Mechanics of the cell

In this lecture, I will describe some mechanical properties of cells. They are dominated by a network of filaments. There are 3 types of filaments actin, microtubules and intermediate filaments. The most important type of filament ~~determining~~ determining the mechanical properties of cells is actin. It forms a gel. In the gel, actin interacts with many proteins. Of particular importance is the molecular motor myosin and crosslinking proteins. The actin gel is called the cytoskeleton
+ Actin Polymerization Inhibitors

In the first part of the lecture, I will introduce the acto-myosin cytoskeleton. I will then illustrate the mechanical properties of cells by discussing a fundamental cellular process: cytokinesis.

I. Cytoskeleton

1. Actin filaments

- Structure: do two protofilaments forming a helix. Polar filaments
- Treadmilling: Actin polymerizes at the + end and depolymerizes at the - end

Polymerization rate k_+ $v_p = k_+ \delta \sim 1 \mu m/s$ k_+ is proportional to actin monomer concentration G actin

down to 1 per/min.

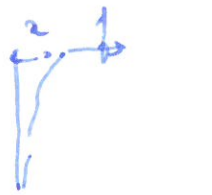
Actin depolymerization rate had

- Actin is a semi-flexible polymer.

$R^{-1} = \frac{d\vec{t}}{ds}$

Bending energy $F = \frac{1}{2} k_B T \, l_p \int_0^L \frac{ds}{R^2}$ Discussed earlier

$l_p \sim 10\,\mu m$ typically for actin $L \ll l_p$. It is almost a rod

Bending: 

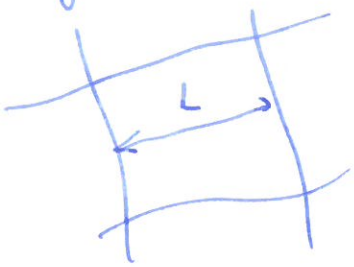
$f = k x \qquad k = \frac{k_B T}{L^2} \mathcal{J}\left(\frac{L}{l_p}\right) \sim k_B T \frac{l_p}{L^3} \sim l_p$

$x = R(l) - R(0)$

Stretching ~~~~~ Thermal fluctuations. Pull an item $k \sim l_p^2 \sim \frac{k_B T l_p^2}{L^4}$ (calculate)

Compression Buckling at a force $F \sim \frac{k T l_p}{L^2}$

2. Actin gels



Shear modulus $\mu = \frac{k_B T}{L^3} \mathcal{J}\left(\frac{l_p}{L}\right)$

If dominated by bending $\mu \sim l_p \sim \frac{k_B T \, l_p}{L^4}$

If dominated by stretching $\mu \sim k_B T \frac{l_p^2}{L^5}$

Rq Role of constants suppose 1 μ mesh

Topological constraints (D. MORSE)
Non linear elasticity and the role of Buckles (M. Lang
Soft mode and hyperelasticity (Mackintosh et al)

At long time an actin gel is viscoelastic and flows like a liquid $\tau \sim 10 - 100$ s

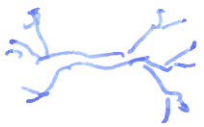
Order of magnitude: Elasticity dominated by bending

$l_p = 10\,\mu m = 10^4\,nm \qquad k_B T = 4 \cdot 10^{-21} J \qquad L = 100\,nm \qquad G \sim 100 - 1000\,Pa$

This gives the elasticity of the cell. The viscosity at long time is $\eta = \mu\tau \sim 10^5$ Pa.s

3. Molecular motors

- Structure
- Consume ATP - Energy release per ATP hydrolysis $\Delta\mu \simeq 25 k_B T$ $\quad ATP \rightarrow ADP + P$ excess ATP
- Processive and non-processive motors : processive motors make many steps before detaching from filaments example myosin V

Non processive motors give an kick and then detatch. They must work by large enough clusters  called minifilament. The example is myosin 2 found in muscle (300 motors in a "thick filament"). In the cytoskeleton the minifilament have 1-2 myosin motors (enough to remain long enough)

- Theory of molecular motors

Eg In an actin gel a minifilament grabs 2 actin filaments and pulls on them

It exerts internal stresses in the actin gel

4. Fluctuation dissipation theorem.

In vitro experiments can be made in vitro with the actin myosin cytoskeleton. (C. Schmidt). Microrheology experiments study the response of a bead immersed in the gel  . One can perform two types of experiments

- Either one measures the instantaneous position $x(t)$ of the bead and its fluctuations

One can deduce the power spectrum $\tilde{C}(\omega) = \int e^{i\omega t} \langle x(t) x(0) \rangle dt$

- One can also measure (with an optical trap) the response to an external force $\tilde{f}(\omega)$. In a linear regime $\langle \tilde{x}(\omega) \rangle = \tilde{\chi}(\omega) \tilde{f}(\omega)$. The response function is a complex number $\tilde{\chi}(\omega) = \chi' + i\chi''(\omega)$. The imaginary part $\chi''(\omega)$ measures the dissipation in the system.

If the system is at thermal equilibrium the fluctuation-dissipation theorem states that $\frac{2\chi''(\omega) k_B T}{\omega} = \tilde{C}(\omega)$

- Two examples: Cytoskeleton in vitro
+ Red blood cell

They are both non-equilibrium systems

- Spectrin network  elastically attached unit active

5. Active gels

In order to study the macroscopic properties of cells, we must build up a hydrodynamic theory valid at long time scales and at large time scales (larger than the mesh size of the actin gel). Close enough to equilibrium, this can be done in a systematic way following Onsager. The main point is to include in the theory molecular motors. We only keep one feature of molecular motors: they consume energy and therefore drive the system out of

The theory uses only symmetry arguments and considers in particular the time reversal symmetry

equilibrium. The force associated to energy consumption is $\Delta\mu$ the energy provided by hydrolysis of 1 ATP molecule. The flux is the number of ATP molecules consumed per unit time Γ. 1 component theory.

We also want to take into account the orientation of actin filaments (remember that actin is polar). We introduce the polarisation $\vec{p} = \langle \vec{n} \rangle$ where $\vec{n}$ is the unit vector along each actin filament and the average is a local average.

The main output of the theory is that in addition to the contributions to the stress of polar liquids, there is an additional contribution (active) $\sigma^a_{ij} = +\zeta \Delta\mu\, p_i p_j$. Experimentally the stress is contractile and ζ is ~~positive~~ negative.. It is not a pressure but a normal stress difference that contracts the actin gel along the polarization $\vec{p}$. If the actin gel is considered as incompressible it dilates the gel in the direction perpendicular to $\vec{p}$

At long times, longer than the visco-elastic relaxation time τ, the deviatoric stress is $\sigma_{ij} = -P\delta_{ij} + \zeta\Delta\mu\, p_i p_j + 2\eta v_{ij}$ $v_{ij} = \frac{1}{2}(\partial_i v_j + \partial_j v_i)$

The theory also provides 2 equations for $\vec{p}$ and Γ the ATP consumption rate.

6. Active matter

The hydrodynamic theory of active gels is based on 4 hypotheses: the system is fluid, it has an orientation (polar or nematic), it consumes energy locally (this is the definition of active systems) and the theory is linear (can be improved). The physicist's hope is that there is universality in all systems with such properties. Some features seem to be indeed "universal"

- Wave propagation
- Giant fluctuations
- Instability of non-flowing steady states

A list of active systems is shown on the slide

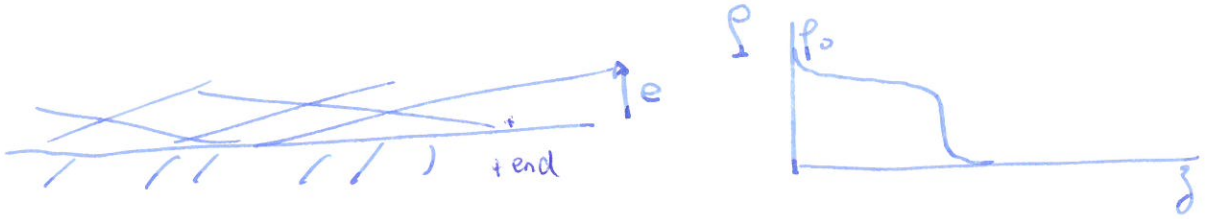
- They are of very different natures and some have nothing to do with biology
- They have very different length scales.

There are several classes of behaviors: dry or wet
conservation or not of momentum
polar or nematic

II. Cortical actin

In most cells actin forms a thin layer (a fraction of µm) in contact with the cell membrane. Actin turns over in this layer

over 300 or so. It is usually assumed that the filaments are quasi parallel to the surface. But randomly oriented in the tangent plane



Take polymerization of actin filaments occurs at the membrane at a velocity v_p (the actin flux of actin in the layer is $\rho_0 v_p$). This layer must be described by the active gel theory.

Actin polymerization proteins

Actin conservation $\frac{\partial \rho}{\partial t} + \frac{\partial}{\partial \zeta} \rho v = -k_d \rho$ where ρ is the actin density, v the velocity and k_d the depolymerization rate.

depolymerization of ρ

An external approximation is to assume that $\rho = \rho_0$ is constant. In a steady state $\frac{\partial v}{\partial t} = -k_d \quad v = v_p - k_d \zeta$. The layer is stationnary but there is an actin velocity from the membrane to the edge. The position of the edge $\zeta = e$ is such that $v = 0 \quad e = \frac{v_p}{k_d}$ $v_p \sim 1\,\mu m/min$ $k_d \sim 1\,min^{-1}$ gives the right order of magnitude. Relate to a non equilibrium wetting problem [illegible]

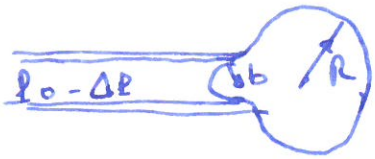
In the plane of the layer (x, y), the only contribution to the stress is the active stress $\sigma^a_{ij} = +\zeta \Delta\mu \, p_i p_j$. If the filaments are randomly oriented $\langle p_i p_j \rangle = \frac{1}{2} \delta_{ij} \qquad \sigma^a_{ij} = -\frac{\zeta \Delta\mu}{2} \delta_{ij} = \sigma^a \delta_{ij}$

The tension in the layer is the integral of the stress (tensile stress) over the thickness $\gamma = -\frac{e \Sigma \Delta\mu}{2}$

The tension is positive so that the cortical layer is under tension. Typically $\gamma = 10^{-3}$ N/m

This is much larger than the membrane tension $\gamma_m = 10^{-5}$ N/m. In many cells the cortex tension dominates mechanical properties

Measurement



P_0 $\Delta P_c = \frac{2\gamma}{b} - \frac{2\gamma}{R}$

If $\Delta\ell > \Delta\ell_c$ the cell is swollen in the pipette

III Cytokinesis

- Shape $\Sigma_0 \Delta\mu = \Sigma_0 \Delta\mu_e + \Sigma_1 \Delta\mu_i \, e^{-\frac{\Delta^2}{2w^2}}$
- Orientation - flow coupling
- Origin of myosin enhancement

Quiescent cytoplasm $V = \frac{4}{3}\pi R_0^3$ total volume

$r = R \sin\theta$

$A = 2\pi(1+\cos\theta) R^2 \times 2$

$V = \frac{4\pi R^3}{3}(1+\cos\theta) + \frac{\pi r^2 \cos\theta R}{3}$

$= \frac{4}{3}\pi R^3 (1+\cos\theta) + \frac{\pi R^3}{3} \sin^2\theta \cos\theta$

$W = T\, 4\pi R^2 (1+\cos\theta) + \lambda\, 2\pi R \sin\theta$. R must be eliminated

by volume conservation

Mechanics and growth of tissues

In these lectures, I will discuss tissue growth and the effect of mechanical stresses on tissue growth. Mechanical effects play an essential role at least in 2 situations: tumor growth (tumors are always confined in space), and development of organisms.

I Macroscopic or hydrodynamic description of tissues.

We want to describe a tissue as a (living material), which we describe on a macroscopic scale (at length scale larger than the size of the cell) and over long times.

The tissue contains cells but also the extra-cellular fluid. We make an effective 1 fluid description, that can be justified quantitatively. There is a velocity field $\vec{v}(\vec{r})$ of the cells.

Compared to classical materials and to the elastic or hydrodynamic theory, the new feature is that a tissue grows by cell division and shrinks due to cell death called apoptosis. The question is

to define a constitutive equation relating the stress σ or p to the deformation or shear rate tensors. The tissue can have a behaviour that is elastic (linear or not), viscous, visco-elastic (possibly non-newtonian) or plastic

1. Cell division and apoptosis

We describe cell division (and cell growth) by a division rate k_d, which depends on the local environment of the cell i.e. the mechanical and biochemical environment. The division rate depends on the concentrations of nutrients, growth factors, oxygen and on the local cell density ρ. If there is a well-defined equation of state, the density is equivalent to the pressure p. Cell death occurs by apoptosis (programmed cell death) at a rate k_a. The growth rate is $k = k_d - k_a$

Cell number conservation reads $\frac{\partial \rho}{\partial t} + \vec{\nabla}(\rho \vec{v}) = [k_d - k_c(\rho)]\,\rho$

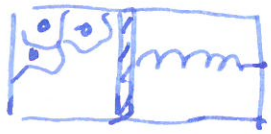
Rq: Cell division and cell death can be considered as stochastic processes. One should then add a noise $\xi(t)$ in the conservation

equation. At long times (compared to the cell division time $1/h_d$) $\xi(t)$ can be considered as a white noise and population dynamics theory

$\langle \xi(t)_{,p} \xi(t')_{,p'} \rangle = \rho (h_d + h_a) \delta(t-t')$. This is multiplicative noise ~~can be considered as a white noise~~

2. Homeostatic pressure

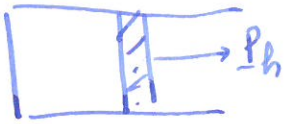
There are several ways to define pressure in a tissue. The hydrostatic pressure is the pressure of the fluid in-between (interstitial fluid) the cells. We consider here the cell pressure defined by the following thought experiment.



where all the walls are permeable to water and all necessary element: nutrients... not cells. There is some analogy with an "osmotic pressure" of the cells.

Many experiments show that the division rate decreases with the cell density or the cell pressure P. The apoptosis rate increases with pressure. There exists a homeostatic state and homeostatic pressure and density P_h such that $h(P_h) = h_d(P_h) - h_a(P_h) = 0$. At this pressure the tissue is on average in a stationary state in the sense that the average number of cells is constant

3- Compressibility of a tissue



One can change the volume without changing pressure

Cells die or divide to compensate for the space. The compressibility $\chi = -\frac{1}{V}\frac{\partial V}{\partial P}$ is then infinite

Rq Calculate the fluctuation $\langle \delta L^2(t) \rangle$ of the piston's position

4- Tissue invasion

By putting into contact 2 tissues with a different homeostatic pressure the tissue with the higher homeostatic pressure invades the other one, independently of the growth kinetics.

Slow thought experiment + movies.

II Tissue fluidization by cell division.

1. Force dipole associated to a dividing cell

When a cell divides a die, it exerts forces on the neighboring cells in a tissue. The sum of these forces vanishes. By making a multipole expansion at lowest order, one can consider that the cell exerts a force dipole

$q^{\alpha\beta} = \int_V d^3 \; -\vec{T} \cdots \vec{d} \cdots +\vec{T}$.

Cells numbered by an index i if they divide

We introduce the force dipole density $\Phi^{\alpha\beta} = \sum_i q_i^{\alpha\beta} \, \delta(\vec{r} - \vec{r}_i)$

The sum is over all dividing cells

2. Force balance in a tissue

At short times, a tissue has an elastic response due to the elasticity of the cells. There is therefore an elastic stress $\sigma^{\alpha\beta}_{el}$ in the tissue. For every dividing cell there is a force dipole $\int_i \left[-\delta(\vec{r}-\vec{r}_i) + \delta[\vec{r}-(\vec{r}_i+\vec{d}_i)] \right]$

The force balance in the tissue reads

$$\partial_\beta \sigma^{\alpha\beta}_{el} + \sum_i \int_i^\alpha \left[-\delta(\vec{r}-\vec{r}_i) + \delta[\vec{r}-(\vec{r}_i+\vec{d}_i)] \right] = 0$$

We expand up to 1st order in d_i the second term

$$\int_i^\alpha \left[\delta[\vec{r}-(\vec{r}_i+\vec{d}_i)] - \delta(\vec{r}-\vec{r}_i) \right] = -\partial_\beta \left[d_{i\beta} \int_i^\alpha \delta(\vec{r}-\vec{r}_i) \right]$$

The force balance can then be written as $\partial_\beta (\sigma^{\alpha\beta}_{el} - Q_{\alpha\beta}) = 0$ where $Q_{\alpha\beta}$ is the force dipole density due to cell division and cell death. Everything happens as if there were in the tissue a total stress $\sigma^{\alpha\beta} = \sigma^{\alpha\beta}_{el} + \sigma^{\alpha\beta}_{int}$ where the internal stress $\sigma^{\alpha\beta}_{int} = -Q_{\alpha\beta}$ is due to cell division and cell death

In the following we decompose the stress into a longitudinal and a transverse component $\sigma_{\alpha\beta} = \sigma \delta_{\alpha\beta} + \tilde{\sigma}_{\alpha\beta}$ where $\tilde{\sigma}_{\alpha\alpha} = 0$

3. Isotropic stress

$\sigma = \sigma^{el} + \sigma^{int}$ is the isotropic part of the stress. Only the derivative with time of σ^{int} is meaningful as σ^{int} is due to cell division and cell

$\frac{d\bar{\sigma}_{ab}}{dt} = K \frac{du}{dt}$ where K is the compressional modulus and $u = u_{rr}$

is the trace of the deformation $\frac{du}{dt} = v = v_{rr} = \vec{\nabla}\cdot\vec{v}$ is the trace of the velocity

gradient $v_{\alpha\beta} = \frac{1}{2}(\partial_\alpha v_\beta + \partial_\beta v_\alpha)$

We write phenomenologically the internal stress as a sum of a term due to cell division and one a term due to cell death $\frac{d\bar{\sigma}_{in}}{dt} = -\rho(k_d q_d + k_a q_a)$ where ρ is the cell density. In the homeostatic state $q_d + q_a = 0$ because on average the state of the tissue is the same after 1 division and we postulate $q_d = -q_a = q$

We assume that this remains true close to the homeostatic state and write

$$\frac{d\bar{\sigma}_{in}}{dt} = -\rho q (k_d - k_a)$$

In the vicinity of the homeostatic state we expand $k = k_d - k_a = \kappa(\sigma + P_h)$.

For stability reasons $\kappa \geq 0$.

Summing everything $\frac{d\bar{\sigma}}{dt} = K v_{rr} - \rho q \kappa (\sigma + P_h)$ and setting $\bar{\sigma} = \sigma + P_h$ the stress difference to the homeostatic state $\frac{d\bar{\sigma}}{dt} + \frac{\bar{\sigma}}{\tau} = K v_{rr}$ where the longitudinal relaxation time is $\tau = 1/(\rho q \kappa)$. There is a relaxation time τ and the tissue behaves as a Maxwell visco-elastic liquid with a "bulk"

viscosity $\zeta = K\tau$ K being the tissue compressibility

Rq - In a usual viscoelastic liquid the pressure does not relax only the traceless part of the stress $\tilde{\sigma}_{\alpha\beta}$.

- If there is no flow $v_{rr}=0$. $\bar{\sigma}$ relaxes to zero exponentially over a time τ. The total stress relaxes toward the homeostatic stress $\sigma = -P_0$

- At long times $\sigma = \eta_b \zeta v_{rr} - P_0$ where ζ_b the bulk viscosity

- For a usual incompressible liquid $v_{rr} = \vec{\nabla}\cdot\vec{v} = 0$. This is not true for a tissue $\frac{\partial \rho}{\partial t} + \vec{\nabla}(\rho\vec{v}) = k_+ \rho$. If $\rho = \text{cst}$ $\vec{\nabla}\cdot\vec{v} = k = k_d - k_a$. It vanishes only in the homeostatic case.

- ~~P3 of the page of ... negative~~ σ

4 - Transverse stress

We use the same strategy for the traceless component of the stress

$\tilde{\sigma}_{\alpha\beta} = \tilde{\sigma}^{el}_{\alpha\beta} + \tilde{\sigma}^{int}_{\alpha\beta}$. The elastic part is $\tilde{\sigma}^{el}_{\alpha\beta} = 2\mu \tilde{u}_{\alpha\beta}$ or

$\frac{d\tilde{\sigma}_{\alpha\beta}}{dt} = 2\mu \tilde{v}_{\alpha\beta}$ $\quad \tilde{v}_{\alpha\beta} = \frac{1}{2}\left(\partial_\alpha v_\beta + \partial_\beta v_\alpha - \frac{2}{3}\delta_{\alpha\beta} v_{rr}\right)$

The internal stress $\tilde{\sigma}^{int}_{\alpha\beta}$ is a traceless tensor. For each cell we can define a vector $\vec{n}$ along the axis of cell division and an orientational tensor $q_{\alpha\beta} = \langle n_\alpha n_\beta - \frac{1}{3}\delta_{\alpha\beta} \rangle$, which is traceless. The average is over neighboring cells

Experimentally, if there is no external stress a cell the axis of cell division is random and $q_{\alpha\beta} = 0$. It has been shown that an external stress orients cell divisions. We assume that the relation is linear $q_{\alpha\beta} = \frac{\tilde{\sigma}_{\alpha\beta}}{\sigma_0}$

We write the derivative of the external stress with time

$$\frac{d\tilde{\sigma}^{\alpha\beta}}{dt} = -\rho\left(k_d \tilde{q}_d + k_a \tilde{q}_a\right) q_{\alpha\beta} = -\rho \frac{\tilde{\sigma}^{\alpha\beta}}{\sigma_0}\left(k_d \tilde{q}_d + k_a \tilde{q}_a\right) = -\frac{\tilde{\sigma}^{\alpha\beta}}{\tau_a}$$

The relaxation time τ_a is of order $1/k_q \sim 1$ day

We obtain $\frac{d\tilde{\sigma}^{\alpha\beta}}{dt} + \frac{\tilde{\sigma}^{\alpha\beta}}{\tau_a} = 2\mu \tilde{v}_{\alpha\beta}$

This is the classical Maxwell constitutive equation for a viscoelastic liquid with a viscosity $\eta = G\tau_a \sim 10^7$ Pa.s. Experimentally, the viscosity is lower $\eta \sim 10^5$ Pa.s. There are other relaxation modes of the stress

We have shown that because of the stress dependance of the orientation of cell division the stress relaxes and over time scales of days, a tissue behaves as a liquid

Rq: Sign of τ_a $\tilde{\sigma}_{\alpha\beta} = \sigma_0 q_{\alpha\beta} + \sigma_1 q_{\alpha\gamma} q_{\gamma\beta}$ → spontaneous planarity (activity) Active tissue

5. Cell diffusion in a tissue

We consider a tissue with no average flow but where there are velocity fluctuations due to noise. There is thus a fluctuating velocity field

$\vec{v}(\vec{r},t)$ such that $\langle \vec{v}(\vec{r},t)\rangle = 0$

We suppose that a cell follows the velocity field its ~~position~~ velocity $\vec{v}(t)$ is $\vec{v}(t) = \vec{v}(\vec{r}(t))$ where $\vec{r}(t)$ is its position at time t.

$$\vec{r}(t) = \int_0^t \vec{v}(t)\,dt \qquad \langle \vec{r}^2(t)\rangle = 2\int_0^t dt' \int_0^{t'} \langle \vec{v}(t)\,\vec{v}(t')\rangle$$

but $\langle \vec{v}(t)\,\vec{v}(t')\rangle = \langle \vec{v}(0)\,\vec{v}(t-t')\rangle$. We find

$$\langle r^2(t)\rangle = 2\int_0^t du \int_0^{t'} \langle \vec{v}(0)\,\vec{v}(u)\rangle\,du = 2t\int_0^{+\infty} \langle \vec{v}(0)\,\vec{v}(t)\rangle dt$$

The diffusion constant is $D = \frac{1}{3}\int_0^{+\infty} dt\, \langle \vec{v}(t=0, \vec{r}=\vec{0})\, v(t, \vec{r}(t))\rangle dt$

We introduce the fourier transform of the velocity $\vec{v}(\vec{r}) = \int e^{i\vec{q}\vec{r}}\,\tilde{v}(\vec{q})\frac{d\vec{q}}{(2\pi)^3}$

$$\langle \tilde{v}(\vec{q},0)\,\tilde{v}^*(\vec{q}',t)\rangle = (2\pi)^3\,\delta(\vec{q}-\vec{q}')\,g(\vec{q},t)$$

$$D = \frac{1}{3}\int_0^{+\infty} \frac{d\vec{q}}{(2\pi)^3} \left\langle e^{i\vec{q}(\vec{r}(t)-\vec{r}(0))} \right\rangle g(\vec{q},t)\,dt$$ where we made a mode coupling approximation. One must therefore calculate the velocity correlation function by introducing noise in the equations

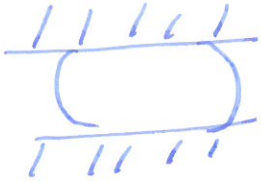
- In the conservation equation (population dynamics)
- In the force balance equation. We assumed that this is white noise at an effective temperature θ

$$D = \frac{1}{3\pi a}\left[\frac{h_d}{\xi} + \theta\left(\frac{\xi q^2 h_d}{\mu}\right)^2\right]$$ which is roughly proportional to h_d. Where a is the cell radius and $\vec{q} = \vec{q}_a + \vec{q}_d$

III Multicellular spheroid

1. Surface tension of a tissue

Spheroids are cell aggregates in general made of cancerous cells that grow and reach a steady size after a few days. They are considered as good models for tumors and are used to test drugs. They are in general spherical and appear as "cell drops" with a radius 500μm → 800 μm. It has been proposed by M. Steinberg that as liquids, spheroids have a surface tension γ. The idea is the same as the classical idea of surface tension of Young and Laplace. Cells there is adhesion between cells and a cell on the surface has less neighbors than in the bulk of the spheroid. The surface tension is then linked to adhesion molecule cadherins. A detailed study though shows that it strongly depends on myosin activity in the cortical actin layer.

Steinberg has measured the surface tension  and found $\gamma \sim 10^{-3}$ N/m.

One can in a similar way define an ~~surf~~ interfacial tension between 2 tissues.

2. Nucleation: secondary tumor

When a metastatic cell escapes from a primary tumor and moves into another tissue, it can "nucleate" a secondary tumor.

Healthy tissue
P_h^s homeostatic

Laplace's law $P_T = P_h^s + \frac{2\gamma}{R}$

The tumor grows if $P_T < P_h^T$ homeostatic pressure or if $P_h^T - P_h^s \geq \frac{2\gamma}{R}$

- The homeostatic pressure of the tumor must be larger than that of the healthy tissue
- There is a critical nucleation radius $R_c = \frac{2\gamma}{P_h^T - P_h^s}$

Secondary tumors are monoclonal: all cells are offsprings of the same cell (metastatic). In order to reach the radius R_c there must be a fluctuation whereby the cancerous cells divide and do not die to reach the radius R_c.

Using the theory of stochastic processes, one can calculate a "splitting probability" that the secondary tumor is larger than R_c. This probability is low.

Heterogeneous nucleation is frequent: tumors ~~start~~ tend to start from surfaces or interfaces.

3. Spheroid growth

- Experiments: one measures the radius $R(t)$ in the presence of an

external pressure. Cell division occurs only at the surface of the spheroid because of nutrient diffusion and mechanical effects

One can make a very naïve model assuming that the cell density is constant. The growth rate $-k = k_d - k_a$ is negative inside the spheroid, otherwise there would be no steady state. Close to the surface in a region of size λ it is increased by δk and equal to $\delta k - k > 0$

Volume conservation reads $\frac{dV}{dt} = -kV + \delta k \lambda n$. We use the volume as a variable $\frac{dR}{dt} = -\frac{kR}{3} + \delta k \lambda$

There is a stationary radius $R_s = \frac{3\delta k \lambda}{k}$ and $R = R_s\left[1 - e^{-\frac{kt}{3}}\right]$

If we fit the experimental curves $-k$ the growth rate decreases with pressure

One can extrapolate to $-k = 0$ to find the homeostatic pressure which is negative. The tissue is under tension

Assuming that the tissue is fluid we calculate the velocity field and the pressure $\vec{\nabla}\cdot\vec{v} = h(r)$ $\quad h(r) = -k \quad r < R-\lambda$

$= \delta k - k \quad R-\lambda < r < R$

If $r < R-\lambda$ $\quad \frac{1}{r^2}\frac{d\,r^2 v}{dr} = -k \quad v = -\frac{kr}{3}$

$R-\lambda < r < R \quad v = \frac{(\delta k - k)r}{3} + \frac{A}{r^2}$

The integration constant is found by the continuity of velocity at $r = R - \lambda$

$$A = -\frac{\delta k (R-\lambda)^3}{3} \qquad N = \frac{(\delta k - k) r}{3} - \frac{\delta k (R-\lambda)^3}{3 r^2}$$

At $r = R$ $v(R) = \frac{dR}{dt}$ $\qquad \frac{dR}{dt} = -\frac{kR}{3} + \frac{\delta k}{3} \frac{R^3 - (R-\lambda)^3}{R^2}$ which gives the same as above if $\lambda \ll R$

If the spheroid behaves as a fluid

$$\eta \nabla^2 v + \bar{\eta} \vec{\nabla}(\vec{\nabla} \cdot \vec{v}) = -\vec{\nabla} P = 0$$ η is the shear viscosity

$\bar{\eta}$ the elongational one

$$\nabla^2 \vec{v} = \vec{\nabla}(\vec{\nabla} \cdot \vec{v}) - \vec{\nabla} \times (\vec{\nabla} \times \vec{v})$$

$$\vec{\nabla}\left[P - (\eta + \bar{\eta}) \vec{\nabla} \cdot \vec{v}\right] = 0 \quad \text{or} \quad P = \text{cst} + (\eta + \bar{\eta}) \vec{\nabla} v$$

The growth rate is constant in both regions and P is constant. It is lower in the center $r < R - \lambda$ and there is a pressure jump if at $r = (R - \lambda)$