

# Supplementary Text S1: Reconstructing stochastic cell population trajectories reveals regulators and heterogeneity of endothelial flow-migration coupling driving vascular remodelling

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## 1 Model description

The movement of endothelial cell (EC) agents from one lattice site to another is described by a step selection function. The step selection function  $f_i^{\tau,t}(\vec{x}|\vec{y})$  describes the probability of an EC agent  $i$  moving from position  $\vec{x}$  at time  $t$  to position  $\vec{y}$  at time  $t + \tau$ . In the normal case we will consider  $\vec{x} = (x_1, x_2)$  and  $\vec{y} = (y_1, y_2)$  as two-dimensional vectors. The step selection function comprises three different aspects of cellular movement, which are (i) biased Brownian movement, (ii) signalling cues, (iii) mechanical cues and the (iv) cellular state. In this model we will neglect cell-cell interactions.

The model simulations are based on the spatial Gillespie algorithm [1], which was originally used for reaction-diffusion systems in molecular dynamics. The model framework has recently been adapted to cellular and animal movement [2, 3]. We will describe cellular movement in terms of rates which express the expected time of an EC agent moving from one lattice site to another. Given that an EC agent  $i$  is at site  $\vec{x}$ , the probability distribution for an agent moving from site  $\vec{x}$ . to site  $\vec{y}$  is given by:

$$f_i^{\tau,t}(\vec{x}|\vec{y}, t) \propto \mu_{i,k}(\vec{x}|\vec{y}) \exp(-\tau\mu_i),$$

The corresponding rates of movement are given by

$$\mu_{i,k}(\vec{x}|\vec{y}, t) = \begin{cases} \frac{\mu_i}{4} \left[ 1 + \alpha \frac{(\vec{x}-\vec{y})}{|\vec{x}-\vec{y}|} \cdot \vec{b}(\vec{x}) \right], & \text{if } |\vec{x} - \vec{y}| = a, \\ 0 & \text{else.} \end{cases} \quad (1)$$

Here,  $\vec{b}(\vec{x})$  determines the bias of an EC agent to move in direction of  $\vec{b}(\vec{x})$ . In case of  $b(\vec{x}) \equiv 0$ , the EC agent becomes a random walker with diffusion coefficient  $D_i = h^2 \frac{\mu_i}{4}$  and the instantaneous velocity is given by  $v = \mu_i h$ , where  $h$  is the grid size.

## 1.1 Distance notations and domains

The simulation is performed on a vasculature from retinal image data. We introduce the following distance notations:

$$d_a(\vec{x}) = \inf_{y \in \Omega_A} d(\vec{x}, y), \quad (2)$$

$$d_v(\vec{x}) = \inf_{y \in \Omega_V} d(\vec{x}, y), \quad (3)$$

$$r(\vec{x}) = \inf_{y \in \Omega_{ON}} d(\vec{x}, y). \quad (4)$$

Here,  $\Omega_A, \Omega_V$  and  $\Omega_{ON}$  are the labelled domains of artery, vein and optic nerve. The normalized vein-artery distance  $\phi_{v-a,rp}$  is computed as follows

$$\phi_{v-a,rp}(\vec{x}) = \frac{d_v(\vec{x})}{d_a(\vec{x}) + d_v(\vec{x})}, \quad (5)$$

The transition of remodelling plexus to sprouting front is described by the radial distance  $r_{plex}(t)$ , which is a function of time

$$r_{rp}(t) = r_{rp}^0 + v_{rp} t. \quad (6)$$

## 1.2 Force field computation from image data

Using these distance notations, the shear stress cue is computed from

$$\vec{b}_{ss} = \vec{a}_{ss} + \vec{v}_{ss} + \nabla U_{ss}, \quad (7)$$

$$U_{ss} = \phi_{v-a,rp} + \frac{1}{4}\phi_{v-a,rp}^2, \quad (8)$$

$$\vec{a}_{ss} = \frac{f_a}{k_a + d_a} \nabla r, \quad (9)$$

$$\vec{v}_{ss} = -\frac{f_v}{k_v + d_v} \nabla r. \quad (10)$$

The directed VEGF-A cue is computed from the distance to the artery mask in the following way:

$$b_{VEGF} = \nabla (d_a^2(x)) + \rho \nabla r. \quad (11)$$

The shear stress cue can overlap into the sprouting front and the VEGFA cue into the remodelling plexus, which defines a competition region between both forces [4]. We define the functions

$$g_{ss}(\vec{x}) = 1 - \frac{r^\gamma(\vec{x})}{(r_{rp} + \rho_{ss})^\gamma + r^\gamma(\vec{x})}, \quad (12)$$

$$g_{VEGFA}(\vec{x}) = \frac{r^\gamma(\vec{x})}{(r_{rp} - \rho_{VEGFA})^\gamma + r^\gamma(\vec{x})}. \quad (13)$$

The resulting shear stress and VEGFA cues are then scaled in the following way

$$\vec{b}_{ss}^E(\vec{x}) = g_{ss}(\vec{x}) \frac{\vec{b}_{ss}(\vec{x})}{|\vec{b}_{ss}(\vec{x})|} \quad (14)$$

and

$$\vec{b}_{VEGFA}^E(\vec{x}) = g_{VEGFA}(\vec{x}) \frac{\vec{b}_{VEGFA}(\vec{x})}{|\vec{b}_{VEGFA}(\vec{x})|}. \quad (15)$$

The resulting cue is then computed from

$$\vec{b}(\vec{x}) = \alpha[\xi \vec{b}_{ss}^E(\vec{x}) + (1 - \xi) \vec{b}_{VEGFA}^E(\vec{x})]. \quad (16)$$

## 2 Bibliography

### References

- [1] Sotiria Lampoudi, Dan T Gillespie, and Linda R Petzold. The multinomial simulation algorithm for discrete stochastic simulation of reaction-diffusion systems. *The Journal of chemical physics*, 130(9):094104, 2009.
- [2] Daria Stepanova, Helen M Byrne, Philip K Maini, and Tomás Alarcón. A multiscale model of complex endothelial cell dynamics in early angiogenesis. *PLoS Computational Biology*, 17(1):e1008055, 2021.
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- [4] Pedro Barbacena, Maria Dominguez-Cejudo, Catarina G Fonseca, Manuel Gómez-González, Laura M Faure, Georgia Zarkada, Andreia Pena, Anna Pezzarossa, Daniela Ramalho, Ylenia Giarratano, et al. Competition for endothelial cell polarity drives vascular morphogenesis in the mouse retina. *Developmental Cell*, 57(19):2321–2333, 2022.

### 3 Parameters

parameter	Value	description
$D$	-	diffusion coefficient
$\alpha$	-	strength of coupling to dual force field
$\xi$	-	fraction of shear stress cue
$\lambda_{ss}$	75 $\mu\text{m}$	overlap of shear stress into sprouting front
$\lambda_{\text{VEGFA}}$	125 $\mu\text{m}$	overlap of shear stress into sprouting front
$a$	0.69 $\mu\text{m}$	size of one grid element
$f_a$	0.05	relative strength of shear stress cue in artery
$k_a$	10 $\mu\text{m}$	-
$f_v$	0.05	relative strength of shear stress cue in vein
$k_v$	10 $\mu\text{m}$	-
$r_{plex}^0$	900 $\mu\text{m}$	initial end of the remodelling plexus and start of sprouting front
$v_{plex}$	5 $\mu\text{m}/h$	speed of sprouting front progression
$\gamma$	10	parameter for steepness of competition zone

Table 1: Parameters used in the model.

parameter	Model-Ctr	Model-Cdc42	Model-Rac1
$\mu_r$	18 steps per h	18 steps per h	18 steps per h
$\alpha$	0.36	0.26	0.32
$\xi$	0.53	0.19	0.34

Table 2: Optimized parameters.