Supplement

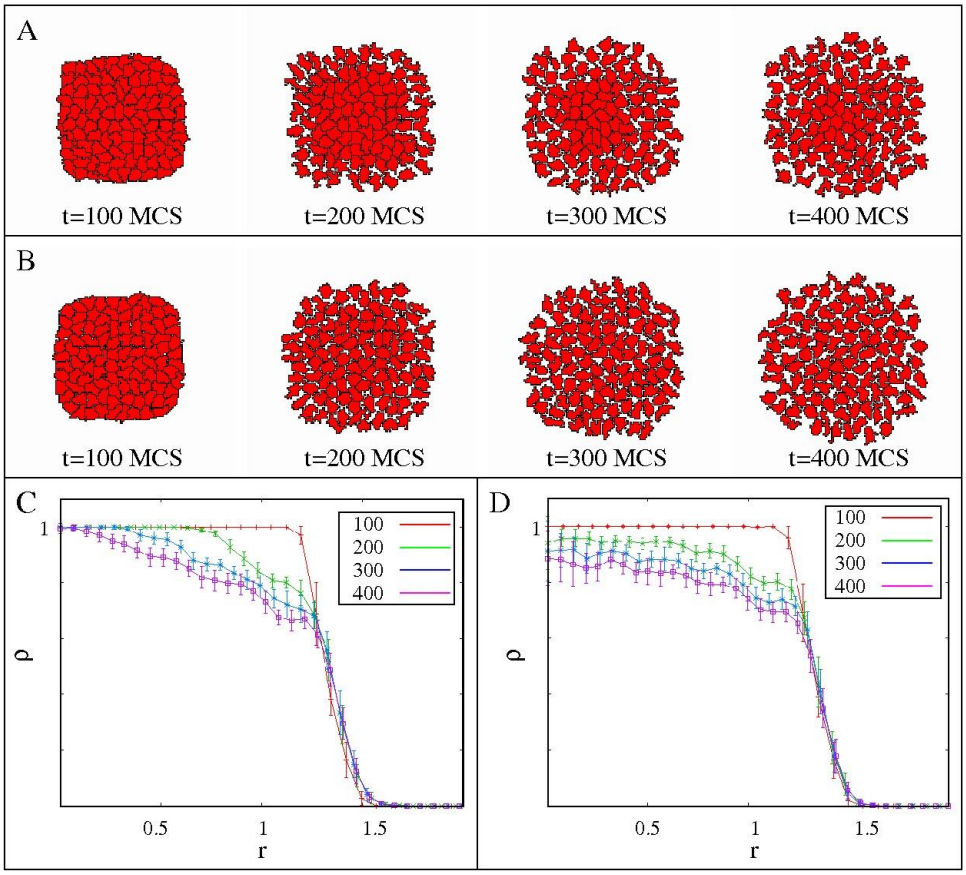

Figure S1. Altered transition rules ensure cell separation inside cell aggregates. The original formulation of the model allows the disintegration of aggregates only from the sides (panel A), similar to the propagation of cracks. Allowing the insertion of a cell-free sub-volume in every attempted step creates a more realistic cell dispersal (panel B). The density profiles of the original (C) and the proposed (D) models reveal the difference in the cell spreading. Colored lines on the graphs correspond to the configurations shown at t=100 MCS, 200 MCS, 300 MCS and 400 MCS. Density (ρ) and distance from the aggregate center (r) are shown compared to the half of the original aggregate size.

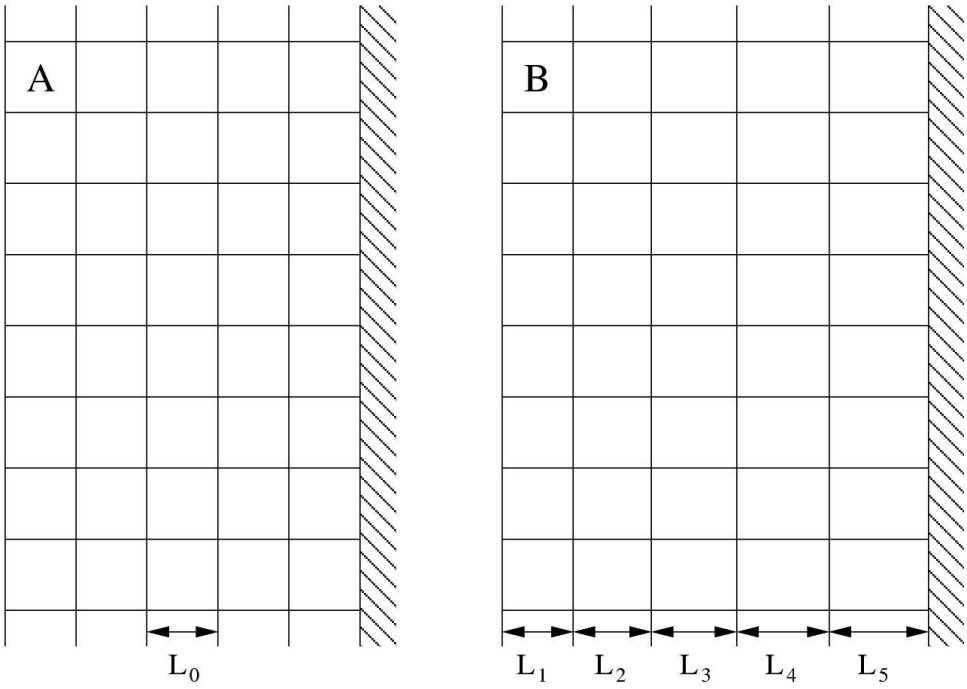

Figure S2. A monolayer consisting of rectangular cells, in equilibrium (A) and by forcing the rightmost surface to move (B).

Let us consider a monolayer of N cells wide, where the equilibrium cell size is L_0. Thus, L_0 minimizes

$$u(L) \sim 2\alpha L + \lambda(L^2 - A_0)^2, \tag{19}$$

resulting in

$$0 = \left.\frac{\partial u}{\partial L}\right|_{L=L_0} = 2\alpha + 4\lambda L_0(L_0^2 - A_0) \tag{20}$$

.

We investigate the behavior of this system if the surface of first cell row is free, while the surface of the last (Nth) cell row is forced to move like in the piston test (see Fig. S2). Assuming steady state cell sizes L_0 perpendicular to the direction of motion, the system is characterized by the average row widths L_i (along the direction of movement), where i is the row index ($1 \le i \le N$). The configuration-dependent goal function (Hamiltonian) of this system is

$$\begin{aligned} u &= \sum_{i=1}^{N} \left[\alpha(L_i + L_0) + \lambda(L_0 L_i - A_0)^2\right] = \\ &= \sum_{i=1}^{N} \left[\lambda L_0^2 L_i^2 + (\alpha - 2\lambda A_0 L_0) L_i\right] + const = \\ &= \lambda L_0^2 \sum_{i=1}^{N} \left[L_i - \left(\frac{A_0}{L_0} - \frac{\alpha}{2\lambda L_0^2}\right)\right]^2 + const. \end{aligned} \tag{21}$$

Using condition (20), the above expression simplifies to

$$u = \lambda L_0^2 \sum_{i=1}^{N} (L_i - L_0)^2 + const. \tag{22}$$

In the following we denote by ℓ_i the extent of cell elongation relative to the equilibrium value: $\ell_i = L_i - L_0$.

We assume that in each elementary step one cell row boundary is moved, thus cells continue to remain in rows. Let us denote the average displacement of the boundary between rows k and $k+1$ by x_k. To calculate this value, we consider the Hamiltonian after the elementary step:

$$u' = \lambda L_0^2 \left(\sum_{i \neq k,k+1} \ell_i^2 + (\ell_k + x_k)^2 + (\ell_{k+1} - x_k)^2 \right) + const. \tag{23}$$

We assume, that the actual movement of the boundary is proportional to x^*_k, the value where $u^0(x_k)$ is minimal:

$$x_k = \epsilon x_k^* \tag{24}$$

where ϵ is the factor expressing the proportionality between x_k and x^*_k and

$$0 = \left. \frac{\partial u'(x_k)}{\partial x_k} \right|_{x_k = x_k^*} = 4x_k^* - 2(\ell_{k+1} - \ell_k) \tag{25}$$

.

Thus,

$$x_k = \epsilon \frac{\ell_{k+1} - \ell_k}{2} \tag{26}$$

.

For our argument it is crucial that $\epsilon \ll 1$ – like in the case of a CPM simulation – within a single elementary step the cell boundary cannot move to the equilibrium position where u^0 is minimal. In the CPM simulation this is a consequence of the stochastic nature of the dynamics as well as of the constraint that only a single lattice unit is changed at each elementary step.

After N elementary steps (26) each row boundary is expected to be updated once, hence the new cell elongations are given as

$$\ell_i' = \ell_i + x_i - x_{i-1} = \ell_i + \frac{\epsilon}{2}(\ell_{i+1} - 2\ell_i + \ell_{i-1}) \tag{27}$$

.

The resulting equation is the Euler-discretized version of the diffusion equation

$$\frac{\partial \ell}{\partial t} = \frac{\epsilon L_0^2}{2\tau} \frac{\partial^2 \ell}{\partial x^2}, \tag{28}$$

where τ is the conversion factor between N elementary steps and a unit of real time. Thus, mechanical perturbations propagate diffusively in this system. The

steady state solution of the diffusion equation is

$$\ell = cx \tag{29}$$

where the coefficient c can be obtained from the boundary condition for the rightmost (driven) row. If we assume that the forced surface moves with a speed v, then during time τ (N elementary steps) it is displaced by $v\tau$. During this N elementary steps the rightmost row is updated once, according to

$$\ell'_N = \ell_N + v\tau - \frac{\epsilon}{2}(\ell_N - \ell_{N-1}). \tag{30}$$

In a steady state $\ell'_N = \ell_N$, thus

$$v\tau = \frac{\epsilon}{2}(\ell_N - \ell_{N-1}) \approx \frac{\epsilon L_0}{2}\frac{\partial \ell}{\partial x} = \frac{\epsilon L_0}{2}c \tag{31}$$

The spatial stretch gradient is then obtained as

$$c = \frac{2v\tau}{\epsilon L_0}, \tag{32}$$

which is independent of the system width or number of rows, N.

Finally we point out that a similar diffusive behavior is exhibited by an overdamped mass and spring chain. In such a system the equation of motion for mass point i is

$$m\frac{d^2x_i}{dt^2} = -\mu\frac{dx_i}{dt} + k(x_{i+1} - x_i - \ell_0) - k(x_i - x_{i-1} - \ell_0), \tag{33}$$

where m is the mass of the particle, μ is the friction coefficient, k is the spring constant and ℓ_0 is the equilibrium spring length. The time scales associated with friction and spring forces are $\tau_f = m/\mu$ and $\tau_s = m/k$, respectively. If the friction is strong, $\tau_f \ll \tau_s$, i.e. $\mu \gg \sqrt{mk}$, then we arrive by the overdamped approximation of eq. (33), analogous to (27):

$$\mu\frac{dx_i}{dt} = k(x_{i+1} - x_i - \ell_0) - k(x_i - x_{i-1} - \ell_0) = k(x_{i+1} - 2x_i + x_{i+1}). \tag{34}$$

This simple one dimensional analysis thus shows that a spatially localized mechanical perturbation propagates through the system as a diffusive front – a behavior is analogous to that of an overdamped elastic system, where the friction force is proportional to the local absolute velocity.

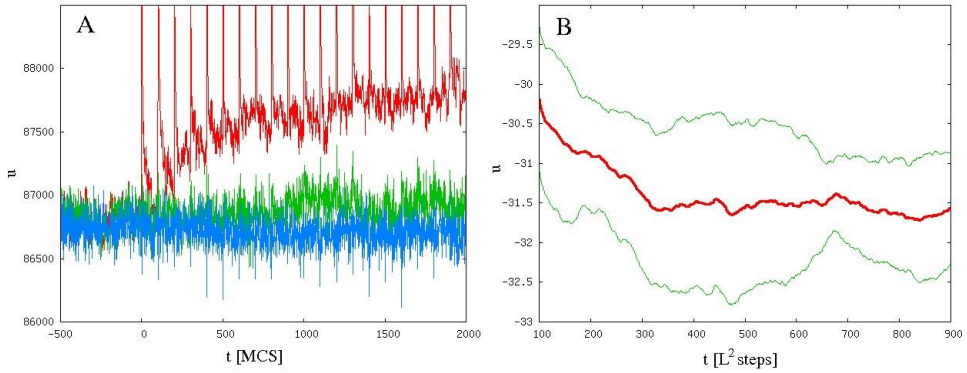

Figure S3. The goal function u during the piston test (A) and the relaxation process (B). A: Values of u during the piston test for systems with no relaxation (red) and either $10L^2$ (green) or $1000L^2$ (blue) relaxation steps inserted at each MCS. Without relaxation, an increase in u is observed. All three systems started from the same relaxed state, piston movement started at t=0 with a speed of 1 lattice site per 100 MCS. B: The goal function u during the relaxation process as the function of the number of relaxation steps, averaged over 5000 relaxation cycles of three independent runs. Green lines show the estimated standard deviation.

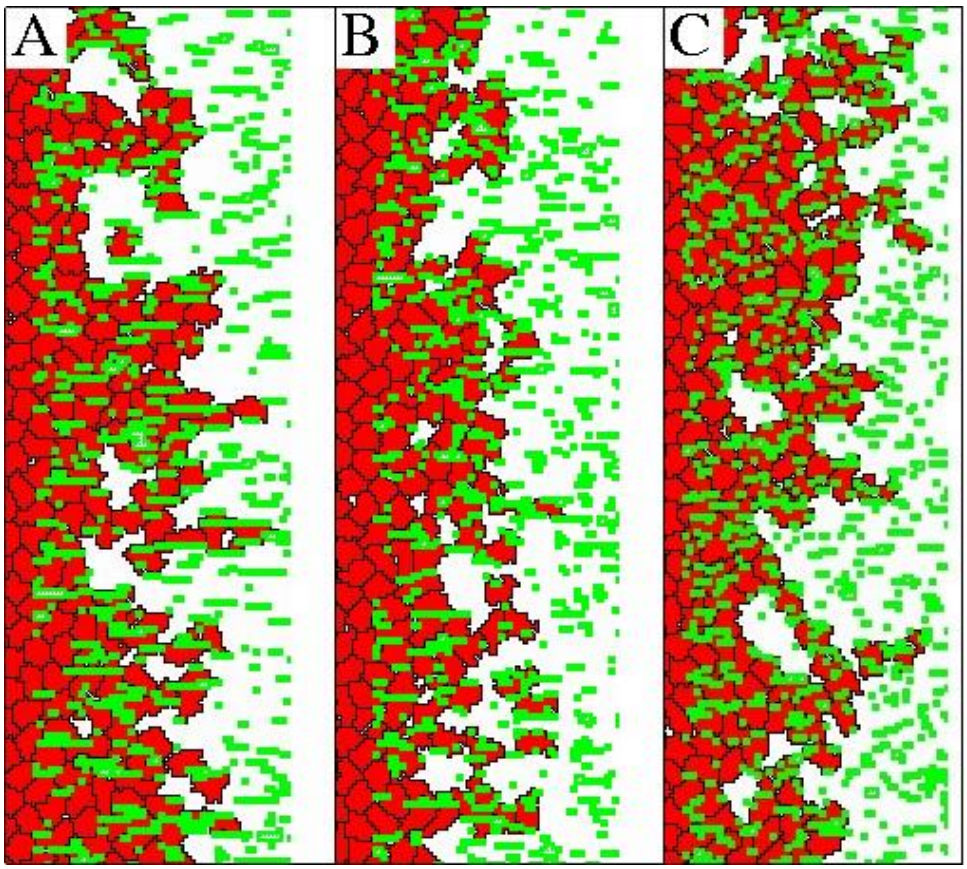

Figure S4. Cells invading matrices with diminishing anisotropy: p_{11}=0.7 (A), 0.6 (B) and 0.5 (C). In all cases cells tend to arrange in linear multicellular structures. Figure panels depict the interface within a 150×450 lattice unit area, cropped from a larger simulation after 1000 MCS computational time. All simulations are carried out in the full model (w 6= 0) with parameters identical to those of simulation 2 in Fig. 9.

Movie legends

Movie 1. Depopulation near the ECM-aggregate interface during matrix invasion. The interface is shown within a 110 × 360 area. Frame-rate is 50 MCS (50 minutes) per frame. Parameters of the simulation are: α = 1, β = 1, γ = −1, Q = 100, P = 0 and N = 2100 cells within a 500 × 500 lattice.

Movie 2. The piston test: comparison of two models that does not (left) and does (right) include mechanical relaxation of the aggregate. 5000 MCS (3.5 days) are shown, with 50 MCS (50 minutes) per frame. Parameters of the simulation are α = 1, β = 0.75, γ = −2, Q = 100, P = 0, and N = 2100 cells within a 500×500 lattice. To ensure relaxation, 500 ×L^2 elementary steps were used after each MCS.

Movie 3. Invasion of non-persistent cells that emigrate from an aggregate. Frame-rate is 50 MCS (50 minutes) per frame. Parameters of the simulation are $\alpha = 1$, $\beta = 0.5$, $\gamma = -1$, $Q = 100$, $P = 0$ and $N = 2100$ cells within a 500×500 lattice. To ensure relaxation, $500 \times L^2$ elementary steps were used after each MCS.

Movie 4. Invasion of actively moving cells that emigrate from an aggregate. Framerate is 50 MCS (50 minutes) per frame. Parameters of the simulation are $\alpha = 1$, $\beta = 0.5$, $gamma = -1$, $Q = 100$, $P = 2$, $T = 20MCS$ and $N = 2100$ cells within a 500×500 lattice. To ensure relaxation, $1000 \times L^2$ elementary steps were used after each MCS.

Movie 5. A cell capable of both degrading and adhering to the ECM does not follow pre-existing tunnels. Instead, the cell invades the ECM and creates a new channel. Frame-rate is 100 MCS (100 minutes) per frame. Parameters of the simulation are $\alpha = 1$, $\beta = 1$, $\gamma = 1$, $Q = 9$, $P = 0$ and a 150×150 lattice.

Movie 6. A combination of active cellular locomotion ($P > 0$) and matrix degradation yields realistic behavior: the cell can both follow a pre-set pattern of ECM channels and initiate a new tunnel. Frame-rate is 50 MCS per frame. Parameters are $\alpha = 1$, $\beta = 1$, $\gamma = 0.5$, $Q = 7$, $P = 2$ and $T = 100$ MCS.