MOX–Report No. 7/2008

Reliable CFD-based Estimation of Flow Rate in Hemodynamics Measures. Part II: Sensitivity Analysis and First Clinical Application

Christian Vergara, Raffaele Ponzini, Alessandro Veneziani, Alberto Redaelli, Danilo Neglia, Oberdan Parodi

MOX, Dipartimento di Matematica "F. Brioschi"
Politecnico di Milano, Via Bonardi 29 - 20133 Milano (Italy)

mox@mate.polimi.it http://mox.polimi.it

Reliable CFD-based Estimation of Flow Rate in Hemodynamics Measures. Part II: Sensitivity Analysis and First Clinical Application

Christian Vergara[1], Raffaele Ponzini[2], Alessandro Veneziani[3], Alberto Redaelli[4], Danilo Neglia[5], Oberdan Parodi[6]

March 17, 2008

[1] -Dept. of Information Technology and Mathematical Methods, Università degli Studi di Bergamo, Italy
-MOX– Modellistica e Calcolo Scientifico
Dipartimento di Matematica "F. Brioschi"
Politecnico di Milano
via Bonardi 9, 20133 Milano, Italy
`christian.vergara@polimi.it`
[2] -Department of Bioengineering, Politecnico di Milano, Italy
-CILEA (Consorzio Interuniversitario Lombardo per l'Elaborazione e l'Automazione), Segrate, Italy
[3] -Dept. of Mathematics and Computer Science, Emory University, Atlanta, GA, USA
-MOX– Modellistica e Calcolo Scientifico
Dipartimento di Matematica "F. Brioschi"
Politecnico di Milano
via Bonardi 9, 20133 Milano, Italy
`alessandro.veneziani@polimi.it`
[4] Department of Bioengineering, Politecnico di Milano, Italy
[5] Institute of Clinical Physiology CNR, Pisa, Italy
[6] -Institute of Clinical Physiology CNR, Pisa, Italy
- Ca' Granda Niguarda Hospital, Milan, Italy

Keywords: Flow rate estimation, Doppler measurements, Womersley number, Sensitivity Analysis, Coronary flow reserve

AMS Subject Classification: 62G99

Abstract

In Ponzini et al. (2006) a new approach has been proposed for estimating in a reliable way blood flow rate from velocity Doppler measurements. In that paper, basic features of the approach and some "*in silico*" test cases were furnished. Here, we give more insights of this approach by performing a sensitivity analysis of the formulae relating blood flow rate to blood velocity. In particular we analyze their sensitivity to the physiological parameters in comparison with the standard formula proposed in Doucette et al. (1992). A first glance at "*in vivo*" validation of the formulae is given too.

1 Introduction

The correct estimation of blood flow rate Q through a vascular surface is a major issue in clinical practice, since it could give important informations about the cardiovascular state of a patient. This can be pursued with a good precision by using invasive approaches, such as the *Electromagnetic flow meter* (see, e.g., Kolin et al. 1968, Elfverson and Larsson 1983) or by considering a mean value across a heart cycle with the *transit time coronary thermodilution* (see, e.g., De Bruyne et al. 2003). Even if these techniques allow to measure directly the flow rate, their difficulty and invasiveness discourage their clinical use. For these reasons, the current elective approach for blood flow analysis is based on the Doppler technique (*Intravascular Doppler velocimetry* analysis, see, e.g, Doucette et al. 1992). Available highly accurate velocity measures at different positions of a vessel make this approach attractive for many clinical applications, such as during catheterisation, in percutaneous transluminal coronary angioplasty (PTCA) and for the determination of coronary flow rate (see, e.g., Kajiya et al. 1987, Johnson et al. 1989, Iliceto et al. 1991, Marcus et al. 1982, Wilson et al. 1985, McGinn et al. 1990, Savader et al. 1997, Doucette et al. 1992). However, Doppler velocimetry analysis cannot measure directly the flow rate. The latter has to be indirectly estimated starting from other available measures.

As a matter of fact, if Γ denotes a section of a vascular district at hand, flow rate Q through Γ is defined as

$$Q = \int_\Gamma \rho \boldsymbol{u} \cdot \boldsymbol{n} d\gamma, \tag{1}$$

where ρ is the blood density (hereafter assumed to be constant), $\boldsymbol{u}$ the blood velocity and $\boldsymbol{n}$ the normal unit vector. In principle, the whole velocity field $\boldsymbol{u}$ on Γ is needed for estimating Q. However, equation (1) can be rewritten in terms of the mean velocity value U as

$$Q = \rho U A \tag{2}$$

where A denotes the area of section Γ. Unfortunately, mean velocity U is not available from measures. On the other hand, Doppler velocimetry analysis provides good measures of the maximum velocity V_M on Γ. Equation (2) requires therefore to be accompained with an appropriate formula relating mean velocity

U to the maximum one V_M. In current clinical practice, as proposed in Doucette et al. (1992), it is usually assumed

$$U = \frac{V_M}{2}. \tag{3}$$

This equation stems from the hypothesis of a parabolic spatial profile for the velocity. For this reason, in the sequel equation (3) will be referred to as *parabolic formula*. Striclty speaking this formula assumes that blood flow is quasi-static, laminar and Newtonian in a rectilinear cylindrical vessel (see Nichols et al., 2005). These assumptions, where at each instant a steady profile is associated with the instantaneous flow rate, is far to be fullfilled in real situations (see e.g. Robertson et al. 2001, Perktold et al. 1998, Shehada et al. 1993, Ferrari et al. 2006). In particular, it has been pointed out by different authors the relevance of blood flow pulsatility on the velocity profiles (Womersley 1955, Hale et al. 1955, Nichols et al. 2005). If we denote by D the vessel diameter, ν the blood viscosity and f the frequency of blood impulse, the adimensional index

$$W = \frac{D}{2}\sqrt{\frac{2\pi f}{\nu}}$$

called *Womersley number*, is used for quantifying the pulsatility of the flow. The higher the value of W the more the assumption of parabolic velocity profile is incorrect (see, e.g., Porenta et al. 1999, Jenni et al. 2000, Jenni et al. 2004, Ferrari et al. 2006, Ponzini et al. 2006). In Ponzini et al. (2006) improved blood flow rate estimates from maximum velocity have been devised by exploiting Computational Fluid Dynamics (CFD) results. The basic idea was to generalize equation (3), by introducing an explicit dependence on the Womersley number of the mean velocity:

$$U = g(V_M, W), \tag{4}$$

where g is a suitable function. For this reason in the sequel formula (4) will be referred to as *Womersley-based formula*. The quantitative determination of function $g(V_M, W)$ in Ponzini et al. (2006) has been carried out by performing about 200 numerical simulations in cylindrical geometries, for different values of the flow rate (prescibed as boundary conditions) and of the Womersley number. Flow rate boundary conditions are prescribed without any biased arbitrary assumption of the velocity profile, according to a mathematical approach recently proposed in Formaggia et al. (2002), Veneziani and Vergara (2005 and 2007). A non-linear least squares approach has been then used for fitting the results (see also Pennati et al. 1996 and 1998). This allows to obtain the parameters for the identification of formula g. Preliminary validation in Ponzini et al. (2006) has been based on *in silico* test cases, i.e. on numerical simulations performed in cases different from the ones used for fitting formula (4). These results show that the new formula improves blood flow rate estimation with respect to (3). In some cases the improvements are remarkable.

In this paper we continue the investigation of this approach through a sensitivity analysis of the formula with respect to the velocity and to the diameter. We show that formula (4) has stability features comparable with (3), apart for values of the Womersley number included in the range $(2.7, 3.1)$. For this reason, we modify formula (4) in this range in order to reduce its sensitivity and we check that this modification does not affect the overall accuracy.

Parabolic and Womersley-based formulae are then applied to a clinical dataset retrieved from the database of the CNR Clinical Physiology Institute of Pisa. These early results show that the Womersley-based formula provide a better agreement with the clinical expectations.

2 Sensitivity Analysis

2.1 Material and Methods

For the sake of accuracy, in Ponzini et al. (2006) three ranges of the Womersley number are considered and associated with three different formulae:

$$\begin{cases} Q = \rho\frac{\pi D^2}{4} g_1(V_M, W) = \rho\frac{1}{2}\frac{\pi D^2}{4} V_M(1 + a_1 W^{b_1}) & \text{for} \quad 0 < W \le 2.7, \\ Q = \rho\frac{\pi D^2}{4} g_2(V_M, W) = \rho\frac{1}{2}\frac{\pi D^2}{4} V_M b_2 \arctan(a_2 W) & \text{for} \quad 3.1 \le W \le 15, \\ Q = \rho\frac{\pi D^2}{4} w g_1(V_M, W) + \rho\frac{\pi D^2}{4}(1-w) g_2(V_M, W) & \text{for} \quad 2.7 < W \le 3.1. \end{cases} \tag{5}$$

Here, a_1, a_2, b_1 and b_2 are the parameters determined by the fitting procedure and $w = w(W)$ is a weight function mixing the formulae for low and high values of W respectively. More precisely, we set (see Ponzini et al. 2006)

$$\begin{cases} a_1 = 0.00417, & b_1 = 2.95272 \\ a_2 = 1.00241, & b_2 = 0.94973 \end{cases},$$

and

$$w(W) = e^{\frac{(W-2.7)^2}{(W-2.7)^2 - 0.4^2}}. \tag{6}$$

Since formulae (5) establish a dependence of the flow rate on the Womersley number W, they are able to describe in a more realistic way different blood flow regimes. We point out that for $W = 0$, that is in steady conditions, we recover the parabolic formula (see $(5)_1$). However, for the same reason they are also more delicate in terms of sensitivity from the data, being estimates possibly polluted by error on maximum velocity V_M, diameter, frequency and viscosity measures. On the contrary, parabolic formula (3) is independent of frequency and viscosity. This means that error in measuring these parameters do not affect the estimate. On the other hand, the same formula is unable to account for flow rate modifications induced by a physical change of viscosity or pulsatility, as we have pointed out previously.

In order to evaluate sensitivity on measurements errors of formulae (5) in comparison to (3) , we introduce in Appendix an index λ, called *amplification* *factor*. If $y(x)$ is the quantity to be estimated depending on the measurable quantity x, the amplification factor reads

$$\lambda = \frac{y'(x)}{y(x)} x, \tag{7}$$

where y' denotes the first derivative of $y(x)$ with respect to x. The amplification factor quantifies the sensitivity of the quantity y on the measure x. Big values of λ means that small perturbations on x (due for example to an error in the measurement) could lead to big perturbations in the estimate y. We point out that the sensitivity of the estimate has not to be confused with its accuracy, that is how this estimate y is "close" to the real value y_{ex}.

Hereafter, we focus our attention on the dependence of our formulae on the measure of the maximum velocity and of the diameter, which are those parameters in formula (5) likely most operator-dependent (while the maximum velocity is the only parameter appearing in formula (3)).

Sensitivity to V_M. All the proposed formulae depend linearly on V_M, i.e. are in the form

$$Q = c(W) V_M$$

where $c(W)$ is a function of the Womersley number (and in particular a costant for the parabolic formula (3)). By resorting to (7), we have for all the formulae considered here

$$\lambda = \frac{c(W)}{c(W) V_M} V_M = 1. \tag{8}$$

Sensitivity of the formulae to maximum velocity measures is therefore the same. A possible error δ on this measure in both cases affects flow rate estimates, with a perturbation of the same order of δ.

Sensitivity to D. Sensitivity on D is even more critical with respect to the operator skillness and experience. Let us consider the different cases at hand separately.

1. *Parabolic formula*: in this case we have from (3)

$$\lambda_{\text{parabolic}} = \frac{\frac{\rho D V_M}{4}}{\frac{\rho}{2}\frac{D^2}{4} V_M} D = 2. \tag{9}$$

2. *Womersley-based formula for small Womersley numbers*: by algebraic manipulation we have

$$\lambda_{g_1} = 2 + b_1 \frac{a_1 W^{b_1}}{1 + a_1 W^{b_1}}. \tag{10}$$

3. *Womersley-based formula for large Womersley numbers*:

$$\lambda_{g_2} = 2 + \frac{a_2 W}{(1 + a_2^2 W^2) \arctan(a_2 W)}. \tag{11}$$

4. *Womersley-based formula for intermediate Womersley numbers¡*: in this case computations are made more difficult by the presence of the weight function w that depends on D through the Womersley number. Let us introduce the following notation:

$$\lambda_{12} = \frac{w g_1'}{(1-w) g_2} D, \quad \lambda_{21} = \frac{(1-w) g_2'}{w g_1} D, \quad \lambda_w = \frac{w'}{w} D, \quad \lambda_{w12} = \frac{(g_1 - g_2) w'}{g_2} D.$$

Then, it is possible to verify that

$$\lambda_{g_3} = 2 + \left(\frac{1}{\lambda_1^{-1} + \lambda_{12}^{-1}} + \frac{1}{\lambda_2^{-1} + \lambda_{21}^{-1}} + \frac{1}{\lambda_w^{-1} + \lambda_{w12}^{-1}} \right). \tag{12}$$

2.2 Forward and backward analysis of perturbations

In this section, starting from theoretical considerations, we provide an application of the results of the sensitivity analysis in order to improve the estimate of the flow rate. In particular, we will show that a perturbation on the measurement of the maximum velocity in a suitable range, leads to a better estimate of the flow rate.

The impact of errors on the computation of a quantity of interest y regarded as a function of the data x can be represented as in Fig. 2. The solid line corresponds to the *exact* calculation of y_{ex} in $\overline{x}$. Approximation procedures affect the result, so that the real process (represented by the dashed line) leads to an approximated value $y_{app}(\overline{x})$. Perturbations on the data on the x-axis change the results, leading to $y_{pert}(\overline{x}) = y_{app}(\overline{x} + \delta)$. We could try to investigate if a perturbation on the data could induce an improvement on the final result. In other words, we look for a perturbation δ that compensates the approximation of the process. The interplay between approximation of results and data perturbations is a classical topic of the so called *backward analysis* (see e.g. Higham 1996). The answer to this question is strictly related to the definition of amplification factor. Actually, we look for $\delta > 0$ such that

$$|y_{\mathrm{ex}} - y_{app}(x + \delta)| < |y_{\mathrm{ex}} - y_{app}(x)|.$$

By exploiting equation (16) in the Appendix and assuming that $x > 0$, $y_{app} > 0$, $y'_{app} > 0$ (and then $\lambda > 0$) and that the approximation process is affected by a constant bias such that $y_{app}(x) < y_{\mathrm{ex}}$, the latter inequality becomes

$$y_{app}(x) - y_{ex} < y_{ex} - y_{\mathrm{app}}(x + \delta) \simeq y_{\mathrm{ex}} - y_{app}(x) \left(1 + \lambda \frac{\delta}{x}\right)$$

$$\Rightarrow 2(y_{app}(x) - y_{\mathrm{ex}}) < -\frac{\lambda\, \delta y_{app}(x)}{x} < 0$$

Then, the previous inequality is solved by

$$\delta < \frac{2(y_{\mathrm{ex}} - y_{app})x}{\lambda\, y_{app}(x)}. \tag{13}$$

In conclusion, a perturbation on the data small enough in fact improves the final estimate.

2.3 Results and Discussion

Sensitivity to D. In Fig. 1 we illustrate the stability index λ of the parabolic and Womersley-based formulae as a function of W. We observe that for $W \leq 2.7$ and $W \geq 3.1$, Womersley-based formulae are slightly more sensitive, as was to be expected since these formulae actually depends on the Womersley number, that in turn depends on the diameter. In particular, for $W < 2.7$ the sensitivity increases with the Womersley number, while for $W > 3.1$ it decreases with W. In this range, the increment of λ is in any case less than 13% of the index of parabolic formula.

On the contrary, for $2.7 < W < 3.1$, we observe that the amplification factor increases up to 68% with respect to the index of parabolic formula. This stems from the fact that in this range of the Womersley number, our formula is given by a weighted linear combination of g_1 and g_2. In the superimposition of the effects the amplification factor is affected by the sum of the two contributions. In order to reduce the sensitivity of the "weighted" Womersley-based formula, we modify the weight function $w(W)$ in (5). In particular, we propose the linear function

$$w(W) = \frac{3.1 - W}{0.4}. \tag{14}$$

From the mathematical viewpoint, this choice introduces a less regular function. Indeed, the Womersley-based formula over the entire range of physiological ranges of Womersley numbers will be only continuous, with discontinuous derivate. However, it reduces the sensitivity to D of the Womersley-based formula in the range $W = (2.7, 3.1)$, as shown in Fig. 1, since it features a slope smaller than with the weight (6). The amplification factor reduces to 38% more than the one of parabolic formula.

It is important to outline that, while the stability of the Womersley-based formula with weight (14) is greatly improved, the accuracy is mantained. This is confirmed by numerical results referring to the same *in silico* validation test cases considered in Ponzini et al. (2006). We apply the original and the modified Womersley-based formulae (given by weights (6) and (14), respectively) to the brachial flow wave test case. The results in Tab. 2, show that the accuracy of the Womersley-based formula is not worsened.

To be more concrete, we detail some examples of clinical relevance (in all the examples we set $\nu = 0.035\,Poise$).

1) Coronary vessel: Let us consider the measure of flow rate in a coronary vessel. We assume that the diameter of such a district is $D = 2\,mm$. In *basal* conditions, frequency $f = 1\,Hz$, consequently $W = 1.34$. For example if the diameter error is 10%, the perturbation induced by the parabolic formula amounts to 20%, while from (10) it follows that the perturbation of the Womersley-based formula amounts to 20.6%.

If we assume that *adenosine* is administered, we have $f = 3\,Hz$ corresponding to $W = 2.32$. In this case the perturbation of the Womersley-based formula amounts to 22.8%.

2) Brachial artery: Let us consider the brachial artery: in this case, a possible value of the diameter is $D = 4.2\,mm$ and then the Womersley number in basal conditions ($f = 1\,Hz$) is $W = 2.81$. In this case we have refer to the weighted formula $(5)_3$, with (14). With a 10% error in the diameter measure, the perturbation of the Womersley-based formula is 37.4% (20% for the parabolic formula).

3) Femoral artery: Here we can assume $D = 10\,mm$. In basal conditions we have $W = 6.69$ and the perturbation of the Womersley-based formula amounts to 21.0%, while under adenosine we have $W = 11.60$ and the perturbation is 20.5%, versus the 20% of the parabolic formula.

Overestimation of the measures. It is worth noting that clinical evidence (see, e.g., Ferrari et al. 2006) suggests that parabolic formula underestimates the real flow rate, $Q_{\text{ex}} > Q_{\text{parabolic}}$. In other words, there is a systematic error with a constant bias (i.e. $Q_{\text{ex}} - Q_{\text{parabolic}} > 0$ constantly). Referring to the section *Forward and backward analysis of perturbations*, in our application the datum x is the diameter or the maximum velocity, whereas the calculation y_{app} is the estimate of the flow rate. Moreover, we remark that $x > 0$, $y_{app} > 0$ (if we focus on downstream fluxes) and $y'_{app} > 0$ for construction. This means that we can apply (13). For example, using one of the *in silico* test case shown in Ponzini et al. 2006, we have $V_M = 4421.0\,mm/s$, $D = 1.2\,mm$, $Q_{ex} = 10000\,mm^3/s$, $Q_{parabolic} = 9876\,mm^3/s$, $W = 1.737$. From (8), (9) and (13), it follows that a measure of the maximun velocity satisfing $\delta < 111.02\,mm/s$ and a measure of the diameter satisfing $\delta < 0.015\,mm$, leads to a better estimate of the flow rate. In this case, as remarked in the previous subsection, perturbations on the measures could at some extent compensate the intrinsic error of parabolic formula. More precisely, we have that small *positive* perturbations on the measures of V_M and D can improve the flow rate estimate based on (3). This has an immediate practical consequence: *when different measures of V_M or D are available it is worth retaining the largest one*, since small overestimations can partially balance the errors intrinsic to the parabolic formula.

In the case of Womersley-based formulae, there is no available experimental evidence of a constant bias in flow rate evaluation, so it is not possible at the moment to give any practical suggestions. Numerical *in silico* results presented in Ponzini et al. (2006 and 2008) suggest however that also this formula features a constant underestimation (even if sensibly reduced with respect to the Doucette's results as will be illustrated in Sect. 3). If these results will be confirmed by *in vivo* validation, then the indication moving towards an overestimated value of the maximum velocity and of the diameter will apply to the Womersley-based formula as well.

3 Some steps to "in vivo" validation

Validation of (5) in Ponzini et al. (2006) was based on CFD results, by performing numerical simulations in geometries and regimes different from the ones used for fitting the formulae. In Ponzini et al. (2008) Womersley-based formulae have been applied to Y-graft bypass. The advantage of *in silico* test cases is that prescription and comparison of data is completely under control. Results obtained in this way show that Womersley-based formulae can significantly improve flow rate estimates in comparison with parabolic formula.

Next step is *in vivo* validation. In what follows we provide a first clinical application of the Womersley-based formula. We point out that this application is just a first preliminary, even if it is an important step in that direction.

Among all the clinical flow rate applications, we have focused on catheter-based Doppler ultrasound velocimetry analysis for the measurement of the coronary flow reserve (CFR). This application is one of the most relevant in clinical application (see Gould et al. 1974, McGinn et al. 1990, Doucette et al. 1992). In particular, the CFR has been intensively used to assess coronary vasomotricity in patients with coronary artery disease (CAD) (see Sambuceti et al. 1997). CFR is known to be defined as the ability of coronary vessels to increase blood flow adjusting it for the myocardium demands for oxygen and energy. CFR can be defined as the ratio between the flow rate Q_S measured in a coronary vessel during maximal vasodilatation and the flow rate Q_R measured in resting conditions, that is

$$\mathrm{CFR} = \frac{Q_S}{Q_R}. \tag{15}$$

Therefore, CFR could represent a clinical diagnostic and prognostic index concerning the coronary vessel inhability to increase flow proportional to increases in myocardial metabolic demand.

We have applied the Womersley-based formula in a blind fashion, to 13 patients (with or without idiopathic dilated cardiomyopathy) of the database of CNR of Pisa, Italy (see Neglia et al. 2007 for details). Patients with idiopathic dilated cardiomyopathy have been chosen since they have shown impaired CFR at positron emission tomography measurements (see Neglia et al. 2002). In particular, in order to compute the flow rate Q_S, adenosine has been administered to these patients.

Using these data, CFR has been estimated using the parabolic and the Womersley-based formula for the computation of the flow rates in (15).

We observe that no ad hoc data acquisition has been needed in order to evaluate the flow rates (and then the CFR) using the Womersley-based formula. An important feature of this formula is actually that it can be used from data commonly measured in the clinical practice.

As shown in Table 1 and in Fig. 3, Womersley-based formula provides an higher value of the estimate of the CFR, with the respect to the one performed by the parabolic formula, in all the patients but one (patient n. 11). We observe that this patient is the only one such that the Womersley number is smaller under adenosine rather then at rest. This is due to the fact that for this patient heart rate is slower under adenosine than in resting conditions.

In particular, the mean value of the CFR obtained with the parabolic formulae is 2.56 ± 0.75, while the one obtained with the Womersley-based formula is 2.65 ± 0.85. This is a good result, in view of the established tendency of parabolic formula to underestimation.

Moreover, in Table 1 the relative differences between the two CFR estimates (ε) are shown. The mean value of ε related to the first 8 patients with idiopathic dilated cardiomyopathy is $2.53\% \pm 2.42\%$, while the mean value in the healthy patients is $3.55\% \pm 4.98\%$. From these results, Womersley-based formula seems to introduce a more significant correction in healthy patients. Because of the small sample size, the two groups are still not well separated.

Data collected so far are however not enough for the construction of a statistically significant data set. Starting from promising results obtained here, we plan to enlarge our data base, in particular including cases with high Womersley number, namely those observed in vessels with larger diameter than that of coronary arteries. In fact, in the present study, formula (5) was applied to arterial vessels with small Womersley numbers. Formula (5) will further improve accuracy of CFR calculation when applied to clinical conditions characterized by elevated heart rates, such as pacing tachycardia, or by medium and large vessels.

Patient	W basal/adenosine	CFR based on (3)	CFR based on (5)	ε
1	2.88/3.19	3.75	4.06	7.64%
2	3.00/3.15	2.25	2.32	3.02%
3	3.53/4.00	2.68	2.75	2.55%
4	2.05/2.44	1.53	1.57	2.55%
5	2.54/2.49	1.55	1.55	0.0%
6	3.24/3.58	3.61	3.68	1.90%
7	2.49/2.73	1.75	1.78	1.69%
8	2.13/2.34	2.28	2.30	0.87%
9	2.68/3.32	1.70	1.92	11.46%
10	2.33/2.54	2.04	2.07	1.45%
11	2.68/2.44	2.84	2.79	-1.79%
12	2.07/2.41	3.52	3.59	1.95%
13	3.00/3.41	3.88	4.07	4.67%

Table 1: CFR estmated with formula (3) and (5) from the data collected at the CNR Clinical Physiology Instiute, Pisa, and relative difference ε =(CFR based on (5)-CFR based on (3))/ CFR based on (5)

	Ed	Ew	Ewmod
W=2.868	18.42%	9.52%	8.03%
W=3.049	18.17%	2.77%	3.33%

Table 2: *In silico* validation: comparison between the relative errors obtained with formulae (3) (Ed), (4) with weight (6) (Ew) and (4) with weight (14) (Ewmod)

Figure captions

Figure 1 Amplification factor λ for Parabolic and Womersley-based formulae as a function of the Womersley number W. Dashed line: index for the original formula featuring the exponential weight function (6) for Womersley numbers in the range $2.7 < W < 3.1$. Solid line: index for the modified formula with the linear weight (14).

Figure 2 Abstract representation of forward and backward impact of data perturbations. Improvement on the result obtained by an approximated process can be the result of a perturbation on the data.

Figure 3 Estimation of the CFR obtained with the parabolic and with the Womersley-based formula: the patients with idiopathic dilated cardiomyopathy (1-8) and the healthy ones (9-13) are separated by the dashed line.

Appendix

Let us consider a generic function $y = y(x)$. Suppose that x could be subject to perturbations δ possibly induced by measurements errors. Our goal is to evaluate the ratio between the relative errors, namely

$$\lambda = \frac{\frac{y(x+\delta)-y(x)}{y(x)}}{\frac{\delta}{x}} = \frac{y(x+\delta)-y(x)}{y(x)}\frac{x}{\delta}.$$

Let us rearrange the latter equation in the following way

$$\lambda = \frac{y(x+\delta)-y(x)}{\delta}\frac{\delta}{y(x)}\frac{x}{\delta} = \frac{y(x+\delta)-y(x)}{\delta}\frac{x}{y(x)}.$$

Now, if we denote by $y'(x)$ the derivative of y with respect to x and let δ tends to 0, we finally obtain

$$\lambda = \frac{y'(x)}{y(x)}x.$$

This amplification factor states the impact of a perturbation on x on the result $y(x)$. In the context of numerical analysis, this index is sometimes called *condition number* of $y(x)$. Observe that from the definition we have for δ small

$$y(x+\delta) \simeq y(x)\left(1 + \lambda\frac{\delta}{x}\right). \tag{16}$$

References

[1] B. De Bruyne, N. H. Pijls, L. Smith, M. Wievegg, and G. R. Heyndrickx. Coronary thermodilution to assess flow reserve: experimental validation. *Circulation*, 2001; 104(17):2003–6.

[2] J. W. Doucette, P. D. Corl, H. M. Payne, A. E. Flynn, M. Goto, M. Nassi, and J. Segal. Validation of a doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation*, 1992; 85(5):1899–911.

[3] J. Elfverson and L. E. Larsson. Superior sagittal sinus blood flow in the dog measured by an electromagnetic flow meter. a comparison with a radioactive gas elimination method. *Clinical Physiology*, 1983; 3(6):545–9.

[4] M. Ferrari, G. S. Werner, P. Bahrmann, B. M. Richartz, and H. R. Figulla. Turbulent flow as a cause for underestimating coronary flow reserve measured by doppler guide wire. *Cardiovascular Ultrasound*, 2006; 4:14.

[5] L. Formaggia, J. F. Gerbeau, F. Nobile, and A. Quarteroni. Numerical treatment of defective boundary conditions for the navier-stokes equations. *Siam Journal on Numerical Analysis*, 2002; 40(1):376–401.

[6] K. L. Gould, K. Lipscomb, and G. W. Hamilton. Physiologic basis for assessing critical coronary stenosis. instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *American Journal of Cardiology*, 1974; 33(1):87–94.

[7] J. F. Hale, Donald Da Mc, and J. R. Womersley. Velocity profiles of oscillating arterial flow, with some calculations of viscous drag and the reynolds numbers. *Journal of Physiology*, 1955; 128(3):629–40.

[8] N. J. Higham *Accuracy and Stability of Numerical Algorithms*. SIAM ed., Philadelphia, 1996

[9] S. Iliceto, V. Marangelli, C. Memmola, and P. Rizzon. Transesophageal doppler echocardiography evaluation of coronary blood flow velocity in baseline conditions and during dipyridamole-induced coronary vasodilation.[see comment]. *Circulation*, 1991; 83(1):61–9.

[10] R. Jenni, P. A. Kaufmann, Z. Jiang, C. Attenhofer, A. Linka, and L. Mandinov. In vitro validation of volumetric blood flow measurement using doppler flow wire. *Ultrasound in Medicine & Biology*, 2000; 26(8):1301–10.

[11] R. Jenni, F. Matthews, S. V. Aschkenasy, M. Lachat, B. van Der Loo, E. Oechslin, M. Namdar, Z. Jiang, and P. A. Kaufmann. A novel in vivo procedure for volumetric flow measurements. *Ultrasound in Medicine & Biology*, 2004; 30(5):633–7.

[12] E. L. Johnson, P. G. Yock, V. K. Hargrave, J. P. Srebro, S. M. Manubens, W. Seitz, and T. A. Ports. Assessment of severity of coronary stenoses using a doppler catheter. validation of a method based on the continuity equation. *Circulation*, 1989; 80(3):625–35.

[13] F. Kajiya, K. Tsujioka, Y. Ogasawara, Y. Wada, S. Matsuoka, S. Kanazawa, O. Hiramatsu, S. Tadaoka, M. Goto, and T. Fujiwara. Analysis of flow characteristics in poststenotic regions of the human coronary artery during bypass graft surgery. *Circulation*, 1987; 76(5):1092–100.

[14] F. J. Klocke. Measurements of coronary flow reserve: defining pathophysiology versus making decisions about patient care. *Circulation*, 1987; 76(6):1183–9.

[15] A. Kolin, G. Ross, Jr. Grollman, J. H., and J. Archer. An electromagnetic catheter flow meter for determination of blood flow in major arteries. *Proceedings of the National Academy of Sciences of the United States of America*, 1968; 59(3):808–15.

[16] M. L. Marcus, D. B. Doty, L. F. Hiratzka, C. B. Wright, and C. L. Eastham. Decreased coronary reserve: a mechanism for angina pectoris in patients

with aortic stenosis and normal coronary arteries. *New England Journal of Medicine*, 1982; 307(22):1362–6.

[17] A. L. McGinn, C. W. White, and R. F. Wilson. Interstudy variability of coronary flow reserve. influence of heart rate, arterial pressure, and ventricular preload.[see comment]. *Circulation*, 1990; 81(4):1319–30.

[18] D. Neglia, A. De Caterina, P. Marraccini, A. Natali, M. Ciardetti, C. Vecoli, A. Gastaldelli, D. Ciociaro, P. Pellegrini, R. Testa, L. Menichetti, A. L'Abbate, W.C. Stanley, F.A. Recchia. Impaired myocardial metabolic reserve and substrate selection flexibility during stress in patients with idiopathic dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*, 2007; 293(6).

[19] D. Neglia, C. Michelassi, M.G. Trivieri, G. Sambuceti, A. Giorgetti, L. Pratali, M. Gallopin, P. Salvadori, O. Sorace, C. Carpeggiani, R. Poddighe, A. L'Abbate, O. Parodi. Prognostic role of myocardial blood flow impairment in idiopathic left ventricular dysfunction. *Circulation*, 2002; 105(2):186-93.

[20] W.W. Nichols, D.A. McDonald, M.F. O'Rourke. *McDonald's blood flow in arteries : theoretical, experimental, and clinical principles*. Hodder Arnold, London, 5th edition, 2005.

[21] G. Pennati, M. Bellotti, E. Ferrazzi, M. Bozzo, G. Pardi, and R. Fumero. Blood flow through the ductus venosus in human fetus: calculation using doppler velocimetry and computational findings. *Ultrasound in Medicine & Biology*, 1998; 24(4):477–87.

[22] G. Pennati, A. Redaelli, M. Bellotti, and E. Ferrazzi. Computational analysis of the ductus venosus fluid dynamics based on doppler measurements. *Ultrasound in Medicine & Biology*, 1996; 22(8):1017–29.

[23] K. Perktold, M. Hofer, G. Rappitsch, M. Loew, B. D. Kuban, and M. H. Friedman. Validated computation of physiologic flow in a realistic coronary artery branch. *Journal of Biomechanics*, 1998; 31(3):217–28.

[24] R. Ponzini, C. Vergara, A. Redaelli, and A. Veneziani. Reliable cfd-based estimation of flow rate in haemodynamics measures. *Ultrasound in Medicine & Biology*, 2006; 32(10):1545–55.

[25] R. Ponzini, M. Lemma, U. Morbiducci, F.M. Montevecchi, A.Redaelli. Doppler derived quantitative flow estimate in coronary artery bypass graft: A computational multiscale model for the evaluation of the current clinical procedure. *Medical Engineering & Physics*, 2008; in press.

[26] G. Porenta, H. Schima, A. Pentaris, S. Tsangaris, D. Moertl, P. Probst, G. Maurer, and H. Baumgartner. Assessment of coronary stenoses by doppler wires: a validation study using in vitro modeling and computer simulations. *Ultrasound in Medicine & Biology*, 1999; 25(5):793–801.

[27] M. B. Robertson, U. Kohler, P. R. Hoskins, and I. Marshall. Flow in elliptical vessels calculated for a physiological waveform. *Journal of Vascular Research*, 2001; 38(1):73–82.

[28] G. Sambuceti, M. Marzilli, P. Marraccini, J. Schneider-Eicke, E. Gliozheni, O. Parodi, A. L'Abbate. Coronary vasoconstriction during myocardial ischemia induced by rises in metabolic demand in patients with coronary artery disease. *Circulation*, 1997; 95(12):2652–9.

[29] S. J. Savader, G. B. Lund, and Jr. Osterman, F. A. Volumetric evaluation of blood flow in normal renal arteries with a doppler flow wire: a feasibility study. *Journal of Vascular & Interventional Radiology*, 1997; 8(2):209–14.

[30] R. E. Shehada, R. S. Cobbold, K. W. Johnston, and R. Aarnink. Three-dimensional display of calculated velocity profiles for physiological flow waveforms. *Journal of Vascular Surgery*, 1993; 17(4):656–60.

[31] A. Veneziani and C. Vergara. Flow rate defective boundary conditions in haemodynamics simulations. *International Journal for Numerical Methods in Fluids*, 2005; 47(8-9):803–816.

[32] A. Veneziani and C. Vergara. An approximate method for solving incompressible navier-stokes problems with flow rate conditions. *Computer Methods in Applied Mechanics and Engineering*, 2007; 196(9-12):1685–1700.

[33] R. F. Wilson, D. E. Laughlin, P. H. Ackell, W. M. Chilian, M. D. Holida, C. J. Hartley, M. L. Armstrong, M. L. Marcus, and C. W. White. Transluminal, subselective measurement of coronary artery blood flow velocity and vasodilator reserve in man. *Circulation*, 1985; 72(1):82–92.

[34] J. R. Womersley. Method for the calculation of velocity, rate of flow and viscous drag in arteries when the pressure gradient is known. *Journal of Physiology*, 1955; 127(3):553–63.

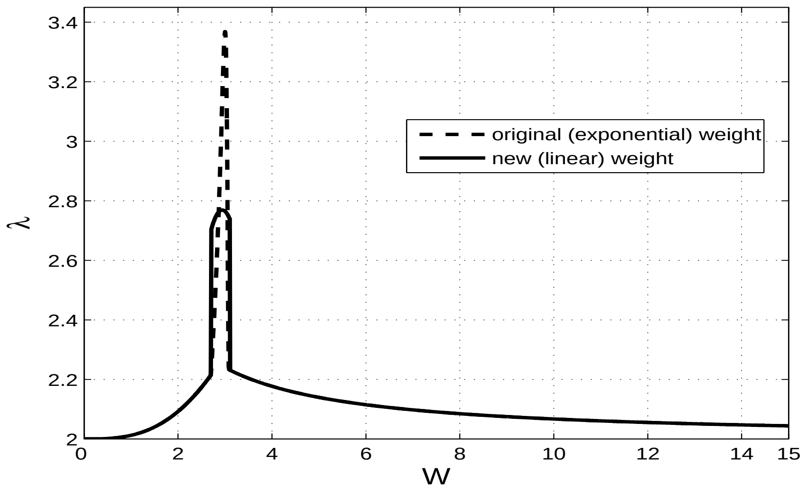

Figure 1:

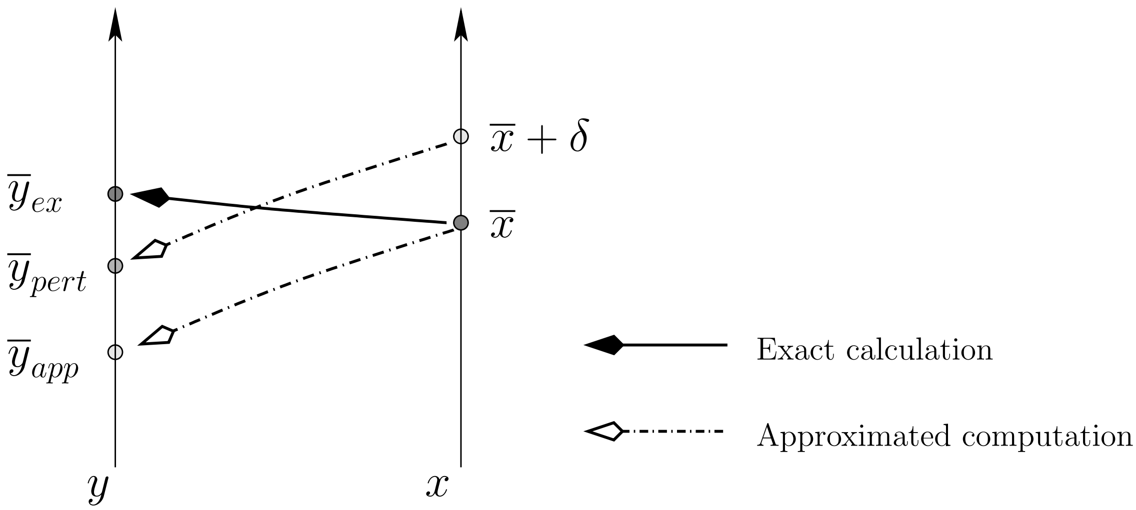

Figure 2: .

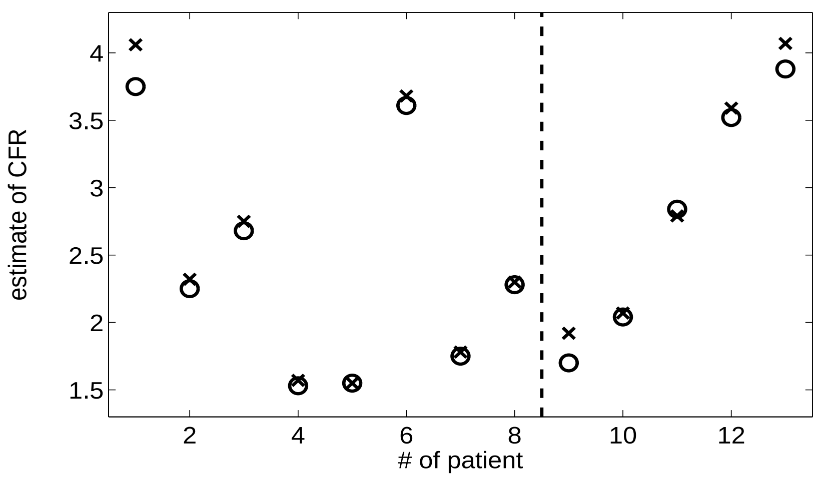

Figure 3:

MOX Technical Reports, last issues

Dipartimento di Matematica "F. Brioschi",
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

7/2008 C. Vergara, R. Ponzini, A. Veneziani, A. Redaelli, D. Neglia, O. Parodi:
Reliable CFD-based Estimation of Flow Rate in Hemodynamics Measures. Part II: Sensitivity Analysis and First Clinical Application

6/2008 E. Fumagalli, L. Lo Schiavo, A.M. Paganoni, P. Secchi:
Statistical analyses of exceptional events: the Italian experience

5/2008 S. Badia, A. Quaini, A. Quarteroni:
Modular vs. non-modular preconditioners for fluid-structure systems with large added-mass effect

4/2008 R. Milani, A. Quarteroni, G. Rozza:
Reduced basis method for linear elasticity problems with many parameters

3/2008 P. Zunino, C. D'Angelo, L. Petrini, C. Vergara, C. Capelli, F. Migliavacca:
Numerical simulation of drug eluting coronary stents: mechanics, fluid dynamics and drug release

2/2008 S. Berrone, M. Verani:
An Adaptive Gradient-DWR Finite Element Algorithm for an Optimal Control Constrained Problem

1/2008 R. Rosso, M. Verani:
Stabilizing rôle of a curvature correction to line tension

26/2007 M. Colecchia, N. Nicolai, P. Secchi, G. Bandieramonte, A.M. Paganoni, L.M. Sangalli, L. Piva, R. Salvioni:
Penile Superficial Squamous cell Carcinoma (SCC) Submitted to CO_2 Laser Excision only: Oncologic Outcome of T1 Disease in 25 Years-Long Experience

25/2007 S. Micheletti, S. Perotto:
Space-Time Adaption for Advection-Diffusion-Reaction Problems on Anisotropic Meshes

24/2007 L.M. Sangalli, P. Secchi, S. Vantini, A. Veneziani:
A Case Study in Functional Data Analisys: Geometrical Features of the Internal Carotid Artery