Eur. Phys. J. E (2012) **35**: 46
DOI 10.1140/epje/i2012-12046-5

THE EUROPEAN PHYSICAL JOURNAL E

Regular Article

Tissue dynamics with permeation

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Received 28 October 2011 and Received in final form 25 May 2012
Published online: 15 June 2012 –

Abstract. Animal tissues are complex assemblies of cells, extracellular matrix (ECM), and permeating interstitial fluid. Whereas key aspects of the multicellular dynamics can be captured by a one-component continuum description, cell division and apoptosis imply material turnover between different components that can lead to additional mechanical conditions on the tissue dynamics. We extend our previous description of tissues in order to account for a cell/ECM phase and the permeating interstitial fluid independently. In line with our earlier work, we consider the cell/ECM phase to behave as an elastic solid in the absence of cell division and apoptosis. In addition, we consider the interstitial fluid as ideal on the relevant length scales, *i.e.*, we ignore viscous stresses in the interstitial fluid. Friction between the fluid and the cell/ECM phase leads to a Darcy-like relation for the interstitial fluid velocity and introduces a new characteristic length scale. We discuss the dynamics of a tissue confined in a chamber with a permeable piston close to the homeostatic state where cell division and apoptosis balance, and we calculate the rescaled effective diffusion coefficient for cells. For different mass densities of the cell/ECM component and the interstitial fluid, a treadmilling steady state due to gravitational forces can be found.

1 Introduction

During development, tissues grow by repeated rounds of cell division in a highly controlled manner [1]. In addition to cell division, coordinated cell death or apoptosis is also part of normal morphogenesis, for example in sculpting the joint of the leg of the fruit fly *Drosophila melanogaster* [2]. Cancerous tissue growth is another extreme case of tissue formation by cell division. Here, cells proliferate abnormally even in adult tissues [3]. More generally, cell division and apoptosis occur at all stages of the life of an organism where dying cells are constantly replaced. Long-standing research has led to deep insights into the respective genetic regulatory pathways and into the biochemical signaling mechanisms involved in cell division and apoptosis [4–7]. However, it is by now well established that morphogenetic processes are also greatly influenced by mechanical conditions (see ref. [8] for an extensive review). As a more direct example of a mechanical perturbation intervening in cell division, it has been shown that the axis of cell division can be oriented by applying an external stress [9–11].

In order to understand the mechanics of tissue formation, various descriptions of the mechanical properties of tissues have been put forward. Cell based computer simulations of tissue growth allow for a great flexibility with respect to the details of single-cell behavior that can be taken into account, and they are able to reproduce *in vitro* experimental data [12,13]. At a mesoscopic scale, growing tissues have been described as a network of cell junctions that can undergo remodeling due to cell division and apoptosis [14,15]. This approach can explain some key aspects of cellular behavior and tissue reorganization, but it is usually quasi-static and thus cannot account for the slow relaxation times of large wavelength modes. Although disregarding details on the cellular scale, a continuum mechanics or hydrodynamic approach allows to capture the multicellular dynamics on large scales [16–18]. In a previous work, we have developed a continuum description of tissues, which describes the stress distribution and the cell flow field induced by cell division and apoptosis events [19]. We showed that a tissue that behaves as an elastic solid on short time scales in the absence of cell division and apoptosis effectively behaves as a viscoelastic fluid with a relaxation time set by the rates of division and apoptosis if present. However, we have considered the tissue as a one-component system not explicitly accounting for the material turnover that is necessarily implied by cell division and apoptosis. Here, we extend our earlier theory to a two-component description of tissue dynamics. The fluxes associated with material turnover give rise to additional mechanical conditions that have not been discussed before.

The idea to describe tissues as a multi-component system is not new and various mathematical models with

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material turnover have been proposed [20–22]. Animal tissues are not only composed of cells. In general, the cells are embedded in the so-called extracellular matrix (ECM) that fills the interstitial space between cells [23]. The ECM is an elastic scaffold consisting of a cross-linked network of fibrous proteins such as collagen, filled by a hydrogel of amino polysaccharides embedding dispersed fibroblast cells. Its important role in development and in healthy tissue homeostasis only begins to emerge [24,25]. Notably, the ECM is constantly remodeled by the embedded cells in response to different cues ranging from mechanical stress to specific signals that are induced, in the case of injury for example [23]. The extracellular space is also penetrated by the interstitial fluid. In normal tissues, it consists mostly of blood plasma filtrate that leaks out of capillaries and is subsequently drained by the lymphatics [26]. In *in vitro* cell aggregates such as multicellular spheroids the interstitial fluid is mostly made up of the culture medium provided. This interstitial flow provides the cells with nutrients and removes metabolic waste.

In order to keep our description simple, we distinguish only two different components constituting a tissue. We address here the dynamics of homogenous three-dimensional confluent tissues with low ECM to cell mass ratio. On the relevant time scales of cell division and apoptosis, the ECM surrounding a cell can be considered as part of that cell, being newly assembled after a cell division or degraded in the case of apoptosis. Thus, we consider the ECM as part of one single cell/ECM tissue component. In addition, we consider the permeating interstitial fluid as the second component independently taken into account. This two-component description extends our previous work in two aspects mainly. First, as the fluid permeates the tissue, friction between the cell/ECM and the fluid phase leads to momentum transfer between the two phases. Furthermore, cell division and apoptosis do not only appear as a source term in the cell number balance equation, but also imply material turnover between the two phases. The aim of this paper is to revisit our previous results in the light of this more detailed description and investigate the effects of permeation in various situations.

The paper is organized as follows. In sect. 2, we detail our two-component description of tissue dynamics. In line with our previous work, we consider the cell/ECM phase to behave as a viscoelastic fluid in the presence of cell division and apoptosis. We consider the interstitial fluid to behave as a purely viscous fluid. We show that friction between the fluid and the cell/ECM phase leads to a Darcy-like relation for the interstitial fluid velocity. We furthermore discuss the dynamics around the homeostatic state introduced in our previous work, where cell division and apoptosis balance at a given pressure [27]. The two-component description allows to clarify the nature of the homeostatic tissue pressure as opposed to the hydrostatic pressure. In sect. 3, we consider the example of a tissue confined in a chamber which is closed at one end with a movable piston. We solve the dynamics in the case of both permeable and impermeable pistons for a tissue close to its homeostatic state. For tissues with low permeability, *i.e.*, high friction between fluid and cell/ECM phase, we find that the pressure induced cell division or apoptosis is limited to a region close to the permeable piston with a characteristic length scale given by the permeability and the effective tissue viscosity. Section 4 presents a discussion of gravitational forces in the context of a two-component description. As an application, we discuss a treadmilling steady state of a tissue under its own gravitational load, which can be found if the cell/ECM phase and the interstitial fluid have different mass densities. In sect. 5, we review the effective diffusion of cells due to stress fluctuations and find that the effective diffusion constant is rescaled by the tissue permeability. The last section is devoted to a discussion of our results.

2 Two-component description of tissues

We describe a tissue as a two-component system and, as argued above, we distinguish: i) a cell/ECM phase that accounts for both the cells in the tissue and the surrounding ECM, which for simplicity we refer to subsequently as cell phase only, and ii) the interstitial fluid that permeates the cell phase. The interstitial fluid is a complex fluid, but here we use a simplified description and consider it as a simple fluid comprising a single effective "molecular" species.

The cell and fluid phases are characterized by the cell number density n^c and the fluid particle number density n^f, respectively, coarse grained over the size of several cells. We introduce the effective cell volume Ω^c (including a portion of the ECM) and the fluid particle volume Ω^f such that

$$n^c\Omega^c + n^f\Omega^f = 1, \tag{1}$$

which implies that cells and fluid fill space completely. The cell volume fraction is defined as $\phi = n^c\Omega^c$, and consequently $n^f\Omega^f = 1 - \phi$.

2.1 Cell number balance and material turnover

The cell number density n^c obeys a balance equation which includes advection due to cell flow as well as an additional source term due to cell division and apoptosis,

$$\partial_t n^c + \partial_\alpha(n^c v^c_\alpha) = n^c(k_\mathrm{d} - k_\mathrm{a}). \tag{2}$$

Here, v^c_α is the velocity field of the cells, and k_d and k_a denote the cell division and apoptosis rates, respectively.

In our description, a cell of volume Ω^c can be converted into Ω^c/Ω^f fluid particles and vice versa when cells die or divide. Here, we assume that cells and the surrounding fluid have the same material mass density, see appendix A. The total volume balance is expressed by

$$\partial_t\left(\frac{\Omega^c}{\Omega^f}n^c + n^f\right) = -\partial_\alpha\left(\frac{\Omega^c}{\Omega^f}n^c v^c_\alpha + n^f v^f_\alpha\right), \tag{3}$$

where v^f_α is the velocity field of the fluid component. Note that this equation has the form of a classical conservation equation $\partial_t n + \partial_\alpha J_\alpha = 0$, where n corresponds to a particle

density and J_α is a particle current. The balance equation for the interstitial fluid thus reads

$$\partial_t n^f + \partial_\alpha (n^f v^f_\alpha) = -\frac{\Omega^c}{\Omega^f} n^c (k_\mathrm{d} - k_\mathrm{a}) - n^c \frac{\mathrm{d}}{\mathrm{d}t}\frac{\Omega^c}{\Omega^f}\,, \quad (4)$$

where $(\mathrm{d}/\mathrm{d}t) = \partial_t + v^c_\gamma \partial_\gamma$ is the convected time derivative at the velocity of the cell flow.

In the following, we consider the system as incompressible. The compressibility of the system is given by $\Xi = -\frac{1}{V}\frac{\partial V}{\partial P}\big|_{N_c,N_f}$, so that with $V = N_c\Omega^c + N_f\Omega^f$ we obtain in the incompressible limit ($\Xi = 0$)

$$0 = -n^c \frac{\partial \Omega^c}{\partial P}\bigg|_{N_c,N_f} - n^f \frac{\partial \Omega^f}{\partial P}\bigg|_{N_c,N_f}. \quad (5)$$

Both volumes Ω^c and Ω^f must decrease with the pressure P. Equation (5) then imposes that they do not depend on pressure when the tissue is incompressible. In the following, we therefore assume that the fluid volume Ω^f is constant; the cell volume Ω^c does not depend on pressure, but can depend on the cell volume fraction ϕ. The pressure P is then determined by the constraint on the total volume flux $v_\alpha = n^c\Omega^c v^c_\alpha + n^f\Omega^f v^f_\alpha$: For an incompressible tissue, eq. (3) leads with the above assumptions to the constraint $\partial_\alpha v_\alpha = 0$; see also appendix A, eq. (A.5).

2.2 Force balance

Internal forces due to cell division or apoptosis as well as external forces applied at tissue boundaries for example can lead to mechanical stresses in the tissue. These stresses are described by the total stress tensor $\sigma_{\alpha\beta} = \sigma^c_{\alpha\beta} + \sigma^f_{\alpha\beta}$, which includes contributions $\sigma^c_{\alpha\beta}$ of the cell phase and $\sigma^f_{\alpha\beta}$ of the fluid. Neglecting inertia, the total force balance on a volume element is written as $\partial_\beta \sigma_{\alpha\beta} = -f^{\mathrm{ext}}_\alpha$, where f^{ext}_α are the external (body) forces acting on the tissue. In the absence of external forces, force balance then requires $\partial_\beta(\sigma^c_{\alpha\beta} + \sigma^f_{\alpha\beta}) = 0$. This implies

$$\begin{aligned} \partial_\beta \sigma^c_{\alpha\beta} + f_\alpha &= 0, \\ \partial_\beta \sigma^f_{\alpha\beta} - f_\alpha &= 0, \end{aligned} \quad (6)$$

where f_α denotes the momentum transfer between the two phases. We assume that it is caused by friction due to the relative flow between the two phases, and we write $f_\alpha = -\kappa(v^c_\alpha - v^f_\alpha)$. The inverse friction coefficient κ^{-1} is the effective permeability or hydraulic conductivity of the tissue.

The stress in the fluid, coarse-grained over several cells, can be expressed as $\sigma^f_{\alpha\beta} = -P^f\delta_{\alpha\beta}$, since the deviatoric stress in the fluid vanishes over length scales large compared to the cells. Therefore, the force balance equations read

$$\begin{aligned} \partial_\beta \sigma^c_{\alpha\beta} - \partial_\alpha P^f &= 0, \\ \kappa(v^c_\alpha - v^f_\alpha) &= \partial_\alpha P^f. \end{aligned} \quad (7)$$

For $v^c \equiv 0$, the second equation is the famous Darcy equation describing flow through porous media [28,29]. Gradients in fluid pressure drive relative interstitial fluid flow through the extracellular matrix.

2.3 Constitutive equations

The material properties of the tissue are characterized by the constitutive equations relating the stresses to other variables or kinematic quantities of the system. In line with our previous work, we consider the cell network to behave as an elastic material in the absence of cell division and apoptosis, and we write

$$\frac{\mathrm{D}}{\mathrm{D}t}\sigma^c_{\alpha\beta} = C_{\alpha\beta\gamma\nu} v^c_{\gamma\nu} + \frac{\mathrm{D}}{\mathrm{D}t}\sigma^s_{\alpha\beta} \quad (8)$$

for the rate of change of the cell stress [19]. Here, $v^c_{\alpha\beta} = (1/2)(\partial_\alpha v^c_\beta + \partial_\beta v^c_\alpha)$ is the strain rate tensor, $(\mathrm{D}/\mathrm{D}t)\sigma_{\alpha\beta} = \partial_t\sigma_{\alpha\beta} + v^c_\gamma\partial_\gamma\sigma_{\alpha\beta} + \omega_{\alpha\gamma}\sigma_{\gamma\beta} + \omega_{\beta\gamma}\sigma_{\alpha\gamma}$ denotes the convected co-rotational time derivative, and $\omega_{\alpha\beta} = (1/2)(\partial_\alpha v^c_\beta - \partial_\beta v^c_\alpha)$ is the vorticity of the cell flow. $\sigma^s_{\alpha\beta}$ is the source stress due to cell division and apoptosis. In the following, we consider that the cell phase is isotropic, *i.e.*, $C_{\alpha\beta\gamma\nu} = \chi\,\delta_{\alpha\beta}\delta_{\gamma\nu} + 2\mu(\delta_{\alpha\gamma}\delta_{\beta\nu} - \delta_{\alpha\beta}\delta_{\gamma\nu}/3)$, where χ and μ are the compressional and the shear modulus, respectively. For the sake of clarity, we separate the cell stress tensor $\sigma^c_{\alpha\beta}$ into an isotropic contribution σ^c and a traceless part $\tilde\sigma^c_{\alpha\beta}$, with $\sigma^c_{\alpha\beta} = \sigma^c\delta_{\alpha\beta} + \tilde\sigma^c_{\alpha\beta}$.

We first discuss the traceless component of the stress. Following our argument developed in ref. [19], the corresponding rate of change of the source stress is given by

$$\frac{\mathrm{D}}{\mathrm{D}t}\tilde\sigma^s_{\alpha\beta} = -\frac{n^c(\tilde d_\mathrm{d} k_\mathrm{d} + \tilde d_\mathrm{a} k_\mathrm{a})}{\sigma_0}\tilde\sigma^c_{\alpha\beta}, \quad (9)$$

where $\tilde d_\mathrm{d}$ and $\tilde d_\mathrm{a}$ are the respective magnitudes of the stress increments related to cell division and apoptosis, and σ_0 is a susceptibility. This leads with eq. (8) to Maxwell viscoelastic dynamics for the anisotropic part of the cell stress,

$$\left(1 + \tau_\mathrm{a}\frac{\mathrm{D}}{\mathrm{D}t}\right)\tilde\sigma^c_{\alpha\beta} = 2\eta\tilde v^c_{\alpha\beta}, \quad (10)$$

where $\tau_\mathrm{a}^{-1} = n^c(\tilde d_\mathrm{d} k_\mathrm{d} + \tilde d_\mathrm{a} k_\mathrm{a})/\sigma_0$ and $\eta = \tau_\mathrm{a}\mu$ is an effective shear viscosity. Note that in the presence of additional stress relaxation mechanisms, the effective shear viscosity could be considerably reduced. The cell phase exhibits the same shear stress relaxation as the whole tissue in our one-component theory [19].

In order to discuss the isotropic part of the cell stress, we first consider the tissue in the absence of cell division and apoptosis. We assume that the cell stress depends on the cell volume Ω^c as well as on the cell number density n^c. In its simplest form, this implies an equation of state $\sigma^c = f(n^c, \Omega^c)$. In order to close the system of equations, we need one more constitutive equation. A simple choice is to assume that cells adjust their volume according to

the cell number density, which implies an additional equation of state $\Omega^c = g(n^c)$. Alternatively, we can write the equations of state of the tissue as

$$n^c = h_1(\sigma^c), \qquad \Omega^c = h_2(\sigma^c), \tag{11}$$

where h_1 and h_2 are positive functions. Note that both cell number density and cell volume may additionally depend on the fluid pressure, which we neglect here. We define the bulk modulus of the tissue by $\frac{\mathrm{d}}{\mathrm{d}t}\sigma^c = -\frac{\bar{\chi}}{n^c}\frac{\mathrm{d}n^c}{\mathrm{d}t}$ or $\bar{\chi} = -n^c\frac{\mathrm{d}h_1^{-1}}{\mathrm{d}n^c}$, respectively. In the absence of cell division and apoptosis, using the cell number balance (2), we obtain $\mathrm{d}\sigma^c/\mathrm{d}t = \bar{\chi}v^c_{\gamma\gamma}$. Comparison with the isotropic part of eq. (8) in the case of vanishing source stress shows that $\chi = \bar{\chi}$.

In a next step, we consider cell division and apoptosis. The rate of change of the isotropic stress is

$$\frac{\mathrm{d}}{\mathrm{d}t}\sigma^c = \chi(v^c_{\gamma\gamma} - k_\mathrm{d} + k_\mathrm{a}), \tag{12}$$

where we again used cell number balance. On the other hand, we can write the rate of change of the source stress as $\mathrm{d}\sigma^s/\mathrm{d}t = -n^c d(k_\mathrm{d} - k_\mathrm{a})$, where d is a pressure increment per cell division. It follows that $d = \chi/n^c$. The constitutive equation for the isotropic part of the cell stress is again analogous to the equation obtained in our one-component description [19].

2.4 Homeostatic state

In constant biochemical conditions, *i.e.*, when tissue growth is not limited by a lack of nutrients, the rates of cell division and apoptosis vary with the cell pressure. It has been argued that a tissue has a characteristic homeostatic pressure at which cell division and apoptosis balance on average [27]. Close to the homeostatic state, we expand the effective cell number growth rate $k_\mathrm{d} - k_\mathrm{a}$ in powers of the isotropic cell stress $\delta\sigma^c = \sigma^c + P^c_\mathrm{h}$ around the homeostatic cell pressure P^c_h,

$$k_\mathrm{d} - k_\mathrm{a} \simeq \frac{1}{\tau}\frac{\delta\sigma^c}{\chi}\,. \tag{13}$$

Together with eq. (12) this leads to Maxwell dynamics for the isotropic part of the stress close to the homeostatic state,

$$\left(1 + \tau\frac{\mathrm{d}}{\mathrm{d}t}\right)(\sigma^c + P^c_\mathrm{h}) = \zeta v^c_{\gamma\gamma}, \tag{14}$$

where $\zeta = \tau\chi$ is an effective bulk viscosity. The same result —relaxation of the isotropic stress at long times— has been obtained previously in the one-component description [19]. However, the two-component description allows for a better understanding of the nature of the homeostatic pressure, which is a mechanical stress exerted by the cells at the homeostatic state on top of the fluid pressure P^f. The examples presented in the next section illustrate this point in more detail.

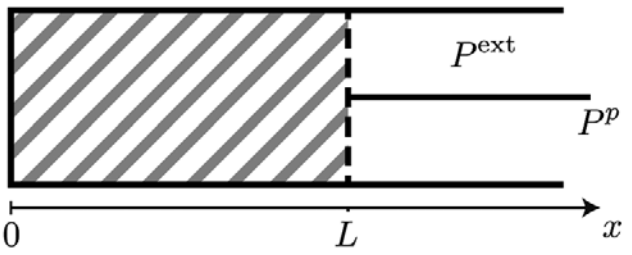

Fig. 1. Sketch of tissue chamber with piston. The tissue is on the left, separated from a fluid reservoir on the other side of the piston. The piston can be considered as being either impermeable or permeable to the extracellular fluid, see text for details.

3 Example: Tissue chamber closed by a piston

In the following, we highlight specific features of tissue dynamics with permeation. As a paradigm, we consider a tissue confined to a chamber with fixed walls and a movable piston closing the chamber, as sketched in fig. 1.

3.1 Steady state of the tissue and piston

We first identify the possible steady states of the system. In the case of both impermeable walls and an impermeable piston exerting a constant external pressure P^{ext}, the total pressure in the tissue chamber has to balance the external pressure, $-\sigma^c + P^f = P^{\mathrm{ext}}$. Since there is no cell flow in a steady state, the cell pressure equals the homeostatic pressure, $\sigma^c = -P^c_\mathrm{h}$, and the fluid pressure adjusts accordingly to $P^f = P^{\mathrm{ext}} - P^c_\mathrm{h}$. This steady state with an impermeable piston exists irrespective of the applied external pressure.

The situation changes if one of the walls or the piston is semi-permeable and allows for fluid exchange. The flow through the wall or piston is related to the hydrostatic pressure drop over the wall; a steady state thus requires $P^f = P^{\mathrm{ext}}$, where P^{ext} is the external hydrostatic pressure. Since the tissue pressure must be equal to its homeostatic value P^c_h, a steady state exists only if an additional force (per unit area) P^p is exerted by the piston. The total pressure in the chamber balances in this case the sum of the external hydrostatic pressure and the additional force applied on the piston, and we find $P^p = P^c_\mathrm{h}$. The force exerted by a semi-permeable piston in the steady state provides therefore a measure of the homeostatic pressure. If the pressures are not balanced, either the piston moves and squeezes the tissue, or the tissue pushes the piston and invades the chamber; there is no other possible steady state. Note that the cell volume and the volume fraction of the interstitial fluid can in principle be calculated from the equations of state of the tissue.

3.2 Tissue and piston dynamics close to steady state

We now consider the case of a semi-permeable piston with a free slip boundary condition on the walls of the chamber

for both the fluid and the cell phase. This choice allows for a one-dimensional treatment of the dynamics. Only the piston is permeable. The pressure exerted on the tissue is again $P^{\rm ext}+P^p$, but now $P^p=P^c_{\rm h}+\delta P$. The position of the piston is given by the length L of the compartment filled by the tissue. Depending on the sign of δP, the piston moves in either direction.

In order to solve for the dynamics of the piston, we need to specify the boundary conditions at $x=L$. The velocity of the piston (the moving boundary) is given by the velocity of the cell flow because the piston is impermeable to cells, $\mathrm{d}L/\mathrm{d}t=v^c_x(L)$. On the opposing wall (located at $x=0$) both the cell phase and the fluid are at rest, $v^c_x(0)=v^f_x(0)=0$. Together with the incompressibility condition, $\partial_x(\phi v^c_x+(1-\phi)v^f_x)=0$, this leads to $\phi v^c_x+(1-\phi)v^f_x=0$. If we consider that the piston has a permeability ν, the boundary condition for the fluid velocity at $x=L$ reads

$$v^f_x(L)-\dot{L}=\nu\left(P^f(L)-P^{\rm ext}\right). \tag{15}$$

Finally, force balance implies

$$-\sigma^c-\tilde{\sigma}^c_{xx}+P^f=P^{\rm ext}+P^c_{\rm h}+\delta P. \tag{16}$$

For slow stress variation, *i.e.*, at long times, the tissue behaves as a liquid and one can keep only the viscous part of the stress variations, and with $\tilde{v}^c_{xx}=\frac{2}{3}\partial_x v^c_x$ we obtain

$$\begin{aligned}\sigma^c&=-P^c_{\rm h}+\zeta\partial_x v^c_x,\\ \tilde{\sigma}^c_{xx}&=\tfrac{4}{3}\eta\partial_x v^c_x,\end{aligned} \tag{17}$$

for the isotropic and the anisotropic part of the cell stress, respectively. Thus, we obtain

$$P^f-\bar{\eta}\partial_x v^c_x=P^{\rm ext}+\delta P, \tag{18}$$

where $\bar{\eta}=\zeta+\frac{4}{3}\eta$ is the longitudinal viscosity. The incompressibility condition combined with the force balance in the fluid (7) gives $\partial_x P^f=\kappa v^c_x/(1-\phi)$, so that by differentiating with respect to x we finally obtain

$$v^c_x-\lambda^2\,\partial^2_x v^c_x=0, \tag{19}$$

where λ is a characteristic length defined by $\lambda^2=\bar{\eta}(1-\phi)/\kappa$. In the following, we assume that ϕ has only a small variation $\delta\phi\ll\phi$ across the tissue, so that we may consider λ as constant when solving (19) for the cell velocity v^c_x. (This argument is made more precise below.) Taking the boundary conditions into account, one finds

$$v^c_x(x)=-\frac{v_0}{\cosh\frac{L}{\lambda}+\alpha\sinh\frac{L}{\lambda}}\sinh\frac{x}{\lambda}, \tag{20}$$

where $v_0=\delta P\lambda/\bar{\eta}$ is a characteristic velocity and $\alpha=\lambda/(\bar{\eta}(1-\phi)\nu)=(\bar{\eta}(1-\phi)\kappa\nu^2)^{-1/2}$ is a dimensionless parameter related to the permeability of the piston.

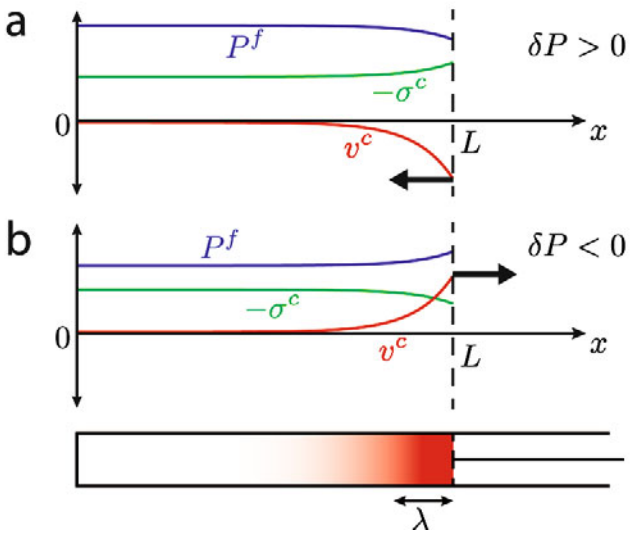

Fig. 2. Tissue dynamics in response to an external force. The force is exerted by a semi-permeable piston, with its position being indicated by the dashed vertical line. Here, we illustrate the case in which the characteristic length λ is small compared to the size of the tissue chamber L. We find that the tissue response is confined to a zone of length λ close to the piston, see text for details. For (a) $\delta P>0$, the cells undergo apoptosis which results in a negative net cell flow as indicated. For (b) $\delta P<0$, the cells are dividing and thus give rise to a net expansion of the tissue.

Depending on the ratio L/λ, we can distinguish two different regimes:

a) $L\gg\lambda$:
If the permeation length is much smaller than the size of the tissue, we find

$$\begin{aligned}v^c_x(x)&=-\frac{v_0}{1+\alpha}e^{(x-L)/\lambda},\\ -\sigma^c(x)&=P^c_{\rm h}+\delta P\frac{\zeta}{\bar{\eta}}\frac{e^{(x-L)/\lambda}}{1+\alpha},\\ P^f(x)&=P^{\rm ext}+\delta P\left(1-\frac{e^{(x-L)/\lambda}}{1+\alpha}\right).\end{aligned} \tag{21}$$

The piston moves at constant velocity $\dot{L}=-v_0/(1+\alpha)$ and most of the tissue is in its stationary state. Only a small region of thickness λ is perturbed, where apoptosis dominates if $\delta P>0$ and division dominates if $\delta P<0$. This is a key result of this work. In this regime, a one-component description of tissues fails to capture the dynamics correctly and permeation must be taken into account. Due to the resistance to flow of the cell phase, fluid pressure builds up on a finite length scale λ. This pressure gradient drives the fluid flow in conjunction with the material turnover implied by cell division or apoptosis, respectively. Examples of flow and pressure profiles are sketched in fig. 2.
For $\alpha\gg1$, the piston does not move and no cell turnover takes place. This limit corresponds to zero

piston permeability and one recovers the stationary state as discussed for an impermeable piston.

b) $L \ll \lambda$:
If the permeation length is much larger than the size of the tissue, to lowest order in x/λ we find

$$v_x^c(x) = -\frac{v_0}{1+\alpha L/\lambda}\frac{x}{\lambda},$$
$$-\sigma^c(x) = P_{\rm h}^c + \delta P\,\frac{\zeta}{\bar\eta}\frac{1}{1+\alpha L/\lambda},$$
$$P^f(x) = P^{\rm ext} + \delta P\frac{\alpha L/\lambda}{1+\alpha L/\lambda}. \qquad (22)$$

In this regime, one recovers the results of the one-component theory with a rescaled pressure difference $\delta P \to \delta P/(1+\alpha L/\lambda)$. This rescaling is due to the fluid pressure drop at $x = L$ caused by the finite piston permeability.
The position of the piston as a function of time is implicitly given by

$$\lambda \ln L/L_0 + \alpha(L - L_0) = -v_0 t. \qquad (23)$$

For large α, *i.e.* $\alpha \gg \lambda/L$, the piston moves with constant speed $\dot L \approx -v_0/\alpha$. In this regime, the finite permeability of the piston limits the velocity with which the tissue turns over. For reasonably small $L \ll \lambda/\alpha$, or for large enough piston permeability, *i.e.*, $\nu \gg L/(\bar\eta(1-\phi))$, this effect becomes negligible and the position of the piston varies according to $\dot L \approx -v_0 L/\lambda$. In this case, one recovers an exponential regime either for growth or for shrinkage.

The cell number density n^c and the cell volume Ω^c can in principle be determined via the equations of state (11). Eventually, one can check that for small δP their variations are small (but always time dependent). The assumption that the variation $\delta\phi$ of the volume fraction is small can now be discussed more precisely: Our calculations are consistent if $\delta\phi = (\mathrm{d}\phi/\mathrm{d}\sigma^c)\delta\sigma^c \ll \phi \approx 1$, where $\delta\sigma^c = \delta P\zeta/[\bar\eta(1+\alpha)]$ in the case of $L \gg \lambda$ and $\delta\sigma^c = \delta P\zeta/[\bar\eta(1+\alpha L/\lambda)]$ in the case of $L \ll \lambda$, and $\mathrm{d}\phi/\mathrm{d}\sigma^c = (\mathrm{d}h_1/\mathrm{d}\sigma^c)\Omega^c + n^c(\mathrm{d}h_2/\mathrm{d}\sigma^c)$ for known h_1 and h_2 (cf. eqs. (11)).

4 Tissue under its own gravitational load

In the previous sections, we neglected gravitational forces, which are supposed to be small compared to other forces. Although they do not necessarily play a role in many biological contexts of tissue dynamics, taking the effects of gravitation into account allows to illustrate key aspects of a multi-component description of tissues.

4.1 Force balance in the presence of gravity as external body force

If gravity is taken into account, the total external body force is given by $f_\alpha^{\rm ext} = \varrho g_\alpha$, where $\varrho = \phi\varrho^c + (1-\phi)\varrho^f$ is the total mass density and g_α is the gravitational acceleration. The force balance for each of the components then reads

$$\partial_\beta\sigma^c_{\alpha\beta} + f_\alpha = -\phi\varrho^c g_\alpha,$$
$$-\partial_\alpha P^f - f_\alpha = -(1-\phi)\varrho^f g_\alpha. \qquad (24)$$

Here, the gravitational force on each of the components corresponds to its mass fraction. The momentum transfer f_α between the two phases comprises now both friction and buoyancy forces, $f_\alpha = -\kappa(v_\alpha^c - v_\alpha^f) - \phi\varrho^f g_\alpha$, so that

$$\partial_\beta\sigma^c_{\alpha\beta} - \kappa(v_\alpha^c - v_\alpha^f) = -\phi(\varrho^c - \varrho^f)g_\alpha,$$
$$-\partial_\alpha P^f + \kappa(v_\alpha^c - v_\alpha^f) = -\varrho^f g_\alpha. \qquad (25)$$

Gravitation enters the force balance equation for the cell phase only for finite density differences $\varrho^c - \varrho^f$, *i.e.*, for different mass densities between cells including ECM and the interstitial fluid. In general, the mass density difference is small, $\varrho^c - \varrho^f \ll \varrho^f$.

Consider a tissue column of arbitrary height with $\varrho^c = \varrho^f$. Does the homeostatic stationary state still exist? Because only its excess weight with respect to the interstitial fluid actually exerts an additional stress on the cell phase, the force balance (25) is readily obeyed for $\sigma^c_{\alpha\beta} = -P^c_{\rm h}\delta_{\alpha\beta}$ and $v^c_\alpha = v^f_\alpha = 0$. Gravitation then simply leads to a barometric profile of the hydrostatic pressure P^f, as can be seen from eq. (25).

4.2 Gravity-induced treadmilling steady state

In the case of a small but finite difference $\delta\varrho \equiv \varrho^c - \varrho^f \ll \varrho^f$ between the mass densities of cells and the fluid, no homeostatic stationary state exists. For a tissue layer close to the homeostatic state, however, a treadmilling stationary state can be found in which apoptosis is induced at the bottom of the tissue layer, balanced by cell division at the upper surface, see fig. 3.

We consider a tissue contained in a box with impermeable lateral walls that are described by full slip boundary conditions and a solid bottom wall at $z = 0$, such that the problem is effectively one-dimensional. The tissue of height h is subject to a force exerted on its upper surface by a semi-permeable membrane or piston similar to the example given in the previous section. In the long time limit, we consider the tissue as viscous and keep only the viscous part of the cell stress variations $\delta\sigma^c = \sigma^c + P^c_{\rm h}$ and $\tilde\sigma^c_{\alpha\beta}$ as given by the constitutive equations (9) and (14), $\tilde\sigma^c_{\alpha\beta} = 2\eta\tilde v^c_{\alpha\beta}$ and $\delta\sigma^c = \zeta v^c_{\gamma\gamma}$. For finite $\delta\varrho$, the divergence of the volume flux is finite in the presence of cell division and apoptosis, see appendix A for a detailed account. However, because the effective cell division rate $k_{\rm d} - k_{\rm a} \propto \delta\sigma^c$ and $\delta\varrho \ll \varrho^f$, the divergence vanishes to second order and we take $\partial_\alpha v_\alpha = 0$. Using the zero flux boundary condition at $z = 0$, we can thus express the fluid velocity as $v^f = -\frac{\phi}{1-\phi}v^c$, where we used $\boldsymbol{v}^c = v^c\boldsymbol{e}_z$ and $\boldsymbol{v}^f = v^f\boldsymbol{e}_z$ (also, $\boldsymbol{g} = -g\boldsymbol{e}_z$ in the following). From the force balance equation of the cell phase we finally obtain

$$\lambda^2\partial_z^2 v^c - v^c = v_0, \qquad (26)$$

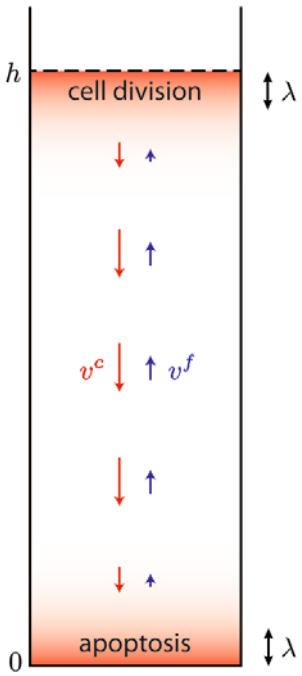

Fig. 3. Sketch of a treadmilling tissue column of height h. Due to a difference in the mass densities of cells and fluid, cells are subject to gravitational forces. We find a solution where cells tend to divide at the top layer of a tissue column and undergo apoptosis at the bottom layer. In between, a constant cell flow maintains the stationary state, together with the opposed interstitial fluid flow.

where we again defined the characteristic length $\lambda^2 = (\zeta + \frac{4}{3}\eta)(1-\phi)/\kappa$ and a characteristic velocity $v_0 = \delta\varrho g\phi(1-\phi)/\kappa$.

The general solution for eq. (26) is given by

$$v^c = -v_0\left(1 + Ae^{\frac{z}{\lambda}} + Be^{-\frac{z}{\lambda}}\right), \tag{27}$$

where A and B are determined from the boundary conditions at $z = 0$ and $z = h$. We look for a steady state where the cell velocity vanishes on both surfaces, $v^c(h) = v^c(0) = 0$, and we find

$$v^c = -v_0\left(1 - \frac{\sinh\frac{z}{\lambda} + \sinh\frac{h-z}{\lambda}}{\sinh\frac{h}{\lambda}}\right). \tag{28}$$

The cell pressure $P^c = -\sigma^c$ follows from the constitutive equation (14) in the viscous limit,

$$P^c = P^c_{\rm h} - \frac{\zeta v_0}{\lambda\sinh\frac{h}{\lambda}}\left(\cosh\frac{z}{\lambda} - \cosh\frac{h-z}{\lambda}\right). \tag{29}$$

For $h \gg \lambda$, the tissue is proliferating in a small layer of thickness λ at the upper surface and undergoing apoptosis in a layer at the bottom of the same thickness. In between, the cells flow with a velocity $v^c \approx -v_0$ from the top to the bottom. If $h \ll \lambda$, the cell velocity is vanishing everywhere to second order, *i.e.* $v^c = \mathcal{O}(\delta\varrho h/\lambda)$, and no relevant turnover takes place.

In order for the steady state to exist, the cell pressure at $z = h \gg \lambda$ has to be balanced by a permeable membrane or piston which exerts a pressure $P^p = P^c{\rm h} - \zeta v_0/\lambda$. The hydrostatic pressure $P^{\rm ext}$ at $z = h$ then enters as a boundary condition for the fluid pressure with $P^f(h) = P^{\rm ext}$. The fluid pressure can be determined from $-\partial_z P^f + \frac{\kappa}{1-\phi}v^c = \varrho^f g$, and we find

$$P^f = P^{\rm ext} + (\varrho^f + \phi\delta\varrho)g(h-z) + \frac{\kappa v_0\lambda}{(1-\phi)\sinh\frac{h}{\lambda}} \times\left(\cosh\frac{z}{\lambda} - \cosh\frac{h-z}{\lambda} - \cosh\frac{h}{\lambda} + 1\right). \tag{30}$$

For $h \gg \lambda$, this expression simplifies to

$$P^f \approx P^{\rm ext} + \varrho^f g(h-z) - \frac{\kappa v_0\lambda}{1-\phi}\left(e^{-\frac{z}{\lambda}} - e^{-\frac{h-z}{\lambda}} + 1\right). \tag{31}$$

As in the first example, the cell number density n^c and the cell volume Ω^c can in principle be determined via the equations of state (11). Eventually, one can check that for small $\delta\varrho/\varrho^f$ their variations are small.

5 Fluctuations

So far we neglected the effect of fluctuations. Whereas this might be appropriate when describing the dynamics on large scales, it does not allow to capture the diffusive behavior of single cells in a tissue which exists even at steady state [30]. In this section, we investigate the role of fluctuations in the homeostatic state along the lines of our earlier work [19], notably including the effects of permeation.

5.1 Stress and velocity fluctuations

In the presence of fluctuations, the balance equations contain additional noise terms describing the fluctuations. To first order, fluctuations in the cell number are described by gaussian white noise ξ^c with zero mean and local correlations in space and time. For a simple birth-and-death process, $\langle\xi^c(\boldsymbol{r},t)\xi^c(\boldsymbol{r}_0,t_0)\rangle = n^c(k_{\rm d}+k_{\rm a})\,\delta(\boldsymbol{r}-\boldsymbol{r}_0)\delta(t-t_0)$. Thus, we rewrite the cell number balance as

$$\partial_t n^c + \partial_\alpha(n^c v^c_\alpha) = n^c(k_{\rm d} - k_{\rm a}) + \xi^c. \tag{32}$$

The fluctuations in the cell number lead to fluctuations in the isotropic part of the cell stress according to (14), which close to the homeostatic state reduces to

$$\left(1 + \tau\frac{\rm d}{{\rm d}t}\right)(\sigma^c + P^c_{\rm h}) = \zeta v^c_{\gamma\gamma} - \frac{\zeta}{n^c_{\rm h}}\xi^c. \tag{33}$$

In addition, fluctuations of the cell orientation and deformation lead to a noise $\tilde{\xi}_{\alpha\beta}$ in the anisotropic part of the stress,

$$\left(1 + \tau_{\rm a}\frac{\rm D}{{\rm D}t}\right)\tilde{\sigma}^c_{\alpha\beta} = 2\eta\tilde{v}^c_{\alpha\beta} + \tilde{\xi}_{\alpha\beta}. \tag{34}$$

Without giving a microscopic description of these fluctuations, we assume that they correspond to a Gaussian white noise with zero mean and delta-correlations in space and time. For an isotropic tissue, these correlations are characterized by a single noise strength θ such that $\langle\tilde{\xi}_{\alpha\beta}(\boldsymbol{r},t)\tilde{\xi}_{\gamma\delta}(\boldsymbol{r}_0,t_0)\rangle = \theta(\delta_{\alpha\gamma}\delta_{\beta\delta}+\delta_{\alpha\delta}\delta_{\beta\gamma}-\frac{2}{3}\,\delta_{\alpha\beta}\delta_{\gamma\delta})\delta(\boldsymbol{r}-\boldsymbol{r}_0)\delta(t-t_0)$. Note that in real tissues, cell division and apoptosis noise could be correlated on finite time and length scales, which we ignore here for simplicity.

5.2 Diffusion in the homeostatic state

As cell division and apoptosis give rise to stress fluctuations, they lead to fluctuations in the cell flow. In order to calculate the diffusion constant of single cells in the tissue, we solve for the cell velocity fluctuations. Incompressibility requires $\partial_\alpha v_\alpha = 0$ and we assume zero volume flux at infinity. Thus, it follows $v_\alpha = 0$ and the fluid velocity field v^f_α can be expressed as $v^f_\alpha = -v^c_\alpha\phi/(1-\phi)$. We decompose all quantities in Fourier modes in space and time according to $f(\boldsymbol{q},\omega) = \int \mathrm{d}t \int \mathrm{d}\boldsymbol{r}\, e^{-i(\boldsymbol{q}\boldsymbol{r}-\omega t)} f(\boldsymbol{r},t)$. We also split the cell velocity field into longitudinal and transverse components, $v^c_\alpha = v^c_\parallel q_\alpha/q + v^c_{\perp\alpha}$. Inserting eqs. (33) and (34) into the force balance, we then obtain

$$\begin{aligned} v^c_\parallel &= \frac{1}{iq}\left[(1-i\omega\tau_\mathrm{a})\zeta(n^c_\mathrm{h})^{-1}\xi^c - (1-\omega\tau)q_\alpha q_\beta\tilde{\xi}_{\alpha\beta}/q^2\right] \Big/ \\ &\quad \left[(1-i\omega\tau_\mathrm{a})\zeta + (1-i\omega\tau)\tfrac{4}{3}\eta + \bar{\kappa}(1-i\omega\tau)(1-i\omega\tau_\mathrm{a})\right], \\ v^c_{\perp\alpha} &= \frac{i}{q}\,\frac{q_\beta\tilde{\xi}_{\alpha\beta}/q - q_\alpha q_\gamma q_\beta\tilde{\xi}_{\gamma\beta}/q^3}{\eta+\bar{\kappa}(1-i\omega\tau_\mathrm{a})}, \end{aligned} \tag{35}$$

where $\bar{\kappa} = \kappa/[(1-\phi)q^2]$. Note the additional term in the denominator for finite κ due to the permeation of the interstitial fluid through the tissue, in comparison to the one-component tissue theory. As $\bar{\kappa} \propto q^{-2}$, friction becomes increasingly important for long wavelength modes.

We make here the approximations that position and velocity fluctuations decouple, and that diffusion is slow compared to the relaxation of the velocity-velocity correlations. A more detailed calculation that does not make this assumption is given in appendix B. With these assumptions, we find that the diffusion constant is given by (see appendix B)

$$D_0 = \frac{1}{6}\int \frac{\mathrm{d}^3q}{(2\pi)^3}\,\hat{C}_{vv}(q,\omega)\bigg|_{\omega=0}. \tag{36}$$

Here, $\hat{C}_{vv}(q,\omega)$ is the velocity-velocity correlation function in the Fourier domain, defined by

$$\langle v_\alpha(\boldsymbol{q},\omega)v_\alpha(\boldsymbol{q}\,',\omega')\rangle = (2\pi)^4\delta(\boldsymbol{q}+\boldsymbol{q}\,')\delta(\omega+\omega')\hat{C}_{vv}(q,\omega). \tag{37}$$

Using (35), we can thus calculate D for an isotropic infinite tissue. The integration over q requires a cut-off at short wavelengths, *i.e.*, at high wave number q_max, which is related to a tracer particle's radius a as $q_\mathrm{max} = \pi/a$. Here, a corresponds to the average radius of a cell. The diffusion constant reads then

$$D_0 = \frac{1}{6\pi a}\left[s\left(\frac{\pi}{a}\lambda\right)\frac{\zeta^2 k_\mathrm{d}/n^c_\mathrm{h} + \frac{2}{3}\theta}{(\zeta+\frac{4}{3}\eta)^2} + s\left(\frac{\pi}{a}\bar{\lambda}\right)\frac{\theta}{\eta^2}\right], \tag{38}$$

where

$$s(x) = 1 + \frac{1}{2(1+x^2)} - \frac{3}{2}\frac{\arctan x}{x} \tag{39}$$

is a factor that accounts for the effects of permeation (see fig. 4 in appendix B for a plot), and $\lambda = \sqrt{(\zeta+\frac{4}{3}\eta)(1-\phi)/\kappa}$ and $\bar{\lambda} = \sqrt{\eta(1-\phi)/\kappa}$ are longitudinal and transverse permeation lengths, respectively. As expected, the finite permeability of the tissue, *i.e.*, finite friction between cells and fluid, leads to a slowing down of diffusion. For $\lambda, \bar{\lambda} \gg a/\pi$, however, one recovers the behavior of the one-component theory, with $s(x \gg 1) \simeq 1$. The correction due to permeation is already less than a factor of two for $\lambda, \bar{\lambda}$ in the range of the size of a cell, with $s(2\pi) \approx 0.7$.

The rescaling of the effective diffusion coefficient of single cells is a third key result of this work. In order to extract tissue mechanical and rheological properties from experimental observations of single cell diffusion, permeation must be taken into account. Additional experiments such as those suggested in the previous section for example may allow to distinguish the various contributions to the measured diffusion constant.

6 Discussion

In this work, we introduced a two-component continuum description of tissues that takes both cells together with the surrounding ECM as well as the interstitial fluid into consideration. The material turnover implied by cell division and apoptosis is thus consistently described without creation of matter *ex nihilo*. The distinction between a cell/ECM and a fluid phase allows to disentangle cell pressure and hydrostatic pressure, and it clarifies the character of the homeostatic tissue pressure introduced in a previous work [27], which taken together is a key benefit of this two-component description. As the interstitial fluid permeates the cell phase, friction between the fluid and cells leads to additional mechanical conditions that cannot be accounted for in a one-component description. It turns out that our earlier one-component description of tissues can be regarded as a friction-less limit case of the two-component theory. We showed, however, that the constitutive equations characterizing the tissue material properties that we obtained previously remain valid for the cell/ECM phase in the two-component description.

Finite friction or permeability implies that fluid flow relative to the cell/ECM phase is proportional to the gradient in hydrostatic pressure, a relation known as Darcy's law which describes fluid flow through porous media. Such pressure gradients can be imposed by boundary conditions or can be due to locally unbalanced cell division or apoptosis, *i.e.*, net material turnover. In the latter case, relative

flows arise that lead to a hydrostatic pressure buildup in the tissue.

In this study, we focussed our analysis on the tissue dynamics close to the homeostatic state in the limit of long times. Here, finite tissue permeability has two main effects. First, the tissue viscosity and the friction coefficient define a characteristic length λ to which the tissue response to mechanical stress is confined. We discussed the dynamics of a semi-permeable piston which exerts an additional force on a tissue confined in a chamber close to homeostatic state. The cells respond to additional cell/ECM phase pressure by apoptosis or cell division, respectively, which leads to relative material flows. If the characteristic length λ is smaller than the length of the chamber, this response is confined to a region of width λ close to the moving piston, beyond which the hydrostatic pressure balances the additional force exerted by the piston and the tissue remains at its homeostatic state. Second, friction between fluid and cell phases effectively slows down the diffusive motion of cells because such motion implies relative material flows due to the volume conservation constraint. Our calculation of the effective diffusion constant shows that the diffusion constant obtained in the one-component theory is rescaled by a factor that depends on the ratio between cell radius and again similar characteristic lengths $\lambda, \bar{\lambda}$ relating the friction coefficient to effective bulk and shear viscosities, respectively. The slowing down becomes negligible for $\lambda, \bar{\lambda}$ much larger than a cell radius.

Furthermore, the two-component theory allows for a coherent description of gravitational forces. For many practical purposes, the mass densities of interstitial fluid and cell/ECM phase, ϱ^f and ϱ^c, respectively, can be considered to be the same. In this case, gravity leads to a hydrostatic pressure gradient without any additional stress on the cell/ECM phase. We show, however, that for a finite density difference $\varrho^c - \varrho^f$ a treadmilling steady state can be found at long times if the characteristic permeation length λ is sufficiently small and the tissue layer sufficiently thick. This example gives an additional illustration of the tissue dynamics with permeation: the cell turnover response to gravitational forces is restricted to a region of width λ due to finite permeability. Interestingly, gravity does not impose a limit on the height of the tissue with the boundary conditions that we consider.

What are the orders of magnitude for these characteristic lengths? A general answer to this question is rather difficult, for several reasons. Both tissue permeability and tissue viscosities are not easily measured and reported values vary over several orders of magnitude. We expect tissue permeability to depend strongly on tissue type, *i.e.*, composition and architecture. Also, the bulk viscosity in the homeostatic state, or equivalently the bulk stress relaxation time, have not yet been measured. Estimating both viscosities to be in the range 10^5–$10^7\,\mathrm{Pa\,s}$ [31] and the inverse permeability to be in the range 10^{11}–$10^{14}\,\mathrm{Pa\,s\,m^{-2}}$ [32], we obtain an order of magnitude for the characteristic length, $\lambda \sim 10^{-5}$–$10^{-2}\,\mathrm{m}$, which ranges from the size of a cell to centimeters. Additional experiments such as the piston experiment suggested here are certainly needed to gain a quantitative understanding of the effects of permeation. These experiments could also clarify to which extent our assumption of the existence of a tissue equation of state as given by eqs. (11) is justified. For example, one could apply first a positive excess piston pressure $\delta P > 0$ and later a negative pressure $\delta P < 0$ and check whether the initial state can be reached with identical cell volume and homeostatic pressure.

Some further remarks are due here. We restricted our description to tissues with a minor contribution of the ECM to a joint cell/ECM phase. Our choice of constitutive equations for the cell phase which relate the isotropic stress in the cell phase to the cell number density is based on this assumption. Thus, we do not intend to describe the interstitial flows that occur in the stroma, a matrix-rich connective tissue with scattered isolated cells [26]. The general approach of multi-component continuum descriptions remains possible though; however, the constitutive equations that model the tissue mechanical properties have to be chosen appropriately. Similarly, our two-component description does not allow to describe active migration of cells in the ECM. To this end, the ECM would have to be described as a third, elastic phase to which the cells can transfer momentum in order to move as done in [33] for a three-component mixture theory. In general, the isotropic cell/ECM stress may also depend on the hydrostatic pressure, a dependence we neglected here. Moreover, we restricted our description of tissue rheology to the linear regime in order to illustrate the key aspects of tissue dynamics with permeation.

Last but not least, our theory predicts an increased interstitial fluid pressure in the center of multicellular tumor spheroids which proliferate at the rim and undergo apoptosis in the rest of the tissue. So far, measurements have been made only in vascularized solid tumors *in vivo* where the contribution of the pressure gradient between vasculature and surrounding tissue cannot be neglected. A spatially resolved measurement of the interstitial fluid pressure in multicellular spheroids would certainly provide a means to access the permeability of the tissue.

Appendix A. Cell number balance, material turnover, and mass conservation

For a discussion of the material turnover that takes mass into account, we introduce the average mass of a cell M^c and the constant fluid particle mass m^f. Note that although m^f is constant, M^c is a function that can vary with time and space. Mass conservation in the tissue is expressed by

$$\partial_t \varrho + \partial_\alpha J^\varrho_\alpha = 0, \tag{A.1}$$

where ϱ = is the total mass density of the tissue and $J^\varrho_\alpha = M^c n^c v^c_\alpha + m^f n^f v^f_\alpha$ denotes the total mass flux. Here, v^c_α and v^f_α denote the velocity fields of the cell and the fluid flow, respectively.

As discussed in the main text, the balance equation for the cell number density n^c reads

$$\partial_t n^c + \partial_\alpha (n^c v^c_\alpha) = n^c (k_\mathrm{d} - k_\mathrm{a}), \tag{A.2}$$

where k_d and k_a denote the cell division and apoptosis rate, respectively. From (A.1) and (A.2) we find a balance equation for the fluid particle density,

$$\partial_t n^f + \partial_\alpha (n^f v^f_\alpha) = -\frac{M^c}{m^f} n^c (k_\mathrm{d} - k_\mathrm{a}) - \frac{n^c}{m^f} \frac{\mathrm{d}}{\mathrm{d}t} M^c, \quad \text{(A.3)}$$

where $(\mathrm{d}/\mathrm{d}t) = \partial_t + v^c_\gamma \partial_\gamma$ is the convected time derivative with respect to the cell flow. It implies that a cell of mass M^c can be converted into M^c/m^f fluid particles and vice versa. For $\varrho^c = \varrho^f$, this corresponds to the scenario discussed in the main text. With (1) we find for the divergence of the total volume flux

$$\partial_\alpha v_\alpha = \left(1 - \frac{\varrho^c}{\varrho^f}\right) \phi \left[(k_\mathrm{d} - k_\mathrm{a}) + \frac{1}{\Omega^c} \frac{\mathrm{d}}{\mathrm{d}t} \Omega^c\right] - \frac{\phi}{\varrho^f} \frac{\mathrm{d}}{\mathrm{d}t} \varrho^c - \frac{1-\phi}{\varrho^f} (\partial_t + v^c_\alpha \partial_\alpha) \varrho^f. \quad \text{(A.4)}$$

Here, $v_\alpha = n^c \Omega^c v^c_\alpha + n^f \Omega^f v^f_\alpha$, and $\varrho^c = M^c/\Omega^c$ and $\varrho^f = m^f/\Omega^f$ are the actual cell and fluid particle mass densities, respectively.

We assume that the tissue is incompressible. Following the discussion after eq. (5), incompressibility implies that the mass densities ϱ^c and ϱ^f do not depend on pressure; for simplicity, we assume them to be constant. Equation (A.4) now becomes a constraint on the volume flux,

$$\partial_\alpha v_\alpha = \left(1 - \frac{\varrho^c}{\varrho^f}\right) \left[\phi (k_\mathrm{d} - k_\mathrm{a}) + n^c \frac{\mathrm{d}}{\mathrm{d}t} \Omega^c\right]. \quad \text{(A.5)}$$

In the case where the mass densities of cells and fluid particles are the same, $\varrho^c = \varrho^f$, the above relation reduces to

$$\partial_\alpha v_\alpha = 0. \quad \text{(A.6)}$$

Appendix B. Detailed calculation of the diffusion constant

In three dimensions, the diffusion constant is defined as

$$D = \lim_{t\to\infty} \frac{\langle \boldsymbol{r}_p^2(t)\rangle}{6t}, \quad \text{(B.1)}$$

where $\boldsymbol{r}_p$ stands for the position of a tracer particle. The position can be expressed in terms of the flow field $v_\alpha(\boldsymbol{r}, t)$ in which the particle moves, and we find

$$D = \frac{1}{3}\int_0^\infty \mathrm{d}t\, \langle v_\alpha(\boldsymbol{r}_p(t), t) v_\alpha(\boldsymbol{r}_p(0), 0)\rangle = \frac{1}{3}\int_0^\infty \mathrm{d}t \int \frac{\mathrm{d}^3 q}{(2\pi)^3} \int \frac{\mathrm{d}^3 q'}{(2\pi)^3} \times \left\langle e^{i[\boldsymbol{q}\boldsymbol{r}_p(t) + \boldsymbol{q}'\boldsymbol{r}_p(0)]} v_\alpha(\boldsymbol{q}, t) v_\alpha(\boldsymbol{q}', 0)\right\rangle. \quad \text{(B.2)}$$

Under the assumptions that particle position and velocity fluctuations decouple, the diffusion coefficient is thus given by

$$D = \frac{1}{3}\int_0^\infty \mathrm{d}t \int \frac{\mathrm{d}^3 q}{(2\pi)^3}\, e^{-q^2 D t} C_{vv}(q, t), \quad \text{(B.3)}$$

where we introduced the velocity-velocity correlation function $C_{vv}(q, t)$ defined by

$$\langle v_\alpha(\boldsymbol{q}, t) v_\alpha(\boldsymbol{q}', 0)\rangle = (2\pi)^3 \delta(\boldsymbol{q} + \boldsymbol{q}')\, C_{vv}(q, t) \quad \text{(B.4)}$$

and assumed a Gaussian distribution of particle position fluctuations,

$$\left\langle e^{i\boldsymbol{q}[\boldsymbol{r}_p(t) - \boldsymbol{r}_p(0)]}\right\rangle = \int \mathrm{d}^3 r \frac{1}{(4\pi D t)^{3/2}} e^{-\frac{r^2}{4Dt}} e^{i\boldsymbol{q}\boldsymbol{r}} = e^{-q^2 D t}. \quad \text{(B.5)}$$

Equation (B.3) allows in principle to calculate the diffusion coefficient without any further approximation. Note however that D is given only in an implicit form. In the main text, we calculated the diffusion constant under the assumption that diffusion is slow compared to the relaxation of the velocity-velocity correlations, an approximation we discuss in detail below.

Appendix B.1. Velocity-velocity correlation function

In order to calculate the velocity-velocity correlations, we solve for the velocity fluctuations in the Fourier domain as driven by the stress fluctations, see eqs. (35) in the main text. We then find the Fourier transform $\hat{C}_{vv}(q, \omega)$ according to

$$\langle v_\alpha(\boldsymbol{q}, \omega) v_\alpha(\boldsymbol{q}', \omega')\rangle = (2\pi)^4 \delta(\boldsymbol{q} + \boldsymbol{q}')\delta(\omega + \omega')\hat{C}_{vv}(q, \omega) \quad \text{(B.6)}$$

which is given by

$$\hat{C}_{vv}(q,\omega) = \frac{2}{q^2}\left[\left(\frac{\zeta}{\bar\eta + \bar\kappa}\right)^2 \frac{k_d}{n_h} \frac{1 + \omega^2\tau_a^2}{1 + \omega^2\tau_1^2 + \omega^4\tau_2^4} + \frac{2}{3}\frac{\theta}{(\bar\eta + \bar\kappa)^2} \frac{1 + \omega^2\tau^2}{1 + \omega^2\tau_1^2 + \omega^4\tau_2^4} + \frac{\theta}{(\eta + \bar\kappa)^2} \frac{1}{1 + \omega^2\tau_3^2}\right]. \quad \text{(B.7)}$$

Here, we defined the three time scales

$$\tau_1^2 = \frac{[\bar\eta\bar\tau + \bar\kappa(\tau + \tau_a)]^2}{(\bar\eta + \bar\kappa)^2} - 2\frac{\bar\kappa\tau\tau_a}{\bar\eta + \bar\kappa},$$
$$\tau_2^2 = \frac{\bar\kappa\tau\tau_a}{\bar\eta + \bar\kappa},$$
$$\tau_3 = \frac{\bar\kappa\tau_a}{\eta + \bar\kappa}, \quad \text{(B.8)}$$

using the abbreviations $\bar\kappa = \kappa/[(1-\phi)q^2]$ and $\bar\eta = \zeta + \frac{4}{3}\eta$ as in the main text, as well as the permeation-independent time

$$\bar\tau = \frac{\zeta\tau_a + \frac{4}{3}\eta\tau}{\bar\eta} = \tau\tau_a \frac{\chi + \frac{4}{3}\mu}{\chi\tau + \frac{4}{3}\mu\tau_a}. \quad \text{(B.9)}$$

In the time domain, the velocity correlations decay exponentially. The respective relaxation times are obtained from the Fourier transforms

$$\int \frac{\mathrm{d}\omega}{2\pi}\, e^{-i\omega t} \frac{1}{1 + \omega^2\tau_3^2} = \frac{1}{2}\frac{e^{-t/\tau_3}}{\tau_3} \quad \text{(B.10)}$$

and

$$\int \frac{\mathrm{d}\omega}{2\pi}\, e^{-i\omega t}\, \frac{1+\omega^2\tau_0^2}{1+\omega^2\tau_1^2+\omega^4\tau_2^4} = \frac{1}{4}\left[\frac{e^{-t/\tilde{\tau}_1}}{\tilde{\tau}_1}\times\left(1+\frac{2\tau_0^2-\tau_1^2}{\sqrt{\tau_1^4-4\tau_2^4}}\right) + \frac{e^{-t/\tilde{\tau}_2}}{\tilde{\tau}_2}\left(1-\frac{2\tau_0^2-\tau_1^2}{\sqrt{\tau_1^4-4\tau_2^4}}\right)\right]. \tag{B.11}$$

Here, two relaxation times $\tilde{\tau}_1$ and $\tilde{\tau}_2$ appear which are given by

$$\tilde{\tau}_1 = \frac{\sqrt{2}\tau_2^2}{\sqrt{\tau_1^2+\sqrt{\tau_1^4-4\tau_2^4}}}, \qquad \tilde{\tau}_2 = \frac{\sqrt{2}\tau_2^2}{\sqrt{\tau_1^2-\sqrt{\tau_1^4-4\tau_2^4}}}, \tag{B.12}$$

where $\tau_1^4 - 4\tau_2^4 \geq 0$ as can be checked with (B.8). Note that all three relaxation times τ_3, $\tilde{\tau}_1$ and $\tilde{\tau}_2$ depend on the wave number q via the q-dependent friction coefficient $\bar{\kappa}$.

Appendix B.2. Calculation of the diffusion constant in the slow diffusion limit

With the approximation that $e^{-q^2Dt} \simeq 1$ for all times t at which the velocity-velocity correlations are finite, eq. (B.3) simplifies to

$$D \simeq \frac{1}{3}\int_0^\infty \mathrm{d}t \int \frac{\mathrm{d}^3q}{(2\pi)^3}\, C_{vv}(q,t) = \frac{1}{6}\int \frac{\mathrm{d}^3q}{(2\pi)^3}\, \hat{C}_{vv}(q,\omega)\Big|_{\omega=0} \equiv D_0. \tag{B.13}$$

In this limit, the diffusion coefficient can be calculated directly from $\hat{C}_{vv}(q,\omega)$, and we obtain

$$D_0 = \frac{1}{12\pi^2}\int_0^{q_{\max}} \mathrm{d}q\, \hat{C}_{vv}(q,\omega)\Big|_{\omega=0} = \frac{1}{6\pi a}\left\{ s\left(\frac{\pi}{a}\lambda\right)\left[\left(\frac{\zeta}{\bar{\eta}}\right)^2 \frac{k_\mathrm{d}}{n_\mathrm{h}^c} + \frac{2}{3}\frac{\theta}{\bar{\eta}^2}\right] + s\left(\frac{\pi}{a}\bar{\lambda}\right)\frac{\theta}{\eta^2}\right\}, \tag{B.14}$$

which is the result presented in the main text. Here, $q_{\max} = \pi/a$ is the high wave number cut-off, where a is a cell radius, and we recall the definitions $\lambda^2 = (1-\phi)\bar{\eta}/\kappa$, $\bar{\lambda}^2 = (1-\phi)\eta/\kappa$ and

$$s(x) = 1 + \frac{1}{2(1+x^2)} - \frac{3}{2}\frac{\arctan x}{x}$$

as introduced in the main text (see fig. 4 for a plot of $s(x)$).

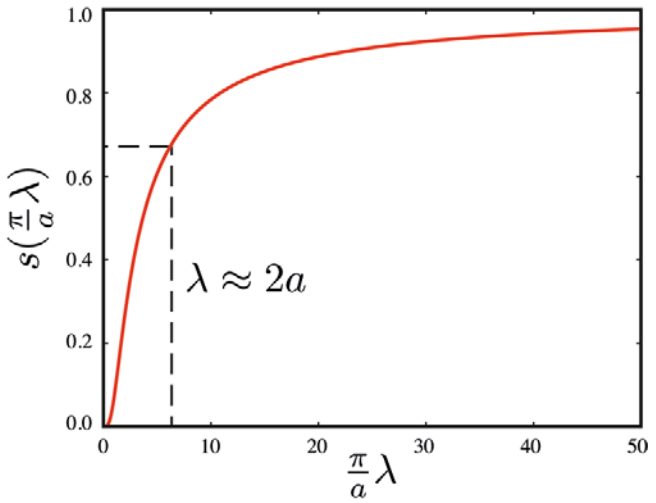

Fig. 4. Scaling of the diffusion coefficient due to finite friction. Note that the scaling factor $s(\frac{\pi}{a}\lambda)$ is already close to one for $\lambda \gtrsim 2a$, *i.e.*, only very low permeability (high friction) of the tissue would seriously dampen cellular diffusion.

Appendix B.3. Validity of the slow diffusion result

The approximation $e^{-q^2Dt} \simeq 1$, or $D \simeq D_0$, holds for all q and on all relevant time scales if

$$q_{\max}^2 D_0 \tau_{\max} \ll 1, \tag{B.15}$$

where $\tau_{\max}$ is the longest relaxation time of the velocity-velocity correlations.

Before we calculate $q_{\max}^2 D_0 \tau_{\max}$, we can already get an estimate for $q_{\max}^2 D$. Using the estimations

$$k_\mathrm{d} = \mathcal{O}(\tau_a^{-1}), \quad n_\mathrm{h}^{c\,-1} = \mathcal{O}(\pi a^3), \quad \theta = \mathcal{O}(\eta^2 k_\mathrm{d}/n_\mathrm{h}^c),$$

we find

$$q_{\max}^2 D_0 \approx \frac{1}{\tau_a}\left[\left(\frac{\chi\tau}{\chi\tau+\mu\tau_a}\right)^2 + \left(\frac{\mu\tau_a}{\chi\tau+\mu\tau_a}\right)^2\right] s\left(\frac{\pi}{a}\lambda\right) + \frac{1}{\tau_a} s\left(\frac{\pi}{a}\bar{\lambda}\right) \lesssim \frac{2}{\tau_a} s\left(\frac{\pi}{a}\lambda\right). \tag{B.16}$$

In order to check the validity of assumption (B.15), we need to compare $\tau_{\max}$ to τ_a and check the role of $s(\frac{\pi}{a}\lambda)$. The longest relaxation time in the problem is given by $\tilde{\tau}_2$. We introduce $\tau_{1'}^2 \equiv \tau_1^2 + 2\tau_2^2$ such that we can express $\tilde{\tau}_2$ as

$$\tilde{\tau}_2 = \tau_{1'} \frac{\sqrt{2}\left(\frac{\tau_2}{\tau_{1'}}\right)^2}{\sqrt{1-2\left(\frac{\tau_2}{\tau_{1'}}\right)^2 - \sqrt{1-4\left(\frac{\tau_2}{\tau_{1'}}\right)^2}}} = \tau_{1'}\left[1-\left(\frac{\tau_2}{\tau_{1'}}\right)^2 - \left(\frac{\tau_2}{\tau_{1'}}\right)^4 + \ldots\right], \tag{B.17}$$

in order to get an estimate for $\tau_{\max} = \tilde{\tau}_2$. Because

$$\left(\frac{\tau_2}{\tau_{1'}}\right)^2 = \frac{(\bar{\eta}+\bar{\kappa})\bar{\kappa}\tau\tau_a}{[\bar{\eta}\bar{\tau}+\bar{\kappa}(\tau+\tau_a)]^2} = \frac{\tau\tau_a[1+(\lambda q)^2]}{[(\lambda q)^2\bar{\tau}+\tau+\tau_a]^2} < 1 \tag{B.18}$$

(even $\ll 1$ for many cases that can be made precise) —and as an upper bound— we therefore consider as slowest relaxation time $\tau_{\max} = \tilde{\tau}_2 \simeq \tau_{1'}$, or directly

$$\tau_{\max} = \tau_{1'}(q_{\max}) = \left.\frac{\bar{\eta}\bar{\tau}+\bar{\kappa}(\tau+\tau_a)}{\bar{\eta}+\bar{\kappa}}\right|_{q_{\max}} = \frac{(\lambda q_{\max})^2\bar{\tau}+\tau+\tau_a}{1+(\lambda q_{\max})^2}\,. \tag{B.19}$$

Note once more that the dependence on q is due to the finite permeability of the tissue; here, we consider the slowest relaxation time for the cut-off wave number $q_{\max}$. The value of $\bar{\tau}$, which turns out to be the relaxation time in the limit of vanishing friction, depends on the ratio of the bulk elastic modulus χ to the shear elastic modulus μ. In the incompressible limit, *i.e.*, for $\chi \gg \mu$, we find $\bar{\tau} \approx \tau_a$. If $\chi \approx \mu$, on the other hand, we obtain $\bar{\tau} \approx 2\tau\tau_a/(\tau+\tau_a)$.

We now discuss approximation (B.15) for various strengths of friction, *i.e.*, different ratios λ/a:

a) friction dominated regime, $\lambda \ll a/\pi$:
Independent of χ/μ, the longest relaxation time is given by $\tau_{\max} = \tau + \tau_a$, and we obtain

$$q_{\max}^2 D_0 \tau_{\max} \approx 2\frac{\tau+\tau_a}{\tau_a} s\left(\frac{\pi}{a}\lambda\right). \tag{B.20}$$

Because $s(x)$ vanishes as x^4, the slow diffusion approximation (B.15) is justified, even for $\tau \gg \tau_a$; in fact, no diffusion is taking place at all.

b) intermediate regime, $\lambda \approx a/\pi$:
In this regime, one can still argue that $\tau_{\max} \approx \tau + \tau_a$, *i.e.*, both relaxation times are present for both $\chi \gg \mu$ and $\chi \approx \mu$. Thus, we find

$$q_{\max}^2 D_0 \tau_{\max} \approx 2\frac{\tau+\tau_a}{\tau_a} s(1) \lesssim \frac{1}{5}\frac{\tau+\tau_a}{\tau_a}\,. \tag{B.21}$$

For $\tau \lesssim \tau_a$, this seems to be sufficiently smaller than one, and one may say that the approximation $D \simeq D_0$ is reasonable. For $\tau \gg \tau_a$, however, this is no longer the case, and the calculation of D needs to be refined.

c) negligible friction, $\lambda \gg a/\pi$:
In this limit, the longest relaxation time depends on χ/μ: For an incompressible tissue ($\chi \gg \mu$), the relaxation time is given by $\tau_{\max} = \tau_a$, and we find

$$q_{\max}^2 D_0 \tau_{\max} = \mathcal{O}(1), \qquad \chi \gg \mu; \tag{B.22}$$

for $\chi \approx \mu$, we have $\tau_{\max} \approx 2\tau\tau_a/(\tau+\tau_a)$, such that

$$q_{\max}^2 D_0 \tau_{\max} \approx \frac{4\tau}{\tau+\tau_a}, \qquad \chi \gg \mu. \tag{B.23}$$

Thus, in the regime of negligible friction, the slow diffusion approximation does not hold in general, and the result for the diffusion coefficient needs to be checked. For a tissue where $\chi \approx \mu$ and $\tau \ll \tau_a$, however, assumption (B.15) turns out to hold and $D \simeq D_0$.

Note that in all possible scenarios the slow diffusion assumption is never grossly violated, *i.e.*, the velocity-velocity correlations never decay much more slowly than the particles diffuse away. Therefore, we would not expect corrections to be strong. In the limit of vanishing friction, this argument can be made more precise.

Appendix B.4. Corrections due to the finite relaxation time in the limit of vanishing friction

Starting from expression (B.3) for the diffusion coefficient, we can carry out the integral over time without any further approximation once we have $C_{vv}(q,t)$, which we find from (B.7) with the transformations (B.10) and (B.11). Thus, we get

$$D = \frac{1}{6\pi^2}\int_0^{\pi/a} \mathrm{d}q\, f(q), \tag{B.24}$$

where $f(q) = q^2\int_0^\infty \mathrm{d}t\, e^{-q^2Dt} C_{vv}(q,t)$ is given by

$$\begin{aligned} f(q) = {} & \frac{1}{2}\left(\frac{\zeta}{\bar{\eta}}\right)^2 \frac{k_{\mathrm{d}}}{n_{\mathrm{h}}^c}\frac{(\lambda q)^4}{[1+(\lambda q)^2]^2}\left[\frac{1}{1+q^2D\tilde{\tau}_1}\left(1+\frac{2\tau_a^2-\tau_1^2}{\sqrt{\tau_1^4-4\tau_2^4}}\right)\right. \\ & \left.+\frac{1}{1+q^2D\tilde{\tau}_2}\left(1-\frac{2\tau_a^2-\tau_1^2}{\sqrt{\tau_1^4-4\tau_2^4}}\right)\right] \\ & +\frac{1}{3}\frac{\theta}{\bar{\eta}^2}\frac{(\lambda q)^4}{[1+(\lambda q)^2]^2}\left[\frac{1}{1+q^2D\tilde{\tau}_1}\left(1+\frac{2\tau^2-\tau_1^2}{\sqrt{\tau_1^4-4\tau_2^4}}\right)\right. \\ & \left.+\frac{1}{1+q^2D\tilde{\tau}_2}\left(1-\frac{2\tau^2-\tau_1^2}{\sqrt{\tau_1^4-4\tau_2^4}}\right)\right] \\ & +\frac{\theta}{\eta^2}\frac{(\bar{\lambda}q)^4}{[1+(\bar{\lambda}q)^2]^2}\frac{1}{1+q^2D\tau_3}\,. \end{aligned} \tag{B.25}$$

Different limits can be recovered from the above expression. In the limit of high friction, $f(q)$ vanishes as $(\lambda q)^4$, where $q \le q_{\max} = \pi/a$. This is in line with the result obtained for D above, eq. (B.14), where $s(x) \propto x^4$ for $x \ll 1$.

Let us discuss the limit of vanishing friction, *i.e.*, small κ. Strictly speaking, friction cannot be neglected for any finite κ as soon as $q < 1/\lambda$. We take this into account by integrating $f(q)$ from a long wavelength, low wave number cut-off $q_c = \lambda^{-1}$ up to the short wavelength, high wave number cut-off $q_{\max} = \pi/a$, which introduces corrections of order $\frac{\pi}{a}\lambda$ due to permeation.

Thus, for $\lambda q \gg 1$, the relaxation times $\tilde{\tau}_1$ and τ_3 vanish, which corresponds to δ-correlated contributions to the

velocity fluctuations in the time domain. Only the relaxation time $\tilde{\tau}_2$ remains finite, with $\tilde{\tau}_2 \to \bar{\tau}$, and we write

$$D = \frac{1}{6\pi^2} \int_{1/\lambda}^{\pi/a} \mathrm{d}q \left(A + B \frac{1}{1 + q^2 D\bar{\tau}} \right). \qquad \text{(B.26)}$$

Here, A and B are constants given by

$$A = \left(\frac{\zeta}{\bar{\eta}}\right)^2 \frac{k_\mathrm{d}}{n_\mathrm{h}^c} \left(\frac{\tau_a}{\bar{\tau}}\right)^2 + \frac{2}{3}\frac{\theta}{\bar{\eta}^2}\left(\frac{\tau}{\bar{\tau}}\right)^2 + \frac{\theta}{\eta^2},$$
$$B = \left(\frac{\zeta}{\bar{\eta}}\right)^2 \frac{k_\mathrm{d}}{n_\mathrm{h}^c} \frac{\bar{\tau}^2 - \tau_a^2}{\bar{\tau}^2} + \frac{2}{3}\frac{\theta}{\bar{\eta}^2}\frac{\bar{\tau}^2 - \tau^2}{\bar{\tau}^2}. \qquad \text{(B.27)}$$

We find that the diffusion constant is thus implicitly defined by

$$D = \frac{1}{6\pi a}\left(A + B \frac{\arctan\left(\frac{\pi}{a}\sqrt{D\bar{\tau}}\right)}{\frac{\pi}{a}\sqrt{D\bar{\tau}}} \right) + \mathcal{O}\left(\frac{a}{\pi\lambda}\right). \qquad \text{(B.28)}$$

For $\frac{\pi}{a}\sqrt{D\bar{\tau}} \ll 1$, we recover the result obtained in the limit of slow diffusion, zero friction,

$$D \simeq \frac{1}{6\pi a}(A + B)$$
$$= \frac{1}{6\pi a}\left[\left(\frac{\zeta}{\bar{\eta}}\right)^2 \frac{k_\mathrm{d}}{n_\mathrm{h}^c} + \frac{2}{3}\frac{\theta}{\bar{\eta}^2} + \frac{\theta}{\eta^2} \right]. \qquad \text{(B.29)}$$

We know that $\frac{\pi}{a}\sqrt{D\bar{\tau}} = \mathcal{O}(1)$ at most. For $\frac{\pi}{a}\sqrt{D\bar{\tau}} = 3$, the arctan-term in eq. (B.28) is of order 0.4, which is significantly different from 1. In this case, we cannot neglect the corrections due to the finite relaxation time. Still in the limit of negligible friction, we find

$$D \simeq D_0 - \left(1 - \frac{\arctan\left(\frac{\pi}{a}\sqrt{D\bar{\tau}}\right)}{\frac{\pi}{a}\sqrt{D\bar{\tau}}}\right)\frac{B}{6\pi a}. \qquad \text{(B.30)}$$

Note that for $\bar{\tau} \simeq \tau \simeq \tau_a$ these corrections are supposedly small; for $\tau \gg \tau_a$, however, the diffusion constant has to be determined graphically or numerically from eq. (B.28) for given values of A and B.

References

1. L. Wolpert, *Principles of Development*, 2nd edition (Oxford University Press, Oxford, 2005).
2. C. Manjón, E. Sánchez-Herrero, M. Suzanne, Nat. Cell Biol. **9**, 57 (2007).
3. R.A. Weinberg, *The Biology of Cancer* (Garland Science, New York, 2006).
4. B. Alberts *et al.*, *Essential Cell Biology*, 3rd edition (Garland Science, New York, 2009).
5. P.M. Domingos, H. Steller, Curr. Opin. Genet. Dev. **17**, 294 (2007).
6. J.M. Kinchen, Apoptosis **15**, 998 (2010).
7. M.R. Buchakjian, S. Kornbluth, Nat. Rev. Mol. Cell Biol. **11**, 715 (2010).
8. T. Mammoto, D.E. Ingber, Development **137**, 1407 (2010).
9. A.J. Maniotis, C.S. Chen, D.E. Ingber, Proc. Natl. Acad. Sci. U.S.A. **94**, 849 (1997).
10. M. Théry, A. Jiménez-Dalmaroni, V. Racine, M. Bornens, F. Jülicher, Nature **447**, 493 (2007).
11. J. Fink, N. Carpi, T. Betz, A. Betard, M. Chebah, A. Azioune, M. Bornens, C. Sykes, L. Fetler, D. Cuvelier *et al.*, Nat. Cell Biol. **13**, 771 (2011).
12. D. Drasdo, S. Höhme, Phys. Biol. **2**, 133 (2005).
13. F. Montel, M. Delarue, J. Elgeti, L. Malaquin, M. Basan, T. Risler, B. Cabane, D. Vignjevic, J. Prost, G. Cappello *et al.*, Phys. Rev. Lett. **107**, 188102 (2011).
14. R. Farhadifar, J.C. Röper, B. Aigouy, S. Eaton, F. Jülicher, Curr. Biol. **17**, 2095 (2007).
15. L. Hufnagel, A.A. Teleman, H. Rouault, S.M. Cohen, B.I. Shraiman, Proc. Natl. Acad. Sci. U.S.A. **104**, 3835 (2007).
16. R. Araujo, D. McElwain, Eur. J. Appl. Math. **15**, 365 (2004).
17. T. Bittig, O. Wartlick, A. Kicheva, M. González-Gaitán, F. Jülicher, New J. Phys. **10**, 063001 (2008).
18. H. Byrne, D. Drasdo, J. Math. Biol. **58**, 657 (2009).
19. J. Ranft, M. Basan, J. Elgeti, J.F. Joanny, J. Prost, F. Jülicher, Proc. Natl. Acad. Sci. U.S.A. **107**, 20863 (2010).
20. T. Roose, P.A. Netti, L.L. Munn, Y. Boucher, R.K. Jain, Microvasc. Res. **66**, 204 (2003).
21. H.M. Byrne, L. Preziosi, Math. Med. Biol. **20**, 341 (2003).
22. L. Preziosi, A. Tosin, J. Math. Biol. **58**, 625 (2009).
23. C. Frantz, K.M. Stewart, V.M. Weaver, J. Cell Sci. **123**, 4195 (2010).
24. R.O. Hynes, Science **326**, 1216 (2009).
25. T. Rozario, D.W. DeSimone, Dev. Biol. **341**, 126 (2010).
26. M.A. Swartz, M.E. Fleury, Annu. Rev. Biomed. Eng. **9**, 229 (2007).
27. M. Basan, T. Risler, J.F. Joanny, X. Sastre-Garau, J. Prost, HFSP J. **3**, 265 (2009).
28. H.P.G. Darcy, *Les Fontaines Publiques de la Ville de Dijon* (Dalmont, Paris, 1856).
29. S. Whithaker, Transport Porous Med. **1**, 3 (1986).
30. J. Mombach, J.A. Glazier, Phys. Rev. Lett. **76**, 3032 (1996).
31. G. Forgacs, R.A. Foty, Y. Shafrir, M.S. Steinberg, Biophys. J. **74**, 2227 (1998).
32. P.A. Netti, D.A. Berk, M.A. Swartz, A.J. Grodzinsky, R.K. Jain, Cancer Res. **60**, 2497 (2000).
33. D. Ambrosi, L. Preziosi, Biomech. Model. Mechanobiol. **8**, 397 (2009).