Supplemental Material

I. SPHERICAL GROWTH

As an example of a tissue growth competition for which we can solve the complete dynamics given by the Eqs. **1-4** of the main text, we examine the growth of a spherical tissue located in the center of a spherical compartment filled with another tissue of lower homeostatic pressure and enclosed by a rigid boundary. For now, we neglect all surface tension effects. The force balance condition (Eq. **2**, main text) in three dimensions takes the form:

$$\begin{aligned} \frac{\partial \sigma'_{rr}}{\partial r} + \frac{2(\sigma'_{rr} - \sigma'_{\theta\theta})}{r} &= \frac{\partial p}{\partial r} \\ \sigma'_{\phi\phi} &= \sigma'_{\theta\theta}, \end{aligned} \tag{1}$$

where r, θ and ϕ are the spherical coordinates, while the constitutive equation (Eq. **3**, main text) reads:

$$\begin{aligned} \sigma'_{rr} &= 2\eta \frac{\partial v}{\partial r} \\ \sigma'_{\theta\theta} &= 2\eta \frac{v}{r}. \end{aligned} \tag{2}$$

The continuity equation (Eq. **1**, main text), together with the expansion of $k_d - k_a$ to first order in $\rho - \rho_h$ (Eq. **4**, main text), gives:

$$\frac{\partial \rho}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2 \rho v\right) = -\kappa(\rho - \rho_h)\rho. \tag{3}$$

These equations need to be solved for the whole system composed of the two tissues, together with the moving boundary between them. Boundary conditions are composed of two parts: (a) in the center and at the rigid external wall, the velocity field vanishes, such that $v(r = 0) = v(r = R) = 0$; (b) at the interface of the two tissues, the velocity field and the stress tensor are continuous. The continuity of the velocity field at the interface leads to the following equation for the time-dependent location $x(t)$ of the tissue boundary:

$$\frac{\partial x}{\partial t} = v(x). \tag{4}$$

The force-balance condition (1) can be integrated using:

$$\frac{\partial \sigma'_{\theta\theta}}{\partial r} = \frac{1}{r}(\sigma'_{rr} - \sigma'_{\theta\theta}) \tag{5}$$

from the constitutive equation (2) to give:

$$2\eta\left(\frac{\partial v}{\partial r}+\frac{2v}{r}\right)=p-p_{\rm ext}. \tag{6}$$

In the absence of surface tension, the integration constant $p_{\rm ext}$ is the external pressure imposed by the rigid wall to satisfy the boundary condition of vanishing velocity. The growth dynamics consisting of Eqs. (3) and (6) for each of the two compartments—together with the moving boundary condition Eq. (4)—can be solved numerically using a finite-difference method (Press *et al.*, 1992). Results with the parameters of Table I are displayed in Fig. **2** of the main text and show how the inner tissue takes over the whole compartment.

In the main text, a constant interfacial tension is introduced between the two tissues. It is shown that this effect leads to the existence of an unstable critical radius in spherical geometry. The growth dynamics with an unstable critical radius is illustrated in Fig. **5** of the main text. However, biologically relevant situations may involve tissues enclosed in membranes whose tensions increase as the inner tissue grows. This is for example the case for some benign tumors that undergo growth arrest due to the extracellular membrane engulfing them. In that case, the surface tension is now dependent on the location x of the boundary between the two tissues. For a purely elastic membrane that is put under tension above a given radius x_0, we have:

$$\gamma(x)=\gamma_0\,\frac{(x-x_0)^2}{x_0^2}\,\theta(x-x_0), \tag{7}$$

where $\theta(x)$ is the heaviside step function. A numerical solution of the growth dynamics with this type of surface tension is presented in Fig. **3** of the main text (parameters are given in Table I together with $\gamma_0=5$ in scaled units).

II. TUMOR GROWTH DYNAMICS WITH REALISTIC PARAMETERS

The growth rate of tumor cells is possibly very slow compared to the viscous relaxation time. In such a case, it can be assumed that the cell density in each compartment is constant. In the absence of surface tension, the pressures in the two compartments balance, leading to an equation relating the two densities:

$$\chi_H^{-1}(\rho_H-\rho_{H,h})+p_{H,h}=\chi_T^{-1}(\rho_T-\rho_{T,h})+p_{T,h}. \tag{8}$$

The change in density in each compartment has contributions coming from the total cell division and apoptosis taking place in the compartment, as well as from the movement of the boundary $x(t)$:

$$\begin{aligned} \dot{\rho_T} &= -\kappa_T \left(\rho_T - \rho_{T,h}\right) \rho_T - 3\,\frac{\dot{x}}{x}\,\rho_T \\ \dot{\rho_H} &= -\kappa_H \left(\rho_H - \rho_{H,h}\right) \rho_H + 3\,\frac{\dot{x}}{x}\,\frac{x^3}{R^3 - x^3}\,\rho_H. \end{aligned} \tag{9}$$

This system of differential equations can be solved numerically. Results with the parameters given in Table II are displayed in Fig. 1.

III. NUTRIENT-LIMITED GROWTH

When studying the nutrient-limited growth of a tumor prior to angiogenesis, the dependences of the cell division and apoptosis rates k_d and k_a on the nutrient and cell densities ρ_n and ρ are constructed using two assumptions: (a) below a given concentration of nutrients per cell c_1, cells stop dividing; (b) below a second, lower concentration of nutrients per cell c_2, cells undergo apoptosis. We model these properties with the following functions[9]:

$$\begin{aligned} k_d &= \frac{\bar{k}_1}{1 + \exp\left(\alpha(\rho - \rho_h + \Delta\rho)\right)} \times \frac{1}{1 + \exp\left(-\beta_1\left(\frac{\rho_n}{\rho} - c_1\right)\right)} \\ k_a &= \frac{\bar{k}_1}{1 + \exp\left(-\alpha(\rho - \rho_h - \Delta\rho)\right)} + \frac{\bar{k}_2}{1 + \exp\left(\beta_2\left(\frac{\rho_n}{\rho} - c_2\right)\right)}. \end{aligned} \tag{10}$$

Here, $\bar{k}_1$ tunes the amplitude of cell division and apoptosis in the system as functions of cell density, as $\bar{k}_2$ tunes how strongly cells die when deprived of nutrients. The parameter α tunes how sharply cell start to die or proliferate as the homeostatic density is passed. It is the same in both functions k_d and k_a, such that $k_d - k_a = 0$ at $\rho = \rho_h$ for large concentrations of nutrients. $\Delta\rho$ sets the amount of cell turnover at homeostatic density. Finally, β_1 and β_2 tune how sharply the cell division and apoptosis rates change as the critical concentrations of nutrients per cell c_1 and c_2 are passed. We illustrate the dependence of k_d and k_a on ρ and ρ_n in Fig. 2, with parameters given in Tables I and III. Since only the difference $k_d - k_a$ enters the growth dynamics (Eq. **1-4**, main text), we illustrate the dependence of this combination on cell density and nutrient concentration in Figs. 3 and 4.

To describe how nutrients are distributed in the system, we suppose that they diffuse freely throughout the system with a given diffusion constant D_n, while being consumed

by living cells for their metabolism and their growth. Metabolism uptake happens at a given rate $\mu\rho_n$ that is proportional to the available concentration of nutrients, and growth dependence is described via an extra consumption term proportional to the number of cell division $k_d\rho$ with a coupling constant λ. For simplicity, we suppose no effect of cell apoptosis on nutrient uptake. We finally suppose that nutrient diffusion is very fast compared to tissue growth, such that only the steady-state diffusion equation needs to be considered:

$$D_n \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial \rho_n}{\partial r}\right) - \lambda k_d \rho - \mu \rho_n \rho = 0. \tag{11}$$

Boundary conditions are as follows: the nutrient concentration is homogeneous and constant in the healthy compartment and the flow of nutrients vanishes at the center of the tumor compartment.

To compute the growth dynamics of a spherical tumor coupled to nutrient diffusion through its surface, we use the same method as in Section I, while solving the steady-state diffusion equation (11) at every timestep. The result with the parameters given in Table III is shown in Fig. **4** of the main text. The characteristic nutrient profile in a tumor that is nutrient-limited in its growth is given in Fig. 5.

IV. STOCHASTIC DYNAMICS

We solve the master equation (Eq. **5**, main text) together with the rates given by Eq. **7** (main text), both analytically and numerically. Imposing an upper sink at $n_{\max}$ in addition to the lower sink at $n_{\min} = 0$, all clusters of cells end up in one of the two sinks when time goes to infinity. The analytic solution—given by Eq. **8** (main text)—gives the splitting probability, namely the probability for a cluster originating from a single cell to reach the upper sink $n_{\max}$ when time goes to infinity. Numerically, we use a Monte Carlo simulation of the master equation **5** (main text) based on the Gillespie algorithm (Gillespie, 1976), which gives information on the temporal evolution of the process leading to the analytic result Eq. **8** (main text) for long evolution times.

The Monte Carlo simulation is implemented according to the following standard procedure: at each step of the growth process (corresponding to a new division or apoptosis event), the algorithm first sets the time delay between this event and the previous one, and then chooses whether apoptosis or division takes place. These two choices are made by

generating two random numbers x_1 and x_2 in the interval $[0, 1]$ using a Mersenne Twister algorithm (Matsumoto and Nishimura, 1998). x_1 determines the time delay δt between two events as:

$$\delta t = -\frac{\log(x_1)}{r_n^+ + r_n^-}, \tag{12}$$

where r_n^+ and r_n^- are the growth and death rates given by Eq. **7** (main text). The stochastic variable x_2 determines whether growth or recession takes place: growth is chosen if $[(r_n^+ + r_n^-)x_2] \leq r_n^+$, recession otherwise.

Parameters are chosen as follows: the upper sink is at $n_{\max} = 10^6$ cells. The parameters that enter the expression for the rates (Eq. **7**, main text) are such that, at very large radii, the tumor divides at a rate of one division per day on average, while having a vanishing probability to shrink. This yields:

$$\kappa_{d/a}\,\chi_T = \frac{k_{n\to\infty}^{+/-} - k_0}{p_{T,h} - p_{H,h}}, \tag{13}$$

with

$$\begin{aligned} k_{n\to\infty}^{+} &= \lim_{n\to\infty} \frac{r_n^+}{n} = 1 \\ k_{n\to\infty}^{-} &= \lim_{n\to\infty} \frac{r_n^-}{n} = 0 \end{aligned} \tag{14}$$

in invert units of days. Here, k_0 is an adjustable parameter in the interval $[k_{n\to\infty}^-, k_{n\to\infty}^+]$ that tunes the amount of stochasticity in the system. Finally, we impose a critical radius r_c corresponding to a critical number of cells n_c at density $\rho_{T,h}$, and choose the surface tension accordingly as:

$$\gamma = \frac{p_{T,h} - p_{H,h}}{2}\left(\frac{3n_c}{4\pi\rho_{T,h}}\right)^{1/3}. \tag{15}$$

The parameters used in Fig. **6** of the main text are given in Table IV.

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[9] Note that the exact form of these functions is not important. Only their qualitative behavior is relevant.

Tables

Parameter	Value	Description
x_0	0.01	initial interface location
ρ_0	1	initial density
v_0	0	homogeneous initial velocity
$t_{\text{evol.}}$	650	total time of evolution in Fig. **2** (main text)
	600	total time of evolution in Figs. **3** and **5** (main text)
	3000	total time of evolution in Fig. **4** (main text) and Fig. 5 here
κ	10	division constant (both tissues)
χ	0.2	compressibility (both tissues)
η	50	viscosity (both tissues)

TABLE I: Parameters used to compute the growth dynamics of spherical tumors in Figs. **2**, **3**, **4** and **5** of the main text and Fig. 5 here. Parameters are scaled in units of the total compartment size R, the homeostatic pressure difference Δp between the two tissues and the homeostatic densities ρ_h which we assume to be identical for the two tissues. Total times are scaled to one in the figures.

Parameter	Value	Description
R	100 μm	total compartment radius (Weinberg, 2007)
x_0	10 μm	initial interface location
ρ_h	0.001 μm^3	homeostatic density (both tissues) (Weinberg, 2007)
Δp	1000 Pa	difference in homeostatic pressures (both tissues) (Helminger *et al.*, 1997)
χ	10^{-7} $\text{Pa}^{-1}\cdot\mu\text{m}^{-3}$	compressibility (both tissues) (Tschumperlin *et al.*, 2004)
$\kappa\cdot\chi\cdot\Delta p$	1 d^{-1}	maximum division rate (both tissues) (Weinberg, 2007)
η	10^4 Pa·s	tissue viscosity (Forgacs *et al.*, 1998)

TABLE II: List of parameters used to compute the growth dynamics of spherical tumors in Fig. 1.

Parameter	Value	Description
c_1	0	nutrients per cell for induction of apoptosis
c_2	0.6	nutrients per cell for arrest of proliferation
$\bar{k}_1$	10	maximum cell division and apoptosis at high nutrient concentration
$\bar{k}_2$	500	apoptosis rate coefficient at starvation
α	10	response coefficient of cell division and apoptosis to cell density
β_1	50	response coefficient of cell division to nutrient concentration per cell
β_2	500	response coefficient of cell apoptosis to nutrient concentration per cell
$\Delta\rho$	0.1	shift in cell division and apoptosis tuning the amount of cell turnover at homeostatic density
D_n	1	nutrient diffusion constant
λ	6	nutrient consumption for proliferation
μ	1000	nutrient consumption for metabolism

TABLE III: Parameters used to generate the plots of Fig. **4** of the main text and Figs. 2-5 here in the coupling of the growth dynamics to nutrients as they enter in Eq. (10).

Parameter	Value	Description
$k^+_{n\to\infty}$	1 d^{-1}	n infinity value of r^+_n/n
$k^-_{n\to\infty}$	0 d^{-1}	n infinity value of r^-_n/n
k_0	0.9 d^{-1}	cell turnover at homeostatic density

TABLE IV: Parameters used in Fig. **6** of the main text.

Figure Legends

FIG. 1: Radius and cell-density as functions of time for a growing tumor in conditions identical to those of Fig. **2** of the main text, but with estimates of realistic parameters. Cell density is one per 10^3 μm^3, and cell division rate is one per day. The homeostatic pressure difference and the tissue viscosity are 10^3 Pa and 10^4 Pa·s, respectively (Helminger *et al.*, 1997; Kruse *et al.*, 2000; Forgacs *et al.*, 1998). Tissue compressibility is 10^{-7} Pa^{-1}·m^{-3} (Tschumperlin *et al.*, 2004). With these parameters, a separation of timescales between the slow cell division and the comparatively fast viscous dynamics occurs, such that we can assume homogeneous cell densities in both compartments. Starting from a single cell and neglecting nutrient coupling, a tumor needs about 100 days to fill a compartment with radius 100μm.

FIG. 2: The cell division rate k_d (A) and the negative apoptosis rate $-k_a$ (B) as functions of the cell density ρ and the nutrient concentration ρ_n, as given by Eq. (10). Parameters are given in Table III.

FIG. 3: Difference $k_d - k_a$ as a function of cell density and nutrient concentration, as given by Eq. (10). Parameters are given in Table III. (A) Top view in grey-scale coding. (B) Three-dimensional view.

FIG. 4: Effect of nutrient concentration on the difference $k_d - k_a$ as a function of cell density. Parameters are given in Table III. At high nutrient concentrations, regulation towards the homeostatic density $\rho_h = 1$ is intact, while at low nutrient concentrations cell division drops significantly. At very low nutrient concentrations, cells undergo apoptosis at a high rate.

FIG. 5: Typical nutrient profile as a function of time in a growing tumor that arrests in a dormant state. The flux at the center vanishes and the outside compartment has a constant concentration. Parameters correspond to those given in Tables I and III.