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1 Experimental and numerical study of platelets rolling on  
2 a von Willebrand factor-coated surface

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9 **Abstract**

Blood platelets circulate in the blood and adhere to wounded vessels to initiate coagulation and healing. The first step of this process is the capture of flowing platelets by adhesive molecules located at the wounded vessel wall. In this article, we study the transport of fixed blood platelets in a microfluidic channel coated with von Willebrand factor (vWF), a large multimeric protein expressed by endothelial cells in the vicinity of wounds. We measure the number of platelets adsorbed at the channel surface as a function of both time and space. Experimental results are compared with a new transport model. We show that transverse diffusion is an important feature of our model, while the rolling behavior of the bounded platelets can be neglected.

10 *Keywords:* Microfluidics, Platelet, Transport, Rolling, Method of  
11 characteristics

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12 **List of abbreviations**

13 EFS: Etablissement Français du Sang

14 PBS: phosphate buffer saline

15 PDMS: polydimethylsiloxane

16 PFA: paraformaldehyde

17 SID: shear-induced diffusion

18 vWF: von Willebrand factor

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20 **Introduction**

21 Platelets are small anucleated blood cells that have an essential role in the  
22 process of hemostasis. In a wounded vessel, platelets adhere to the wall through  
23 ligand-receptor interactions and initiate coagulation. The large multimeric pro-  
24 tein von Willebrand factor (vWF) is such a ligand [1]. At high shear rates, vWF  
25 unfolds and exposes platelet-binding domains [2, 3]. The resulting platelet-vWF  
26 bonds are transient, causing platelets to roll along a vWF-expressing wall [4, 5].

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27 vWF can also mediate firm adhesion through interaction with activated integrin  
28  $\alpha_{IIb}\beta_3$  [6]. Cell rolling is well documented for platelets [7] but also leukocytes  
29 [8] and tumour cells [9]. Clinicians need reliable platelet function assays, either  
30 for the diagnosis of bleeding disorders [10] or the monitoring of anticoagulant  
31 treatments. Microfluidics is a convenient way to manipulate small blood samples  
32 [11] and devices have been developed to assess the effects of anti-platelet treat-  
33 ments with measurements of the concentration platelets bound to the surface  
34 of a micro-channel [12, 13, 14].

35 In this article, we study the flow of fixed platelets in a vWF-coated microflu-  
36 idic chamber. The local concentration of platelets adhering to the wall,  $C_s$ , is  
37 measured and found to be a decreasing function of the distance  $x$  between the  
38 channel entrance and the position of observation. This phenomenon, called axial  
39 dependency, has been observed in experiments involving whole blood [15]. To  
40 the best of our knowledge, although several theoretical and numerical studies  
41 focused on the diffusivity of platelets in the transverse direction[16, 17, 18] or  
42 on the adhesion mechanism[10], no predictions have been made regarding the  
43 axial dependency of platelet concentration.

44 We present a basic model for the transport of blood platelets in the micro-  
45 channel. This model involves specific cell-wall interactions and can include  
46 advection, diffusion in the transverse direction and cell rolling. The relative im-  
47 portance of the different features of this model is explored through comparison  
48 with experimental observations. Physical parameters, such as platelet attach-  
49 ment and detachment rates  $K_{on}$  and  $K_{off}$ , are used as fitting parameters and we  
50 compare their values with experimental measurements or simulated estimations  
51 when available.

## 52 **Experimental Methods**

### 53 *Microfluidics*

54 Microchannels are fabricated using standard soft lithography techniques [19]  
55 and have a rectangular cross-section of fixed width  $W = 400 \mu\text{m}$  and length  
56  $L = 4 \text{ cm}$ , and variable height  $H \in [14, 63] \mu\text{m}$ . After plasma treatment,  
57 channels are sealed on a glass slide, filled with a phosphate buffer saline (PBS,  
58 Lonza) solution containing  $20 \mu\text{g.mL}^{-1}$  vWF (Wilfactin, LFB Biomedicaments,  
59 Les Ulis, France) and incubated overnight at  $4^\circ\text{C}$ . Prior to the experiment, the  
60 channel is rinsed with PBS in order to remove unbound vWF.

61 The cell reservoir is connected to the channel with capillary tubing (internal  
62 diameter  $228 \mu\text{m}$ ). The homogeneity of the suspension in the entrance reservoir  
63 is maintained by gentle agitation. The flow is driven by a pressure control system  
64 (Fluigent MFCS-4C). Platelet perfusions are then performed at a wall shear rate  
65 compatible with the unfolding of immobilized vWF ( $\dot{\gamma} = 1400 - 1800 \text{ s}^{-1}$ ).

### 66 *Biological Material*

67 Blood platelets isolated from whole blood are provided by Etablissement  
68 Français du Sang (EFS) as the following agreement (CPSL C UNT- 06/EFS/029),

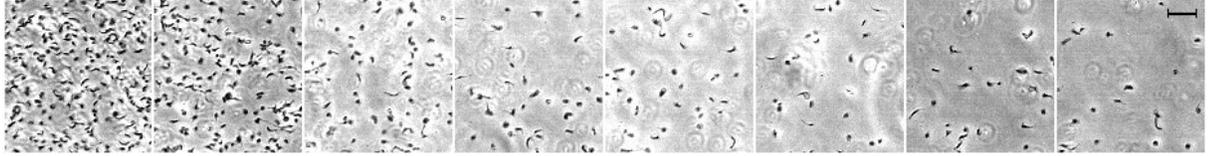


Figure 1: Photographs of the surface of the micro channel after 95 minutes experiment. Positions are equally spaced and separated by 1mm. The first picture is acquired  $x = 0.6$  mm away from the channel entrance. Scale bar represents  $20 \mu\text{m}$ .

69 prepared as described by Dunois-Lardé and co-workers [20], then fixed with  
 70 paraformaldehyde (PFA), rinsed and diluted in PBS to reach a concentration  
 71 of  $1.4 \cdot 10^8 \text{ mL}^{-1}$ . The goal of fixation is to preserve as much as possible the  
 72 structure of platelets but to avoid further metabolic reactions, thus preventing  
 73 effects such as on-chip activation [21].

#### 74 *Videomicroscopy*

75 We use a Leica DMI 6000 B inverted microscope, equipped with a 40x magni-  
 76 fication dry lens focused on the glass surface of the chip, and a camera (Photron  
 77 Fastcam SA3) at an acquisition rate of 0.5 fps with a 20 ms shutter to mea-  
 78 sure the rolling velocity of adherent cells. During the kinetics measurements,  
 79 only snapshots are acquired. As the motorized stage navigates between several  
 80 pre-recorded positions along the whole channel length in less than 2 minutes,  
 81 the experimental error associated with time is  $\Delta t = 1$  min. We define channel  
 82 entrance, denoted  $x = 0$ , as the center of the  $750 \mu\text{m}$ -wide hole where inlet tub-  
 83 ing is inserted. The precision for position is therefore of the order of  $300 \mu\text{m}$ .  
 84 Images are analysed with ImageJ software, using a routine to automatically  
 85 count the number of adherent cells in a microscope field. In the case of dense  
 86 surface coverage, the program fails to separate entangled platelets. Such images  
 87 are analysed independently by two experimentalists. The discrepancy between  
 88 their two counts was used to estimate the measurement error on platelet surface  
 89 concentration  $\Delta C_s \sim 20\% C_s$ .

#### 90 **Experimental observations**

91 Figure 1 shows photographs of the channel surface after 95 minutes of per-  
 92 fusion, showing evidence of the axial dependency of platelet adsorption. The  
 93 exposure time is long, so that only platelets bound to vWF appear sharp. Flow-  
 94 ing platelets are not visible.

95 Figure 2 illustrates the diversity of behaviours observed at the surface. Po-  
 96 sitions of surface-adsorbed platelets are shown, with time colour-coded from  
 97 purple to red. Some platelets roll along the surface, creating rainbow-like pat-  
 98 terns, while others are stationary and appear white. Events of platelet adhesion  
 99 and desorption from the surface also occur, generating incomplete rainbows.

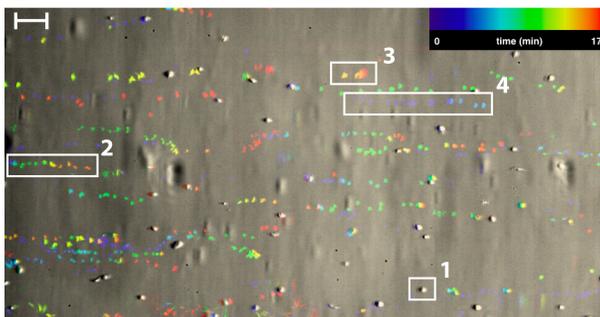


Figure 2: Superposition of pictures from a video focused on the surface of the micro-channel. The colors from blue to red corresponds to the time, the scale is  $20\mu\text{m}$ . Both stationary platelets (frame 1) and rolling platelets (frame 2) can thus be observed. One adhesion event is identified in (frame 3) as the first time this platelet is measured in the middle of the experiment. Likewise a desorption event is seen (frame 4) as the platelet disappears from the surface before the end of the experiment.

## 100 Model

101 Based on the above observations, we develop a model which describes the  
 102 transport of blood platelets in the channel. Our goal is here to understand the  
 103 physical phenomena governing the repartition of platelets between volume and  
 104 surface along the channel. Three types of dynamical events are involved in the  
 105 model: adhesion, desorption and rolling.

## 106 Equations

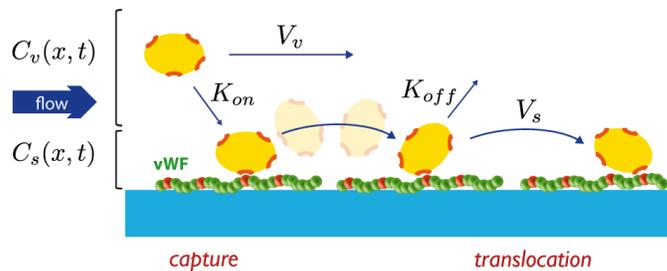


Figure 3: Interactions of platelets with the vWF-coated wall. Platelets in the volume are advected with a speed  $V_v$  and can bind with the vWF with a coefficient  $K_{on}$ . Adherent platelets can roll with a speed  $V_s$  and detach with a coefficient  $K_{off}$ .

107 As shown in Figure 3, we define a small control volume and consider the  
 108 number of platelets in this volume and on the surface, respectively noted  $n_v$

109 and  $n_s$ . The mass balance sketched in Figure 4 involves their time variations:

$$\begin{cases} n_v(x, t + dt) \\ = n_v(x, t) + n_{v,in} - n_{v,out} - n_{exch} + n_{diffusion} \\ n_s(x, t + dt) \\ = n_s(x, t) + n_{s,in} - n_{s,out} + n_{exch} \end{cases} \quad (1)$$

110 where  $n_{v,in}$  and  $n_{v,out}$  (resp.  $n_{s,in}$  and  $n_{s,out}$ ) are the number of cells that enter  
 111 and exit the volume (resp. surface) due to advection (resp. rolling) during  $dt$ .  
 112  $n_{exch}$  represents the number of cells exchanged between surface and volume.  
 113 The additional source term  $n_{diffusion}$  will be discussed later.

The exchange term  $n_{exch}$  is composed of two parts. The formation of bonds between vWF and platelets on the one hand is described by the adhesion rate  $K_{on}$ , depending linearly on the number  $n_v$  of available platelets, and limited by the presence of platelets already on the surface. On the other hand, for the detachment of platelets, with a rate  $K_{off}$ , from the surface, only a linear dependency with the number of adsorbed platelets is considered, as platelet suspensions are dilute enough in our experiments:

$$n_{exch} = K_{on} dt n_v (1 - n_s/n_{s,max}) - K_{off} dt n_s$$

114 with  $n_{s,max}$  the maximum number of platelets that can adhere to the control  
 115 surface.

We rewrite equation (1) using the volume and surface concentration of platelets:

$$\begin{aligned} n_{v,in} &= C_v(x, t) V_v dt h dy \\ n_{v,out} &= C_v(x + dx, t) V_v dt h dy \\ n_{s,in} &= C_s(x, t) V_s dt dy \\ n_{s,out} &= C_s(x + dx, t) V_s dt dy \end{aligned} \quad (2)$$

116 Here,  $h$  represents the thickness of the fluid layer interacting with the surface.  
 117 In an extremely shallow channel, all platelets in the bulk interact with the walls  
 118 and the concentration  $C_v$  in the exchange layer is equal to the average bulk  
 119 concentration in the channel. In some situations however, the influence of the  
 120 wall may not reach the core of the flow. The region involved in the exchanges  
 121 with the wall is more shallow than the channel. There, new platelet adhesion  
 122 events can induce a significant decrease of the volume concentration  $C_v$ . This  
 123 depletion can be compensated by a diffusive term. Calling  $D$  the diffusion  
 124 coefficient,  $n_v^\infty$  the quantity of platelets in the bulk, above the exchange layer,  
 125 and  $l_D$  the typical distance over which diffusion occurs, we get:  $n_{diffusion} =$   
 126  $D dt / l_D^2 (n_v^\infty - n_v)$ .

Introducing the partial derivatives of the concentration with respect to time

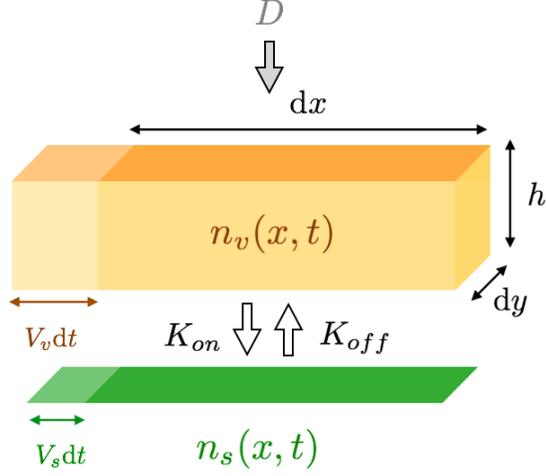


Figure 4: The wall surface in green and the volume in orange respectively contain  $n_s(x, t)$  and  $n_v(x, t)$  platelets at the time  $t$  in the space between  $x$  and  $x + dx$ . The platelets in the lighter region enter these spaces between  $t$  and  $t + dt$ .

and space, we get:

$$\begin{cases} \frac{\partial C_v}{\partial t} + V_v \frac{\partial C_v}{\partial x} = -J + \frac{D}{l_D^2} (C_v^\infty - C_v) \\ \frac{\partial C_s}{\partial t} + V_s \frac{\partial C_s}{\partial x} = hJ \\ J = K_{on} C_v \left( 1 - \frac{C_s}{C_{s,max}} \right) - K_{off} \frac{C_s}{h} \end{cases} \quad (3)$$

- 127  $C_s$ ,  $C_v$  and  $C_v^\infty$  are respectively the surface concentration, the volume concentration in the exchange layer and the volume concentration in the bulk;  $C_{s,max}$   
 128  
 129 the maximal concentration on the surface at the packing limit.

Initially, both the surface and the volume of the channel are empty:

$$\begin{cases} C_v(x, t = 0) = 0 \\ C_s(x, t = 0) = 0 \end{cases} \quad (4)$$

At the channel entrance, new platelets are injected in the volume only:

$$\begin{cases} C_v(x = 0, t) = C_v^\infty \\ C_s(x = 0, t) = 0 \end{cases} \quad (5)$$

130 *Dimensionless equations*

From equation (3), we can apply a series of basic transformations described in the Appendix A to reach the following dimensionless equations:

$$\begin{cases} v_t + v_x = -j + d(v^\infty - v) \\ s_t + \epsilon s_x = j \\ j = v(1 - s) - \alpha s \end{cases} \quad (6)$$

131 and boundary conditions:

$$\begin{cases} v(x, t = 0) = 0 \\ s(x, t = 0) = 0 \\ v(x = 0, t) = v^\infty \\ s(x = 0, t) = 0 \end{cases} \quad (7)$$

132 where  $v$ ,  $s$  and  $v^\infty$  are the dimensionless concentrations  $C_v$ ,  $C_s$  and  $C_v^\infty$   
 133 respectively, and the subscripts represent partial derivation with respect to di-  
 134 mensionless time and space. The parameters  $d$ ,  $\epsilon$  and  $\alpha$  are defined as a non-  
 135 dimensional diffusion coefficient  $d = \frac{D}{l_D^2 K_{on}}$ , the ratio of longitudinal velocities

136  $\epsilon = \frac{V_s}{V_v}$  and the ratio of exchange rates  $\alpha = \frac{K_{off}}{K_{on}}$ .

137 Here the system is composed of two half-spaces  $v$  and  $s$ , where a same object  
 138 has different speed 1 and  $\epsilon$  and an exchange value  $j$  between the half-spaces.  
 139 The diffusion can be easily added or neglected. These dimensionless coupled  
 140 equations thus offer the opportunity to generalise this study to any similar  
 141 system.

142 *Analytical approach*

143 The equations (6) represent the transport of a population in two interact-  
 144 ing spaces with different characteristic speeds. We apply here the method of  
 145 characteristics to these coupled equations. Briefly, three subspaces are defined  
 146 in the  $(t, x)$  plane, as shown in Figure 5: a yellow domain where  $x > t$ , a grey  
 147 domain where  $\epsilon t < x < t$  and a blue domain where  $x < \epsilon t$ . The boundaries of  
 148 these subspaces are lines of constant speed, as 1 and  $\epsilon$  are the non-dimensional  
 149 speeds of the cells in the volume and at the surface respectively. We can define  
 150 two sets of characteristic curves in the  $(t, x)$  space, one for each concentration  
 151  $v$  and  $s$ . The set of curves  $\mathcal{K}_1$  is defined by  $\frac{dx}{dt} = 1$  (blue lines in Figure 5) and  
 152 the equation  $\frac{dv}{dt} = -j(s, v) + d(v^\infty - v)$  is true on them; the set of curves  $\mathcal{K}_\epsilon$   
 153 is defined by  $\frac{dx}{dt} = \epsilon$  (red lines in Figure 5) and associated with  $\frac{ds}{dt} = j(s, v)$ .

154 Let us consider the blue sub-space defined by  $x < \epsilon t$  and the point  $M_1(t_1, x_1)$   
 155 as shown in Figure 6. Since the evolution of  $v$  is known on the characteristic  
 156 lines of slope 1 and that of  $s$  on lines of slope  $\epsilon$ , the values  $v_1$  and  $s_1$  at  $M_1$  only  
 157 depend on the initial values of  $v$  and  $s$  at  $M_0$  and  $M'_0$  and on the distance on  
 158 each characteristic, that is to say on  $x_1$ .

159 If  $\tilde{M}_1$  is also in the sub-space and at the same height  $x_1$  as  $M_1$ , then the  
 160 solutions  $v$  and  $s$  are identical to those of  $M_1$ , since they derive from the values

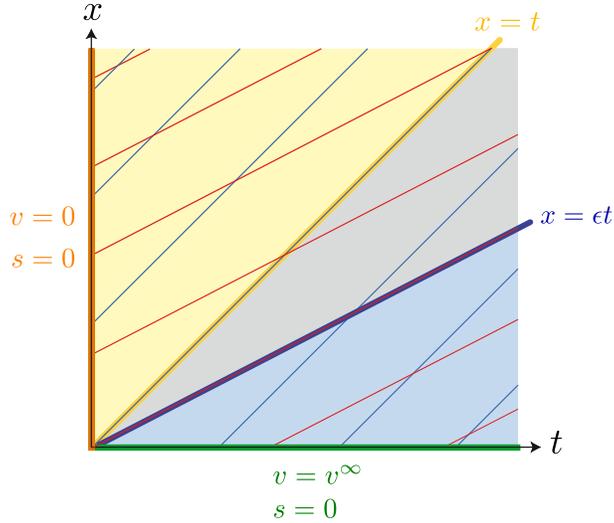


Figure 5: Characteristic curves defined from the coupled equations (6) in the  $(t, x)$  space. Three sub-spaces are presented here: in yellow the sub-space defined by  $x > t$ , in blue the sub-space  $x < \epsilon t$  and grey the sub-space between the two and where most of the interesting physics of the system resides.

161 measured in  $\tilde{M}_0$  and  $\tilde{M}'_0$ , that are the same as in  $M_0$  and  $M'_0$ . Thus all points  
 162 at a position  $(t, x_1)$  with  $t > x_1/\epsilon$  share similar values of the concentrations  
 163  $s$  and  $v$  since they originate from a similar boundary condition  $v = v^\infty$  and  $s = 0$ .  
 164 This means that, for each position  $x$ , the system reaches a stationary state for  
 165  $t > x/\epsilon$ . Experimentally, this fact is confirmed for small positions. For large  
 166 positions, no stationary state is observed, because the condition  $t > x/\epsilon$  is not  
 167 achieved during the course of the experiment.

168 A similar approach shows that the sub-space defined by  $t < x$  has solutions  
 169 that do not vary with position. If diffusion is neglected ( $d = 0$ ), then the  
 170 concentrations in this subspace are zero, as no object can move faster than the  
 171 highest speed in the system and the only source of platelets is the injection at  
 172 the origin of the channel ( $v(t, x = 0) = v^\infty$ ). When diffusion is considered, it  
 173 is the only source of cells in this subspace. The solution still does not change  
 174 with respect to the position, because the diffusion coefficient is a constant and  
 175 the boundary conditions are the same all along the channel.

176 Figure 7 shows how, having explored these asymptotic regimes, we can sketch  
 177 the shape of kinetics and axial dependency curves. The region explored in  
 178 experiments corresponds to the grey zone and not to the asymptotic regimes  
 179 described above. The temporal resolution of our experiments does not allow us  
 180 to capture the delay between starting times at different positions. For example,  
 181 for two positions  $x_1$  and  $x_2$ , we expect kinetics curves to start with a delay  
 182  $\tau = \frac{x_2 - x_1}{V_v}$ . If  $V_v$  is  $1 \text{ mm}\cdot\text{s}^{-1}$ , which is the order of magnitude of the average  
 183 bulk velocity, then even for the largest possible separation  $x_2 - x_1 = 4 \text{ cm}$ , we

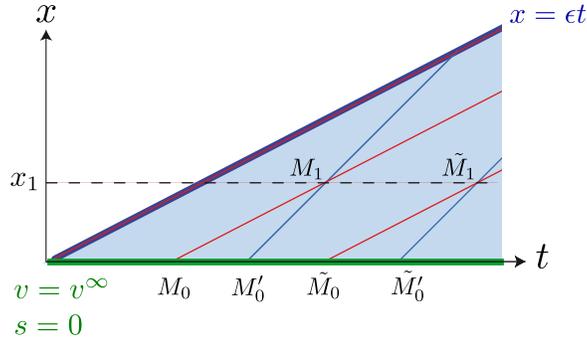


Figure 6: Details of the sub-space defined by  $x < et$  where  $M_0$  and  $M'_0$  (respectively  $\tilde{M}_0$  and  $\tilde{M}'_0$ ) are the boundary conditions relative to  $M_1$  (respectively  $\tilde{M}_1$ ). On the horizontal axis, values of  $v$  and  $s$  are fixed to  $v^\infty$  and 0. From these values, the solution at the point  $M_1(t_1, x_1)$  can be calculated. This solution is similar to the one at the point  $\tilde{M}_1(\tilde{t}_1, x_1)$  as they originate from the same set of equations and previous states. Thus, all points on the line  $x = x_1$  at times larger than  $x_1/\epsilon$  share the same values of  $v$  and  $s$ , and the solution is stationary in this subspace.

184 find  $\tau < 1$  min. In spite of this, the overall shape of kinetics curves resembles  
 185 that of experimental ones.

### 186 *Numerical resolution*

187 In order to explore the intermediate zone, we use a time-step numerical  
 188 method to solve equation 6. We compute volume and surface platelet concen-  
 189 trations for all values of  $x$  and  $t$ , and not only in asymptotic cases. The programs  
 190 are written in *Matlab* and run on a recent Intel-based desktop computer.

191 The equations involve seven parameters.  $d$ ,  $\epsilon$  and  $\alpha$  describe the physics  
 192 of the system, while the other four render time  $t$ , position  $x$  and the two concen-  
 193 trations  $C_v$  and  $C_s$  dimensionless. We look for the set of parameters which  
 194 yields the simulation closest to the experimental points. We can thus describe  
 195 this as minimizing a score function in a seven-dimensional space. The score  
 196 value  $r$  is a simple distance between simulated and experimental points. Since  
 197 the parameters do not appear explicitly in the score function, we can not run  
 198 a classical optimisation search. Indeed, a whole simulation must be re-run for  
 199 each set tested. We thus wrote a simplified search process, sketched in Figure  
 200 8.

201 We start the search with a limited number of different values for each par-  
 202 ameters and test all possible combinations. All parameters are varied on a  
 203 logarithmic scale with the exception of  $C_{s,max}$  which is tested on a linear scale.  
 204 We then select the two sets which lead to the best fits between simulation and  
 205 experiments but differ by more than one parameter. All combinations are tested  
 206 for the two previously selected sets. At each iteration, we keep the two best fits  
 207 and use them as input for the next refinement. Every three iterations, the dif-

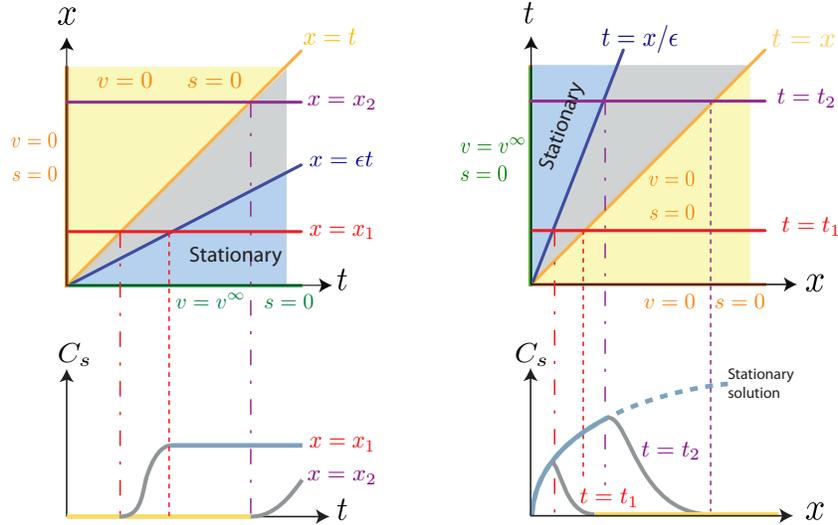


Figure 7: A kinetics (resp. axial dependency) curve is built by intersecting a horizontal line with the  $(t, x)$  (resp.  $(x, t)$ ) diagram. Significant variations occur when this line crosses the grey region, connecting with the two asymptotic solutions at times (resp. positions) defined by the dashed lines.

208 ference between the input values and the tested parameters is reduced so we  
 209 can reach a greater precision for the result.

210 The selection of the two best fits aims to avoid finding a local minimum of  
 211 our score function instead of the global minimum we are looking for. This search  
 212 pattern, and in particular the fact that we limit our search to nine iterations,  
 213 determines the maximum values each parameters can reach. An a-posteriori  
 214 verification is performed: the values found at the end of the search should not  
 215 be at the border of the search range.

	$C_{s,max}$ ( $\text{mm}^{-2}$ )	$V_v$ ( $\text{mm}\cdot\text{s}^{-1}$ )	$V_s$ ( $\text{mm}\cdot\text{s}^{-1}$ )	$K_{on}$ ( $\text{s}^{-1}$ )	$K_{off}$ ( $\text{s}^{-1}$ )	$D$ ( $\text{mm}^2\cdot\text{s}^{-1}$ )	$h$ (mm)
min	$5 \cdot 10^3$	$1.7 \cdot 10^{-5}$	0	$1.7 \cdot 10^{-6}$	$10^{-12}$	0	$10^{-7}$
max	$13.6 \cdot 10^4$	373	373	37.3	37.3	$10^2$	1

Table 1: Extreme values used in the search process.

## 216 Discussion

217 We start by using a simplified model without diffusion. Table 1 contains the  
 218 range of variation for all the other parameters. Figure 9 shows that the model  
 219 provides an overall shape consistent with experimental measurements, consisting  
 220 of an initial increase followed by saturation, close to the channel entrance. The

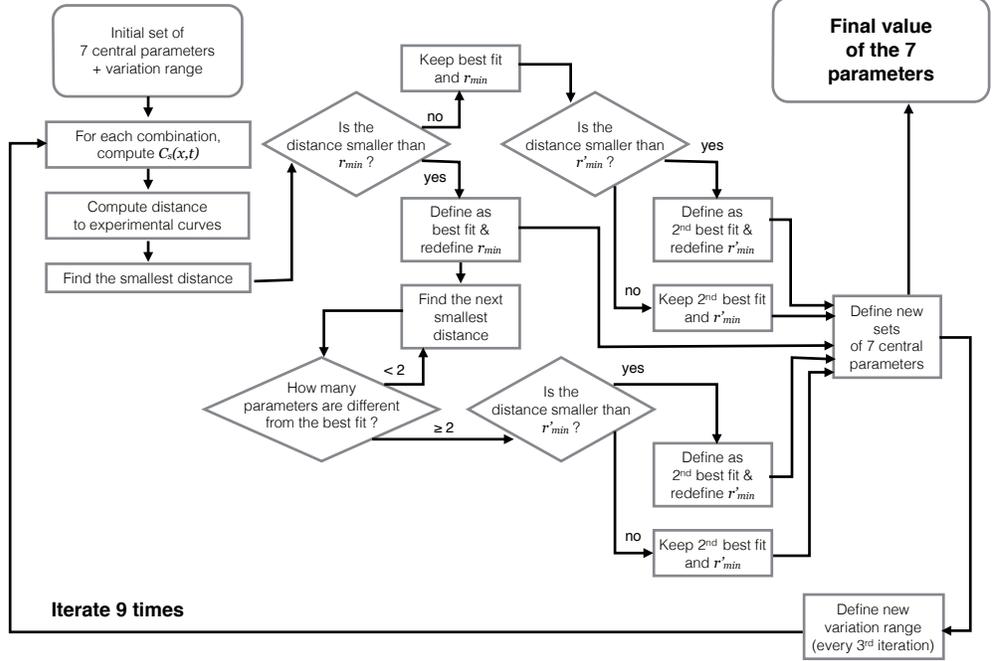


Figure 8: Flow chart representing the fitting process.

221 saturation is no longer observed further away from the entrance ( $x > 4$  mm).  
 222 For distant positions, experimental curves are concave while numerical ones  
 223 are convex. Before trying to refine the model to better adjust the shape of  
 224 experimental curves, let us discuss the order of magnitude obtained for the  
 225 model parameters, presented in Table 2.

226  $C_{s,max}$  is defined as the threshold beyond which no new platelets can adsorb  
 227 to the surface. This situation may occur when all the vWF binding sites are  
 228 used, or if the platelet close packing limit is reached. As the surface is densely  
 229 coated in vWF, we expect the second situation to be the limiting factor. Con-  
 230 sidering platelets as discs of average diameter  $3.1 \mu\text{m}$  [22], the maximal 2D  
 231 packing fraction is reached when  $C_{s,max} \simeq 12 \cdot 10^4 \text{ mm}^{-2}$ . The value found  
 232 with our algorithm  $1.7 \cdot 10^4 \text{ mm}^{-2}$  is smaller than this estimation. This can be  
 233 easily explained, as many platelets in our sample have a shape more complex  
 234 than a discoid, and the packing of such objects cannot be as compact as that of  
 235 discs. Also, in the vicinity of adherent platelets, perturbations of the local flow  
 236 may prevent new platelets from being captured by the surface.

237 The adsorption rate of the model is taken as  $K_{on} = 0.24 \text{ s}^{-1}$ . This value is

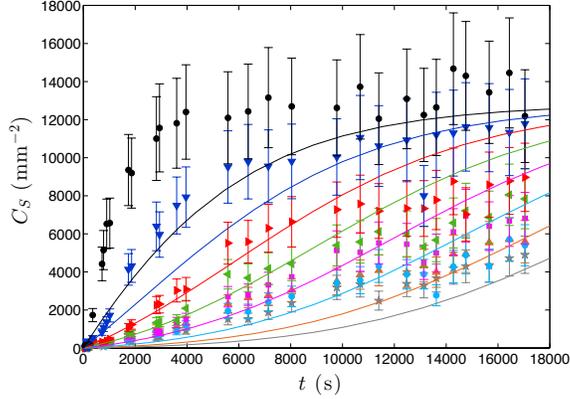


Figure 9: Temporal evolution of the surface concentration of platelets at different positions in the channel:  $x = 0.6$  mm ( $\bullet$ ),  $x = 1.6$  mm ( $\blacktriangledown$ ),  $x = 2.6$  mm ( $\blacktriangleright$ ),  $x = 3.6$  mm ( $\blacktriangleleft$ ),  $x = 4.6$  mm ( $\blacksquare$ ),  $x = 5.6$  mm ( $\bullet$ ),  $x = 6.6$  mm ( $\blacktriangle$ ),  $x = 7.6$  mm ( $*$ ). Solid lines represent numerical predictions obtained by neglecting diffusion.

238 consistent with the rate constant associated with the transition of free platelets  
 239 from the volume to a surface bounded state, that was estimated by Fitzgibbon  
 240 et al. [23]:  $r_{2-3} \simeq 0.07 - 0.4 \text{ s}^{-1}$ . When modeling the adhesion of platelets to  
 241 subendothelial matrix, Leiderman and Fogelson [24] find a value of  $1 \text{ s}^{-1}$ . In  
 242 this situation, platelet adhesion is mediated by a larger number of molecules  
 243 than vWF alone, which can explain this larger adhesion rate.

244 The desorption rate  $K_{off}$  is found to be much smaller than  $K_{on}$ :  $K_{off} \simeq$   
 245  $6 \cdot 10^{-5} \text{ s}^{-1}$ . This small value is due to the dense coating of vWF which forms  
 246 several bonds with each platelet, that have to be simultaneously broken for the  
 247 platelet to be released. Experimental measurements with platelet-rich plasma  
 248 on a non-adhesive surface yield a value  $k_{off} \simeq 5 \cdot 10^{-2} \text{ s}^{-1}$  [25]. It is reasonable  
 249 that the value we measure on an adhesive surface much smaller.

250 The length  $h$  is the height in the volume where platelets can interact with  
 251 the surface and form bonds. We find  $h \simeq 0.1 \mu\text{m}$  which is in agreement with  
 252 the size used by Fitzgibbon et al. [23]:  $L = 0.2 \mu\text{m}$ . This also corresponds to  
 253 the diameter of the repeating units constituting the vWF protein [2]. Because  
 254  $h$  is smaller than the size of a single platelet, the volume concentration in the  
 255 layer of thickness  $h$  should rather be considered as a probability for a platelet  
 256 from the bulk to reach the surface and adhere to it.

257 The advection velocity  $V_v$  is found to be  $0.36 \text{ mm} \cdot \text{s}^{-1}$ . The average fluid  
 258 velocity in the channel is much larger  $\bar{V} \sim 6 \text{ mm} \cdot \text{s}^{-1}$ . But in the exchange layer  
 259 located close to the channel bottom the velocity can be estimated as  $V_v = \dot{\gamma}h/2$ .  
 260 This yields a prediction for  $V_v \sim 0.6 \text{ mm} \cdot \text{s}^{-1}$ , that is in fair agreement with  
 261 the value provided by the fit.

262 The rolling velocity  $V_s$  is the only parameter whose fitted value seems in-  
 263 consistent. The typical velocity of rolling platelets is  $1$  to  $10 \mu\text{m} \cdot \text{s}^{-1}$ , which is  $5$

264 orders of magnitude beyond the numerical result. The decrease in average ve-  
 265 locity could be explained by the presence of platelets activated prior to fixation  
 266 and incapable of rolling. This is consistent with experimental observations of a  
 267 few immobile platelets.

268 *Influence of diffusion*

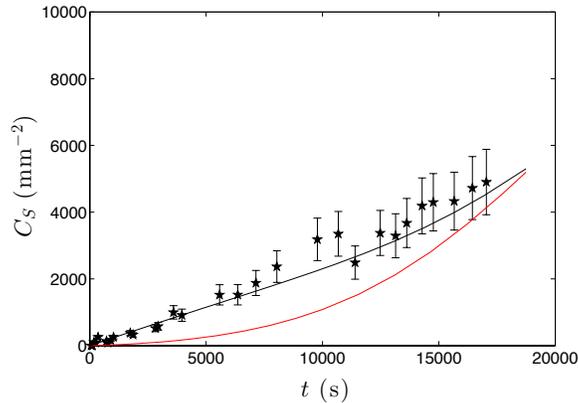


Figure 10: Adsorption kinetics 7.6 mm away from the channel entrance. Experimental data are compared with numerical simulations obtained with a simple model neglecting (in red) or taking into account diffusion (in black).

269 Far from the entrance, our model fails to capture the curvature of kinet-  
 270 ics curves. This underestimation of platelet adsorption suggests that a source  
 271 term is missing from the initial model. A possible explanation is that platelets  
 272 diffuse from the core of the channel towards the walls. Brownian diffusion is  
 273 parametrized by the coefficient  $D_B = k_B T / (6\pi\eta R) \sim 2 \cdot 10^{-13} \text{ m}^2\text{s}^{-1}$ , with  
 274 the water viscosity  $\eta_{water} \sim 10^{-3} \text{ Pa} \cdot \text{s}$  and the particle radius  $R \sim 10^{-6} \text{ m}$ .  
 275 Shear-induced diffusion (SID) is defined as an effective diffusive motion of par-  
 276 ticles in a shear flow. It increases with shear rate and depends on the shape  
 277 of diffusing objects [26]. The SID coefficient is written  $D_{SID} = \dot{\gamma} R^2 f(\phi)$ , with  
 278  $\dot{\gamma} = 1400 \text{ s}^{-1}$  the local shear rate, and  $\phi \sim 0.5 \cdot 10^{-3}$  the volume fraction of the  
 279 particles. For anisotropic particles, the function  $f$  is different than for spheri-  
 280 cal particles and the diffusivity is more important [18]. In the dilute limit the  
 281 diffusivity is proportional to  $\phi$  and we can estimate the diffusion coefficient for  
 282 plate-like objects [26]:  $D_{SID} = \dot{\gamma} R^2 6.9 \phi \sim 6.2 \cdot 10^{-12} \text{ m}^2\text{s}^{-1}$ . It thus appears  
 283 that shear-induced diffusion should predominate over Brownian diffusion in our  
 284 system.

285 The Peclet number  $Pe = \frac{\tau_{diff}}{\tau_{conv}}$  compares diffusion and convection time  
 286 scales. Here,  $Pe = \frac{V_v l_D^2}{DL}$ , with  $l_D$  the typical distance over which diffusion  
 287 occurs in the transverse direction and  $L \sim 10^{-3} \text{ m}$  the distance between two  
 288

289 measurements. Here we consider that  $l_D$  is of the order of the channel thickness  
 290  $H \sim 10^{-5}$  m [27]. We get  $Pe \sim 2$ , indicating that diffusion cannot be neglected.

291 When diffusion is taken into account, numerical curves lose their convexity,  
 292 as illustrated in Figure 10. The best fit is obtained for  $D = 5.9 \cdot 10^{-12}$  m<sup>2</sup>s<sup>-1</sup>,  
 293 which is in fair agreement with theoretical predictions. The value of parameters  
 294 obtained with this full model, presented in the second line of Table 2, remain  
 295 consistent with the estimations presented in the previous paragraph.

#### 296 *Influence of the rolling behaviour*

297 Even when diffusion is taken into account, the value of  $V_s$  deduced from  
 298 the model remains extremely low. In the equation expressing transport at the  
 299 surface, the term  $V_s \frac{\partial C_s}{\partial x} \sim V_s \frac{C_{s,max}}{L}$  can balance the desorption term  $K_{off} C_s$  if  
 300  $V_s \sim K_{off} L$ , that is of the order of  $0.1 \mu\text{m}\cdot\text{s}^{-1}$ . The adjusted values of  $V_s$  are  
 301 several orders of magnitude smaller. This seems to indicate that rolling can be  
 302 neglected in our problem. In supplementary Figure 12, we adjust experimental  
 303 data with new numerical simulations in which rolling velocity is set to 0. Of  
 304 course, in a different system where the velocity contrast between surface and  
 305 volume is smaller, we could expect a significant contribution from rolling to  
 306 surface coverage. Again, the values of all parameters stay in the same order  
 307 of magnitude, although they may vary by a factor 2 or 3. Thus the rolling  
 308 behaviour of platelets seems negligible in this case. Nevertheless, it may very  
 309 well be fundamental for the formation of blood clots, such as in microfluidic  
 310 models of stenosis and coagulation [12, 28].

#### 311 *Influence of the non-linearity*

Experimental values of  $C_s$  never exceed  $15000 \text{ mm}^{-2}$ , a much smaller value  
 than those obtained for  $C_{s,max}$  in the best fits. We further simplify the model  
 by suppressing the non-linear surface saturation term:

$$1 - \frac{C_s}{C_{s,max}} \simeq 1$$

312 in equation (3). Far from the channel entrance, the linear model yields results  
 313 that are very similar to the ones obtained with the full model. As seen in  
 314 supplementary Figure 13, results are less satisfying close to the channel entrance,  
 315 where the surface coverage is maximal. As suppressing the non-linear term  
 316 represents a significant gain of time, this linear model could be interesting for  
 317 applications where a prediction of surface coverage far from the channel entrance  
 318 is desired.

#### 319 *Influence of desorption*

320 Since the desorption rate  $K_{off}$  is much smaller than that of the adsorption  
 321 rate  $K_{on}$ , we also attempt to adjust experimental curves while neglecting desorption.  
 322 The results are displayed in Figure 11: the obtained numerical curves  
 323 increase fast and clearly fail to grasp the trend towards saturation exhibited  
 324 by experimental data. In fact, although both rates share the same dimension,

	$C_{s,max}$ ( $\text{mm}^{-2}$ )	$V_v$ ( $\text{mm} \cdot \text{s}^{-1}$ )	$V_s$ ( $\text{mm} \cdot \text{s}^{-1}$ )	$K_{on}$ ( $\text{s}^{-1}$ )	$K_{off}$ ( $\text{s}^{-1}$ )	$D$ ( $\text{mm}^2\text{s}^{-1}$ )	$h$ (mm)
no diffusion	$1.7 \cdot 10^4$	0.36	$3.6 \cdot 10^{-11}$	0.24	$0.6 \cdot 10^{-4}$	0	$0.9 \cdot 10^{-4}$
full	$3.8 \cdot 10^4$	0.10	$1.0 \cdot 10^{-10}$	0.18	$3.6 \cdot 10^{-4}$	$5.9 \cdot 10^{-6}$	$2.7 \cdot 10^{-4}$
no rolling	$6.1 \cdot 10^4$	0.04	0	0.05	$3.4 \cdot 10^{-4}$	$1.7 \cdot 10^{-6}$	$7.8 \cdot 10^{-4}$
linear	$5.4 \cdot 10^4$	0.03	$3 \cdot 10^{-13}$	0.04	$3.2 \cdot 10^{-4}$	$1.7 \cdot 10^{-6}$	$9.3 \cdot 10^{-4}$
no desorption	$1.2 \cdot 10^5$	0.01	0	0.03	0	$0.7 \cdot 10^{-6}$	$2.7 \cdot 10^{-3}$
literature	$1.2 \cdot 10^5$			0.07 - 1	0.05	$6.2 \cdot 10^{-6}$	$2 \cdot 10^{-4}$
reference	[22]			[23, 24]	[25]	[26]	[2, 23]

Table 2: Parameters value for the different models tested

325 they should not be directly compared with one another. The exchange rate  $J$   
326 involves two terms,  $K_{on}C_v$  and  $K_{off}\frac{C_s}{h}$  that are actually of the same order of  
327 magnitude when computed with the fitting parameters. It is thus necessary to  
328 keep the desorption term in the analysis.

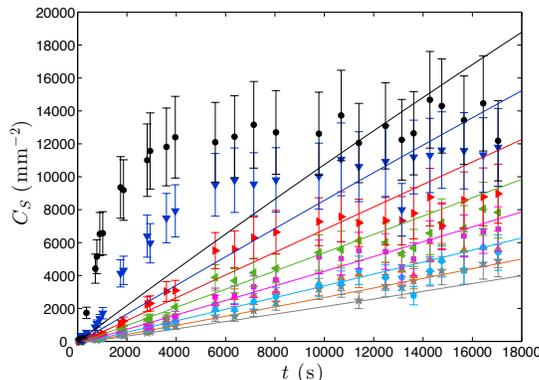


Figure 11: Temporal evolution of platelet surface concentration at different positions in the channel:  $x = 0.6$  mm ( $\bullet$ ),  $x = 1.6$  mm ( $\blacktriangledown$ ),  $x = 2.6$  mm ( $\blacktriangleright$ ),  $x = 3.6$  mm ( $\blacktriangleleft$ ),  $x = 4.6$  mm ( $\blacksquare$ ),  $x = 5.6$  mm ( $\bullet$ ),  $x = 6.6$  mm ( $\blacktriangle$ ),  $x = 7.6$  mm ( $*$ ). The experimental points with their error bar are compared with the model obtained when no desorption is considered (lines).

### 329 Variability

330 The weak contribution of rolling to the transport of platelets along the chan-  
331 nel may be explained by the fact that some of the adherent platelets are activated  
332 and do not translocate. This feature is likely to vary from one sample to an-  
333 other. In supplementary Figure 14, we show that the shape of adhesion kinetics  
334 changes when experimental conditions are varied, but the main features, such as  
335 axial dependency and saturation close to the entrance, are conserved. Param-  
336 eters such as channel height, platelet sample, platelet concentration and wall  
337 shear rate are varied (see supplementary Table 3). While the model without

338 rolling remains in fair agreement with experimental data for other samples, the  
339 adjusted diffusion coefficient can be as much as three orders of magnitude lower  
340 than the one measured for sample A. In shear-induced diffusion, the apparent  
341 diffusion coefficient strongly depends on the particules' size and aspect ratio.  
342 Platelets have a roughly discoidal shape, but for some patients, blood also con-  
343 tains incompletely formed, larger platelets that have a dumbbell shape. It can  
344 therefore be understood that shear-induced diffusion plays a significant role in  
345 platelet transport for some, but not all patients.

346 We also notice that the adjusted value of  $K_{on}$  is small for this particular  
347 sample (sample B). This is consistent with the measured values of platelet con-  
348 centration that remain low even at long times, indicating that the affinity of  
349 platelets from this sample for vWF is smaller than usual.

350 For yet another example (sample C), the shape of kinetics curves and results  
351 of fitting are more similar to the ones obtained with sample A, as well as the  
352 values of the fitting parameters. The shape of curves at intermediate positions  
353 however is not well reproduced by the simulations. The axial dependency is  
354 very marked in this experiment, and the values of  $C_s$  measured at positions far  
355 from the entrance are almost uniformly equal to 0. These data with extremely  
356 low values bias the fitting process, that becomes therefore less efficient in the  
357 regions of finite  $C_s$ . The choice of the observation positions for this experiment  
358 is not optimal. A more accurate fitting could be performed by selecting only  
359 the experimental data containing significant information.

## 360 Conclusions

361 We presented in this article an experimental set-up and an associated model  
362 to study the transport of fixed blood platelets in a micro channel with coated  
363 walls. In spite of the variations that we observe between models or between  
364 experiments, some of the conclusions are repeatable. In all three examples,  
365 we find that the thickness of the exchange layer  $h$  is of the order of a few  
366 hundred nanometers. The adsorption and desorption constants  $K_{on}$  and  $K_{off}$   
367 extracted from this work characterize the behavior of whole cells and not of  
368 single bonds. The desorption rate  $K_{off}$  is always much smaller than  $K_{on}$  but  
369 desorption is not negligible and accounts for the saturation observed close to the  
370 channel entrance. In some samples, shear-induced diffusion needs to be taken  
371 into account and the diffusion coefficient  $D$  found by adjusting experimental  
372 data is in agreement with theoretical predictions. To further improve the fitting,  
373 we would need to take into account the fact that diffusion occurs across the cell-  
374 free layer, whose thickness is not uniform. By choosing a constant characteristic  
375 length for diffusion, we underestimated the diffusive flux towards the surface  
376 close to the channel entrance, where the cell-free layer is extremely thin and the  
377 concentration gradient large.

378 When whole blood is used instead of a platelet suspension, the surface is  
379 covered much more rapidly [15]. This is due to margination effects : red blood  
380 cells present in the core of the vessel flow push platelets towards the surface,  
381 increasing their availability in the vicinity of the walls [17]. We assume that our

382 model could remain valid in such a situation, if an effective diffusion coefficient  
 383 depending on red blood cell concentration and deformation replaced the shear-  
 384 induced diffusion coefficient.

385 We also quantified axial dependency and showed that concentration profiles  
 386 exhibit extremely sharp decreases close to the channel entrance. Measurements  
 387 of the surface concentration in adsorbed platelets is therefore highly sensitive to  
 388 a small error in position. We therefore think that experiments where observa-  
 389 tions are made on a single location in the channel should be handled with care,  
 390 and that measurements made at several positions should be preferred.

391 Although sophisticated multiscale models exist, practical applications could  
 392 make use of less costly micro scale simulations [29]. This paves the way towards  
 393 more efficient simulations of cell suspension dynamics.

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 397 who prepared the platelets; Antoine Blin and Hyacinthe Buisson who performed  
 398 preliminary experiments; and Olivier Dauchot for inspiring discussions.

#### 399 **Appendix A: Dimensionless equations**

The goal is to render the following coupled equations dimensionless:

$$\begin{cases} \frac{\partial C_v}{\partial t} + V_v \frac{\partial C_v}{\partial x} = -J + \frac{D}{l_D^2} (C_v^\infty - C_v) \\ \frac{\partial C_s}{\partial t} + V_s \frac{\partial C_s}{\partial x} = hJ \\ J = K_{on} C_v \left(1 - \frac{C_s}{C_{s,max}}\right) - K_{off} \frac{C_s}{h} \end{cases}$$

We first focus on the two concentrations and apply the following transfor-  
 mation:

$$\begin{aligned} C_v &\leftarrow \frac{C_v h}{C_{s,max}} = v \\ C_s &\leftarrow \frac{C_s}{C_{s,max}} = s \end{aligned}$$

The transversal dimension  $h$  is naturally used to bridge the gap between the  
 surface and volume concentrations as it is characteristic of the dimension that  
 differ between the two concentrations. The equations thus transform into:

$$\begin{cases} \frac{\partial v}{\partial t} + V_v \frac{\partial v}{\partial x} = -\tilde{J} + \frac{D}{l_D^2} (v^\infty - v) \\ \frac{\partial s}{\partial t} + V_s \frac{\partial s}{\partial x} = \tilde{J} \\ \tilde{J} = \frac{Jh}{C_{s,max}} = K_{on} v (1 - s) - K_{off} s \end{cases}$$

We then render time and position dimensionless using the characteristic speed  $V_s$  and characteristic time  $1/K_{on}$ .

$$\begin{aligned} t &\longleftarrow t K_{on} \\ x &\longleftarrow x K_{on} / V_v \end{aligned}$$

which leads to the following coupled equations:

$$\begin{cases} v_t + v_x = -j + \frac{D}{l_D^2 K_{on}} (v^\infty - v) \\ s_t + \frac{V_s}{V_v} s_x = j \\ j = \tilde{J}/K_{on} = \frac{Jh}{C_{s,max} K_{on}} = v(1-s) - \frac{K_{off}}{K_{on}} s \end{cases}$$

The dimensionless physical parameters appear directly in the above expression and we identify them:

$$\begin{aligned} d &= \frac{D}{l_D^2 K_{on}} \\ \epsilon &= \frac{V_s}{V_v} \\ \alpha &= \frac{K_{off}}{K_{on}} \end{aligned}$$

400 This leads to the following system:

$$\begin{cases} v_t + v_x = -j + d(v^\infty - v) \\ s_t + \epsilon s_x = j \\ j = v(1-s) - \alpha s \end{cases} \quad (8)$$

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Exp	$H$ ( $\mu\text{m}$ )	PLT source batch number	$[PLT]$ ( $\text{mL}^{-1}$ )	$\dot{\gamma}$ ( $\text{s}^{-1}$ )
A	23	1	$1.4 \cdot 10^8$	1400
B	23	2	$2.8 \cdot 10^8$	1800
C	63	3	$1.4 \cdot 10^8$	1800

Table 3: Conditions corresponding to the experimental results. Three different batches of platelets were tested. We varied channel height  $H$ , platelet concentration in the suspension  $[PLT]$  as well as wall shear rate  $\dot{\gamma}$ . Sample A corresponds to data shown in Figures 9 to 13, samples B and C to data shown in Figure 14.

## 491 Supplementary Material

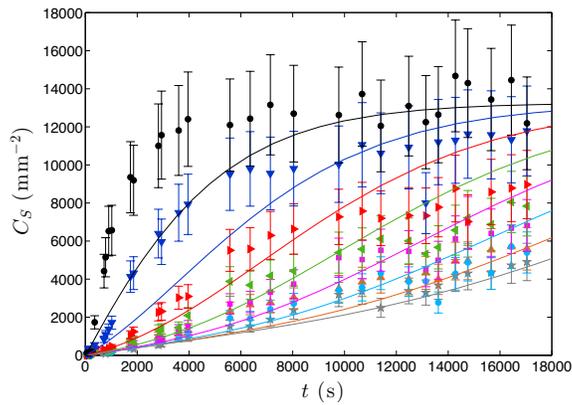


Figure 12: Temporal evolution of platelet surface concentration at different positions in the channel:  $x = 0.6$  mm ( $\bullet$ ),  $x = 1.6$  mm ( $\blacktriangledown$ ),  $x = 2.6$  mm ( $\blacktriangleright$ ),  $x = 3.6$  mm ( $\blacktriangleleft$ ),  $x = 4.6$  mm ( $\blacksquare$ ),  $x = 5.6$  mm ( $\bullet$ ),  $x = 6.6$  mm ( $\blacktriangle$ ),  $x = 7.6$  mm ( $*$ ). The experimental points with their error bar are compared with the model obtained when no rolling is considered (lines).

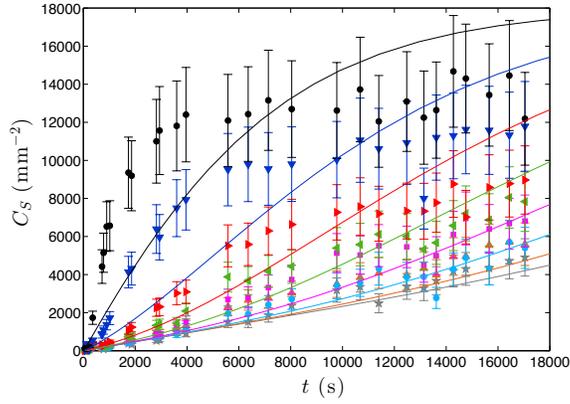


Figure 13: Temporal evolution of platelet surface concentration at different positions in the channel:  $x = 0.6$  mm ( $\bullet$ ),  $x = 1.6$  mm ( $\blacktriangledown$ ),  $x = 2.6$  mm ( $\blacktriangleright$ ),  $x = 3.6$  mm ( $\blacktriangleleft$ ),  $x = 4.6$  mm ( $\blacksquare$ ),  $x = 5.6$  mm ( $\bullet$ ),  $x = 6.6$  mm ( $\blacktriangle$ ),  $x = 7.6$  mm ( $*$ ). The experimental points with their error bar are compared with the linear model (lines).

Exp	$C_{s,max}$ ( $\text{mm}^{-2}$ )	$V_v$ ( $\text{mm}\cdot\text{s}^{-1}$ )	$K_{on}$ ( $\text{s}^{-1}$ )	$K_{off}$ ( $\text{s}^{-1}$ )	$D$ ( $\text{mm}^2\text{s}^{-1}$ )	$h$ (mm)
B	$3.8 \cdot 10^4$	0.01	$7.2 \cdot 10^{-3}$	$1.4 \cdot 10^{-4}$	$1.8 \cdot 10^{-10}$	$1.1 \cdot 10^{-3}$
C	$6.8 \cdot 10^4$	0.12	0.16	$8.0 \cdot 10^{-4}$	$2.5 \cdot 10^{-6}$	$4.9 \cdot 10^{-4}$

Table 4: Parameters obtained by fitting data shown in Figure 14 with a model neglecting rolling.

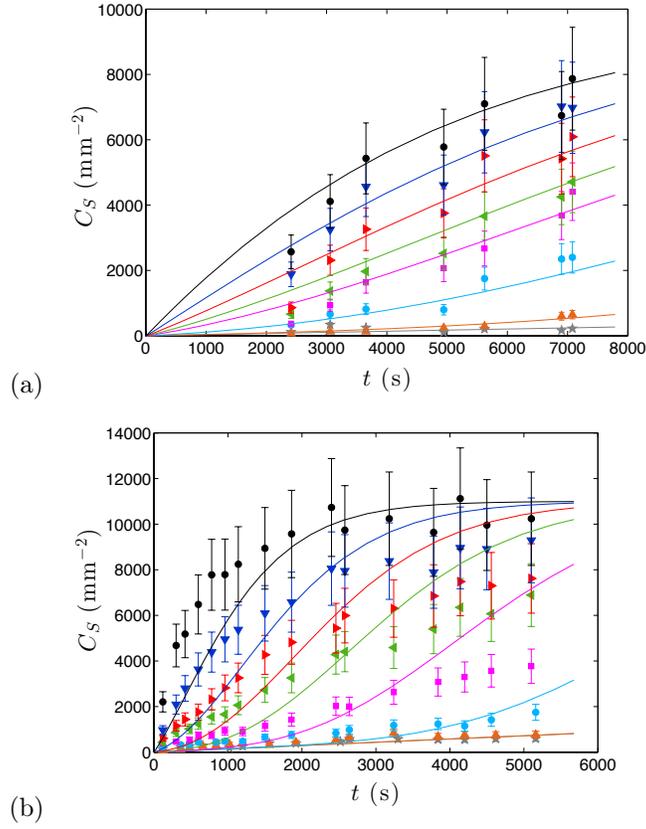


Figure 14: Adjustments of two extra experimental kinetics with the model neglecting rolling. The experimental parameters are listed in Table 3. (a) Curves obtained for sample B at positions  $x = 0.5$  mm (●)  $x = 1$  mm (▼),  $x = 1.5$  mm (▶),  $x = 2$  mm (◄),  $x = 2.5$  mm (■),  $x = 4$  mm (●),  $x = 7$  mm (▲),  $x = 38$  mm (\*). (b) Curves obtained for sample C at positions  $x = 0.5$  mm (●)  $x = 1$  mm (▼),  $x = 1.5$  mm (▶),  $x = 2$  mm (◄),  $x = 3$  mm (■),  $x = 5$  mm (●),  $x = 10$  mm (▲),  $x = 30$  mm (\*).