):2363–2372.