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# A biomechanical model for cell sensing and cell migration

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## 1 Introduction

A fascinating aspect of how cells interact to create multi-cellular structures is largely stochastic [1, 2]. The combined complexity and randomness involved in such processes makes it difficult to unravel the interwoven ingredients needed for various multi-cellular structures to emerge [3, 4]. However, for emergence to happen, each cell needs to behave in a sufficiently coherent manner [5]. Therefore by studying cells individually in a controlled environment we may hope to identify a few key ingredients. Although single cell migration is stochastic, it can nonetheless be influenced by the inherent properties of the substrate. Known examples include, cell to substrate adhesion properties [6], substrate stiffness [7], substrate topology [8] and the shape of the adhesion patterns drawn on the substrate [2].

The effect of adhesion properties on cell motility was reported in 1997 by Palecek *et al.* [6] and largely confirmed by other groups since then [9]. Interestingly, experiments showed that, as the mean detachment force increases, the mean cell speed would initially increase, then peaked and finally declined [6].

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21 On the other hand, directional migration bias can be observed in some instances when single cells are allowed to  
22 migrate between adhesion patterns. Vecchio *et al.* [2] reported a significant bias as single cells moved between trian-  
23 gular patterns coated with fibronectin [10]. Understanding how cells perceive and react to their surrounding should  
24 ultimately enable us to better comprehend how biological processes such as tissue formation and angiogenesis take  
25 place. We therefore chose to use a numerical model as a tool to test our hypothesis and the limits of our theoretical  
26 understanding.

27  
28 Various types of numerical models can already be found in the literature. Each type has its own advantages and  
29 drawbacks. Lattice based models, such as Cellular Potts Models and cellular automata are defined on a grid, which  
30 artificially constraints the cell behavior, notably when it comes to accurately model the impact of mechanics in the  
31 system [11, 12, 13]. Others are point based models, which have the advantage of being simple, on the other hand,  
32 it means that no intracellular mechanics is taken into account and external mechanics is also limited [14]. Finally,  
33 more complex mechanical cellular models such as the one presented by [15, 16, 17] are numerically too costly and  
34 too complex, making them impracticable to study cellular migration and behavior on large scales.

35  
36 We therefore developed an agent based cellular model with moderate complexity, making it computationally light  
37 and fast enough to run a moderately large number of simulation on a regular computer within a reasonable time frame,  
38 while being rich enough to take into account some aspect of the intracellular mechanics. The model is composed of  
39 nodes and branches. The nodes connect the branches to each other and can interact with the substrate, while the  
40 branches transmit and generate forces between nodes. This design allows for the emergence of a dynamic cellular  
41 structure. The behavior of the model was then tested on homogeneous substrates with various adhesion conditions  
42 so as to identify the key parameters needed to recreate the hump like curve found by [6] and by [9]. In addition, the  
43 model was also tested on triangular shape adhesion patterns to identify relevant parameters involved in directional  
44 biases [10], [2].

45

## 46 2 Cell model

### 47 2.1 Overall cell structure

48 Our cell model is constructed to account for the overall cell dynamics based on the interactions between cytoskeletal  
49 fibres and adhesion points. It is composed of branches and nodes that form a hierarchical tree like structure meant  
50 to represent the mechanical structure of the cell by emulating its center (nucleus), membrane protrusions, adhesions  
51 and mechanosensors. Each node  $N_i$  has an order  $i$  (from 1 to 2) that indicates its degree of separation from the central  
52 node  $N_0$ . The parent node of  $N_i$  is node  $N_{i-1}$ . Node  $N_0$  has no parent node. Several  $N_i$  nodes can radiate from a node  
53  $N_{i-1}$  and each branch  $B_i$  connects the two nodes  $N_i$  and  $N_{i-1}$ .

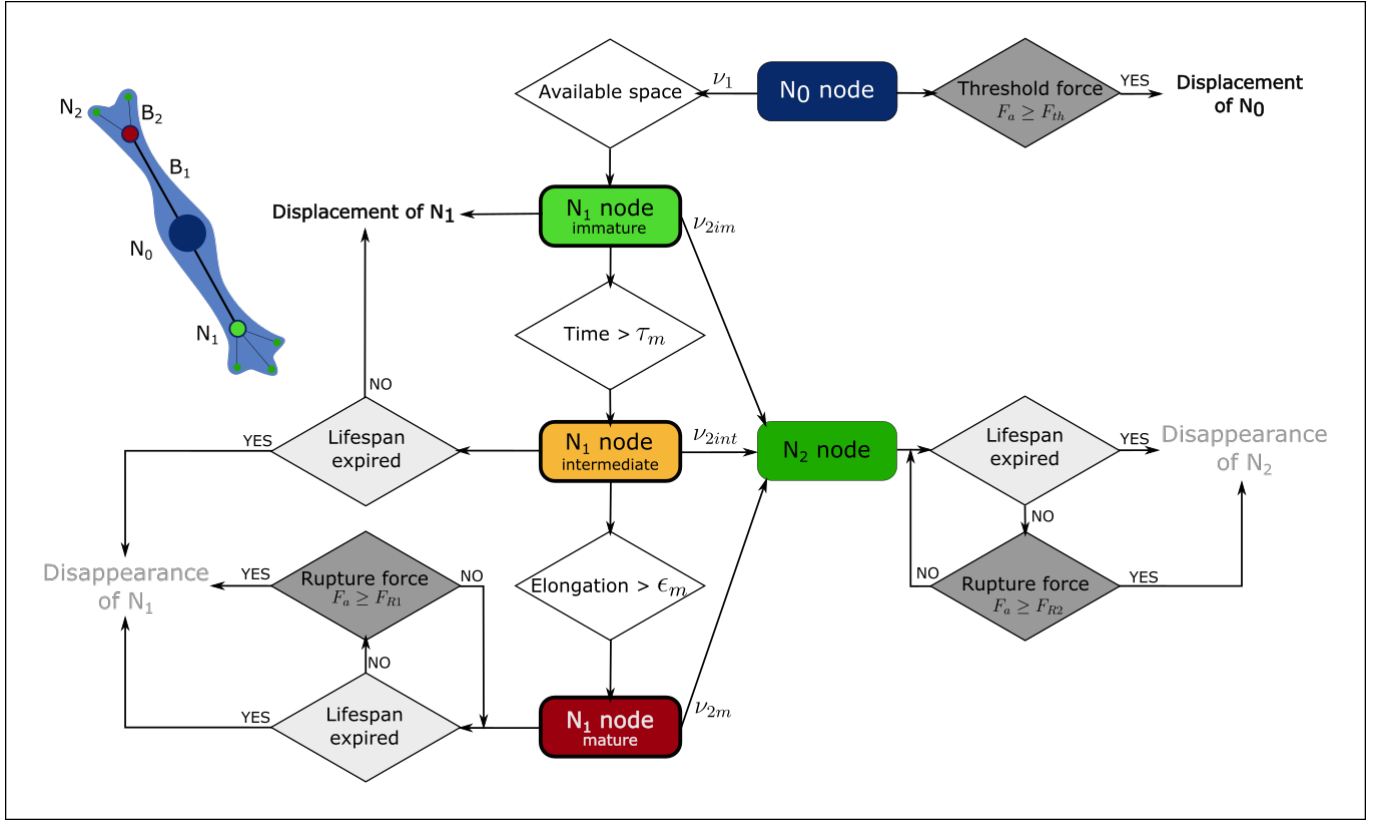
- 54 • The  $N_0$  node represents the cell center, (*i.e.* the cell nucleus). This point is unique and it is used to locate the  
55 cell.
- 56 • The  $N_1$  node represents a cell adhesion as the tip of a protrusion emanating from the cell centre.  $N_1$  nodes have  
57 the potential to mature and exist under three different forms of increased maturity (described below) in order  
58 to account for the evolving nature of the cell adhesions.
- 59 • The  $N_2$  node represents a protruding mechanosensor. Those nodes typically represent membrane extensions,  
60 such as filopodia, that probe the cell environment.

61 The number, position and properties of nodes and branches are dynamically regulated, such that the cell generates  
62 or deletes nodes and branches. The latter transmit and generate forces thus enabling nodes to move and pull on the  
63 substrate. The cell can consequently spread, adhere, pull and move. The behavior of each node is dependent on its  
64 order, thus enabling the emergence of a coherent system. The rules regulating each node type are summarized in  
65 Figure 1 and are detailed below.

### 66 2.2 Nodes generation

#### 67 $N_1$ nodes

68 Several  $N_1$  nodes can be generated during the cell's life time. The frequency and the location at which they are  
69 generated is regulated in a probabilistic manner. Therefore, to determine how many  $N_1$  nodes should be generated  
70 during the current time step, we first need to calculate the occurrence of independent events that will attempt to



**Figure 1:** The cell structure is composed of nodes and branches,  $N_0$ , the root node is at the center,  $B_1$  branches connect the root node to  $N_1$  nodes and  $B_2$  branches connect the latter to  $N_2$  nodes. The flowchart shows how nodes evolve over time. The  $N_0$  node is bound to the substrate and moves if the adhesion force  $F_a$  is greater than the threshold force  $F_{th}$ . It generates  $N_1$  nodes if space is available.  $N_1$  nodes are initially immature, then intermediate and finally mature. The respective function of each  $N_1$  state is to: explore (if immature), assess if it can become mature (if intermediate) and bind to the substrate (if mature). During each maturation state a  $N_1$  node respectively generates  $N_2$  nodes at an average stochastic rate of  $\nu_{2im}$ ,  $\nu_{2int}$  and  $\nu_{2m}$ . The function of the  $N_2$  nodes is to probe the environment and contribute to the movement of the cell's leading edge. Therefore, immature and intermediate  $N_1$  nodes move, while mature  $N_1$  nodes are bound to the substrate. Immature  $N_1$  nodes transition to an intermediate state after reaching the age of  $\tau_r$ , while the mature state is reached once the  $B_1$  branch is strained above  $\epsilon_m$ . When the adhesion force  $F_a$  of a  $N_1$  or  $N_2$  node is greater than the respective rupture force  $F_{R1}$ ,  $F_{R2}$  there is rupture and the node disappears and its child nodes with it.

71 generate them. To do so, we define the mean frequency  $\nu_1$  at which these independent events occur around the cell.  
 72 But, to avoid overcrowding of  $N_1$  nodes in one area, an exclusion angle  $\delta\theta_1$  is defined around the  $B_1$  branch, so as to  
 73 prevent new  $N_1$  nodes from forming too close to their already existing counterparts (Fig. 2). From there we can then  
 74 calculate  $\lambda_1$ , the expected rate of occurrence during a time step  $dt$ :

$$\lambda_1 = \nu_1 dt \quad (1)$$

75 Then we use a pseudo-random variate generator that follows the Poisson's distribution with  $\lambda_1$  as input. The ob-  
 76 tained random variate integer  $j_1$  is the number of events that will attempt to create a  $N_1$  node during the current time  
 77 step. If  $j_1$  is greater than zero and if there is room to create a new node, then a new node is created at a fixed initial  
 78 distance  $l_{10}$  from  $N_0$  and at a randomly generated angle  $\theta_1$  (fig. ??). Where the latter is a random variate pulled from  
 79 a uniform distribution over the angular domain that remains available. This process is repeated  $j_1$  times or until there  
 80 is no more room to create another node because the angular domain is fully inhibited.

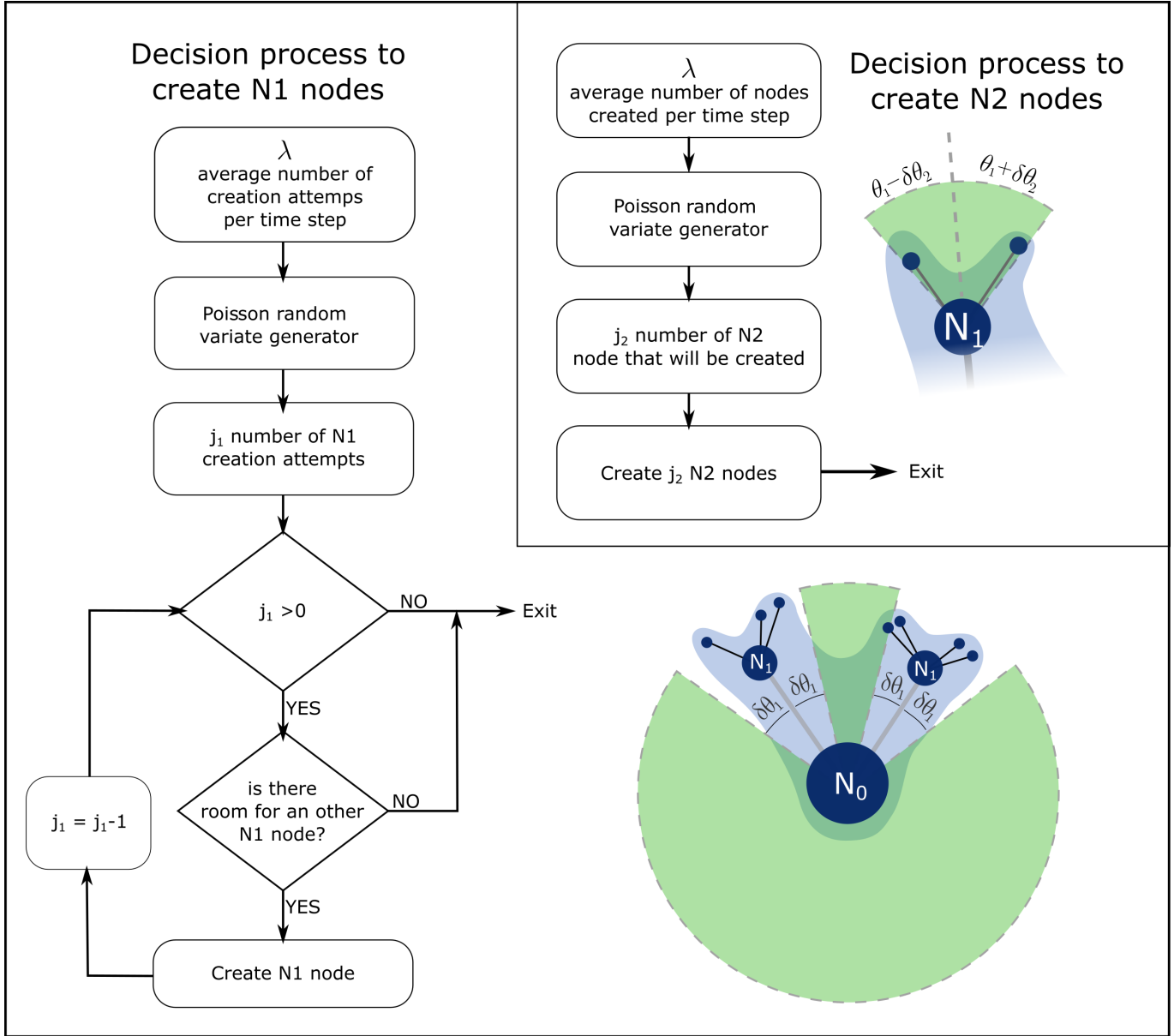
81

82  *$N_2$  nodes*

83  $N_2$  nodes can be considered as membrane spikes that probe the cell environment.  $N_2$  nodes are stochastically emitted  
 84 by the parent  $N_1$  node with a mean frequency  $\nu_2$  that depends on the maturation level of  $N_1$ . An immature  $N_1$  emits  $N_2$   
 85 nodes with a higher frequency to actively probe the environment and orient the cell displacement. As it matures, the  
 86  $N_1$  node reinforces its adhesion strength to the substrate and emits  $N_2$  nodes with a lower frequency to progressively  
 87 reduce the probing activity and stabilize the adhesion. The expected rate of occurrence  $\lambda_2$  of a new  $N_2$ , during a time  
 88 step  $dt$ , is:

$$\lambda_2 = \nu_2 dt \quad (2)$$

89 a Poisson's variate generator is used to define the number of  $N_2$  nodes that are created during the time step with  $\lambda_2$   
 90 as input. Then the angle with which each new  $N_2$  appears, is defined using a uniform-random variate generator that  
 91 follows a uniform distribution. The sample space is defined between  $\theta_1 \pm \delta\theta_2$ . The new  $N_2$  node is thus created at the  
 92 angle  $\theta_2$  and fixed at an initial distance  $l_{20}$  from the position of the parent  $N_1$  node (Fig. 2).



**Figure 2:** Nodes creation. *Left and bottom:* decision process to create  $N_1$  nodes at each time step. A  $N_1$  node located at an angle  $\theta_1$  will inhibit the formation of new  $N_1$  nodes in the angular domain surrounding the  $B_1$  branch i.e.  $\theta_1 \pm \delta\theta_1$ . *Top right:* Decision process to create  $N_2$  nodes at each time step in an angular domain surrounding the  $B_1$  branch i.e.  $\theta_2 \pm \delta\theta_2$ . Areas in green represents the zone where a new node can be created.

93 **2.3 Nodes displacement**

94 Our model aims at describing the cell movement and displacement dynamics. Therefore the nodes that all adhere to  
 95 the substrate with various degrees, that depend on their type and maturation level, can be displaced by the mechanical  
 96 forces applied on them through the branches.

97

98 Each branch (of index  $i$ ) that is connected to a node exerts a force  $\mathbf{F}_i$  on the node such that the net force applied by the  
 99  $n$  branches on the node is the sum of these forces. If the node is bound to the substrate the adhesion force  $\mathbf{F}_a$  prevents  
 100 the node from moving such that:

$$\mathbf{F}_a = - \sum_{i=1}^n \mathbf{F}_i \quad (3)$$

101 On the other hand, when the node is able to move, according to the quasi-static approximation the acceleration is  
 102 negligible. Thus using Newton's second law, and by stating that the friction force  $\mathbf{F}_v = -\alpha\mathbf{v}$  is always opposed to the  
 103 node's displacement with velocity  $\mathbf{v}$ , we have:

$$-\alpha\mathbf{v} = \sum_{i=1}^n \mathbf{F}_i \quad (4)$$

104 where  $\alpha$  is the friction coefficient of the node with the substrate. It depends on the node type and maturation level.  
 105 The node's new position at the next iteration noted  $\mathbf{x}_N^{t+dt}$  is thus given by:

$$\mathbf{x}_N^{t+dt} = \mathbf{x}_N^t + \mathbf{v}dt \quad \text{with} \quad \mathbf{v} = \frac{1}{\alpha} \sum_{i=1}^n \mathbf{F}_i \quad (5)$$

106 In our model,  $N_2$  nodes play the role of sensors that interact with the substrate to probe its mechanical and/or  
 107 adhesive properties in order to orientate the cell displacements. Several  $N_2$  nodes are simultaneously linked by  $B_2$   
 108 branches to their parent node  $N_1$  on which they pull.  $B_2$  branches are assumed to be short elastic actin spikes with  
 109 elastic coefficient  $\kappa_2$ . They are emitted with an initial length  $l_{20}$  and they are characterized by a predefined Cauchy  
 110 strain  $\epsilon_{20}$  such that the resting length  $l_{2r}$  of the spike is smaller than its initial length, *i.e.* :

$$\epsilon_{20} = \frac{l_{20} - l_{2r}}{l_{2r}} > 0 \quad (6)$$

111 As a consequence the spike is initially stretched and will attempt to return to its rest length. This will cause the branch  
 112 to pull on both nodes, giving rise to a positive elastic force  $F_{el}$  along the  $\overrightarrow{N_1N_2}$  axis since the  $N_2$  node is fixed (bounded  
 113 to the substrate) and the  $N_1$  node is free to move (at least in its non mature states):



$$F_{el} = \max(0, \kappa_2(l_2(t) - l_{2r})) \quad \text{with} \quad l_{2r} = \frac{l_{20}}{1 + \epsilon_{20}} \quad (7)$$

114 The resulting force on the parent node  $N_1$  is calculated as the sum of the elastic contributions of each  $B_2$  branches  
 115 with equation (4). The  $N_1$  node is then displaced according to equation (5) to its new position which corresponds to  
 116 the location where the highest resulting tension is developed.

## 117 2.4 Nodes maturation

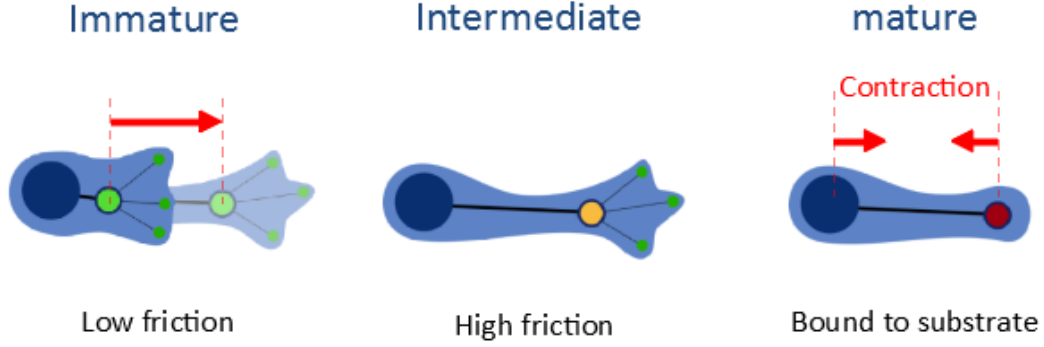
118 The  $N_1$  nodes represent the adhesion points on which the cell actin fibres, represented by the  $B_1$  branches, take support.  
 119 Before the cell is able to move, the adhesion initially composed of integrins, should reinforce by the recruitment of  
 120 new proteins such as talin and paxillin. Further proteins are recruited for the nucleation and binding of actin fibres,  
 121 including vinculin,  $\alpha$ -actinin, FAK, VASP, Arp2/3. The fibres can then generate increasing forces on the adhesion  
 122 that reaches maturation under the form of a focal adhesion through the recruitment of zyxin and tensin. Reciprocally  
 123 the mature adhesions can resist higher tensions from the cytoskeletal fibres. This bi-directional maturation process  
 124 between adhesion and cytoskeletal fibres is important to realistically describe the cell sensing ability and its evolving  
 125 biomechanics. Indeed, depending on the mechanical nature (rigidity) of the substrate the maturation process will be  
 126 more or less efficient depending on the level of forces attained by the cell fibres.

127 We consider in the model three level of maturation for the  $N_1$  nodes and its associated  $B_1$  branch: immature,  
 128 intermediate and mature states. Each state is characterized by an enhanced adhesiveness to the substrate and by an  
 129 enhanced potential of force generation (Fig. 3).

- 130 • *Immature state*: the  $N_1$  node is free to move and is displaced by the forces exerted by the  $N_2$  nodes emitted at  
 131 a high rate  $v_{2im}$ . Consequently its friction with the substrate is initially small with coefficient  $\alpha_{01}$  and linearly  
 132 increases with time to reach at time  $\tau_t$  the value  $\alpha_{int}$  which characterizes the friction of the intermediate state.  
 133 The friction evolution between the immature and intermediate states is thus given by:

$$\alpha_1(t) = \frac{\alpha_{int} - \alpha_{10}}{\tau_t} t + \alpha_{10} \quad (8)$$

134 As a concomitant event, the  $B_1$  branch is progressively reinforced by actin fibres recruitment, that leads to a



**Figure 3:** Illustration of the maturation stages of the  $N_1$  node. The immature node, characterized by a low friction with the substrate, is displaced by the traction of the  $N_2$  nodes. After some pre-defined time the  $N_1$  node reaches the intermediate maturation state characterized by an increased friction with the substrate. It finally reaches maturation if the  $B_1$  branch is sufficiently elongated by the tensions from the  $N_2$  nodes. The mature adhesion is bounded to the substrate and the  $B_1$  branch becomes contractile to generate higher forces on the  $N_0$  node in order to allow the cell to translocate by taking support on the  $N_1$  node to move forward.

135 linearly increasing stiffness from  $\kappa_{10}$  (immature state) to  $\kappa_{11}$  (intermediate state):

$$\kappa_1(t) = \frac{\kappa_{11} - \kappa_{10}}{\tau_t} t + \kappa_{10} \quad (9)$$

136 The branch initially corresponds to an unstretched spring of length  $l_{01}$  that can bear tension and compression  
 137 depending on the node displacement  $l_1(t)$ . The elastic restoring force in the branch is then given by:

$$F_{el} = \kappa_1(t)(l_1(t) - l_{01}) \quad (10)$$

138 • *Intermediate state:* it is attained when the  $N_1$  node reaches the age  $\tau_t$  for which the values of the friction  
 139 coefficient and branch stiffness are kept constant as:

$$\alpha_1(t) = \alpha_{int} \quad \text{and} \quad \kappa_1(t) = \kappa_{11} \quad (11)$$

140 The increased friction coefficient of the node  $N_1$  makes it resist more to the displacement from the pulling  $N_2$   
 141 nodes. Moreover, the production rate of  $N_2$  nodes is concomitantly reduced with  $v_{2int} < v_{2im}$ . This reduces  
 142 significantly the exploration potential of the branch. At this stage, the  $B_1$  branch corresponds to a bundle of  
 143 actin fibres for which the rest length is reassessed and given by  $l_1(\tau_t)$ . The elastic restoring force in the branch

144 is now given by:

$$F_{el} = \kappa_{11}(l_1(t) - l_1(\tau_t)) \quad (12)$$

145 • *Mature state*: the transition to this state only occurs if the  $B_1$  branch elongation from its new resting length  
146  $l_1(\tau_t)$  reaches the elongation target  $\epsilon_m$ , *i.e.* if:

$$\frac{l_1(t) - l_1(\tau_t)}{l_1(\tau_t)} \geq \epsilon_m \quad (13)$$

147 This condition is not necessarily reached, so not all  $N_1$  mature to this final state. If they do, two major  
148 transitions affect the node and branch. First, the node is fixed, bound to the substrate, in order to be able to  
149 sustain cell translocation that is required for the cell displacement. The production rate of  $N_2$  is further reduced  
150 with  $v_{2m} < v_{2int}$ . Second, the branch becomes contractile, through myosin recruitment, and corresponds to a  
151 stress fibre which is able to generate the force required for the cell translocation, *i.e.* the force that will allow  
152 the  $N_0$  node to move. The contractile force is given by:

$$F_c = \gamma_{max} \left(1 - e^{-\frac{\|\mathbf{F}_a\|}{F_\gamma}}\right) \quad (14)$$

153 where  $\gamma_{max}$  is the stall force of the adhesion,  $F_\gamma$  is a characteristic force constant, and  $\|\mathbf{F}_a\|$  is the norm of the  
154 adhesion force. By convention, if  $\mathbf{F}_c$  is positive, it pulls on  $N_0$  whereas it pushes when it is negative. The total  
155 force in the branch is the sum of the elastic contribution  $F_{el}$  (Eq. (12)) and contractile one  $F_c$  (Eq. (14)). The  
156 cell translocation occurs if the adhesion force  $F_a$  (Eq. (3)) is bigger than a threshold force  $F_{th}$ .

## 157 2.5 Nodes disappearance

158 Nodes can disappear in two different ways. First they have a limited lifespan and they spontaneously disappear when  
159 this time limit is reached. The lifespan depends on the node type (see Table 1). Second the nodes that are bound to  
160 the substrate can be broken if the resulting tension force exerted on the node exceed the rupture force. In both cases,  
161 when the node disappears, the connecting branch and child nodes also disappear instantaneously.

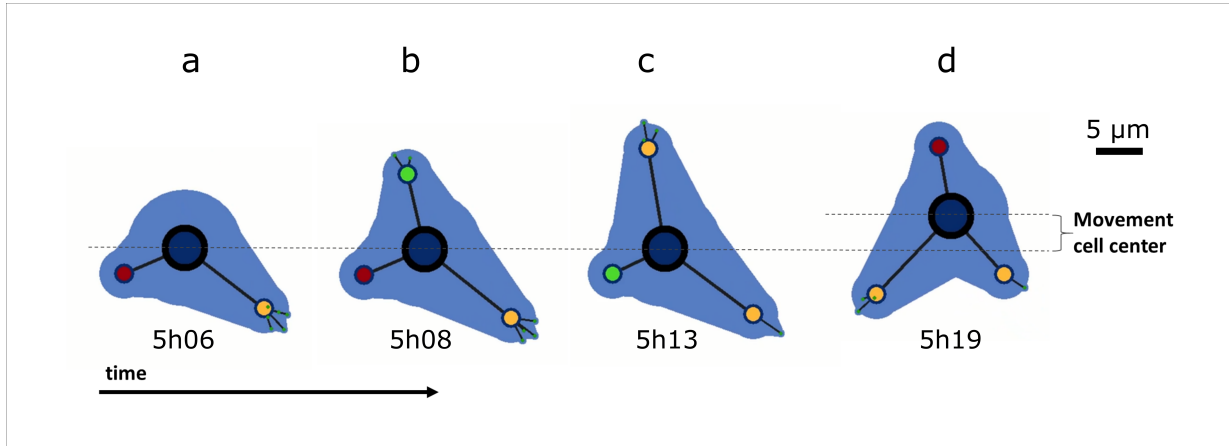
## 162 **3 Results**

### 163 **3.1 General cell behavior**

164 The model aims at genericity, *i.e.* at representing potentially any cell types. A particular cell type can be generated  
165 by adjusting the parameters in order to obtain a specific cell shape (from round shape to stellar shape) and specific  
166 behavior defined by the cell motile potential for example. Cells as different as keratocytes and glial cells can be  
167 generated. For the simulations presented here, the model parameters (given in Table 1) were defined based on a set of  
168 predefined constraints to represent an average unspecified cell, as follows:

- 169 1. *cell shape*: the observation of isolated cells in two-dimensional cell culture shows that the cell shapes usually  
170 exhibit a limited number of main protrusions, rarely exceeding 4 branches (endothelial cells [ref] or fibroblasts  
171 [ref]). We fixed this limit as a first constraint with the parameter  $\delta\theta_1$ . The ability to form membrane spikes to  
172 probe the environment is in the other hand defined by the parameter  $\delta\theta_2$ .
- 173 2. *cell size*: the branches length  $l_{01}$  and  $l_{02}$ , used to define  $B_1$  and  $B_2$ , were set to correspond to a protrusion and  
174 spike lengths respectively so that the maximum size of the cell does not exceed  $50\mu m$  to remain within the  
175 values of an average cell size.
- 176 3. *cell force generation*: the cell mechanical properties defined by the cell stiffness coefficients ( $\kappa$ ) and adhesion  
177 coefficients ( $\alpha$ ) were set so that the cell can develop the required range of forces, typically around  $50nN$ . The  
178 progressive increased in force generation associated to the maturation of the adhesions and fibres is obtained by  
179 making these parameters evolve along the 3 maturation states.
- 180 4. *cell motile dynamics*: time parameters such as adhesions production rates ( $\nu$ ) and adhesion lifespans ( $\tau$ ) con-  
181 tribute to the dynamics of the cell. But more importantly, the adhesions rupture forces ( $F_R$ ) and the threshold  
182 force required for cell translocation ( $F_{th}$ ) determine the level of interaction of the cell with its substrate and its  
183 ability to easily detach in order to move.

184 A suitable set of parameters that responds to these constraints and to the admissible range of values from the litera-  
185 ture has been semi-empirically determined (see Table 1). The simulation realized with the so-defined parameters is  
186 presented in figure 4.



**Figure 4:** Cell deformation and migration observed over a 13 minutes period of a long lasting simulation of 72 hours. The cell mainly exhibits a characteristic triangular shape, with dynamical movements of extension/retraction of its protrusions (branches). Colour code for  $N_1$  node states: green for immature, yellow for intermediate and red for mature. The cell envelop in blue is represented for cosmetic purpose only, since this model does not describe the cell membrane nor the cytoplasm.

187 Figure 4 shows a typical sequence of cell shape changes, in relation to the maturation of the nodes, and leading to  
 188 the cell displacement. The simulation exhibits three different outcomes for the  $N_1$  nodes: (i) a mature node disappears  
 189 and is instantaneously replaced by an immature node (node on the left of the cell), (ii) a node is displaced, but the  
 190 branch is not sufficiently elongated to reach the maturation criterion (node on the right of the cell), (iii) a node pro-  
 191 gressively and successfully evolves through the three maturation stages and eventually the contraction of the mature  
 192 branch leads to the cell displacement (node on the top of the cell).

193

#### 194 *Adhesions dynamics*

195 Cell deformations and migration have been simulated over 72 hours. The different events related to the nodes dynam-  
 196 ics, including maturation and turnover, have been recorded. Figure 5a shows the cause of the  $N_1$  nodes disappearance:  
 197 among the 642  $N_1$  nodes generated, 366 (57%) disappear at the intermediate stage as their lifespan expired and 273  
 198 (43%) reach the mature state. Only 20% of the mature  $N_1$  nodes attain their time limit, all the other mature nodes  
 199 break because of the tensions forces applied on them. This relatively high contribution of the rupture force reveals that  
 200 only a limited amount of mature adhesions  $N_1$ , are strong enough to resist the branch contractility as focal adhesions  
 201 would. If the adhesion is strong enough to support cell translocation the cell will move, if it is not strong enough the  
 202 adhesion breaks (rupture). On the other hand, the main cause of death of the 8815 generated  $N_2$  nodes is the expiration  
 203 of their lifespan that accounts for 82% of the disappearances (Fig. 5b). Indeed, the role of  $N_2$  nodes is to dynamically

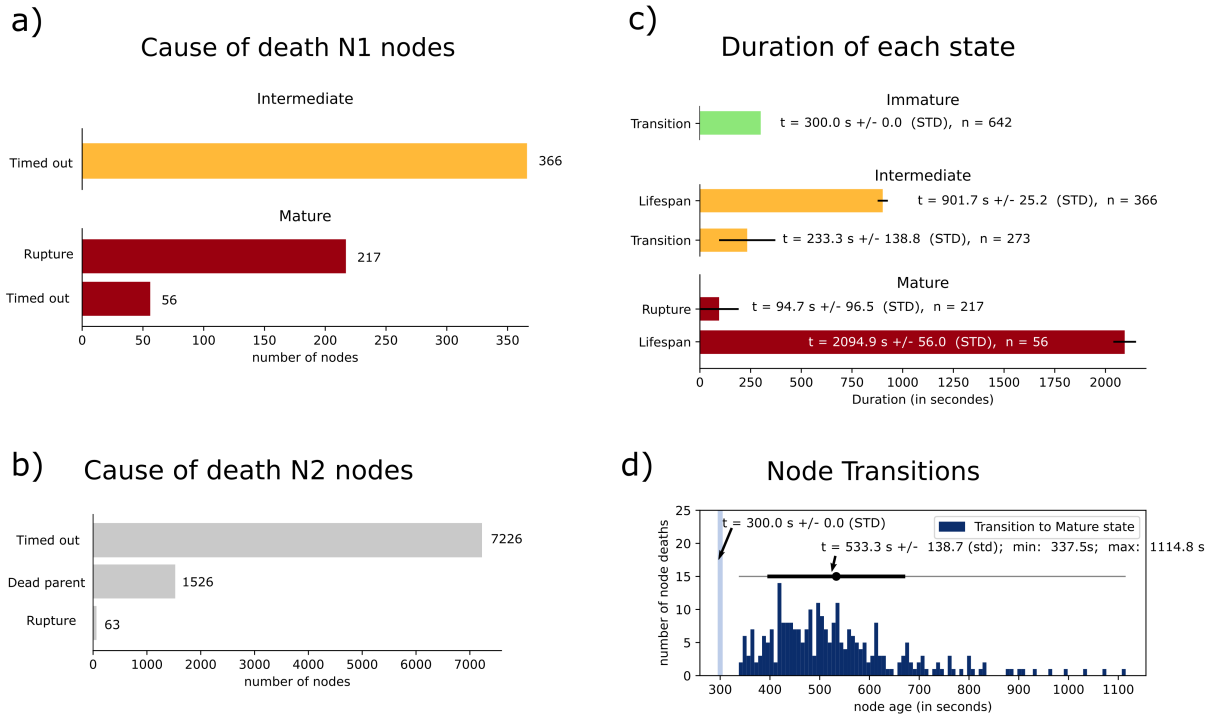
204 probe the environment. Their lifespan has been fixed short enough to favour this rapid dynamics, but long enough for  
205 the  $B_2$  branches to exert tension forces to relocate the  $N_1$  node in the region of interest (in the case of a heterogeneous  
206 substrate).

207 The maturation dynamics of the  $N_1$  node is highlighted in figures 5c and 5d. All the 642  $N_1$  nodes formed during  
208 the 72 hour simulation mature to the intermediate state since this transition is unconditional as soon as the node  
209 is 300 seconds old. At the intermediate state, the lifespan of the  $N_1$  nodes is around 900 seconds. However if the  
210 branch  $B_1$  elongates sufficiently, the node matures and this can occur over a vast period of time (as shown in fig  
211 5d) with an average time of  $233 \pm 139s$ , *i.e.* well before reaching the lifespan limit. This ensures that a sufficient  
212 amount (about 43%) of  $N_1$  nodes will mature. Once maturation is reached, an enhanced force competition - with the  
213 addition of a contractile force component - takes place in the branch. Rupture of the  $N_1$  nodes occurs on a relatively  
214 short window period of  $95 \pm 96s$  after the node reaches maturation. The remaining nodes reach their time limit of  
215 about 2000 seconds.

216

### 217 *Force generation*

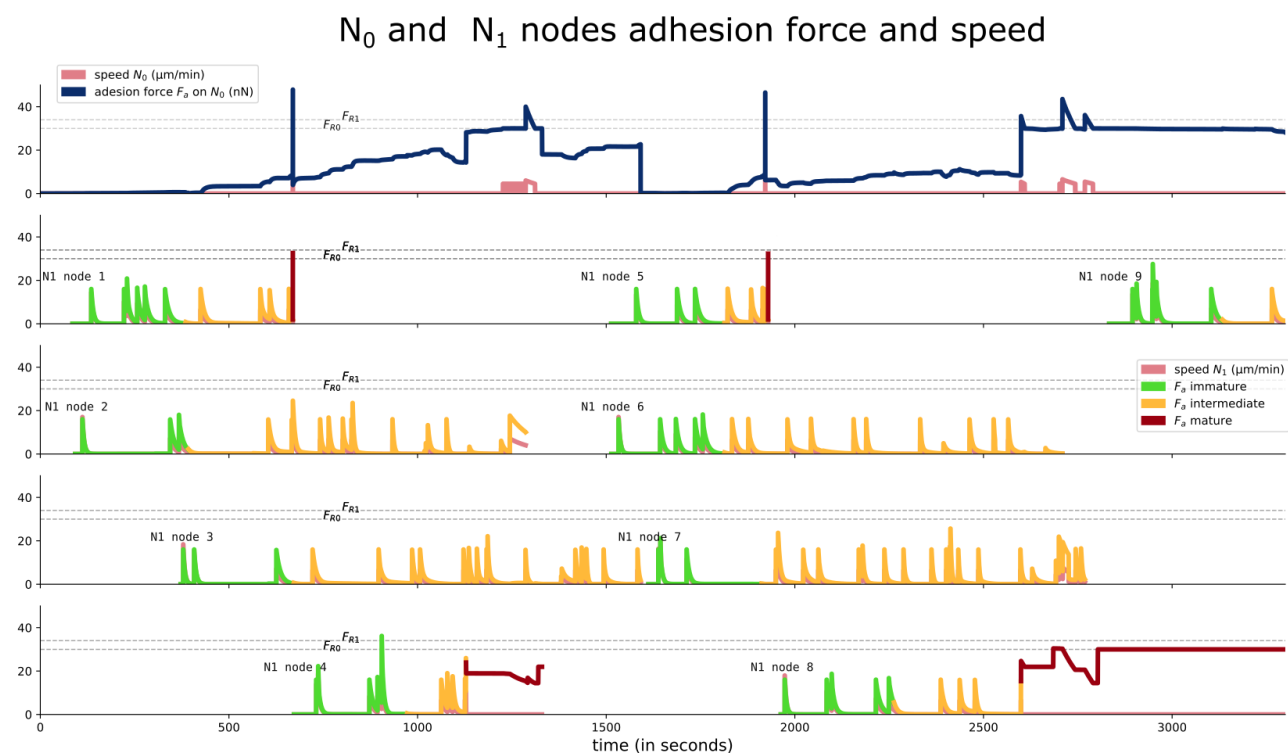
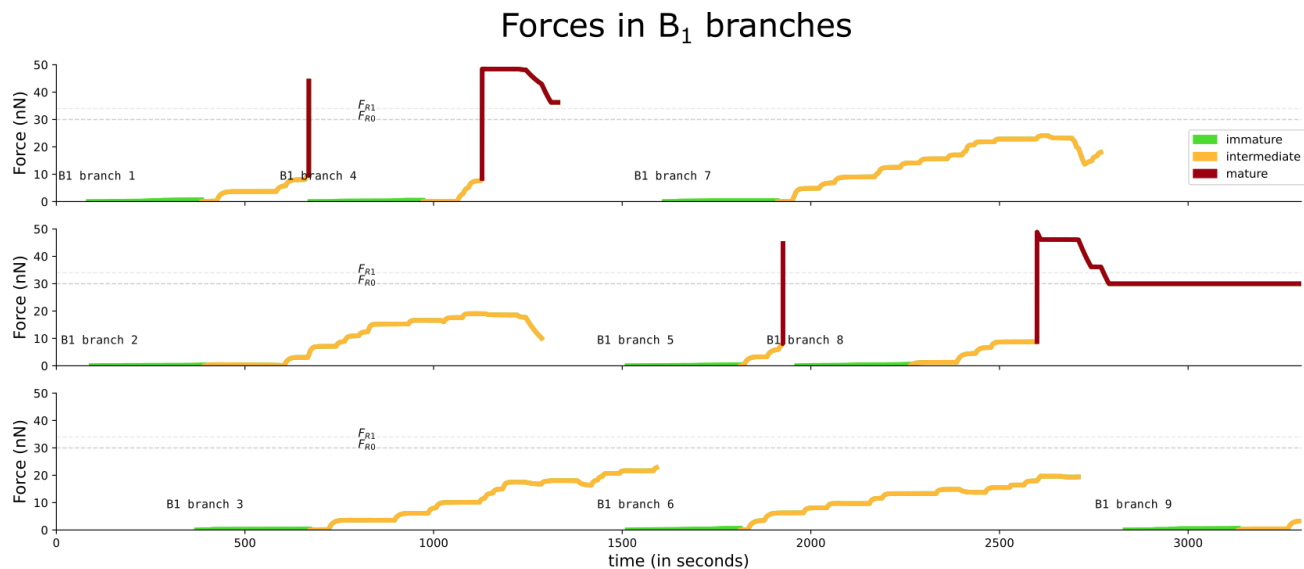
218 Adhesions and branches mature concomitantly. The maturation of the branch is characterized by the progressive  
219 increase of the force it can generate on its nodes. Figure 6 displays the evolution of the forces generated in the branches  
220 and exerted on the nodes during a sequence of a single cell movements of about one hour in order to highlight how  
221 the forces in the branches drive the nodes displacement dynamics and the cell migration. Figure 6, upper graph shows  
222 that at the immature stage, the forces in the  $B_1$  branches remain very small despite the linear increase of the elasticity  
223 coefficient with time. After 300s the elasticity coefficient of the branch stops evolving and the branch resting length  
224 is redefined to its acquired length. These new conditions define the intermediate state of the branch where the force  
225 progressively increases, often above 20nN, because of the branch elongation due to the  $N_1$  node displacement under  
226 the traction of the  $B_2$  branches (not represented). If the  $B_1$  branch elongation reaches the elongation threshold  $\epsilon_m$  then  
227 the  $B_1$  branch attains the mature state and becomes contractile. This acquired contractility generates a jump of about  
228 40nN in the branch force. This value has been defined so as to generate a level of force on  $N_0$  sufficiently high to  
229 displace this node, *i.e.* for the cell to migrate. Figure 6, lower graph shows the resulting forces applied by the branches  
230 on the nodes. Forces applied on the  $N_1$  nodes appear as a succession of spikes of about 20nN in intensity. This spike  
231 profile is explained by the  $N_1$  node displacement that dissipate the resulting force from the  $B_1$  and  $B_2$  branches. Force



**Figure 5:** Nodes dynamics for a single cell over a 72 hour simulation. a) cause of death for the intermediate and mature  $N_1$  nodes; b) cause of death of the  $N_2$  nodes; c) durations at which the transitions to the more mature states occur, effective durations of the nodes lifespan and mean duration at which a mature node breaks (STD stands for standard deviation of the mean); d) recorded  $N_1$  node transition events in function of the node age. All immature to intermediate transitions happened at the age of 300s, while all intermediate to mature transitions happened afterwards. The horizontal grey line spans from the earliest to the latest transition, while the black spot and bar show mean transition age and its standard deviation. We note that the node age is the sum of the times spent in each state. Colour code for  $N_1$  node states: green for immature, yellow for intermediate and red for mature.

232 dissipation is possible as long as  $N_1$  is free to move, *i.e.* when it is in its immature or intermediates state. At the  
233 mature state, the  $N_1$  node is bounded to the substrate to resist the contractile force. If the force on the node reaches  
234 the threshold  $F_{R1}$  then the node breaks and instantly dissipates the force (two occurrences for node 1 and node 5 in the  
235 figure). In both cases the sudden force increase in the branch is sufficient to reach the threshold force  $F_{th}$  on the  $N_0$   
236 node required for the cell to move (*i.e.* non-zero speed) just before the times 750s and 2000s. All other cases of cell  
237 displacements (*i.e.* non-zero speed) occurred when at least one branch becomes contractile to increase the resulting  
238 force on the  $N_0$  node above the  $F_{th}$  threshold.





**Figure 6:** Upper graph: evolution of the force intensity in the different  $B_1$  branches. The branches are displayed on 3 graphs to avoid overlapping of the co-existing branches. During the one-hour observation period 9 branches are observed with in average 3 co-existing branches. The colour code represents the maturation state of the branch: immature (green), intermediate (yellow), mature (red). Lower graph: evolution of the intensity of the resulting forces applied on the  $N_0$  (first row) and  $N_1$  nodes (rows 2 to 4). The  $N_1$  nodes are displayed on 4 graphs to avoid overlapping of the co-existing nodes. During the one-hour observation period 9  $N_1$  nodes are observed. The colour code represents the maturation state of the  $N_1$  node: immature (green), intermediate (yellow), mature (red). The horizontal grey dotted lines in each graphs represent the force thresholds  $F_{R0} = F_{th}$  for  $N_0$  to move and  $F_{R1}$  for  $N_1$  to break.

### 239 3.2 Cell migration on a homogeneous substrate

240 To test the model we first perform cell migration simulations on a homogeneous substrate. Figure 7 (upper left graph)  
241 presents the superimpositions of 50 single cell trajectories recorded over 72 hours. The homogeneous distribution of  
242 the trajectories is coherent with a typical random migration behaviour, meaning that our model does not introduce any  
243 migration bias. We then tested the influence of the force attachment of the cell to the substrate. The cell attachment  
244 force corresponds to the threshold forces triplet  $(F_{th}, F_{R1}, F_{R2})$  than can change depending on the biochemical nature  
245 of the substrate, *i.e.* on the cell matrix fibres composition, characterized by the amount of ligands and/or the strength  
246 of the adhesive bonds with which the cell can interact. To change the cell-substrate affinity, *i.e.* the cell attachment  
247 force, we introduce the parameter  $\delta$  to modulate the force magnitude as  $\delta \times (F_{th}, F_{R1}, F_{R2}) = (\delta F_{th}, \delta F_{R1}, \delta F_{R2})$ . We  
248 then compare  $\delta = 1$  which is the reference simulation with  $\delta = 1.5$  which means a 50% increase of the attachment  
249 force. Figure 7 (upper right graph) shows that the cell exploration zone is significantly reduced while maintaining its  
250 random migration characteristic.

251 If  $\delta$  is changed from 0.25 to 2.0, the average cell speed evolves with a bell shape (Fig.7, lower graph) which is  
252 in agreement with experimental facts [6]. For  $\delta < 1$  the cell remains unable to move since the attachment force is  
253 too weak for the cell to take support on the substrate. The level of forces developed by the branches systematically  
254 break the adhesions that cannot strengthen and reach maturation to allow the cell to move. Once the attachment  
255 force is strong enough for  $\delta > 1$  then the cell can move. For  $\delta = 1.125$  the average cell speed reaches its maximum  
256 close to  $8\mu\text{m}/\text{h}$ , and decreases progressively for increasing values of  $\delta$ . When the attachment force is higher, then the  
257 cell adhesions reach maturation however the forces developed in the branches are not high enough to reach the cell  
258 translocation threshold which limits the cell migration.

259 Since the level of force for cell translocation can only be reached once the  $N_1$  adhesion is mature, we further tested  
260 the influence of the mature  $N_1$  adhesion lifespan  $\tau_m$  (Fig.7, lower graph). As expected, when the adhesion lifespan is  
261 shorter ( $\tau_m/2 = 17\text{min}$ ), there is a higher turnover of the adhesions which allows the cell to move more often, thus  
262 increasing the average migration speed. In the other hand when the lifespan is longer ( $2 \times \tau_m = 70\text{min}$ ), then the  
263 cell adhesion and its associated branch which does not reach the translocation threshold force remains stuck until the  
264 adhesion is released as it reaches its time limit. This is slowing down the cell migration speed. In the extreme case  
265 where the adhesion lifespan  $\tau_m$  is infinite, the only way to break the adhesion is for the associated branch to reach the  
266 translocation threshold. The lack of adhesion turnover reduces drastically the average migration speed by a factor two

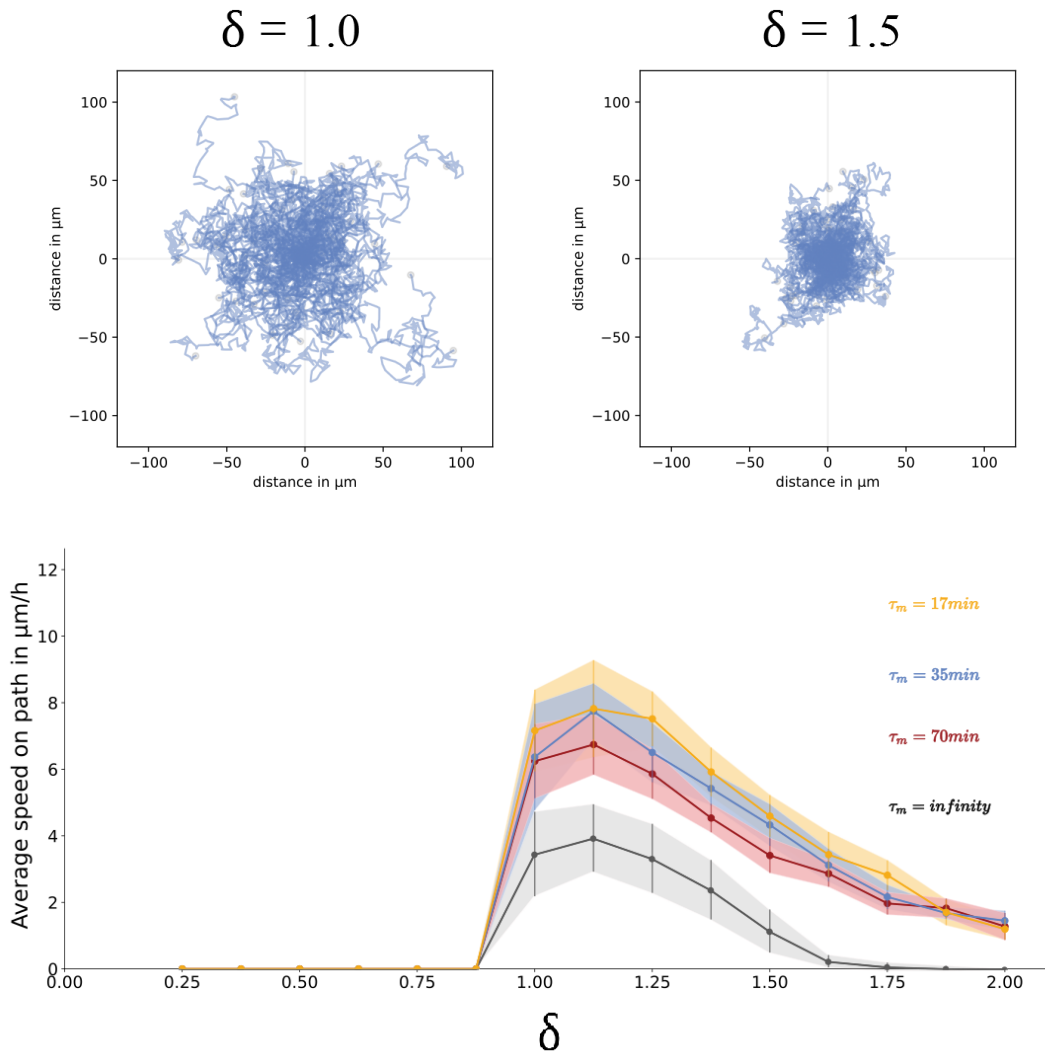
267 (the maximum speed is  $4\mu\text{m}/\text{h}$ ), however the cell remains able to migrate.

268

269 *Confrontation to experimental data*

270 From a qualitative stand point, the bell shape relationship between the cell speed and cell attachment to the substrate  
271 is well described [6].

272 [9].



**Figure 7:** Upper graphs: Cell trajectories on a homogeneous substrate for two cell detachment conditions  $\delta = 1.0$  and  $\delta = 1.5$ . Fifty trajectories of a single cell moving for 72 hours are superimposed in each graph. Lower graph: Average cells speed as a function of the parameter  $\delta$  representing the cell detachment condition. Each point of the curves corresponds to 10 trajectories of a single cell moving for 12 hours. Each coloured curve corresponds to a different value for  $\tau_m$ , the lifespan of mature  $N_1$  nodes.  $\tau_m = 35\text{ min}$  is the reference simulation used in the two upper graphs.

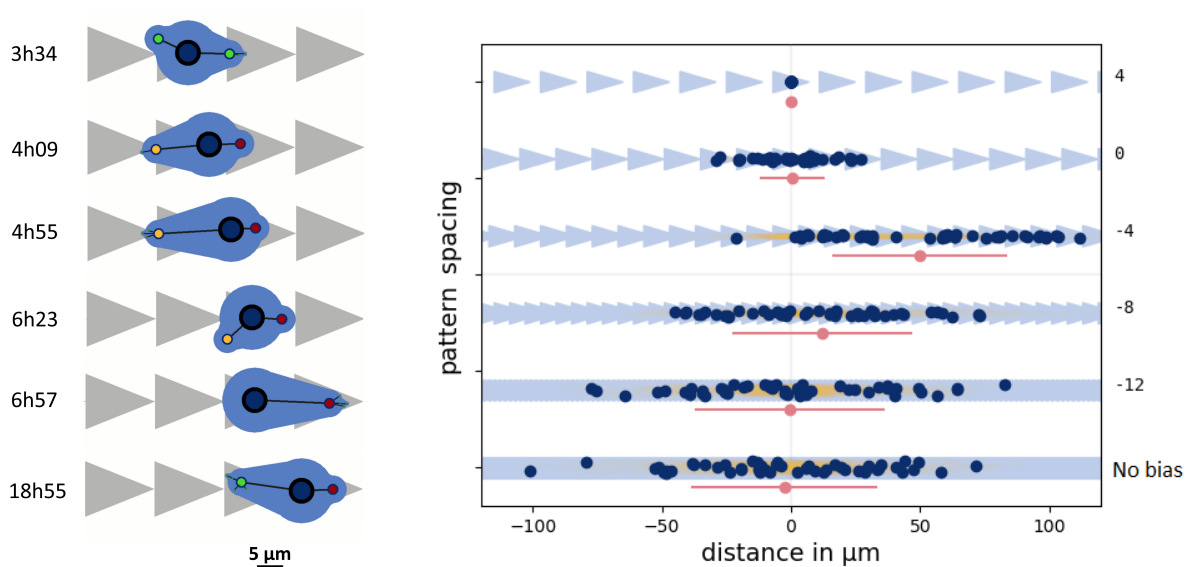
### 273 3.3 Constrained cell migration on adhesive patterns

274 Engineered adhesive patterns, typically coated with fibronectin, are often used to constrain the cell shape in order  
275 to study the resulting cytoskeletal organization. They can also be used to investigate the factors influencing the cell  
276 displacements. Inspired by the study of Vecchio *et al.* [2], we challenged our cell model by constraining the cell  
277 migration on a stripe of adhesive triangular patterns. By varying pattern spacing, the aim is to determine if the pattern  
278 can favour a migration direction on our virtual cell. The triangular shape presents an adhesive asymmetry for the cell  
279 surface adherence between the left and the right side of the patterns. The question is *will the cell follow the arrows ?*

280  
281 For the simulations, the nodes  $N_1$  and  $N_2$  can only form if in contact with the pattern. Each triangle of the pattern  
282 is  $10\mu\text{m}$  high and  $20\mu\text{m}$  long (Fig. 8). The gap distance between consecutive triangles is set for each simulations.  
283 It varies from  $-12\mu\text{m}$  to  $4\mu\text{m}$  with an increment of  $4\mu\text{m}$  from one simulation to another. A negative value of the gap  
284 distance means that the triangles overlap with this length. We also considered a pattern of reference with no bias,  
285 corresponding to a continuous adhesive stripe.

286  
287 Figure 8 (left) exhibits a sequence of cell movement and displacement on the adhesive pattern with a gap distance  
288 between consecutive triangles equals to zero. The cell forms branches that can reach the triangles on the left or on  
289 the right. However the inhibition condition for node and branch formation implemented in the model (see Fig. 2),  
290 limits the formation of a single branch per triangle (the triangle is not big enough to accommodate two  $N_1$  nodes). As  
291 a consequence, the direction for the cell displacement is not the resultant of the force competition between left and  
292 right, since the forces tend to equilibrate with one branch on each side. On the other hand it mostly depends on the cell  
293 probability to form some adhesions, which is directly related to the differential length of the arcs corresponding to the  
294 intersection of the circle of radius  $l_{01}$  with the adhesive surface at each side of the cell. This is a strong difference with  
295 the experiments of Lo Vecchio *et al.* where the differential quantities between both sides of the cell is the adhesion  
296 area. Indeed the longer the arcs does not mean/correspond to the largest adhesion area.

297  
298 To quantify the cell migration properties, Lo Vecchio *et al.* [2] proposed the calculation of a coefficient informing  
299 on the direction bias of the cell trajectory. This coefficient is calculated from the quantities  $N_+$  and  $N_-$  that correspond  
300 respectively to the number of steps made by the cell in the positive direction (following the tips of the triangles)  $N_+$



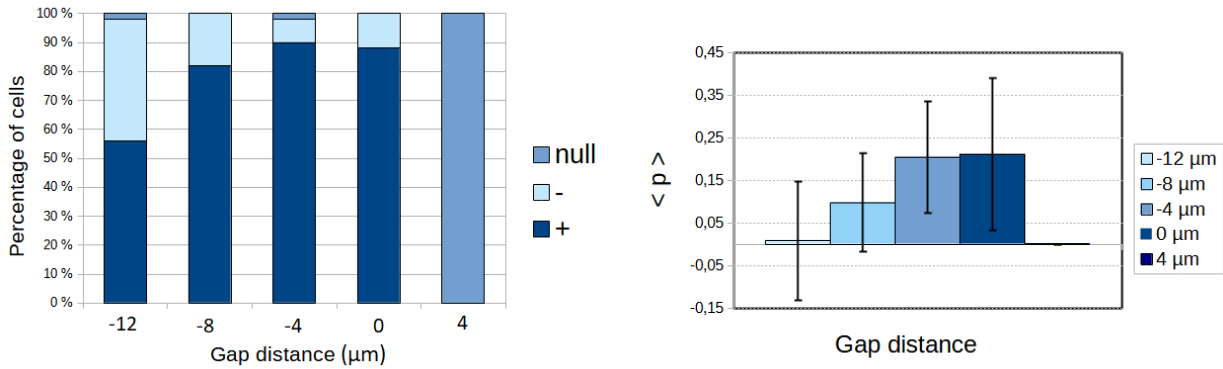
**Figure 8:** Left graph: cell displacement on triangular adhesive patterns. Right graph: each single cell was left to move on the pattern and its position after 72 hours is represented by a dark blue dot. The positions of 50 cells are displayed for each pattern spacing value. The average position and standard mean displacement are respectively represented by a red dot and line. The simulations are reproduced for different triangular pattern spacing from  $4\mu m$  until there is a continuous adhesive strap (meaning no direction bias).

301 and in the negative direction (opposite direction)  $N_-$ .

$$p = \frac{N_+ - N_-}{N_+ + N_-} \quad (15)$$

## 302 4 Discussion

303 When the cells were allowed to migrate freely on a uniform substrate, as expected, no directional bias was observed.  
 304 However, adhesion conditions clearly impacted cell movement. The model was able to represent the experimentally  
 305 observed bell shaped curve [6]. To do so, required matching the adhesion condition on  $N_1$  nodes by adapting  
 306 ing the value of  $F_{R1}$ . The involvement of this parameter makes sense because it can be used to represent the strength  
 307 of the adhesion between the cell and the substrate, which is changing experimental parameters such as fibronectin  
 308 density and adhesion rupture force [6, 9]. However, to obtain the desired result, required a sufficiently long lifespan  
 309  $\tau_m$  for mature  $N_1$  nodes. These findings are coherent since the adhesion of slower moving cells are more stable and  
 310 such behavior are found on rigid substrate or with increased fibronectin density. Thus changing a single mechanical



**Figure 9:** Left graph: percentage of cells ending their trajectories in the left side (-), right side (+) or same position (null) from their initial position, as a function of the gap distance. Right graph: average direction bias of the cell trajectories ( $\langle p \rangle$ ) as a function of the gap distance. Measurements in both graphs were made from 50 cells migrating for 48 hours.

311 parameter to represent the interaction with the substrate was enough to recreate the well documented behavior.

312

313 Vecchio et al. 2020 experimentally observed that, cells moved from one pattern to the next with a clear directional  
 314 bias towards the right [2]. The model showed that it was able to generate a migration bias based on the spacing,  
 315 height and length of the triangular pattern. To reproduce the observed behavior, we thus selected a parameter set that  
 316 enabled cells to move from one pattern to the next and also showed a clear directional bias from left to right (fig8).  
 317 Interestingly as the tips of the triangles became

318 However, while on the one hand, Vecchio et al. 2020, find that increasing spacing between the triangle patterns  
 319 promoted directional bias to the right, on the other hand, in the model's case the bias was reduced ([2]). This can in  
 320 part be explained by the fact that the model becomes less mobile as the inter-pattern distance increases. In the future,  
 321 trying to improve the model on that count could be a valuable way to better understand the mechanism that allows  
 322 cells to move from one pattern to the next.

323

324 Despite its relative simplicity, we were able to create an agent based modeling scheme, that does not depend  
 325 on a lattice. Moreover, the model takes into account both unicellular and extracellular mechanical forces, as well as  
 326 substrate properties and reacts accordingly.

327

328 Performance wise, all computation was fast. 1h of single cell computation could be calculated in 0.2-20 seconds  
 329 (without visualization) depending on settings. However, in the slowest simulations, the biggest performance hits

330 where caused by recording high amounts of data to disk, which could be optimized if needed. In addition, parallel  
331 optimization could be further implemented to process high cell count simulation in real time or even faster. The  
332 recorded computation speed suggests that the model could be implemented to study various multi-cellular phenomena  
333 such as morphogenesis, tissue patterning and angiogenesis, which was previously performed via a grid dependent  
334 modeling schemes [13, 18]. These simulation could therefore include a few hundred or even a few thousand cells,  
335 while delivering results within a reasonable time frame. In addition, the simplicity of the modeling paradigm makes  
336 it flexible enough to be adapted for various scenarios, which makes it a promising modeling framework for the future.

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<b>Parameter</b>	<b>Description</b>	<b>Value</b>	<b>unit</b>
$v_1$	production rate of $N_1$	0.01	$s^{-1}$
$v_{2im}$	production rate of $N_2$ from immature $N_1$	0.015	$s^{-1}$
$v_{2int}$	production rate of $N_2$ from intermediate $N_1$	0.015	$s^{-1}$
$v_{2m}$	production rate of $N_2$ from mature $N_1$	0.00001	$s^{-1}$
$\tau_t$	duration of $N_1$ immature state	5	<i>min</i>
$\tau_{int}$	lifespan of intermediate $N_1$	15	<i>min</i>
$\tau_m$	lifespan of mature $N_1$	35	<i>min</i>
$\tau_2$	lifespan of $N_2$	200	<i>s</i>
$l_{10}$	initial length of $B_1$	7	$\mu\text{m}$
$l_{20}$	initial length of $B_2$	4	$\mu\text{m}$
$\epsilon_m$	maturation Cauchy strain of $B_1$	0.5	-
$\epsilon_{20}$	initial Cauchy strain of $B_2$	0	-
$\kappa_{10}$	initial stiffness of $B_1$	0.1	$nN/\mu\text{m}$
$\kappa_{11}$	stiffness of $B_1$	3.5	$nN/\mu\text{m}$
$\kappa_2$	stiffness of $B_2$	12	$nN/\mu\text{m}$
$\alpha_0$	friction coefficient of $N_0$	400	$nN \cdot s/\mu\text{m}$
$\alpha_{10}$	initial friction coefficient of $N_1$	50	$nN \cdot s/\mu\text{m}$
$\alpha_{int}$	friction coefficient of intermediate $N_1$	150	$nN \cdot s/\mu\text{m}$
$\alpha_m$	friction coefficient of mature $N_1$	165	$nN \cdot s/\mu\text{m}$
$\alpha_2$	friction coefficient of $N_2$	8	$nN \cdot s/\mu\text{m}$
$\gamma_{max}$	contractility of $B_1$	40	<i>nN</i>
$F_\gamma$	force constant	30	<i>nN</i>
$F_{th}$	Threshold force for $N_0$ displacement	30	<i>nN</i>
$F_{R1}$	Rupture force of $N_1$	34	<i>nN</i>
$F_{R2}$	Rupture force of $N_2$	17	<i>nN</i>
$\delta\theta_1$	inhibition angle for $N_1$	$\pi/2$	-
$\delta\theta_2$	apparition angle for $N_2$	$\pi/6$	-

**Table 1:** Model parameters

## References

- [1] David B. Brückner, Alexandra Fink, Christoph Schreiber, Peter J. F. Röttgermann, Joachim O. Rädler, and Chase P. Broedersz. Stochastic nonlinear dynamics of confined cell migration in two-state systems. *Nature Physics*, 15(6):595–601, June 2019.
- [2] Simon Lo Vecchio, Raghavan Thiagarajan, David Caballero, Vincent Vigon, Laurent Navoret, Raphaël Voituriez, and Daniel Riveline. Collective Dynamics of Focal Adhesions Regulate Direction of Cell Motion. *Cell Systems*, 10(6):535–542.e4, June 2020.
- [3] Roeland M.H. Merks, Sergey V. Brodsky, Michael S. Goligorsky, Stuart A. Newman, and James A. Glazier. Cell elongation is key to in silico replication of in vitro vasculogenesis and subsequent remodeling. *Developmental biology*, 289(1):44–54, January 2006.
- [4] Graeme Donald Snooks. A general theory of complex living systems: Exploring the demand side of dynamics. *Complexity*, 13(6):12–20, July 2008.
- [5] Adam Shellard and Roberto Mayor. Supracellular migration – beyond collective cell migration. *Journal of Cell Science*, 132(8), April 2019.
- [6] Sean P. Palecek, Joseph C. Loftus, Mark H. Ginsberg, Douglas A. Lauffenburger, and Alan F. Horwitz. Integrin-ligand binding properties govern cell migration speed through cell-substratum adhesiveness. *Nature*, 385(6616):537–540, February 1997.
- [7] Elisabeth G. Rens and Roeland M. H. Merks. Cell Shape and Durotaxis Follow from Mechanical Cell-Substrate Reciprocity and Focal Adhesion Dynamics: A Unifying Mathematical Model. *arXiv:1906.08962 [cond-mat, physics:physics, q-bio]*, June 2019.
- [8] Kwang Hoon Song, Sung Jea Park, Dong Sung Kim, and Junsang Doh. Sinusoidal wavy surfaces for curvature-guided migration of T lymphocytes. *Biomaterials*, 51:151–160, May 2015.
- [9] David Caballero, Raphaël Voituriez, and Daniel Riveline. Protrusion Fluctuations Direct Cell Motion. *Biophysical Journal*, 107(1):34–42, July 2014.

- 364 [10] David Caballero, Raphaël Voituriez, and Daniel Riveline. The cell ratchet: Interplay between efficient protrusions and adhesion determines cell motion. *Cell Adhesion & Migration*, 9(5):327–334, September 2015.
- 365
- 366 [11] Sonja E. M. Boas, Yi Jiang, Roeland M. H. Merks, Sotiris A. Prokopiou, and Elisabeth G. Rens. Cellular Potts Model: Applications to Vasculogenesis and Angiogenesis. In Pierre-Yves Louis and Francesca R. Nardi, editors, *Probabilistic Cellular Automata: Theory, Applications and Future Perspectives*, Emergence, Complexity and
- 367
- 368
- 369 Computation, pages 279–310. Springer International Publishing, Cham, 2018.
- 370 [12] Margriet M. Palm, Marchien G. Dallinga, Erik van Dijk, Ingeborg Klaassen, Reinier O. Schlingemann, and Roeland M. H. Merks. Computational Screening of Tip and Stalk Cell Behavior Proposes a Role for Apelin Signaling in Sprout Progression. *PLOS ONE*, 11(11):e0159478, November 2016.
- 371
- 372
- 373 [13] A. Stéphanou, S. Le Floc’h, and A. Chauvière. A Hybrid Model to Test the Importance of Mechanical Cues Driving Cell Migration in Angiogenesis. *Mathematical Modelling of Natural Phenomena*, 10(1):142–166, 2015.
- 374
- 375 [14] Filippo Stefanoni, Maurizio Ventre, Francesco Mollica, and Paolo A. Netti. A numerical model for durotaxis. *Journal of Theoretical Biology*, 280(1):150–158, July 2011.
- 376
- 377 [15] Patrick Cañadas, Valerie M. Laurent, Christian Oddou, Daniel Isabey, and Sylvie Wendling. A cellular tensegrity model to analyse the structural viscoelasticity of the cytoskeleton. *Journal of Theoretical Biology*, 218(2):155–
- 378
- 379 173, September 2002.
- 380 [16] Jean-Louis Milan, Sandrine Lavenus, Paul Pilet, Guy Louarn, Sylvie Wendling, Dominique Heymann, Pierre Layrolle, and Patrick Chabrand. Computational model combined with in vitro experiments to analyse mechanotransduction during mesenchymal stem cell adhesion. *European Cells & Materials*, 25:97–113, 2013.
- 381
- 382
- 383 [17] Jean-Louis Milan, Ian Manificier, Kevin M. Beussman, Sangyoon J. Han, Nathan J. Sniadecki, Imad About, and Patrick Chabrand. In silico CDM model sheds light on force transmission in cell from focal adhesions to
- 384
- 385 nucleus. *Journal of Biomechanics*, June 2016.
- 386 [18] M. Dorraki, A. Fouladzadeh, A. Allison, C. S. Bonder, and D. Abbott. Angiogenic Networks in Tumors—Insights via Mathematical Modeling. *IEEE Access*, 8:43215–43228, 2020.
- 387