Text S1: Cellular Potts Model

The CPM describes biological cells as domains on a regular lattice. Each cell has its own identity σ and is represented as a set of lattice sites sharing the same index. Therefore, every lattice site $\vec{x}$ is a part of one specific cell that has its particular identity $\sigma(\vec{x})$. Any lattice site that does not belong to any biological cell type is typically considered as a medium with a cell identification number $\sigma = 0$. In addition to the unique identification number, every cell in the CPM is marked with a label $\tau(\sigma) > 0$ to identify a biological cell type.

The classical implementation of the CPM employs a modified Metropolis Monte-Carlo algorithm to describe amoeboid movement. The dynamics of the cells is described by a globally defined effective Hamiltonian, H, which usually is the sum of terms representing cell adhesion and volume or surface constraints. Once the Hamiltonian is defined, the system evolves by applying the following procedure at each Monte Carlo Step (MCS).

A number of lattice sites equal to the size of the lattice are randomly visited. Every randomly selected lattice site $\vec{x}$ attempts to copy its cell index $\sigma(\vec{x})$ into a randomly chosen adjacent lattice site $\vec{x}'$. The probability of accepting or rejecting an index change attempt is based on the following transition rule:

$$P\left(\sigma(\vec{x}) \rightarrow \vec{x}'\right) = \begin{cases} 1 & ,\Delta H\left(\sigma(\vec{x}) \rightarrow \vec{x}'\right) < 0 \\ e^{\frac{-\Delta H\left(\sigma(\vec{x}) \rightarrow \vec{x}'\right)}{T}} & ,\Delta H\left(\sigma(\vec{x}) \rightarrow \vec{x}'\right) \geq 0 \end{cases} \quad (1)$$

where $\Delta H\left(\sigma(\vec{x}) \rightarrow \vec{x}'\right)$ represents the change in the Hamiltonian due to the copy attempt, and the parameter T represents the effective fluctuation amplitude or active motility of the cells in the system. In absence of such fluctuations (i.e., when T approaches 0) the system tends to get stuck in local minima. Equation 1 describes that if the index-change attempt would decrease the value of a globally defined Hamiltonian, the copy attempt is accepted with a probability of 1. However, if the value of H would increase due to the copy-attempt, then the system follows Boltzmann probability to accept or reject a copy-attempt.

Although the basic Hamiltonian can be extended with numerous terms exhibiting specific cellular behaviours, there are at least two basic components in a typical Hamiltonian for every variation of the CPM: a bond energy term responsible for cell-cell adhesion and a surface area constraint term responsible for maintaining a constant cell surface area.

$$H = H_{bond} + H_{surface} \quad (2)$$

The cell-cell and cell-medium interactions take place through bonding energies. The bonding energy between two cells is proportional to the size of the interface between both cells and is given by the formula:

$$H_{bond} = \sum_{(\vec{x},\vec{x}')} J_{\tau(\sigma(\vec{x})),\tau\left(\sigma(\vec{x}')\right)} \left(1 - \delta_{\sigma(\vec{x}),\sigma(\vec{x}')}\right) \quad (3)$$

Here, $J_{\tau(\sigma(\vec{x})),\tau\left(\sigma(\vec{x}')\right)}$ is the bonding energy between two neighbouring cell types $\tau(\sigma(\vec{x})$ and $\tau(\sigma(\vec{x}')$, and $\delta_{\sigma(\vec{x}),\sigma(\vec{x}')}$ is the Kronecker delta term that ensures the elimination of contributions from the neighbouring lattice sites belonging to the same cell. If $\sigma(\vec{x}) = \sigma(\vec{x}')$, the delta function returns a value of 1 and 0 otherwise.

The surface area constraint energy term in the Hamiltonian specified in equation (2) is given by:

$$H_{surface} = \sum \lambda_a (a_\sigma - A_\sigma)^2 \quad (4)$$

Where a_σ represents the current surface area, and A_σ is the prescribed target surface area of the cell σ. The coefficient λ_a denotes the surface area elasticity or stiffness of the cell. Any deviation in the current surface area of a cell from its specified target area (in case a cell is stretched or compressed) penalizes the Hamiltonian with a coefficient λ_a.

Text S2: Parameter analysis

Although the results presented in this study are obtained using the parameter values shown in the Table 1, we have performed additional parameter studies to investigate the effects of certain parameters towards the migration and proliferation of the SMCs. Most of the parameter sweep analyses were carried out in a previous work using a small strip of tissue (1). From that study, the SMC-SMC, SMC-Medium and the SMC-IEL adhesion energies were turned-out to be the most important parameters. A complete explosion of the vessel integrity was observed using a very high SMC-Medium energy whereas a very low SMC-SMC energy does not allow the cells to detach from each other and migrate. Therefore a balance between the both was observed to be essential. Although many parameters e.g. cell-cell adhesions, surface tension between cells, have a huge impact on the overall model response but there seems to have almost no quantitative data available for such parameters that can be used to choose the right value of these parameters. Therefore, based on the detailed analysis of varying adhesion and cohesion energies carried out in (1), we finally chose to use the parameters specified in Table 1 as these were the best parameters to maintain vessel integrity and allowed us to model the process of stent deployment as well as well to observe the migration of the SMCs. For more details on the selection of adhesion energies, the reader is referred to (1).

For the purpose of the current study, we have investigated the influence of the λ parameter (specified in equation 4) on the cells migration. This parameter defines the elasticity or stiffness of the cell and a value $\lambda = 50$ is used as a default value for the SMCs to produce the results presented in this study. Figure S1 shows the effects of varying this λ parameter on the migration of SMCs using injury scenario Inj2_90. It is clear from figure S1A that increasing the λ parameter substantially increases the number of migrated SMC considering an identical injury. Moreover, the same effect can also be observed while counting the number of neointimal cells where a higher value of λ results in a faster regrowth of the tissue (Figure S1B). Regardless of the

increasing migration and proliferation, the shape of the cells becomes irregular with a high value of λ. The fact behind an increased migration and proliferation is that a higher value of λ makes cells rigid and they do not freely change shapes during the copy attempt. This rigidity in the cell surface / volume produces small gaps between the cells, allowing cells to get in touch with the substrate (medium) and based on the rules, if the SMC is attached to a medium, it continues to migrate and proliferate. Therefore, they continue to proliferate.

Another important parameter that seems to play an important role in the final results is the choice of the IEL fenestrae size and its density. The results reported in this paper are produced by using a hole size of 2 pixels (2.669 μm) (taken from (2)) with a gap density of 5.89 gaps/100 μm (obtained from (3). However, we did vary these values to observe their influence on the SMCs proliferation. The gap density of 5.89 gaps/100 μm was the upper limit reported in (3) but we also tried 1.5 gaps/100 μm which was the lowest value stated in the same study. The hole size was varied between 2–7 pixels to observe the changes in the cells proliferation. Simulations were run using Inj_BA and Inj2_90 scenario to compare the growth trends and the results are reported in Figure S2. It is clear from these analyses that a lower value of the hole size (2 or 3 pixels) produce different results among Inj_BA and Inj2_90 groups. However, no dissimilarities were observed by using a larger fenestration size. This is due to the fact that larger fenestrae allow cells to migrate and proliferate easily in the Inj_BA scenario and since these holes are large enough, therefore, stenting does not produce much difference and finally results in similar growth curves. An additional thing to be noticed from the figure S2 is that the no perceptible differences in the growth response were observed by varying the gap density, however lower gap density resulted in a slightly slower growth when compared to the group of larger gap density using holes size 2 or 3 pixels (figure S2A and S2B).

To further clarify the role of stenting on the IEL fenestration, we measured the absolute distances between the centres of mass of two IEL cells which are next to each other. We calculated this distance prior to stenting (Inj_BA case where no struts were deployed) and also in all the injury scenarios presented in this paper. A mean value of this absolute distance for every injury scenario is shown in Figure S3 and this figure clearly demonstrates that an increase in the mean distance was observed with an increase in the strut deployment depth (injury). The increase in the mean distance between the injury groups is not much larger because only the cells near the struts mostly tend to observe high displacements while the others far away from the struts suffer with lower dislocations. However, figure S3 clearly shows that the maximum value of the distance observed between two IEL cells tends to increase with an increase in the strut deployment depth, and due to this increase in the hole size near the struts, we observe more SMCs migrating through these enlarged holes. We also investigated the influence of the elastic coupling strength (λ) between the IEL cells during stent deployment (Figure S4). By using a very low λ value, we observed that the springs become very flexible and due to this, it was not possible to maintain a prescribed distance between the IEL cells. Moreover, with a very high value of λ, the springs become too stiff and we did not observe any enlargements in the IEL hole size due to the deployment.

Simulated data and source code

The simulated data and the source code can be retrieved from:
http://persistent-identifier.org/?identifier=urn:nbn:nl:ui:18-23391

Reference:

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