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Lagrangian methods for blood damage estimation in cardiovascular devices - How numerical implementation affects the results

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Summary

This paper evaluated the influence of various numerical implementation assumptions on predicting blood damage in cardiovascular devices using Lagrangian methods with Eulerian computational fluid dynamics. The implementation assumptions that were tested included various seeding patterns, stochastic walk model, and simplified trajectory calculations with pathlines. Post processing implementation options that were evaluated included single passage and repeated passages stress accumulation and time averaging. This study demonstrated that the implementation assumptions can significantly affect the resulting stress accumulation, i.e., the blood damage model predictions. Careful considerations should be taken in the use of Lagrangian models. Ultimately, the appropriate assumptions should be considered based the physics of the specific case and sensitivity analysis, similar to the ones presented here, should be employed.

Keywords

Blood damage model; computational fluid dynamics; Lagrangian methods; cardiovascular devices; numerical modeling

1. Introduction

Cardiovascular devices are known to cause thromboembolic complications that requires anticoagulant therapy. Experimental studies related this blood damage to elevated flow shear stress levels and exposure time of the blood constituents to it [1,2]. Most of the suggested blood damage or hemolysis models follow a power law formulation of the form suggested by Blackshear et al. [3]:

$$D=C\tau^{\alpha}t^{\beta} \quad (1)$$

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where D is an index of damage, τ is the shear stress, t is the exposure time, and C , α , and β are model coefficients [3–7].

Our group employed the linear hemolysis model ($C=\alpha=\beta=1$; [5]) to study mostly platelet activation, employed in numerical simulations of blood flow in various cardiovascular devices, e.g., mechanical heart valves (MHV) [8–10] and mechanical circulatory support (MCS) devices [11,12]. For this purpose, we have employed multiphase discrete phase model (DPM) and calculated the Lagrangian trajectories for a large number of platelets. While these simulations in devices provided invaluable quantification of the thrombogenic potential of these devices, the influence of numerical implementation methods on such models was never methodologically examined. The aim of this paper is to evaluate how the numerical implementation of Lagrangian damage models, when coupled with traditional Eulerian CFD model, affect their results. These effects are evaluated with sensitivity studies using our linear stress accumulation model. We would like caution that the ability of Lagrangian damage models to predict accurate blood damage is highly dependent on their degree of complexity, and that accurate predictive capabilities may become elusive and need to be validated in complex series of in vitro experiments. However, a very important utility of Lagrangian damage models is in comparative type of studies (e.g., for comparing the thrombogenic performance of two similar designs of a certain device with the same numerical methodology). In such studies the comparison may eliminate the effects of a priori implementation assumptions while still maintaining the predictive capabilities of the model.

2. Methods

We have conducted a comparison of several numerical implementation methods and studied their influence on the results of Lagrangian cell damage models. Nine dedicated simulation models were used for these comparisons. These models use two flow regimes: (i) laminar flow through coronary stent and (ii) turbulent flow through mechanical heart valve. These two devices represent typical cases for implementation assumptions that can affect the results. For both cases, the Lagrangian trajectories were calculated by employing DPM with particle injection. Spherical particles, representing naturally buoyant platelets with diameter of $3\ \mu\text{m}$ and the density of the surrounding fluid, were released at the entrance to the device. The trajectory of a platelet is calculated from the force balance between the inertia and drag forces acting on the particle, in a Lagrangian reference frame. The stress history of these platelet particles were registered along their corresponding flow trajectories and rendered to calculate the linear stress accumulation (SA) for each platelet trajectory. The SA that is used herein is defined as the integral of the stress over time that can be numerically approximated as the summation of the instantaneous stress magnitude and exposure time product [5]:

$$SA = \int_0^{T_{\text{traj}}} \sigma dt \approx \sum \sigma \cdot \Delta t \quad (2)$$

where T_{traj} is the trajectory duration, t is time and Δt is the time step. Obviously, other non-linear models can also be employed in a similar manner to test the effect of various implementation methods. The contribution of the various stress tensor components is rendered into a scalar stress as first suggested by Bludszuweit [13] and then applied by Apel et al. [14] and our group [8]. The scalar stress is based on comparison of the work for element deformation in uni-axial shear flow with the work for 3-D deformation:

$$\sigma = \sqrt{\frac{\sigma_{xx}^2 + \sigma_{yy}^2 + \sigma_{zz}^2 - \sigma_{xx}\sigma_{yy} - \sigma_{yy}\sigma_{zz} - \sigma_{zz}\sigma_{xx} + 3(\tau_{xy}^2 + \tau_{yz}^2 + \tau_{zx}^2)}{3}} \quad (3)$$

where for the turbulent cases, the stress tensor includes both the viscous and the Reynolds stresses, while the Reynolds stresses are approximated based on Boussinesq's eddy viscosity hypothesis:

$$\sigma_{ij} = \mu \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) - \overline{\rho u_i u_j} \approx \mu \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) + \frac{2}{3} \rho k \delta_{ij} - \mu^t \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \quad (4)$$

where μ is the viscosity, $\frac{\partial u_i}{\partial x_j}$ is the mean velocity gradient, ρ is the density, $\overline{\rho u_i u_j}$ is the Reynolds stress, k is the turbulent kinetic energy, and μ^t is the turbulent viscosity.

The statistical distribution of the SA reached by thousands of platelets along their multiple trajectories is collapsed into a Probability Density Function (PDF) [9]. The PDF method describes the statistical distribution of the likelihood that SA values will be reached by individual platelet trajectory, representing the 'thrombogenic footprint' of the device and facilitates easy comparison between different devices or their design iterations. Although, this representation of 'thrombogenic footprint' of a device was suggested for comparison of different device designs, here it is employed in somewhat non-traditional way for comparing the effect of different implementation assumptions. This use allows us to focus on how the implementation assumptions affect the results. The amount of particles that were released, approximately 11,500, was chosen based on refinement study to assure that the PDF of the SA is not sensitive to this size.

While both types of models were solved with transient flow equations, for simplification purposes and in order to make the models more comparable, the boundary conditions were constant. In all the models the blood was assumed non-compressible and Newtonian with density of 1060 m³/kg and viscosity of 0.035 Pa.s. The laminar flow cases were modeled for typical coronary arteries dimensions (diameter of 3.3mm) with inlet velocity of 0.3 m/s that represents a Reynolds number of 150 [15,16]. The stent has a length of 8 mm and thickness of 100 μ m [17] with domain length of 100 mm that was meshed with 2.2 million polyhedral cells - based on sensitivity study that focused on the recirculation zones (Figure 1). The duration of the simulation was 1.5 s, based on the number of particles that were trapped in the between the struts of the stent, with a fixed time step of 3 ms. The chosen amount of particles allows capturing the trapped particles phenomena with hundreds of particles that

were trapped for the entire simulation duration. Turbulence in the mechanical valve was modeled by employing a shear stress transport (SST) $k-\omega$ model with low Reynolds number correction. This model was chosen for its ability to represent the phenomena found in any type of unsteady Reynolds averaged Navier Stokes (URANS) and is suitable for this type of flow in valves [8]. The diameter of the straight tube and the valve was 19 mm. The mesh and time discretization, as well as the boundary conditions, were based on the work of Alemu and Bluestein [8] while employing constant inlet velocity with the peak systolic magnitude. The domain length was 100 mm and it was meshed with 950,000 polyhedral and 150,000 hexahedral cells where the thickness of the first boundary layer was chosen according to turbulence intensity [8]. The duration of simulation was 3 s and the fixed time step was 1 ms [8]. All the models were solved in ANSYS Fluent 16.1 (ANSYS Inc., Canonsburg, PA).

3. Influence of straight tubes

There are cases where there is a need to compare the device not just to another designs, but also to a control case. An example for such a case is a stent for treatment of a stenosed artery that can be compared with an idealized blood vessel. This idealized vessel, which can be easily modeled as a straight tube, should obviously have lower thrombogenicity than similar vessel with a stent. However, this assumption cannot be easily inferred from a simple SA calculation and comparing its distribution for the two cases. Comparison of the PDF of the SA distribution of coronary flow through a stent and a straight tube control (Figure 2) illustrates this. It can be easily noticed that the main mode of the SA distribution is very similar in the two cases, but paradoxically in the 'tail' higher SA range there is higher probability for higher SA in the straight tube. This is especially pronounced for the SA range with values higher than 3.5 Pa·s (Figure 2 insert), which is sometimes considered as a threshold for platelet activation [4,5,18].

This specific case illustrates how such a bias may arise for the simple case of a flow simulation in a straight tube. Obviously, this is special case and the demonstrated bias cannot necessarily be reproduced in other, more complex, cardiovascular devices. In straight tube with ideal laminar flow the platelets are flowing in straight lines along their corresponding laminae where they are exposed to constant stresses. Those platelets flowing closest to the wall are the slowest and are also exposed to the highest wall shear stresses, thus their SA is disproportionally much higher than those of other platelets flowing faster in lower shear stress laminae. This bias is even more pronounced given that there are more platelets residing in the near wall region because of the longer circumference and the use of boundary layer meshing in the near wall region (see subsection 3.2). The inclusion of a device such as a stent eliminates this phenomenon because as the stents struts induce disturbed flow patterns, the platelets are not trapped in the same lamina anymore. On the other hand, in the stent model the particles that flow through the recirculation zones between the struts are also trapped and exposed to higher stresses and for longer durations. However, the mixing effect releases most of these particles to other laminae, and thus, reducing their total SA. The two practical conclusions from this numerical experiment is that: (i) SA should be used to compare various designs, but not necessarily used for comparing to a healthy case control and (ii) that the SA calculation for comparative purposes should include only the flow region of the device itself without the inlet and outlet tubes, as those may mask the differences.

Other implementation methods that affect this phenomenon and may be used to better analyze the results are presented in the following subsections.

3.1. Single and repeated passages

The platelets flow through the device along various trajectories with different durations, or exposure times, and lengths. The SA calculation may assume a single passage, i.e., that every platelet passes only once through the device, or that it is repeatedly flowing through the device but entering it in a random location for each consecutive passage. There are advantages and disadvantages for each approach when comparing the SA in a device using PDF, thus they should be implemented according to the purpose of the comparison.

In the single passage method [9] each particle has different exposure time (T_{traj} in Equation (2)) and therefore the SA values can better differentiate modes and help in identifying regions of elevated SA. For this reason, this option is usually used for design optimization where studying local effects of certain geometric features of the device. The main disadvantages of this method is that comparison between particles with different exposure times is biased not only against those in the boundary layers (as demonstrated in the straight tube case), but also against slow particles that are exposed to lower stresses. One possible way to address this while still comparing only a single passage, is to average the SA by the time (as discussed in subsection 3.3).

The repeated passages approach [19] as calculated herein is performed as post processing of single passage results by randomly seeding back the exiting particles. It is important to keep the seeding pattern even, as otherwise the location will not be completely randomized. For example, if the seeding pattern is denser in the boundary layers there will be higher probability of particles seeded in this region. The SA is calculated based on the same total duration (T):

$$SA = \sum_{i=1}^{n-1} \left(\int_{T_i}^{T_{i+1}} \sigma dt \right) \quad \text{where } T = T_n \quad (5)$$

Another option is to use the same high number of repetitions for all the trajectories and to assume that randomization will eventually equalize the total duration in all the repeated passages. If this assumption is used, it is important to examine whether there are no trapped platelets in the domain at the end of the solution because these platelets would be 'teleported' from their final location to the device entrance at the beginning of the next passage. Both options for repeated passages better replicate in-vitro recirculation experiments where repeated passages are inherent to the flow through the device. Therefore, repeated passages are more relevant for either the validation of the simulations or for device performance evaluation. The main disadvantage of this method is that because of the randomizing and the cumulative averaging by the large number of repeated passages, the PDF distributions approach a characteristic Gaussian 'bell curve' distribution. This makes it difficult to distinguish between different modes that specific design features of the device may yield. The magnitude of the SA is obviously higher than that of a single passage SA,

but it is a better representation of the thrombogenic potential of entire bulk of the platelets in a flow loop.

Figure 3 presents such comparison between laminar flow through the straight tube and the coronary stent, where the SA is calculated using the repeated passages approach. The total duration was set to the simulation duration, 1.5 s, and 100,000 possible trajectories were calculated. Similar to other repeated passages SA [19], the PDFs' shape obtains an almost Gaussian distribution. While the modes of the two cases appear similar, the repeated passages SA does indicate the additional SA due to the stent. In this case, the tail of repeated passages SA of the stent continue up to 163 Pa·s while it reached only 55 Pa·s in the straight tube.

3.2. Seeding patterns

As mentioned before, it is undesirable to release more particles in the near-wall region because in straight tubes the contribution of these particles to the SA would overwhelm all others. This is especially acute when using the default options in some commercial CFD solvers, where in most cases the particles are released on the nodes of the mesh, resulting in much denser seeding in the wall boundary layer. This seeding pattern could also bias any type of flow simulation if the repeated passages method is employed (see subsection 3.1). This bias is further demonstrated below, for three cases of the same straight tube simulation but with different seeding patterns.

All three models that are presented herein employ dedicated seeding patterns which are not released from the mesh nodes. A concentric circular seeding pattern (marked in blue in Figure 4) is the pattern that is used throughout this paper. It is based on an even spacing between the particles in the radial and circumferential directions. A Cartesian seeding pattern (red in Figure 4) uses the same even spacing as in the concentric pattern, but is defined along the vertical and horizontal directions instead. A boundary layer seeding pattern (green in Figure 4) is similar to the concentric circular seeding pattern, but the two rings that are closest to the wall are replaced with five boundary layers that are defined by growth factor of 1.2. All the three cases have similar amount of particles, approximately 11,500.

Comparison of the PDF of the SAs of these three seeding patterns are presented in the top panel of Figure 4. As expected, the boundary layer has the highest probability for SA larger than 3.5 Pa·s. The main modes of the two evenly distributed seeding patterns are similar, while obviously there is lower probability for platelets to reside in the core flow in the boundary layer seeding. The Cartesian seeding has the lowest probability for SA greater than 3.5 Pa·s. This likely happens because the first layers of platelets near the wall are not arranged in equi-distant rings from the wall, rather those have variable distances based on their Cartesian coordinates.

3.3. Comparison of trajectories based on time averaging

Another option for comparing the SA of different trajectories while accounting for their various durations is to time average the integration in Equation (2):

$$\text{Time averaged SA} = \overline{\text{SA}} = \frac{1}{T_{\text{traj}}} \int_0^{T_{\text{traj}}} \sigma dt \approx \frac{1}{T_{\text{traj}}} \sum \sigma \cdot \Delta t \quad (6)$$

Although it might be argued that this method is conceptually similar to the repeated passages method, this method can be used to differentiate the trajectories and can be used without PDF. One example for such a use is for comparing the SA with the Hellums et al. [2] platelet activation level threshold (Figure 5). Since these activation levels were measured for various exposure times and shear stress levels, this type of comparison accounts for both the trajectory duration and the $\overline{\text{SA}}$ of each platelet. The resulting $\overline{\text{SA}}$ dots cloud distribution (straight tube - green, stent - red) can then indicate how far from the activation level threshold each platelet SA value reached by the end of its individual trajectory is located. For almost any exposure time, larger maximum $\overline{\text{SA}}$ is found in the stent model as compared to the straight tube. These are clearly the cases that bring the platelets closer to the Hellums et al. [2] activation level threshold. This type of comparison graphically represents the ‘thrombogenic potential’ more pronouncedly than the traditional PDF plot, at least in this special case of the stent and the straight tube models. Moreover, unlike the SA that cannot be compared with any activation threshold, the separation of the $\overline{\text{SA}}$ and time allows to compare the shear stresses and exposure time locus. The main disadvantage of this $\overline{\text{SA}}$ method is that the temporal changes are ignored, however it should be emphasized that these changes are also ignored in normal integration and they can only be accounted for if the entire stress-time loading waveforms are compared.

A step further from time averaging the SA values can be to make them non-dimensional. Longest and Kleinstreuer [20] suggested the following non-dimensional SA that they have termed the platelet stimulation history (PSH):

$$PSH = \frac{1}{\tau_{\text{mean}} \cdot \tau_{\text{waveform}}} \int_0^{T_{\text{traj}}} \sigma dt \quad (7)$$

where τ_{mean} is the mean wall shear stress of the vessel and T_{waveform} is the input waveform time-period. These two parameters represent the entire flow field rather than the platelet itself and its trajectory, thus the PSH is closer to normalization of the SA than to traditional non-dimensionalization in fluid mechanics. A possible means to attribute a physical meaning for such non-dimensional SA (NDSA) parameter is to represent the ratio between the external flow stresses that are applied on the platelet and the internal structural stresses within the platelet:

$$NDSA = \frac{\text{External flow stresses}}{\text{Internal mechanical stresses}} \approx \frac{\overline{\text{SA}}}{\bar{\sigma}_{\text{structure}}} = \frac{1}{\bar{\sigma}_{\text{structure}} \cdot T_{\text{traj}}} \int_0^{T_{\text{traj}}} \sigma dt \quad (8)$$

Obviously, $\sigma_{structure}$ cannot be directly calculated from the current Lagrangian methods. Future use of multiscale simulations that model the platelet trajectory, its deformation and its fluid-structure interaction with the surrounding plasma [21] could be employed for the calculation of $\sigma_{structure}$. As an approximation, it is possible to assume that $\sigma_{structure}$ has the same order of magnitude as a platelet's ultimate stress. The ultimate stress of platelets is approximately 3000 Pa, established by experiments of the maximum extension length [22] and the linear stress strain curve [23] of untreated human platelets.

4. Lagrangian methods with turbulence models

When there is a need to numerically model turbulent flow, the most computationally efficient approach is the unsteady Reynolds-averaged Navier-Stokes (URANS), with multiple transport equations to approximate the Reynolds stresses. This averaging can affect both the way that the flow stresses are calculated (Equation (4)) and the resulting Lagrangian trajectory. Other turbulence models, that do not approximate the flow based on mean and fluctuating components, could be too computationally expensive for Lagrangian damage models. Intuitively, the Reynolds stresses should have a very significant contribution to the SA. Figure 6 confirms that for the case of turbulent flow in a mechanical heart valve. It should be noted that the use of Reynolds stresses for predicting blood damage is somewhat controversial, ranging from a conjecture that they should be ignored [24] to experimental measurements that clearly indicate that Reynolds stresses are related to blood cell damages [25,26]. Although the Reynolds stresses term cannot exert a viscous shear on a cell, it expresses a momentum exchange that can contribute to the platelet activation process which involves transduction of these stresses through the membrane to the platelet microtubular system and cytoskeleton.

One possible way to account for the turbulent fluctuations in the trajectory calculation is to use a discrete random walk model [27] for the interaction with the turbulent eddies. This method was previously employed by our group for SA calculation [8,10,28]. In this method the particle interactions with the fluid eddy can be estimated from the velocity fluctuations, which are related to the local turbulence kinetic energy and the eddy lifetime. The eddy lifetime is related to the Lagrangian integral time scale T_L . For the current case of mechanical heart valve with the assumption of 10% turbulence intensity in the inlet [8] the specific dissipation rate in the inlet can be approximated as $\omega = 49 \text{ s}^{-1}$ and the time scale as $T_L = 0.034 \text{ s}$. Figure 7 compares PDFs of SA with random walk model and without it. The stochastic model increased the SA levels and there is lower probability that the SA will be in the first mode, but the two PDFs curves are close. Although the stochastic model adds some 'noise' to the trajectory, this process might also reduce the SA because it smooths out the stress levels in a similar way to the randomization in the repeated passages approach Figure 3. The stochastic models might play larger role when employed to cases such as pulsatile flow in MHVs. It could especially be pronounced during the late systole with the onset of transition to turbulence during the deceleration phase before the valve closes. However, this is not the focus of the work presented here, which concerns the general effects of the implementation assumptions rather than specific cases such as pulsatile flows through MHV.

5. Coupled fluid-particle interaction

Depending on the numerical solver that is used, sometimes it is impossible to employ two-way particle-blood interaction coupling. Pathlines, that represent the trajectories of fluid particles, can be calculated in post-processing from the velocity field of each time step or during the solution as one-way fluid-to-particle coupling. Intuitively, it might be assumed that the two types of coupling will have little influence on such small neutrally buoyant particles like the ones that represent platelets. This assumption was tested in the current section by comparing two-way DPM coupling with pathlines, which in this case were calculated using one-way DPM coupling (Figure 8). These cases were also compared with instantaneous pathlines at the last time step. The instantaneous pathlines (that in some commercial CFD packages are called ‘pathlines’) are calculated as trajectories but from the velocity field of only a single time step. Obviously, the SA of the instantaneous pathlines is very different from that of the transient trajectories, but it is presented here to illustrate this difference. The fully coupled DPM has the lowest SA values, probably resulting from including the drag forces that shift the particles away from the high shear stress regions.

Expert commentary

In this paper we evaluated the influence of various implementation assumptions on Lagrangian calculation of stress accumulation (SA) for predicting blood damage. In this specific comparative study, the SA was computed assuming a linear SA summation law, but similar results are expected to be found when employing any other power law model formulation (where the cumulative damage is calculated from the multiplication of stress and time with different powers). The implementation assumptions included various seeding patterns, stochastic walk model, and simplified trajectory calculations with pathlines. Post processing implementation options that were evaluated included single passage and repeated passages SA, and time averaging.

As clearly demonstrated in this study, the implementation assumptions can significantly affect the resulting SA, i.e., the blood damage model predictions. Some of the results were somewhat counterintuitive, showing for example that the stochastic walk model has only limited effect on the SA. Clearly, careful considerations should be taken in the use of Lagrangian models that are case or scenario specific. In cases where more demanding models may be too computationally prohibitive while having only a limited effect on the results, some simplifying assumptions may be used. Ultimately, the appropriate assumptions should be considered based on the physics of the specific case and sensitivity analysis, similar to those employed in the case studies presented here.

Some additional considerations were not included in this study. Brownian motion was not considered because the particles are larger than submicron scales [29], while it still might be argued that particle size of 3 μm is close to this threshold and that the Brownian forces may become significant in low Reynolds laminar flow. Collisions between the particles were also neglected. Other effects on the Lagrangian trajectories could be a result of the blood vessel motion. For example, trapped particles between the struts of the coronary stent might be released when the artery contract. This effect cannot be numerically modeled without employing more complex fluid structure interaction (FSI) considerations or experimentally

obtained data, yet it may have a significant influence on the higher SA ‘tail’ range of the PDF because these particles have longer exposure time and they are subjected to the highest stress levels.

Five-year view

In the next five years, with the advent of high performance computing (HPC) resources that will allow solving more complex models in a reasonable time, there are several key directions that might be pursued. The debate over the use of URANS and the correct way to account for Reynolds stresses and the stochastic motion might be resolved by the use of direct numerical simulation (DNS), where the Navier–Stokes equations are solved without averaging or approximating the turbulence. This method requires mesh resolution which is in the diminutive Kolmogorov turbulent energy cascade scale, with the Lagrangian trajectories calculated using similar temporal and spatial resolutions. Mesh-free models, such as dissipative particle dynamics (DPD), where the entire continuum is discretized into particles in the molecular scale and particles interaction can be defined by force laws, might also be employed. Similar to DNS, these kind of models will not require special consideration of turbulence. In addition, it will be possible to calculate the Lagrangian trajectories directly from the particles without introducing additional phase and, as mentioned before, it will model the platelet deformation and internal stresses that can be used for non-dimensional SA (NDSA). Finally, erosion models, that are currently available for DPM, could be modified to include the blood damage model. In such application, the blood damage will be coupled with the CFD solution instead of being calculated in post-processing. It will make the use of more complex models possible. For example, if the blood constituent changes its shape it could affect the flow or the particle could be broken into several smaller particles such as happens in hemolysis or in platelet microparticle shedding.

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References

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers

1. Hellums, J.; Hardwick, R. Response of platelets to shear stress-a review. In: Gross, D.; Hwang, N., editors. *The Rheology of Blood, Blood Vessels and Associated Tissues*. Sijthoff and Noordhoff Leiden; 1981. p. 160-183.
2. Hellums JD, Peterson DM, Stathopoulos NA, Moake JL, Giorgio TD, Hartmann A, Kuschinsky W. Studies on the Mechanisms of Shear-Induced Platelet Activation. *Cerebral Ischemia and Hemorheology*. 1987Springer Berlin Heidelberg:80–89. Experimental criterion for platelet activation
3. Blackshear, PI; Dorman, FD.; Steinbac, Jh. Some Mechanical Effects That Influence Hemolysis. *Transactions American Society for Artificial Internal Organs*. 1965 Apr.11:112&. [PubMed: 14330962] First attempt to associate blood damage with flow stress
4. Boreda R, Fatemi R, Rittgers S. Potential for platelet stimulation in critically stenosed carotid and coronary arteries. *J Vasc Invest*. 1995; 1(1):26–37.

5. Bluestein D, Niu L, Schoepfoerster RT, Dewanjee MK. Fluid mechanics of arterial stenosis: relationship to the development of mural thrombus. *Ann Biomed Eng.* 1997; 25(2):344–356. [PubMed: 9084839] First time our group suggested the stress accumulation concept
6. Giersiepen M, Wurzinger LJ, Opitz R, Reul H. Estimation of shear stress-related blood damage in heart valve prostheses--in vitro comparison of 25 aortic valves. *Int J Artif Organs.* 1990; 13(5):300–306. [PubMed: 2365485]
7. Song X, Throckmorton AL, Wood HG, Antaki JF, Olsen DB. Computational fluid dynamics prediction of blood damage in a centrifugal pump. *Artif Organs.* 2003; 27(10):938–941. [PubMed: 14616540]
8. Alemu Y, Bluestein D. Flow-induced platelet activation and damage accumulation in a mechanical heart valve: numerical studies. *Artif Organs.* 2007; 31(9):677–688. [PubMed: 17725695]
9. Xenos M, Girdhar G, Alemu Y, et al. Device Thrombogenicity Emulator (DTE)--design optimization methodology for cardiovascular devices: a study in two bileaflet MHV designs. *J Biomech.* 2010; 43(12):2400–2409. [PubMed: 20483411] First time our group suggested the use of PDF as 'thrombogenic footprint'
10. Yin W, Alemu Y, Affeld K, Jesty J, Bluestein D. Flow-induced platelet activation in bileaflet and monoleaflet mechanical heart valves. *Ann Biomed Eng.* 2004; 32(8):1058–1066. [PubMed: 15446502]
11. Girdhar G, Xenos M, Alemu Y, et al. Device thrombogenicity emulation: a novel method for optimizing mechanical circulatory support device thromboresistance. *PLoS One.* 2012; 7(3):e32463. [PubMed: 22396768]
12. Marom G, Chiu WC, Crosby JR, et al. Numerical model of full-cardiac cycle hemodynamics in a total artificial heart and the effect of its size on platelet activation. *J Cardiovasc Transl Res.* 2014; 7(9):788–796. [PubMed: 25354999]
13. Bludszuweit, C. A theoretical approach to the prediction of haemolysis in centrifugal blood pumps. University of Strathclyde; 1994. (Ed.^(Eds))
14. Apel J, Paul R, Klaus S, Siess T, Reul H. Assessment of hemolysis related quantities in a microaxial blood pump by computational fluid dynamics. *Artif Organs.* 2001; 25(5):341–347. [PubMed: 11403662]
15. Jaffe RB, Glancy DL, Epstein SE, Brown BG, Morrow AG. Coronary arterial-right heart fistulae. Long-term observations in seven patients. *Circulation.* 1973; 47(1):133–143. [PubMed: 4265596]
16. He X, Ku DN. Pulsatile flow in the human left coronary artery bifurcation: average conditions. *J Biomech Eng.* 1996; 118(1):74–82. [PubMed: 8833077]
17. Sadauskas, M. Multilink RX Ultra stent geometry files. Dublin Institute of Technology; 2014. (Ed.^(Eds))
18. Einav S, Bluestein D. Dynamics of blood flow and platelet transport in pathological vessels. *Ann N Y Acad Sci.* 2004; 1015(1):351–366. [PubMed: 15201174]
19. Slepian MJ, Alemu Y, Girdhar G, et al. The Syncardia() total artificial heart: in vivo, in vitro, and computational modeling studies. *J Biomech.* 2013; 46(2):266–275. [PubMed: 23305813]
20. Longest PW, Kleinstreuer C. Numerical simulation of wall shear stress conditions and platelet localization in realistic end-to-side arterial anastomoses. *J Biomech Eng.* 2003; 125(5):671–681. [PubMed: 14618926]
21. Zhang P, Gao C, Zhang N, Slepian MJ, Deng Y, Bluestein D. Multiscale Particle-Based Modeling of Flowing Platelets in Blood Plasma Using Dissipative Particle Dynamics and Coarse Grained Molecular Dynamics. *Cel. Mol. Bioeng.* 2014; 7(4):552–574.
22. Smith C 2nd, Burris S, Weiss D, White J. Comparison of bovine and human platelet deformability, using micropipette elastimetry. *American journal of veterinary research.* 1989; 50(1):34–38. [PubMed: 2919825]
23. Leung S, Lu Y, Bluestein D, Slepian M. Dielectrophoresis-Mediated Electrodeformation as a Means of Determining Individual Platelet Stiffness. *Ann Biomed Eng.* 2015
24. Ge L, Dasi LP, Sotiropoulos F, Yoganathan AP. Characterization of hemodynamic forces induced by mechanical heart valves: Reynolds vs. viscous stresses. *Ann Biomed Eng.* 2008; 36(2):276–297. [PubMed: 18049902]

25. Sallam AM, Hwang NH. Human red blood cell hemolysis in a turbulent shear flow: contribution of Reynolds shear stresses. *Biorheology*. 1984; 21(6):783–797. [PubMed: 6240286] Related blood cell damages to turbulent (Reynolds) stresses
26. Jones SA. A Relationship between Reynolds Stresses and Viscous Dissipation - Implications to Red-Cell Damage. *Ann Biomed Eng*. 1995; 23(1):21–28. [PubMed: 7762879]
27. Gosman AD, Ioannides E. Aspects of Computer-Simulation of Liquid-Fueled Combustors. *Journal of Energy*. 1983; 7(6):482–490.
28. Bluestein D, Li YM, Krukenkamp IB. Free emboli formation in the wake of bi-leaflet mechanical heart valves and the effects of implantation techniques. *J Biomech*. 2002; 35(12):1533–1540. [PubMed: 12445606]
29. Li A, Ahmadi G. Dispersion and Deposition of Spherical-Particles from Point Sources in a Turbulent Channel Flow. *Aerosol Science and Technology*. 1992; 16(4):209–226.

Key issues

- When comparing a single passage SA in a device to a control case, e.g., as in the case of a stented artery compared to an artery without one, the SA may become biased with higher values for the control because the closest particles to the wall are trapped in the much slower boundary layer flow and higher shear stress levels. In the presence of a device the disturbed flow patterns prevent this bias from occurring.
- Repeated passages SA helps to eliminate SA bias for the case of laminar flow in straight tubes but are less useful for optimizing the device design for reduced thrombogenicity (lower SA)
- Seeding pattern can amplify a straight tube SA bias, as it will be augmented in denser seeding regions. In the absence of flow mixing this will not necessarily be eliminated by repeated passages.
- Time averaging and non-dimensionalizing the SA might help comparing trajectories with varying exposure times with the full range of the platelet activation level locus.
- The addition of stochastic walk model to represent the turbulence effects on the trajectories slightly increasing the SA levels relative to trajectories that doesn't account for fluctuations
- Coupled DPM trajectories and pathlines show similar SA distribution but with different magnitudes
- Instantaneous pathlines cannot be used for comparison of devices with turbulent flow, even if the boundary conditions are constant

Figure 1.
Schematic description of the domains and zoom into the mesh of the laminar and turbulent flow models

Figure 2.

Comparison of probability density functions (PDFs) of the stress accumulation (SA) from a single passage of particles flowing through straight tube and a coronary stent

Figure 3. Comparison of probability density functions of the stress accumulation from repeated passages of particles flowing through straight tube and a coronary stent

Figure 4.

Comparison of probability density functions (PDFs) of the stress accumulation (SA) in straight tubes with concentric circular (blue), Cartesian (red), and concentric circular with boundary layer (green) seeding patterns. Examples for the seeding patterns with zoom-in near the wall are presented on the bottom row.

Figure 5.
Comparison of time averaged stress accumulations for particles flowing through straight tube and a coronary stent and the shear stress activation levels that were measured by Hellums et al. [2]

Figure 6.

Comparison of probability density functions of the stress accumulation based on viscous stress alone and viscous with Reynolds stresses from a single passage of platelets flowing through a mechanical heart valve

Figure 7. Comparison of probability density functions of the stress accumulation based on normal particle path and stochastic walk model from a single passage of particles flowing through mechanical heart valve

Figure 8.

Comparison of probability density functions of the stress accumulation based on two-way coupled discrete phase model (DPM), pathlines, and instantaneous pathlines at the last time step from a single passage of particles flowing through mechanical heart valve