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1 **Modelling and simulation of flow and agglomeration in deep veins valves using**
2 **Discrete Multi Physics.**

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9

10 **Abstract**

11 The hemodynamics in flexible deep veins valves is modelled by means of discrete
12 multi-physics and an agglomeration algorithm is implemented to account for blood
13 accrual in the flow. Computer simulations of a number of valves typologies are carried
14 out. The results show that the rigidity and the length of the valve leaflets play a crucial
15 role on both mechanical stress and stagnation in the flow. Rigid and short membranes
16 may be inefficient in preventing blood reflux, but reduce the volume of stagnant blood
17 potentially lowering the chances of thrombosis. Additionally, we also show that in
18 venous valves, cell agglomeration is driven by stagnation rather than mechanical stress.

19 **Keywords:** Discrete Multi-Physics, Smoothed Particle Hydrodynamics, biological
20 venous valve, Clot, Deep Venous Thrombosis.

21

22 **1. Introduction**

23 Deep venous thrombosis (DVT) is a dangerous and painful condition in which blood
24 thrombi form in deep veins. Such thrombi contain blood cells (including red blood cells
25 and platelets) within a mesh of coagulated protein which is predominantly fibrin. If one
26 of these aggregates detaches from the vein, it can reach the lungs resulting in a life-
27 threatening complication known as pulmonary embolism (PE). In the UK alone, DVT
28 and PE (designated together as venous thromboembolism, VTE) cause an estimated
29 25,000 deaths annually which exceeds the number of deaths from breast cancer, AIDS
30 and road traffic accidents combined (Hunt 2009).

31 One of the factors exacerbating DVT is prolonged immobility (e.g. bed ridden after
32 surgery, limb paralysis and long-haul flights), where the insufficient efficacy of the
33 muscle pump, which normally assists blood flow through the leg veins, leads to sluggish
34 flow. Stasis and low flow states are classically associated with a high probability of
35 thrombus formation (Reitsma et al., 2012). Because of this, it is likely that specific flow
36 patterns in veins, especially around the valve flaps, can play a fundamental role in the
37 formation of thrombi (Bovill and van der Vliet, 2011). Since hydrodynamics is affected
38 by the valve characteristics, the valve characteristics can also affect thrombus
39 agglomeration but the actual mechanisms remain unclear.

40 Moreover, once a person has developed DVT and has been successfully treated, he or
41 she is likely to develop other thrombus in the future, suggesting that the person's
42 specific valve geometry or flexibility may also contribute to the solid blood formation.

43

44 By providing hydrodynamic information of the blood flow around the valve, computer
45 simulations can improve our understanding of the link between fluid dynamics and
46 DVT. Computational blood dynamics has been widely and successfully used for cardiac
47 valves (e.g. De Hart et al., 2000; Fenlon and David, 2001; Van Loon et al., 2004;
48 Buxton and Clarke, 2006; Watton et al., 2007; Van Loon 2010; Astorino et al., 2012;
49 Espino et al., 2012; Bahraseman et al., 2014; Al-Azawy et al., 2015; Borazjani 2015;
50 Halevi et al., 2015; Kamensky et al., 2015; Marom 2015; Miandehi et al., 2015; Bavo et
51 al., 2016), but with a few exceptions so far little attention has been given to venous
52 valves (e.g. Wijeratne and Hoo 2008; Keijsers et al., 2015). In the majority of the
53 venous valve simulations, the valve is fixed and the complex interaction between the
54 flow and the moving leaflets is lost. Recently, flexible structures were investigated with
55 the Fluid Structure Interaction (FSI) method (Simao et al., 2016). Nevertheless, analyses
56 remain often limited to few cycles or implemented with one symmetrical leaflet. One of
57 the reasons is related to the intrinsic difficulty of the FSI to simulate the leaflets' contact
58 at the end of the closing phase. A few studies (e.g. Van Loon et al. 2010, Kamensky et
59 al. 2015) used additional contact algorithms to account for the mechanical contact of
60 leaflets. However, the implementation of these algorithms is complex and the frequency
61 of the re-meshing close to the contact point remains an issue.

62 In this work, we use the Discrete Multi-Physics (DMP) approach developed in
63 Alexiadis (2015) to model both the fluid dynamics and the flexible leaflets. This
64 approach was previously used for cardiac valves (Ariane et al., 2017). In this previous
65 paper, based on both dimensionless analysis and direct numerical simulations, we have
66 shown that size and rigidity of the leaflets, together with inlet velocity, are key
67 parameters and have determined which factors most affect the hydrodynamics around

68 the valve. For comparison, we focus on these parameters in this study, to specific flow
69 patterns and stress profiles in a venous valve system using the DMP approach.

70 Other advantages of the approach proposed here is that, contrary to FSI simulation, it
71 can account for a complete valve closure without the use of a stabilisation algorithm.

72 Finally, using DMP gives the possibility of introducing an agglomeration algorithm that
73 transforms a portion of the liquid into a solid. Other studies (e.g. Simao et al., 2016)
74 simulated cell aggregates by tweaking the viscosity of the liquid, but with the method
75 proposed here we can form actual solid structures within the liquid phase. By
76 introducing the agglomeration algorithm, we identify among the regions where thrombi
77 are most likely to form and which have the highest growth probability.

78

79 **2. Modelling**

80 **2.1. Modelling approach**

81 The DMP modelling technique used in this work is based on the so-called discrete
82 multi-hybrid system (DMHS). In the DMHS model, the liquid is represented by
83 Smoothed Particle Hydrodynamics (SPH) particles (Monaghan 1994; Morris et al.,
84 1997; Liu and Liu 2003), while the solid structure is divided into many notional
85 particles linked by computational springs (to model the elastic modulus of the solid),
86 computational hinges (to model the flexural modulus) and computational dashpots (to
87 model the viscous material behaviour). Mathematically, this is similar to the treatment
88 of molecular bonds used in Molecular Dynamic (MD) simulations. In the original paper
89 where the DMHS was first proposed (Alexiadis 2014), this part of the model was
90 referred to as Coarse Grained Molecular Dynamics (CGMD) to highlight its MD origin.
91 Here we prefer the term Mass-Spring Model (MSM) as the scales involved are
92 macroscopic. Readers can refer to Appendix A for details and to (Ariane et al., 2017)
93 for application of this methodology to biological valves.

94 **2.2. Geometry**

95 In this study, we use a 2D schematic representation of the leg venous valve (Wijeratne
96 and Hoo 2008) as illustrated in Fig. 1. The channel radius is $Z = 0.004$ m, the radius of
97 the valve chamber is $R = 0.007$ m and its length is $Y = 0.04$ m. Three different lengths L
98 of the membrane are studied: long (0.0256 m), medium (0.0175 m) and short (0.01 m).
99 In order to distinguish different parts of the geometry, we refer to the region between

100 the two leaflets as the ‘opening region’ and to the two regions between the wall and the
101 leaflet as ‘sinus regions’. Fig. 1 shows the location of the opening region and one of the
102 two sinus regions (the other is symmetric and located above the upper leaflet).

103 **Fig. 1.** Illustration of the venous valve 2D geometry and particle representation.

104 The leaflets are represented by (solid) MSM particles joined together by springs and
105 hinges (fig. 1) as discussed in Appendix A. SPH particles are used for the fluid and
106 stationary (solid) particles for the walls. Three layers of particles are used for the
107 channel and two for each leaflet.

108 There are two types of parameters required for the simulations: model parameters and
109 simulation parameters. The first group consists of internal parameters used by the SPH
110 and MSM solvers (Table 2); the second refers to the operative conditions detailed
111 below.

112 **2.3 Simulation conditions**

113 The Young’s modulus E and the flexural modulus F of the membrane are the results of
114 the MSM particles joined together by numerical springs and hinges. The relation
115 between the spring (k_b) and hinge (k_a) constants and the actual Young’s modulus and
116 the flexural modulus is given in Ariane et al. (2017). A viscous coefficient is added to
117 the MSM springs to confer viscoelastic properties to the membrane as in a Kelvin–
118 Voigt material.

119 Periodic boundary conditions are used at the inlet/outlet and we implement the same
120 pulsatile flow (purely oscillatory) used by (Wijeratne and Hoo 2008) and imposing to
121 each liquid particle the acceleration g as shown in equation 1

$$122 \quad g = g_0 \sin(2\pi ft), \quad (1)$$

123 with amplitude g_0 (given in Table 1), time t and oscillation frequency $f = 1/T$ (with T the
124 period oscillation). We use equation 1 as a simple means of forcing alternating flow in
125 the valve, but the real oscillation is not sinusoidal and the frequency is not constant. We
126 chose $T = 4$ s, which is long enough to ensure full closure. Here we limit the total time
127 of calculation with 4 full cycles (opening and closing) which correspond to 16 s.
128 Previous work (Wijeratne and Hoo 2008) used $T = 3$ s and simulated only one full
129 cycle. When the muscles contract, the blood within the veins is compressed and the
130 valve opens; when the muscles dilate, the valve closes preventing backward flow. The
131 blood velocity depends on the force of the muscle contraction and, in general, it is
132 related to the level of physical activity of a specific person. In order to account for three
133 levels of physical activity, we take into account three values of g_0 (0.1 m s^{-2} , 0.25 m s^{-2}
134 and 0.4 m s^{-2}), which result in three different flows with maximum velocities in the inlet
135 channel of 0.03 m s^{-1} (low physical activity), 0.07 m s^{-1} (intermediate case), 0.13 m s^{-1}
136 (high level of physical activity) respectively. The low velocity is from (Simao et al.,
137 2016), the intermediate velocity is from (Wijeratne and Hoo 2008) and we include the
138 third highest velocity to account for high levels of physical activity. In all cases, the
139 flow is laminar.

140 The length and the flexibility of the membrane vary from person to person (Mühlberger
141 et al., 2008; Moore et al., 2011). In order to investigate a variety of individual
142 variations, we consider three membrane lengths (0.0256 m, 0.0175 m, and 0.01 m). The
143 longest length is from (Wijeratne and Hoo 2008) and the shortest length is chosen as the
144 minimum size allowing a complete closure of the leaflets. Regarding the flexibility and

145 the stiffness, in our previous paper (Ariane et al. 2017), the literature review for the
 146 aortic valve has shown that the membrane has three dynamic regimes based on the
 147 membrane stiffness (Bavo et al. 2016; Ledesma et al. 2014; De Hart et Al. 2000; Van
 148 Loon et al. 2006). In the simulation, we vary the stiffness of the valve according to these
 149 regimes (see Table 1).

150 **Table 1.** List of simulations with fluid velocities and membrane parameters.

Variation of the membrane length and the velocity with $k_a = 0.01J$		
Length of the membrane L [m]	V [m s ⁻¹]	Designation
Short L= 0.01 m	0.03	L0.01/V0.03/ k_a 0.01
	0.07	L0.01/V0.07/ k_a 0.01
	0.13	L0.01/V0.13/ k_a 0.01.
Medium L= 0.0175 m	0.03	L0.0175/V0.03/ k_a 0.01
	0.07	L0.0175/V0.07/ k_a 0.01
	0.13	L0.0175/V0.13/ k_a 0.01.
Long L= 0.0256 m	0.03	L0.0256/V0.03/ k_a 0.01
	0.07	L0.0256/V0.07/ k_a 0.01
	0.13	L0.0256/V0.13/ k_a 0.01
Variation of the membrane flexibility with L = 0.0256m and V = 0.07 m s⁻¹		
Angular coefficient k_a [J]	Designation	
0.0001	L0.0256/V0.07/ k_a 0.0001	
0.002	L0.0256/V0.07/ k_a 0.002	
0.005	L0.0256/V0.07/ k_a 0.005	
0.02	L0.0256/V0.07/ k_a 0.02	
0.05	L0.0256/V0.07/ k_a 0.05	

151

152 **2.4 Agglomeration algorithm**

153 In order to understand the agglomeration dynamics, we introduce in the model the
154 agglomeration algorithm developed in Ariane et al. (2017) (a brief overview of the
155 method can be found in Appendix B). At this stage, our focus is to understand if
156 *hydrodynamics alone* favours agglomeration at different locations. The actual
157 biochemical process of thrombus formation is an extremely complex phenomenon (e.g.
158 Pantelev et al., 2015) and it is beyond the scope of this article.

159 Specific particle points are used as agglomeration seeds. The algorithm every N time-
160 steps checks all the fluid particles at a distance R_{MAX} from the seeds and, with a certain
161 probability P , transforms some of these particles into solid agglomerate-particles.

162 In the simulations, the values of N , R_{MAX} and P are given in Table 2. These values do
163 not correspond to the real time-scale of agglomeration but were chosen in order to
164 accelerate agglomeration and to observe significant growth in few cycles. Since our
165 goal is to determine where agglomeration is more likely, this ‘accrual acceleration’ does
166 not affect the validity of the results, as long as the timescale of agglomeration is longer
167 than the timescale of the flow.

168

169 **Table 2.** Model parameters used in the simulations.

SPH (eq.s A.5–A.7)	
Parameter	Value
Number of SPH wall particles (3 layers)	5360
Number of SPH valve particles (2 layers)	(1) 1026, (2) 702, (3) 402
Number of SPH fluid particles	(1) 89592, (2) 89726, (3) 90012
Mass of each particle (fluid)	$1.05 \cdot 10^{-5}$ kg
Mass of each particle (wall and valve)	$2 \cdot 10^{-5}$ kg
Initial distance among particles Δr	$1 \cdot 10^{-4}$ m
Smoothing length h	$2.5 \cdot 10^{-4}$ m
Artificial sound speed c_0	10 m s ⁻¹
Density ρ_0	1056 kg m ⁻³
Time step Δt	10^{-7} s
CGMD (eq.s A.10–A.11)	
Parameter	Value
Angular coefficient k_a	See Table 1
Hookian coefficient k_b	$1 \cdot 10^6$ J m ⁻²
Viscous damping coefficient k_v	0.01 kg s ⁻¹
Equilibrium distance r_0	$1 \cdot 10^{-4}$ m
Equilibrium angle θ_0	$\pi/2$ rad
BOUNDARIES (eq. A.15)	
Constant K	$4 \cdot 10^{-4}$ J
Repulsive radius r^*	$1 \cdot 10^{-4}$ m
SOLID FORMATION (Section Formation of solid aggregates)	
Number of time step for solid formation N	$0.5 \cdot 10^6$ s
R_{\max}	$2.5 \cdot 10^{-4}$ m
Agglomeration probability P	50 %
Max bonds per solid particle	4
(a) long, (b) medium, (c) short membrane	

170

171

172 **3. Results and discussion**

173 **3.1 Stress and residence time**

174 According to (Simao et Al., 2016), causes of DVT among young people remain
175 unknown in most of half of the cases. When the origin of DVT is known, thrombus
176 initiation is often associated with blood coagulability, changes in the vessel wall or
177 immobility (Esmon 2009). In the case of immobility, low velocity and high residence
178 time are the most causes of blood aggregation (Menichini et Al. 2016, Bovill et Al.
179 2011). Although, shear stress can also play a role in platelet aggregation and activation.
180 In fact, components of the coagulation cascade and platelets can be activated in all shear
181 stresses, just mechanisms will be different. For instance, at low shear stress, platelets
182 adhere to fibrinogen, whereas at high shear stress to von Willebrand factor (Ikeda et al.,
183 1991). Likewise, abnormal shear stress distribution can initiate and accelerate the
184 formation of thrombi (Hou et Al., 2015). In the arterial setting, high stress could be an
185 activator of platelet aggregation (Zhang et al., 2002). However, arterial and venous
186 thrombi are structurally different. In arteries, high shear may induce platelet activation
187 and formation of what is sometimes called *white thrombi* with few red cells in it. In
188 veins, the thrombus is red with many red cells trapped in coagulated proteins. In this
189 case, coagulation seems to be the dominant process, suggesting a slower, time
190 dependant, accrual.

191 The following discussion focuses on both mechanical stress and residence time, to
192 account for the two factors that are most generally related to thrombus formation
193 (Zhang et al., 2002).

194 3.1.1 Mechanical stress

195 Our DVT calculations show that shear stress is high only in the opening region and
196 almost negligible everywhere else (Fig. 2a). Clinical experience, however, indicates that
197 thrombi do not form in the opening region, where shear stress is high, but rather in the
198 sinus region (Bovill and van der Vliet 2011) where it is at its lowest (Ju et al., 2016).
199 These observations suggest that *total mechanical stress* (T_{tot}), rather than shear stress
200 (T_{shear}) should be investigated and our results show that, in this case, T_{tot} is high on
201 both sides of the membrane (Fig. 2b).

202 In a fluid, the *total mechanical stress* (or total mechanical force) is the sum of shear
203 stress (or viscous forces), inlet pressure (or pressure force, P_{tot}) and gravity (or Body
204 force, ignored here). Fig. 2c shows the pressure profile and indicates that the higher
205 *total mechanical stress* on the membrane cannot be justified by pressure alone. When a
206 solid body moves in the fluid (acceleration or deceleration), it generates additional
207 forces (virtual mass force) that simultaneously move the volume of the surrounding
208 fluid. These inertial forces so-called *added forces* explain the higher T_{tot} on the
209 membrane in the sinus region.

210 **Fig. 2.** Shear stress (a), total mechanical stress (b), pressure (c), and velocity magnitude
211 (d) for $L0.0256/V0.03/k_a0.01$

212 3.1.2. Residence time in the sinus

213 In Lagrangian approach, displacement is used as a proxy for residence time and the
214 following discussion is based on this parameter instead of residence time.

215 As shown in Fig. 2d, the velocity in the sinus region is low compared to that of the
216 opening region; as a consequence, the residence time of fluid particles in this region is
217 higher. Fig. 3 illustrates this point. We highlight the particles initially in the sinus in
218 blue and we track their position during the simulation. At the end of four cycles, a
219 fraction of the particles has left the sinus, while the rest remains confined in this region.
220 In Fig. 3, the particles are coloured according to their *displacement*, defined as the
221 distance travelled by each particle during the simulation. Blue particles do not move
222 very much and are substantially stagnant; red particles have higher velocity and show
223 higher displacement.

224 **Fig. 3.** Simulation snapshots illustrating the fluid motion of the particles initially in the
225 sinus at different times (beginning of each new cycle): for L0.0256/V0.03/k_a0.01;
226 particles coloured according to their displacement.

227 In the sinus, we can identify two areas of high fluid displacement. The first (called
228 ‘mixing region’ in Fig. 3) corresponds to the recirculation region created by the
229 backflow (Fig. 4). The second (called ‘compression region’ in Fig. 3) is below the
230 membrane and corresponds to the part of the fluid displaced by the oscillating
231 movement of the membrane. There is a fundamental difference between the two
232 regions. While in the mixing region the fluid particles are actually moved out of the
233 sinus by the backflow, in the compression region the particle only oscillates around the
234 same point due to the alternate motion of the membrane.

235 **Fig. 4.** Velocity profile in the sinus area (vectors) for L0.0256/V0.03/k_a0.01.

236 Despite the fact that both regions show high displacement, the actual residence time is
237 high only in the compression region.

238 Displacement alone, therefore, is not enough to distinguish between regions of low and
239 high residence time. In order to account for this, in the next section, we introduce the
240 time-averaged displacement as a more accurate proxy for the residence time.

241 **3.2. Parametric study**

242 In this section, we investigate how T_{tot} and displacement are affected by (i) membrane
243 flexibility, (ii) leaflet length and (iii) level of physical activity (fluid velocity).
244 According to our simulations, all of these three parameters are particularly significant
245 for the performance of the valve. Comparing the effect of these parameters among
246 different setups, however, is not straightforward because it changes in space and time.
247 To compare results with respect to the same reference point, we identify the fluid
248 particle in the sinus region with the highest mechanical stress and for every setup we
249 measure stress and displacement at this location. In this way, we carry out all our
250 measurements at the same relative position. However, as indicated in Fig. 5a and 5b,
251 displacement and T_{tot} also change with time. To account for this, in the case of
252 displacement (Fig. 5a), we use the time-average instead of the instantaneous
253 displacement. In the case of T_{tot} (Fig. 5b), we use the maximal rather than the average
254 stress because agglomeration is more affected by the peak of the stress rather than its
255 average.

256 **Fig. 5.** Time evolution of the local fluid displacement (a) and total mechanical stress
257 magnitude (b) for the particle of maximal stress (L0.0256/V0.03/ k_a 0.01).

258 We can also quantify how both these parameters oscillate with time by calculating their
259 standard deviation; in the subsequent Figs, the error bars indicate the standard
260 deviation.

261 3.2.1. Effect of membrane flexibility

262 The flexibility of the membrane depends on its flexural modulus. In Ariane et al. (2017)
263 we showed that the flexural modulus is mostly affected by the k_a , for this reason, in this
264 section we focus on how time-averaged displacement and maximal stress vary with this
265 parameter.

266 In Fig. 6, both average displacement and T_{tot} decrease as the membrane flexibility
267 increases to a value $k_a = 0.02$ J because mechanical deformation is lower for rigid
268 membranes. However, the displacement for very rigid membranes ($k_a = 0.05$ J)
269 increases. The reason for this can be understood by comparing Fig. 7a and 7b: at $k_a =$
270 0.05 J, the leaflets maintain a straight profile during the closure phase (Fig. 7a), while at
271 $k_a = 0.02$ J they bend under the flow (Fig. 7b). When the leaflets bend, they partially
272 shield the sinus region from the backflow and reduce the velocity (and therefore the
273 displacement). Conversely, very flexible membranes ($k_a < 0.005$ J) highly deform and
274 fluctuate under the flow (Fig. 7c). This explains the higher standard deviation in Fig. 6
275 and the irregular profile of Fig. 6b for $k_a < 0.005$ J.

276 **Fig. 6.** Time-averaged displacement (a) and total mechanical stress (b) versus k_a (valve
277 flexibility) for cases: $L = 0.0256$ m, $V = 0.07$ m s⁻¹ and k_a from 0.0001J to 0.05J.

278 **Fig. 7.** Simulation snapshots illustrating the fluid motion of the particles initially in the
279 sinus for long valve, $V = 0.07$ m s⁻¹ and three flexibilities: (a) $k_a = 0.05$ J, (b) $k_a = 0.02$ J,
280 and (c) $k_a = 0.0001$ J, particles coloured according to their displacement.

281 3.2.2. *Effect of membrane length and inlet velocity*

282 Fig. 8 shows the effect of the inlet velocity on the displacement and stress for three
283 membrane sizes. For medium or long membranes, as expected, higher velocities are
284 associated with higher stress and displacement. The short membrane, however, behaves
285 differently.

286 **Fig. 8.** Evolution of displacement (a) and total mechanical stress magnitude (b) with
287 the maximum inlet velocity.

288 Contrary to the medium and long membrane (see Fig. 2), in short membranes, the
289 highest stress (see Fig. 9) is located at the tip rather than the middle of the valve. At the
290 tip, the motion of the particles depends on the hydrodynamics at the opening region
291 rather than that at the sinus region and, therefore, they are easily transported away by
292 the flow and the displacement increases significantly.

293 **Fig. 9.** Total mechanical stress (a), velocity magnitude (b), vector velocity (c), and
294 displacement (d) in the short valve case for $L0.01/V0.07/k_a0.01$.

295 **3.3. Agglomeration**

296 The main physical parameters that affect agglomeration are the residence time and
297 mechanical stress. The simulations highlight two key locations: one at the sinus side of
298 the membrane, where stress is the highest (point P_1 in Fig. 10), and the other at the
299 valve/wall connection where the residence time is the highest (point P_2 in Fig. 10).

300 The higher mechanical stress at P_1 pushes particles closer, increasing the number of
301 particles inside R_{MAX} ; however, because the velocity is higher, these particles remain

302 inside R_{MAX} only for a short time. At P_2 , the opposite happens: the mechanical stress is
303 lower, but also, because the velocity is low (and, therefore, the residence time is high)
304 and the particles remain inside R_{MAX} for longer.

305 High stresses and high velocities, therefore, have opposite effects on agglomeration.
306 Fig. 10 shows faster growth at P_2 , suggesting that residence time may be more
307 important for aggregation propagation in the venous valve than mechanical stress.

308 **Fig. 10.** Solid aggregates in the sinus region at two different times for
309 $L0.0175/V0.07/k_a0.01$.

310 **Conclusions**

311 This article presents a discrete multi-physics model for both blood dynamics and
312 leaflets mechanics of a leg venous valve. In the simulations, we focused on mechanical
313 stress and flow stagnation (high residence time) in the sinus region because these two
314 factors have been linked to the onset of blood solid formation. The model is
315 subsequently coupled with an agglomeration algorithm to account for the formation and
316 propagation of solid aggregates in the flow.

317 The results show that the flexibility and the length of the membrane play a crucial role
318 in both stress and flow stagnation. Rigid membranes do not close completely and,
319 therefore, they may be inefficient in preventing blood reflux. However, they also allow
320 for a larger flow exchange between the sinus region and the central flow reducing
321 stagnation and, potentially, lowering the chances of thrombosis. Similarly, short
322 membranes reduce the volume of the sinus region, which also decreases stagnation.

323 We also focused on the issue in venous valves and whether it is mechanical stress or
324 stagnation that favours cell agglomeration which may lead to thrombosis.

325 In order to compare the role of these two factors, we identified the location in the sinus
326 with the highest stress and that with the highest stagnation. We placed an agglomeration
327 seed in each of these two locations and implemented our agglomeration algorithm.

328 The growth of the agglomerate at the point of maximum stagnation was considerably
329 higher than that at the point of maximal stress. This implies that, in the case of the
330 venous valve, stagnation can be more important than mechanical stress in thrombus
331 formation and propagation.

332 This result, combined with the fact that membrane flexibility and length determine the
333 level of stagnation in the sinus, highlights the potential for personalised diagnostics in
334 the fight against deep venous thrombosis. In principle, length and stiffness could be
335 evaluated in clinical setting using existing diagnostic methods. Currently, they are not
336 evaluated, but based on our results, if they were added, in the future, to the toolkit of
337 physicians they could, potentially, help predicting the likelihood of DVT.

338 These data, in fact could be introduced into our discrete multi physics model to predict,
339 for that particular valve, the location of maximum stagnation and provide information
340 that, potentially, could be converted into a probability of thrombus formation for a
341 specific individual.

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345 **Supporting Information**

346 A Appendix

347 B Appendix

348 **References**

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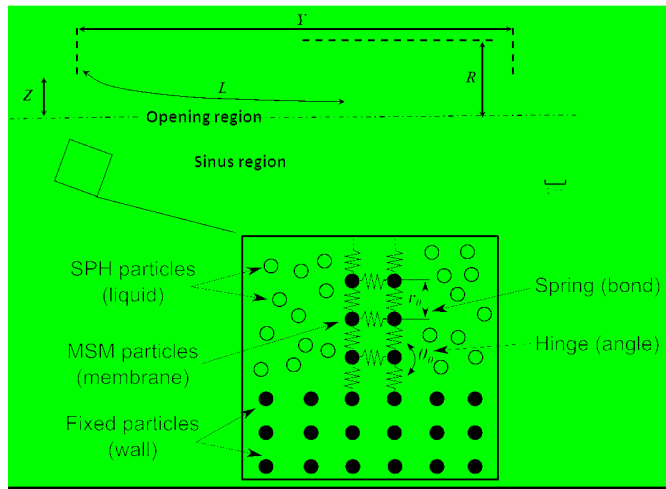
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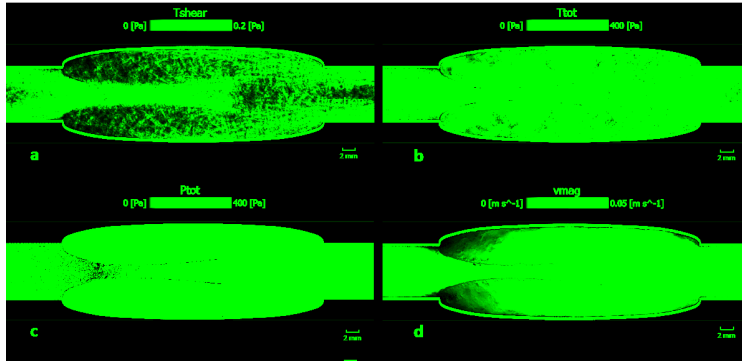
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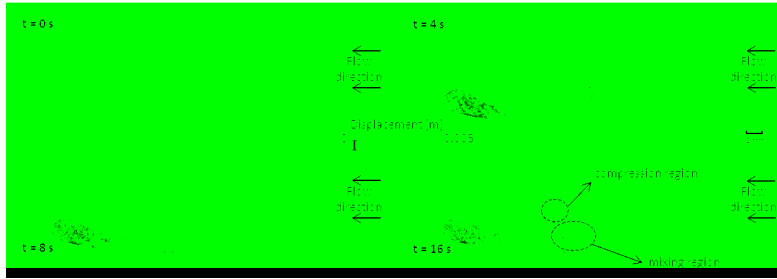
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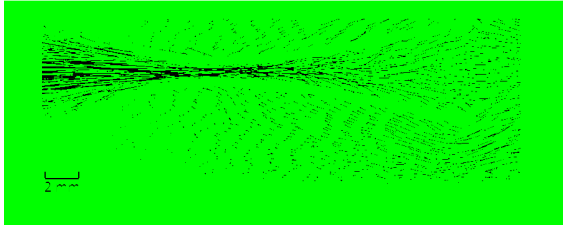
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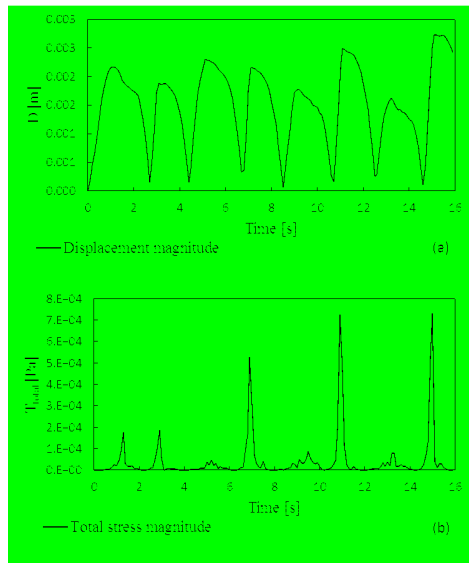


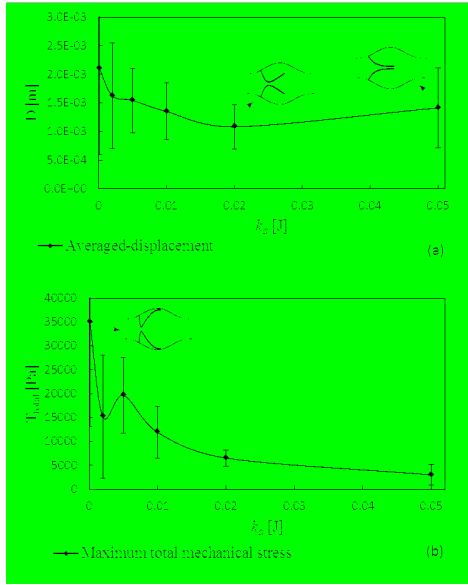
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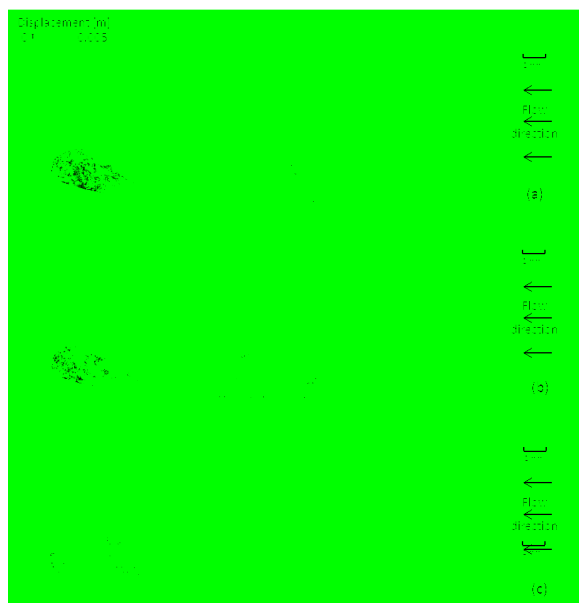


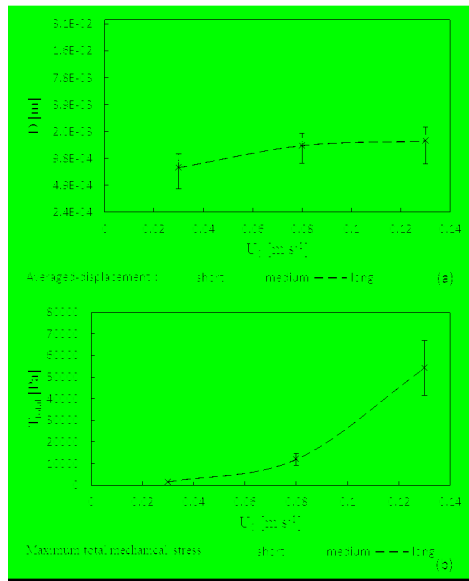


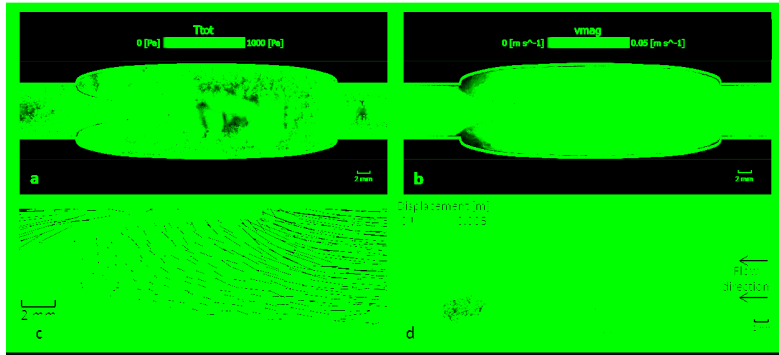
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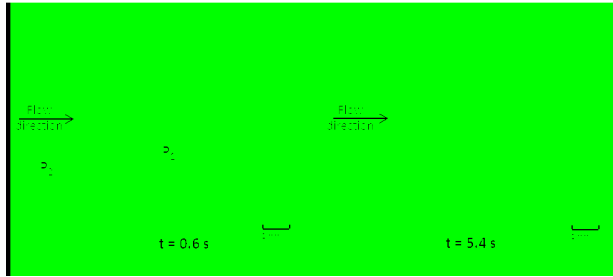












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Highlights:

- Development of a discrete multi-physics model for both the blood dynamics and the leaflets mechanics in a leg venous valve.
- The model accounts for the hydrodynamics, the valve deformation with contact closure, and the solid aggregation at the same time.
- The key role of the flexibility and the length of the valve in both stress and flow stagnation are investigated.
- In venous valve, stagnation can be more important than stress in thrombus formation and propagation.