A computational model for prediction of clot platelet content in flow-diverted intracranial aneurysms: Supplementary material

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1 Governing equations

We based our model of thrombin generation and platelet activation on the models presented in [6, 10]. Since these models don't include fibrin generation, we used the mathematical model of fibrin generation presented by Anand *et al.* [1]. To model the bulk aggregation of platelets, we modified a representation of platelet aggregation at the site of injury originally proposed by Leiderman and Fogelson [8], called the LF-model.

To assess the likelihood of formation of a fibrin and platelet rich clot, a macroscopic model for post-FD thrombosis in the aneurysm was made based on the previous models of haemostatic thrombosis [1, 6] and platelet deposition [8, 10]. Mathematical description of the models used to simulate transport phenomena and biochemical reactions are given below. Following the common practice in biochemical reaction modelling, where the rate of occurrence of event, x, requires an appropriate concentration of a particular species, C_i, i.e., the concept of cooperativity, the Hill function, a sigmoidal activation function of form $\phi_x^i = C_i^n/(C_i^n + C_{i,50}^n)$, was used [5]. In this equation, C_i is the concentration of species i, $C_{i,50}$ is the concentration of species i where the half-maximal activation (half saturation) occurs, and the exponent n, called the Hill coefficient, reflects the steepness and switch-like character of the sigmoid. In this study, we set $n = 4$ where we needed a narrow switch like response to availability of a specie, and set $n = 2$ when a wider and smoother response was required.

1.1 Fluid flow

Three dimensional momentum equations for incompressible and Newtonian fluid, the Navier-Stokes equations, were used to describe blood flow.

$$\rho\frac{\partial \boldsymbol{u}}{\partial t} + \rho(\boldsymbol{u}\cdot\nabla)\boldsymbol{u} = -\nabla p + \mu\nabla^2\boldsymbol{u} - \mu\Phi(k_f, k_p)\boldsymbol{u}. \tag{1}$$

In (1), $\boldsymbol{u}$ and p represent the velocity vector and pressure, respectively. Blood was assumed to be a Newtonian fluid with constant density, $\rho = 1066$ kg/m^3 and viscosity, $\mu = 0.0035$ Pa.s [13]. To account for the effect of clot on the fluid velocity field, without modelling the fluid-structure interaction, the blood clot was treated as a porous medium with both fibrous (fibrin strands) and granular (bound platelets) components. A Darcy term, $\mu\Phi(C_f, C_p)\boldsymbol{u}$, was added to the momentum equations. The function $\Phi(C_f, C_p)$ was defined as

$$\Phi(C_f, C_p) = \frac{1}{k_{fi}}\phi_p^{fi} + \frac{1}{k_{bp}}\phi_p^{bp}, \tag{2}$$

where k_{fi} and k_{bp} are permeabilities of the clot due to fibrin fibres and bound platelets, respectively. The Hill functions ϕ_p^{fi} and ϕ_p^{bp} were used ensure that there is no flow restriction in regions

with no fibrin or platelet aggregates, while flow restriction increases to half of its maximal value as fibrin and platelet concentrations approaches $C_{fi,50}$ and $C_{bp,50}$, respectively. According to Anand et al. [1], the concentration of a fibrin gel at plasma level fibrinogen concentration was assumed to be greater than 600 nM, i.e., a fibrin gel was assumed to be formed when concentration of fibrin reached 600 nM. Based on this and the measurments done by Wufsus et al. [14], we set $C_{fi,50} = 600$ nM, $C_{bp,50} = 7 \times 10^5$ platelets/μm^3, $k_{fi} = 1.2 \times 10^{-1} \mu$m^2, and $k_{bp} = 3.1 \times 10^{-1} \mu$m^2. We also set $n = 4$ to ensure a sharp boundary between the clot and blood while maintaining the numerical stability. We calculated the fluid residence time as described by Rayz et al. [9] and shear rate was calculated using the associated built-in variable in CFX.

1.2 Fluid-phase chemical species

We denote by C_{pt}, C_{th}, C_{at}, C_{fg}, C_{fi}, the bulk concentrations of prothrombin, thrombin, anti-thrombin, fibrinogen, and fibrin, respectively. Transport of each species was modelled using the advection-diffusion-reaction equation:

$$\frac{\partial C_i}{\partial t} + (\boldsymbol{u} \cdot \nabla) C_i = D_i \nabla^2 C_i + S_i, \tag{3}$$

where C_i is the species concentration, D_i is the diffusion coefficient, and S_i is the reaction term.

Thrombin generation was assumed to occur on the surface of resting and activated platelets and the platelets bound to the clot. The kinetics of the reactions was assumed as second order chemical reactions with kinetic constants k_{th}^{rp}, k_{th}^{ap}, and k_{th}^{bp}, respectively. Thrombin inhibition by anti-thrombin was also modelled as a second order reaction with kinetic constant, k_{th}^{at}. Thrombin-mediated fibrin generation was assumed to occur according to Michaelis-Menten kinetics with k_{fi}^{th} and $k_{m,fi}^{th}$ as kinetic constants. The reaction source terms in (3) were formulated for each species as:

$$S_{pt} = -k_{th}^{rp} C_{rp} C_{pt} - k_{th}^{ap} C_{ap} C_{pt} - k_{th}^{bp} C_{bp} C_{pt} \tag{4}$$

$$S_{th} = k_{th}^{rp} C_{rp} C_{pt} + k_{th}^{ap} C_{ap} C_{pt} + k_{th}^{bp} C_{bp} C_{pt} - k_{th}^{at} C_{at} C_{th} \tag{5}$$

$$S_{at} = -k_{th}^{at} C_{at} C_{th} \tag{6}$$

$$S_{fg} = -S_{fi} = -k_{fi}^{th} C_{th} C_{fg} / (k_{m,fi}^{th} + C_{fg}). \tag{7}$$

1.3 Platelet activation and binding

Transport of resting, C_{rp}, and activated, C_{ap}, platelets were modelled using (3). The same equation was solved for bound platelets, C_{bp}, but advection and diffusion terms were removed to prevent platelets from being transported once recruited by the clot.

Platelet activation by thrombin and already activated platelets were modelled as first order reactions with k_{pa}^{th} and k_{pa}^{ap} as kinetic constants of activation by thrombin and activated platelets, respectively. Platelet activation by thrombin was assumed to occur when thrombin concentration was greater than 9.11×10^{-1} nM [10]. This was modelled by multiplying the associated reaction source by a Hill activation function, ϕ_{pa}^{th} with $C_{th,50} = 9.11 \times 10^{-1}$ nM and $n = 4$ to ensure a steep and switch-like response around the threshold concentration.

Leiderman and Fogelson [8] assumed platelet aggregation and deposition at the site of injury to be proportional to the free platelet concentration and value of a binding affinity function, a Hill function, representing proximity of free platelets to already bound platelets. Fibrin generation was not considered by Leiderman and Fogelson [8]. In the present model, we considered thrombin-induced fibrin generation and its effect on platelet trapping and aggregation. We

Table 1: Model parameter values

Biochemical reactions kinetic constants					
k_{th}^{rp}	6.50×10^{-10} U PLT^{-1}s$^{-1}\mu$M^{-1}	[10]	k_{th}^{ap}	3.69×10^{-9} U PLT^{-1}s$^{-1}\mu$M^{-1}	[10]
k_{th}^{bp}	6.50×10^{-10} U PLT^{-1}s$^{-1}\mu$M^{-1}	[10]	k_{th}^{at}	7.083×10^{-3} μM^{-1}s^{-1}	[10]
k_{fi}^{th}	59.00 s^{-1}	[1]	$k_{m,fi}^{th}$	3160 nM	[1]
k_{pa}^{th}	0.50 s^{-1}	[6]	k_{pa}^{ap}	0.30 nM^{-1}s^{-1}	[6]
k_{pa}^{bp}	0.30 nM^{-1}s^{-1}	[6]	k_{pb}	1.00×10^{4} s^{-1}	[8]
Diffusion coefficients					
D_{pt}	5.21×10^{-7} cm^{2}s^{-1}	[1]	D_{th}	6.47×10^{-7} cm^{2}s^{-1}	[1]
D_{at}	5.57×10^{-7} cm^{2}s^{-1}	[1]	D_{fg}	3.10×10^{-7} cm^{2}s^{-1}	[1]
D_{fi}	2.47×10^{-7} cm^{2}s^{-1}	[1]	D_{rp}	2.50×10^{-7} cm^{2}s^{-1}	[8]
D_{ap}	2.50×10^{-7} cm^{2}s^{-1}	[8]			

assumed platelet recruitment and deposition to depend on the concentration of free platelets and value of a function representing fibrin-platelet. We used a second order Hill function ϕ_{pb}^{fi} with $C_{fi,50} = 60$ nM, i.e., 10% of the threshold concentration at which fibrin clot is said to be formed, i.e., 600 nM. According to the above, the reaction source terms for resting and activated platelets were formulated as:

$$S_{rp} = -k_{pa}^{th}\phi_{pa}^{th}C_{rp} - k_{pa}^{ap}C_{rp} \tag{8}$$

$$S_{ap} = k_{pa}^{th}\phi_{pa}^{th}C_{rp} + k_{pa}^{ap}C_{rp} - k_{pb}\phi_{pb}^{fi}C_{ap} \tag{9}$$

$$S_{bp} = k_{pb}\phi_{pb}^{fi}C_{ap}. \tag{10}$$

2 Model parameters

Our model includes eight biochemical species and nine biochemical reactions. Values of reaction rate constants were taken from the experimental literature and are reported in Table 1. The parameter k_{pb} represents the rate of aggregation and deposition in the presence of fibrin. To our knowledge, this parameter has not been measured experimentally. Leiderman and Fogelson [8] estimated a fixed value for this parameter and reported only some change on the platelet density distribution in response to up to 100-fold increases of this value. We used the same value as Fogelson and Leiderman [8] and remark that as long as the value maintained though all the experiments, despite the limited effect on platelet aggregation densities, it will not influence the case-to-case comparisons made based on the platelet aggregation density.

Values of diffusion coefficients for all species were taken from the experimental literature. The shear dependent diffusion augmentation effect of red blood cells on the diffusion of platelets was considered by two orders of magnitude increase in the expected value in normal Brownian motion [12, 8]. Platelets were assumed to be static once bound to the clot, therefore, in Table 1, no diffusion coefficient is reported for the bound platelets.

3 Computer model of the phantom experiment and the flow diverters

We built a computer model of the phantom using ANSYS Design Modeler v16.2 (Ansys Inc., Canonsburg, PA, USA). Geometric models of the deployed FD's were created using Fast Virtual Stenting (FVS) method [7]. According to the study [3], each FD consisted 24 wires of 40 μm thickness and mean porosities of the FD's in their deployed configuration were 72% and 65% for FD-4.5 and FD-4.0, respectively. Since we were only interested in the effect of FD's on the intra-aneurysmal flow, to reduce the computational costs, the FD models were clipped and portions of the FD's laying entirely on the vessel wall were removed. The effect of partial stent modelling on intra-aneurysmal haemodynamics was proven negligible in previous studies [2].

4 Numerical simulations

Volumetric meshes were generated using ANSYS ICEM CFD v16.2 (Ansys Inc., Canonsburg, PA, USA). Element sizes in the core region of the domain were set according to the @neurIST processing tool chain, where mesh independence tests on non-stented aneurysms were performed as described in [13]. Stuhne and Steinman [11] suggested that the mesh resolution in the vicinity of the stent wires needs to be about one-third of the wire's radius to achieve an accurate flow solution around the struts. In this study, a mesh independence test was performed with three levels of refinement around the struts maintaining the mesh size in the core region. A coarse mesh (maximum edge size of 0.02 mm on the wires), a medium resolution mesh (maximum edge size of 0.01 mm on the wires), and a fine mesh (maximum edge size of 0.005 mm on the wires) were considered, while the fine mesh used as the reference in the test. Mesh independence was performed based on the inflow rate at the aneurysm neck and the sac-averaged concentrations of the fibrin and platelets, and mesh independence was assumed to be reached when the solutions differed less than 1% from the reference-mesh solutions. Mesh independence was obtained for the medium resolution mesh, where tetrahedral elements with maximum edge size of 0.2 mm and five layers of prismatic elements with a maximum edge size of 0.1 mm were used to discretise the core region of the computational domain. This resulted in volumetric meshes with 13 and 12 million total number of elements for the FD-4.0 and FD-4.5 cases, respectively.

Two sets of simulations were performed for each of the FD-4.0 and FD-4.5 cases: (i) unsteady pulsatile flow simulation of intra-aneurysmal haemodynamics before and after stent placement with no thrombosis model included. This was done to enable comparisons with PIV measurements reported by Gester et al. [3] at the peak systole; and (ii) non-pulsatile flow simulation of intra-aneurysmal haemodynamics and biochemistry before and after stent placement. According to Gester et al. [3], in-vitro experiments were performed based on a pulsatile flow waveform with a time-averaged flow rate of 220 mL/s obtained from measurements reported by Hoi et al. [4]. We prescribed the same waveform as the inlet boundary condition in the first set of simulations. In the second set of simulations, we prescribed a non-pulsatile flow of 220 mL/s as the inlet boundary condition. The concentration of each species at the inlet was set at their normal value in blood. The inlet concentrations of thrombin and fibrin were set to zero [1]. Prothrombin, anti-thrombin, and fibrinogen were assumed to have inlet concentrations of 1400, 2410, and 7000 nM [1]. The concentration of resting platelets at the inlet was set to 2×10^8 platelets per millilitre and 5% of this concentration was assumed as the level of background platelet activation [10]. All model variables were initialised using a steady-state simulation with all the reaction terms off. After initialisation, unsteady simulations of the reactive flow were

performed. In all simulations, the mean Reynolds number at the inlet was 338; no turbulence modelling was performed; a Poiseuille profile was imposed at the inlet; wall distensibility was not considered (rigid-wall assumption); and, a zero-pressure condition was prescribed at the outlet.

The coupled momentum and transport equations for biochemical species were solved in ANSYS CFX v16.2 (Ansys Inc., Canonsburg, PA, USA) using a finite volume method. CFX's Finite Rate Chemistry combustion built-in model was used to simulate blood flow in which thrombosis biochemical reactions occur. Second-order-accurate discrete approximations were used both in space and time, i.e., a second-order advection scheme and a second-order backward Euler transient scheme. In the first set of simulations, unsteady simulations were run for 3 cardiac cycles and results from the last cycle used in the analyses. The cardiac cycle was discretised in time into 200 equal steps. The time-step size was set according to the @neurIST processing toolchain where time-step size independency tests were performed as described by Villa-Uriol et al. [13]. In the second set of simulations, CFX's automatic time-scale control was used in the steady-state initialisation simulations. Simulations of the coupled flow and thrombosis were run for 30 seconds of simulation time using CFX's adaptive time-stepping with minimum, maximum, and initial time-steps of 0.0001 s, 0.05 s, and 0.01 s. Solutions of the steady-state simulations and those of unsteady simulations at each time step converged when maximum residual of the computational domain was less than 5×10^{-4}.

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