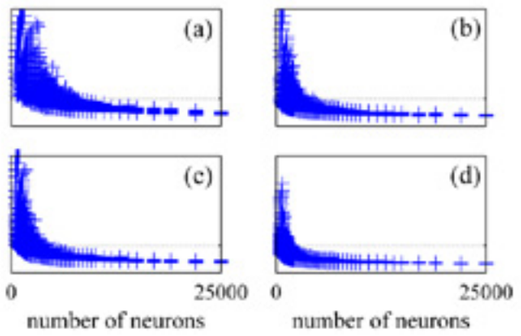

Figure 7.—Larger population sizes produce more robust working memory systems. Each graph represents the value of M/m obtained for randomly generated connectivity matrices as a function of the total number of neurons in the population (between 500 and 25000), the percentage neurons belonging the activity pattern (5% in **(a)** and **(b)**, and 10% in **(c)** and **(d)**), and the connectivity rate (10% in **(a)** and **(c)**, and 20% in **(b)** and **(d)**). For each population size, 500 samples are drawn. The dashed line marks the value M/m=4 below which the variability in the synaptic conductances becomes better contained within the calculated bounds.

tions each neuron in the pattern receives from other neurons in the pattern, the average synaptic efficacy must be $\geq 5 \times 10^{-5}/m$. On the other hand, a neuron outside the activity pattern must not be activated by the neurons in the pattern; i.e. it must not receive more than a total synaptic conductance of $20 \times 10^{-5}\mu S$. If M is the maximum number of connections each exterior neuron receives from neurons belonging the pattern, than the average synaptic efficacy must be $\leq 20 \times 10^{-5}/M$. Thus, the average synaptic efficacy must be between $5 \times 10^{-5}/m$ and $20 \times 10^{-5}/M$ which is only possible if $5 \times 10^{-5}/m \leq 20 \times 10^{-5}/M$. This means that $M/m \leq 4$.

As the population size grows, the fluctuations in the number of input synapses each neuron receives becomes less relevant (scales with $1/\sqrt{N}$) and the excitation reaching neurons inside the memory pattern, and outside, becomes more homogeneous. Less variability in the total synaptic conductances means that corruption of the memory activity pattern becomes less probable. A comparison of the population sizes required to obtain highly robust working memory systems, as a function of the pattern size and *ConnRate*, is shown in Fig. 7.

5. Final remarks

We have shown how detailed biophysical models and their numerical analysis can be used to shed light to complex problems in neurobiology. These type of models are not simply a mathematical challenge: their proximity to biology makes them ideal to construct new hypothesis, produce predictions, catalyze new experiments and ultimately improve our understanding of how our brains can process and store information.

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Modeling and simulation of the human cardiovascular system

by **Alexandra Bugalho de Moura*** and **Adélia Sequeira****

Abstract.—The use of mathematical modeling and numerical simulation to study blood circulation and related pathologies is an active interdiciplinary field of research. It has a great social and economical impact mainly due to cardiovascular diseases, that represent one of the leading causes of death and morbidity in industrialized countries.

Due to the complexity of the human cardiovascular system, the use of computational models to study blood flow in healthy and pathological situations is a challenge to mathematicians and engineers. Nevertheless, it constitutes nowadays a reliable tool which is increasingly used in clinical applications, such as the placement of stents in arteries with atherosclerotic plaques, or the understanding of aneuerysm growth and rupture.

In this article some of the fundamental aspects of mathematical modeling and numerical simulation of blood circulation will be described, highlighting in particular the pathological case of cerebral aneurysms.

1. Simulating blood circulation: a challenge to mathematicians

Over the last years, the development and application of mathematical models, seconded by the use of efficient and accurate numerical algorithms, has allowed for impressive progresses in the understanding of the human cardiovascular system, in both healthy and pathological situations [5,12,9]. The developments in scientific computation techniques and computers capacity have also contributed to patient-specific studies, providing valuable clinical information in the perspective of diagnosis, treatment or surgical planning [5,15,12,9,13,14]. Indeed, the increasing demand from the medical community for scientifically rigorous investigations of cardiovascular diseases has been a major impulse to the progress in this field. However, modeling and simulating the human circulation still remains a very difficult and challenging task. The geometrical structure of the vascular tree and the heterogeneous composition of blood, the mechanical and biochemical interactions between blood and the vessel walls, the pulsatile nature of blood flow, together with auto-regulation processes and the link between global and local circulation, are extremely complex physiological phenomena. Therefore, it is impossible to construct a three-dimensional (3D) mathematical model of the circulatory system including all those characteristics, and therefore simplifications are mandatory. On the other hand, it is recognized that cardiovascular pathologies, like atherosclerosis or aneurysms, are closely related with local hemodynamics, such as areas of flow

Keywords.—Mathematical modeling, numerical approximation, computer simulations, computational fluid dynamics (CFD), blood flow, cardiovascular system, fluid-structure interaction, geometrical multiscale modeling, aneurysm.

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reversal or low and oscillatory wall shear stress [5,7,2,12]. The progress in the power of modern computers along with the progress in imaging, visualization and geometry reconstruction techniques, as well as the improvement of sophisticated numerical algorithms, allow for the development and analysis of highly complex models. The final goal is to set up patient-specific models and simulations incorporating data and measurements taken from each single patient, that will be able to predict the results of medical diagnosis and therapeutic planning with reasonable accuracy and using non-invasive means. This is a highly multidisciplinary field of research, requiring the collaboration between mathematicians, bio-engineers and medical doctors.

2. Mathematical models for the cardiovascular system

It is known that cardiovascular diseases are associated to local hemodynamics [7,5,2], that is, to local blood flow dynamics in specific regions of the cardiovascular tree. Strictly speaking, blood is not a fluid, but a suspension of particles in a fluid named plasma [8]. However, in medium to large sized vessels, blood can be considered as an incompressible continuum fluid described by the incompressible Navier-Stokes equations, accounting for the conservation of momentum and mass (1).

2.1. The fluid equations

Given $\Omega \subset \mathbb{R}^3$ an open and bounded domain of interest, usually a portion of a vessel, and $I =]0, T]$ the time interval, the continuity and momentum equations for incompressible and isothermal fluids are given by:

$$\begin{cases} \rho\left(\dfrac{\partial \mathbf{u}}{\partial t} + \mathbf{u}\cdot\nabla\mathbf{u}\right) - \operatorname{div}\boldsymbol{\sigma}(\mathbf{u}, P) = 0, & \text{in } \Omega, \forall t \in I, \\ \operatorname{div}\mathbf{u} = 0, & \text{in } \Omega, \forall t \in I, \end{cases} \tag{1}$$

where ρ is the density of blood, assumed constant since the fluid is considered incompressible, and $\mathbf{u}$ and P are the unknown velocity and pressure fields, respectively. The fluid flow is interily known if the velocity vector and the pressure at each spacial point and instant of time are known. $\boldsymbol{\sigma}(\mathbf{u}, P)$ is the so called Cauchy stress tensor, defining the internal forces of the fluid, hence its rheology [8]. Blood is often considered to be a Newtonian fluid in large to medium sized vessels, meaning that it flows like water: the internal tangential forces are proportional to the velocity gradient, with the constant of proportionality being the fluid viscosity,

$$\boldsymbol{\sigma}(\mathbf{u}, P) = -P\mathbf{I} + 2\mu\mathbf{D}(\mathbf{u}),$$

where μ is the constant viscosity, and $\mathbf{D}$ is the strain rate tensor given by

$$\mathbf{D}(\mathbf{u}) = \frac{1}{2}\left(\nabla\mathbf{u} + \nabla\mathbf{u}^T\right). \tag{2}$$

However, blood exhibits non-Newtonian properties, mainly due to the mechanical characteristics of red blood cells [8,9]. The shear-thinning behavior of blood is one of its main non-Newtonian properties, characterized by the decrease of the apparent viscosity with increasing shear rate. In this case, the viscosity is not constant and depends on the shear rate:

$$\dot{\gamma} = \sqrt{\frac{1}{2}\mathbf{D}(\mathbf{u}) : \mathbf{D}(\mathbf{u})}. \tag{3}$$

To account for this property of blood, a generalized Newtonian rheological model can be considered [8,9,13,14] with the Cauchy stress tensor given by:

$$\boldsymbol{\sigma}(\mathbf{u}, P) = -P\mathbf{I} + 2\mu(\dot{\gamma})\mathbf{D}(\mathbf{u}).$$

Different viscosity functions $\mu(\dot{\gamma})$ define different generalized Newtonian models that can be of shear-thinning, shear-thickening, or yield stress type, according to the behavior of the apparent viscosity with respect to the shear rate. One of the most used shear-thinning generalized Newtonian models for blood is the Carreau model, for which the viscosity function is given by:

$$\mu(\dot{\gamma}) = \mu_\infty + \left(\mu_0 - \mu_\infty\right)\left(1 + (\lambda\dot{\gamma})^2\right)^{\frac{n-1}{2}}, \tag{4}$$

where $\lambda > 0$, and $n \in \mathbb{R}$ are constants, and the coefficients μ_0 and μ_∞ are the asymptotic viscosity values at low and high shear rates, respectively. In this case, since the blood is shear-thinning, we have $\mu_0 > \mu_\infty > 0$. All these parameters should be obtained from curve fitting to experimental data. In particular, in several works [9,13,14] the parameter values of the viscosity function were estimated from experimental viscosity data obtained for normal human blood: $\mu_0 = 0.456$ Poi, $\mu_\infty = 0.032$ Poi, $\lambda = 10.03$ s, and $n = 0.344$. Different experimental data will give rise to different parameter values.

2.2 Initial and boundary conditions

In order to be well-posed, i.e., to have a unique solution that depends continuously on the data, equations (1) and (3) must be endowed with initial and boundary conditions. The initial condition is given by $\mathbf{u} = \mathbf{u}_0$, for $t = 0$, in Ω. Due to the lack of in vivo data usually $\mathbf{u}_0 = \mathbf{0}$. This means that the simulation starts with a zero solution and it is necessary to compute the solution for several time instants in order to have clinically relevant solutions.

Regarding the boundary conditions, two types of boundaries should be considered (see Fig. 1): the physical artery wall, and the artificial boundaries resulting from the truncation of the domain. Indeed, due to the geometrical complexity of the cardiovascular system, the computational cost of 3D simulations, and the fact that 3D detailed information is usually needed only in specific regions of interest, the portion of the artery at study should be truncated.

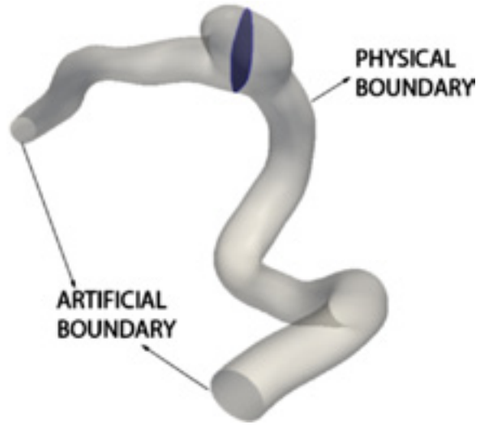

Figure 1.—The 3D computational domain of interest (blood vessel with an aneurysm), showing the physical boundary formed by the artery wall and the inflow and outflow artificial sections due to the truncation of the domain.

On the physical boundary, that we denote by Γ_w, boundary conditions are prescribed using physical arguments. If the movements of the vessel wall due to the blood flow load are not considered, i.e., if the artery wall is assumed to be rigid, then at that boundary the velocity is zero $\mathbf{u} = \mathbf{0}$, describing the total adherence of the fluid to the wall (no-slip condition). This simplifying hypothesis is assumed very often [2,9,12,13,14,15].

2.3 Compliance of the artery wall: fluid-structure interaction (FSI)

If the compliance of the wall is taken into account, the velocity of the fluid on the wall should be the same as the velocity of the moving wall: $\mathbf{u} = \mathbf{g}$, where $\mathbf{g}$ is the wall velocity given by a mathematical model that describes its motion [10,4]. The vascular wall is a very complex soft tissue, composed of several different layers, and it is very difficult to devise appropriate and accurate models describing their dynamical behavior. This is still a subject of active research and, for that reason, the simplest 3D linear hyperelastic model is often applied (see [10,4,11] and references therein):

$$\rho_w \frac{\partial^2 \boldsymbol{\eta}}{\partial t^2} - \operatorname{div}_0(\mathbf{P}) = \mathbf{0}, \qquad \text{on } \Omega_s^0, \tag{5}$$

where Ω_s^0 is the computational domain of the structure artery wall in the reference configuration[1], $\boldsymbol{\eta}$ is the displacement vector with respect to the reference configuration Γ_w^0, ρ_w is the wall density, div_0 stands for the divergence operator with respect to the Lagrangian coordinates and $\mathbf{P} = \mathbf{P}(\boldsymbol{\eta}) = \mathbf{FS}$ is the first Piola-Kirchhoff tensor (see [10,4]), with $\mathbf{S} = \mathbf{S}(\boldsymbol{\eta})$ the second Piola-Kirchhoff tensor and $\mathbf{F} = \mathbf{F}(\boldsymbol{\eta}) = \mathbf{I} + \nabla_0\boldsymbol{\eta}$ the deformation gradient tensor.

To have a description of the bood-vessel interaction problem, the fluid equations (1) and (3) are coupled with the structural equations (5). That is achieved by imposing the following matching conditions on Γ_w^t,[2] for all $t \in I$:

$$\begin{cases} \mathbf{u} = \dot{\boldsymbol{\eta}}, \\ -(\boldsymbol{\sigma}(\mathbf{u}, p) + p_{ext}\mathbf{I})\cdot\mathbf{n} = \boldsymbol{\Phi}\cdot\mathbf{n} \end{cases} \tag{6}$$

where p_{ext} is a given external pressure which, without loss of generality, is considered to be zero, $\boldsymbol{\Phi}$ is the stress exerted by the structure on the fluid and $\mathbf{n}$ is the outward unit vector to Γ_w^t. In (6) the first equality is the no-slip condition that guarantees the total adherence of the fluid to the structure ($\dot{\boldsymbol{\eta}}$ is the wall movement velocity), while the second equality establishes the continuity of the normal stresses.

{1} As it is customary in solid mechanics, the structure equations are written in the reference configuration (Lagrangian frame), while the fluid equations are set up in the current configuration (Eulerian frame), see for instance [10].

{2} Notice that now the fluid domain changes in time, due to the wall motion: $\Omega = \Omega^t$, and $\Gamma_w = \Gamma_w^t$.

It is necessary to provide appropriate initial conditions to the structure, compatible with the FSI problem. The dependence of the fluid domain on the structure equations solution makes it very difficult to guarantee the well-posedness of the FSI problem, which is still an open problem [10,4].

2.4 Artificial boundaries: the geometrical multiscale approach

The prescription of boundary conditions on the artificial sections constitutes a great challenge, since they cannot be deduced from physical arguments, and in vivo data on the flow rate or pressure are very difficult to obtain. The artificial sections can be divided into two types, the inflow sections, closer to the heart and also called upstream sections (usually the computational domain only has one inflow section), and the outflow sections, closer to the systemic circulation and also called downstream sections (it is common to have more than one in the computational domain). Very often standard boundary conditions, such as Neumann homogeneous conditions at outflow sections, are imposed: $\sigma(\mathbf{u}, P) \cdot \mathbf{n} = \mathbf{0}$. However, these conditions do not account for the remaining parts of the cardiovascular system. The computational solution is highly dependent on the choice of the boundary conditions on the artificial sections, so that such solutions can become not reliable and their use in clinical applications are compromised. Indeed, the cardiovascular system is closed, and the local hemodynamics greatly depends on the systemic circulation (see e. g. [12]). For that reason, the global behavior of blood flow should be taken into account in local 3D simulations. In order to do that, models of different geometrical scales, with different levels of accuracy and computational cost are considered, according to the level of detail required. This approach leads to the so called *Geometrical Multiscale Modeling* of the cardiovascular system [6,10].

In regions where detailed information is necessary, 3D models are applied. These are the most computationally costly and can only be applied to small regions of the vasculature.

If the purpose is to simulate large arterial trees, 1D simplified models should be used [3,6,10,4,11,1]. These models are obtained from the 3D FSI problem by averaging and assuming cylindrical geometry of the vessels. The 1D models are less accurate, providing only average quantities such as flow rate and mean pressure, yet they

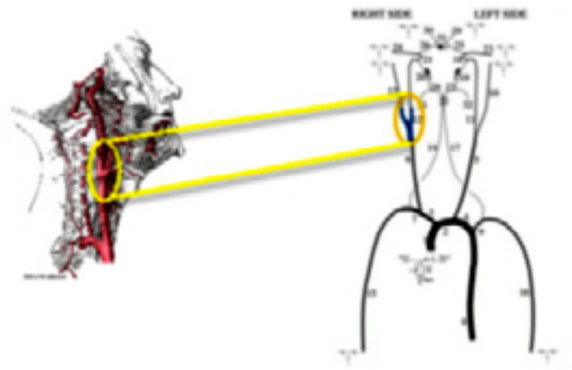

Figure 2.—Schematic of the coupling of a 3D model of the carotid bifurcation with a 1D arterial network, and with 0D models at its extremities to take into account the capillaries resistance.

are much less expensive from the computational view point and describe very well the wave propagation nature of blood flow in arteries [10,4,11]. Indeed, the 1D model for blood flowing in arteries is given by an hyperbolic system of equations, that in physiological situations is under a sub-critical flow regime.

Simpler lumped parameter models can be derived from the 1D models by further averaging in space, resulting in a system of ordinary differential equations (ODEs) [3,6,12]. Since lumped parameter models do not depend on space, they are also named 0D models. They describe the variation in time of the averaged pressure and flow rate in a specific region of the circulatory system, such as the venous bed, the pulmonary circulation, or the heart. There is a strong analogy between lumped parameter models and electric networks. Indeed the flow rate can be seen as the electric current and the mean pressure as the voltage. Furthermore, the lumped parameters are precisely the resistance, related with the blood viscosity, the inductance, related with the blood inertia, and the capacitance, related with the wall compliance.

Coupling together models of the three different levels gives rise to the geometrical multiscale modeling of the cardiovascular system. The couplings are achieved by imposing the continuity of mean pressure and flow rate [6,10,4]. In this manner, reduced 1D or 0D models can be coupled to the artificial sections of the 3D model in order to provide proper boundary conditions, accounting for the remaining parts of the cardiovascular system [10,4,11,12]. This procedure allows to perform reliable computational simulations of local blood flow with clinical impact. Fig. 2 illustrates the coupling of all the three hierarchical models. The region of interest is the carotid bifurcation, which often undergoes atherosclerotic plaques.

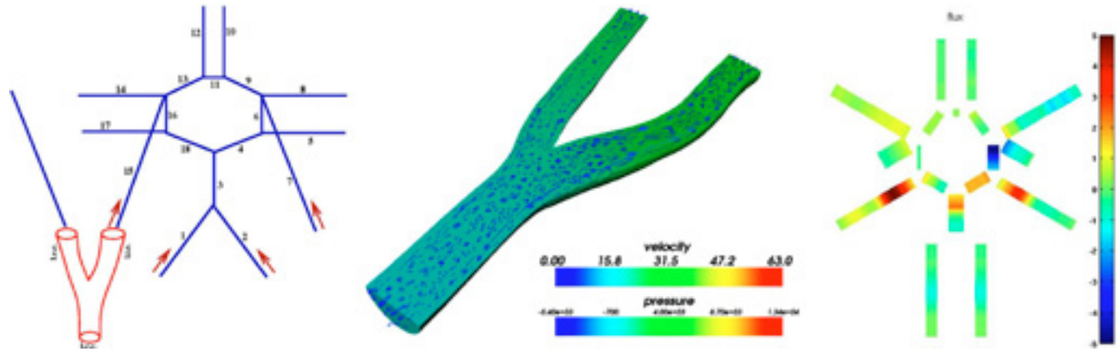

Figure 3.—Realistic 3D carotid bifurcation coupled to the circle of Willis. Left: scheme of the coupling between the 3D carotid bifurcation and 1D reduced models. The internal carotid downstream section is coupled to a 1D network of the circle of Willis, while the external carotid downstream section is coupled to a single 1D tube. Center: pressure [dyn/cm^2] and velocity [cm/s] solution in the 3D carotid bifurcation. Right: the values of the flow rate [cm^3/s] in the circle of Willis [10,11].

In Fig. 3, the numerical solution of the coupling of a 3D FSI model of the carotid bifurcation with a 1D model of the circle of Willis is represented (taken from [10,11]). The 1D description of the circle of Willis properly accounts for the absortion and propagation of pressure waves, so that the 3D simulation on the carotid bifurcation is reliable.

Although they are less detailed, the reduced 1D and 0D models provide very useful simulations at very low computational cost, and are often applied as stand alone models, not necessarily coupled with 3D models. For instance in [1], 1D models are used to study anatomic variations of the circle of Willis, and in [3], 1D models and a 0D model for the heart are applied to study the circulation effects of amputating one leg.

In [13,14] the sensitivity of the numerical fluid solution in cerebral aneurysms to changes on the outflow conditions is studied, including the use of reduced models. In [12] the geometrical multiscale approach is used to obtain reliable results with clinical applications in heart paediatric surgery.

3. Numerical simulation of hemodynamics in cerebral aneurysms

Cerebral aneurysms are pathological dilations of the cerebral vascular wall, which induce modifications in the mechanical properties of the artery wall, including its weakning that may lead to rupture. The rupture of cerebral aneurysms causes sudden death in 50% of the patients, and provokes permanent disabilities in a great number of the remaining cases. It is a silent pathology, without any symptomatology until rupture, except for a very small number of cases. It is therefore a devastating disease that is believed to affect approximately 5% of the population. The causes for initiation, growth and rupture of cerebral aneurysms are still unknown, although it is accepted that there is a correlation between aneurysm progression or genetic and hemodynamic factors [2,5,15]. In what concerns the hemodynamic factors, the numerical simulations play a very important and unique role in the comprehension of this disease, allowing in particular to obtain patient-specific reliable results and their visualization in a non-invasive way [9,13,14,15]. Through computational simulations it is also possible to easily compute hemodynamic indicators, such as the wall shear stress (WSS), that are very difficult to measure in vivo or in vitro. Precisely, the WSS and other related quantities, such as the WSS gradient, are known to be determinant in the initiation, growth and rupture of aneurysms [2,15]. Thus, numerical simulations have

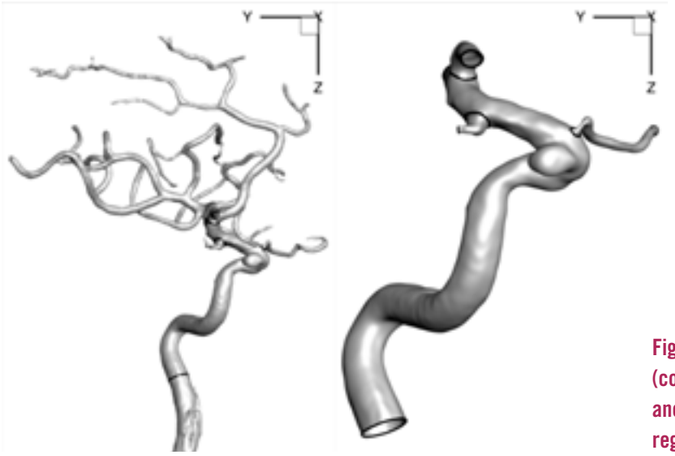

Figure 4.—Reconstructed geometry from CTA (computed tomography angiogram) of a cerebral aneurysm (left), and definition of the computational region of interest (right) [13].

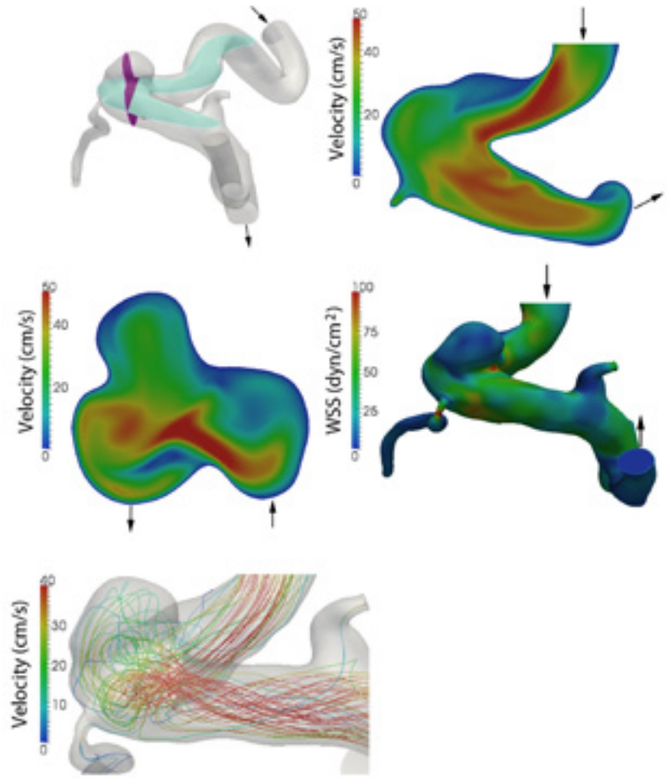

Figure 5.—Illustration of the chosen cross-sections (top-left), velocity magnitude (cm/s) in both cross-sections (top-right and middle-left), WSS magnitude (dyn/cm^2) (middle-right), and velocity pathlines coloured by the velocity magnitude (bottom). Note that the velocity cross-section that includes the aneurysm is such that the upstream flow is on the right and downstream flow on the left [13].

nowadays an increasing impact in the clinical practice of patients with cerebral aneurysms. They lead to a better understanding of the disease and try to predict its natural progression, namely its rupture and consequent potential letal bleeding, contributing also to its treatment. Therefore, computer simulations constitute a tool to support medical and clinical decision, both in the analysis and diagnosis of anatomic and physiological results, as well as in the prediction of surgical outcomes and post surgical complications. The results may also contribute to improve treatment and surgical techniques, such as endovascular surgery.

As already mentioned, the hemodynamics highly depends on the morphology of the blood vessels, that is, on its geometry, being thus specific of each patient. In particular, for the study of cerebral aneurysms, reliable simulations depend not only on the choice of appropriate mathematical models and accurate numerical algorithms, but also on their application in patient-specific computational geometries, obtained from medical acquisition, as for instance computational tomography (CT). In order to have patient-specific computational domains, it is necessary to reconstruct the medical images, which consists essentially in three steps [9,13,14]:

(1) Segmentation: identification of the region of interest in the grey scale medical image. In this case it is important to distinguish between lumen and artery wall;

(2) Surface reconstruction: mathematical definition of the 3D surface, usually performed by means of the marching tetrahedra algorithm (see [9,13,14] and references therein);

(3) Smoothing: the 3D reconstructed surface has non physiological irregularities related with the medical image quality, which has noise due to its acquision, that should be eliminated through a smoothing process usually carried out by a bi-Laplacian algorithm [9,13,14].

Once one has the reconstructed medical image (see Fig. 4, left) [13], it is necessary to define the computational region of interest, where to perform the 3D numerical simulations (see Fig. 4, right) [9,13,14]. Afterwards, it is necessary to define a computational 3D mesh, by decomposition into simpler geometrical figures, usually tetrahedra, in which the numerical algorithms are applied. In order to attain accurate solutions in patient-specific simulations, it is essential to have a large number of very small elements, usually in the order of millions.

From the simulation results of the velocity and pressure fields, it is possible to compute the hemodynamic indicators associated to aneurysm risk of growth and rupture, such as the WSS and its variations. In Fig. 5 are depicted the numerical results of the simulation performed in the geometry of Fig. 4, taken from [13]. It is possible to observe that the region of higher WSS is the neck of the aneurysm, precisely where the flux of the main vessel occurs, as it can be seen by the pathlines, while the lower values of WSS are found within the aneurysm sac.

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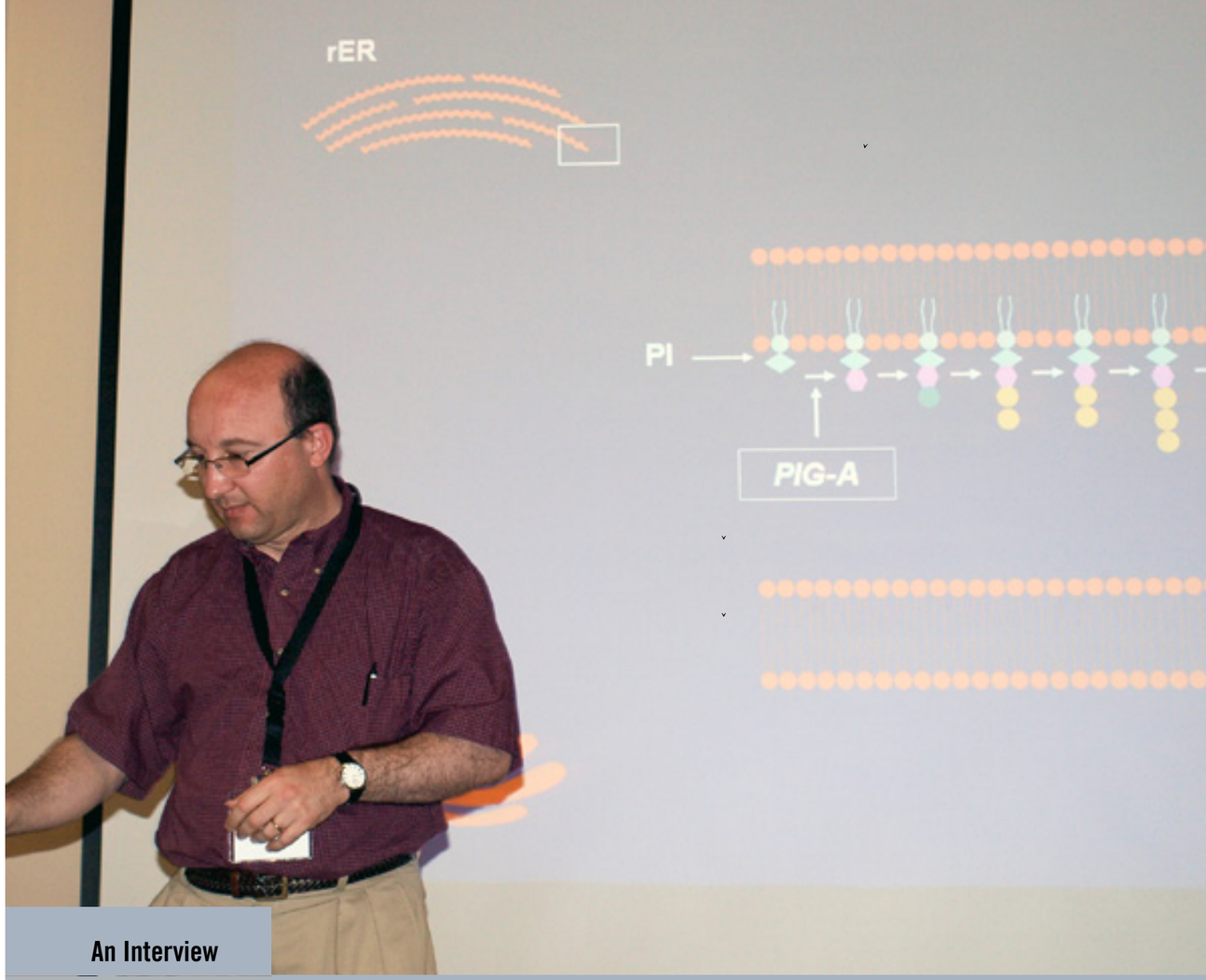

An Interview

with David Dingli

by **Francisco Santos** and **Fabio Chalub** [Universidade Nova de Lisboa]

David Dingli was in Evora for the Summer School "Dynamic Models in Life Sciences", where he presented a set of lectures called "Hematopoietic Stem Cells and Hematopoiesis". In these lectures, he introduced the audience to the state-of-the-art in the dynamics of stem cells, and their relation to blood disorders. After the conference he gave this interview to Francisco Santos and Fabio Chalub, summer school co-organizers.