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$$\boxed{\begin{array}{l}\text{Boulder Summer School 2024}\\ \text{Active contractility of adherent cells}\end{array}}$$

Most important aspect of biological systems:
weak interactions, high & constant temperature ($\approx 300K$)

$\Rightarrow$ molecules constantly bump into each other

$\Rightarrow$ basis of biochemistry

$$\boxed{\begin{array}{c}\text{interaction energy}\\ k_B T = 4 \cdot 10^{-21} J = 4\, pN\, nm = \frac{1}{40} eV\end{array}}$$

dynamics

equipartition: $\frac{1}{2} m v^2 = k_B T \Rightarrow v \approx 10 \frac{m}{s}$

Stokes-Einstein relation: $D = \frac{k_B T}{6 \pi \eta R} \approx \frac{(10\, \mu m)^2}{s}$

for proteins in water

($R = nm$, $\rho = \frac{kg}{dm^3}$, $m = \frac{4\pi}{3} \rho R^3$, $\eta_{H_2O} = 10^{-3} Pa \cdot s$)

$D_r = \frac{k_B T}{8 \pi \eta R^3} = \frac{1}{10\, ns}$

interesting

Interactions are weak because

$\rightarrow \varepsilon = 80$ high polarizability, strong screening by water molecules and ions

$\rightarrow$ fast rotation weakens anisotropic interactions

$$\langle U_{dipole} \rangle_{rot} \sim \int d(\cos\theta)\, U e^{-\beta U} \sim \frac{\mu^4}{\varepsilon^2 T r^6}$$

$\sim \frac{\mu^2}{\varepsilon r^3}$

thermal average, otherwise $\langle U_{dipole} \rangle_{rot} = 0$, Taylor expansion

$\rightarrow$ entropic interactions, esp. water bridges in aqueous solvent, $F = U - TS \approx k_B T$

cell size + number

$\langle x^2 \rangle = 6 D t \Rightarrow$ limits cell size (2)

signaling time $1\,s \Rightarrow$ cell size $10\,\mu m$

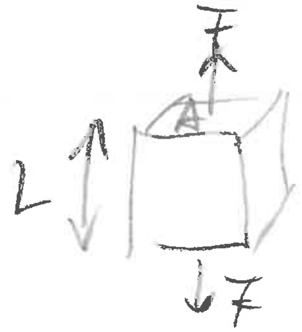
How many cells in our body?

$$\left(\frac{1\,m}{10\,\mu m}\right)^3 = 10^{15}$$

close to correct number $3 \cdot 10^{13}$

mechanics

High temperature also sets the scale for cell mechanics!



$$\frac{F}{A} = \sigma = E \underbrace{\frac{\Delta L}{L}}_{=:\varepsilon \text{ strain}}$$

stress

Young's modulus

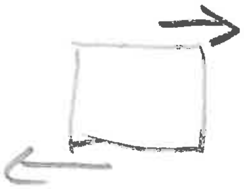
$$[E] = [\sigma] = Pa$$

$$E = \frac{U}{a^3} = \frac{k_B T}{(10\,nm)^3} = k\,Pa$$

cells are soft!

Spring constant $k = \frac{F}{\Delta L} = \frac{E \cdot A}{L}$

σ and E should be similar for appreciable deformation ($\varepsilon \approx 1$)



$\dot{\varepsilon}$ strain rate

$$\sigma = \eta \dot{\varepsilon}$$

Compare atomic crystals: $E = \frac{eV}{A^{\circ 3}} = GPa$

$$[\eta] = Pa \cdot s$$

$$\tau = \frac{\eta}{E} = 10\,s \quad \text{relaxation time}$$

$$\eta = E \cdot 10\,s = 10^4\,Pa \cdot s$$

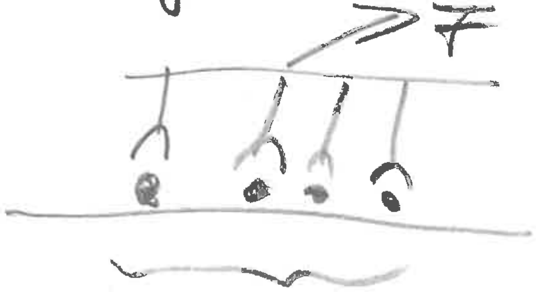
$$= 10^7\,\eta_{water}$$

cells are highly viscous!

Cell adhesion and traction forces:

Single bonds can sustain only $F = \frac{k_B T}{nm} = pN$

⇒ adhesion clusters share force between many molecules



N bonds

$$\underbrace{F_c}_{} = \overset{pN}{F_b}\; \overset{\# bonds}{N_t}\; \mathrm{plog}\left(\frac{k_{on}}{N_t e}\right)$$

[Bell Science 1978]

"focal adhesion"

binding rates

1000 molecules can sustain nN and need μm^2 of area

$$\Rightarrow \quad \sigma = \frac{nN}{\mu m^2} = \frac{10^{-9}\, N}{10^{-12}\, m} = kPa$$

⇒ matches exactly the stiffness of other cells and the extracellular matrix

⇒ explanation of focal adhesions!

Other estimate for substrate stiffness / traction stress:

$$\sigma = E = \frac{k\, L}{A} = \frac{nN}{\mu m}\,\frac{\mu m}{\mu m^2} = kPa \quad ✓$$

Substrate Energy $\frac{F^2}{2k} \sim \frac{(\sigma A)^2}{EA/L} = \overset{\frac{\sigma}{E} \approx 1}{\frac{\sigma^2}{E}} A L \approx \overset{= F}{(\sigma A)} L = nN \cdot \mu m = fJ$ per adhesion

whole cell: $\times 1000$ $E \approx pJ$

Viscoelasticity

Cells are soft objects that deform and flow.

One can combine elasticity and viscosity in two different ways.

1) Viscoelastic fluid → Maxwell model

$C = E \cdot A$, $C_\eta = \eta \cdot A$ } 1d moduli

$F_d = C_\eta \dot{\varepsilon}_d \qquad F_s = C \varepsilon_s$

$F_d = F_s = F$

$\varepsilon = \varepsilon_d + \varepsilon_s \Rightarrow \dot{\varepsilon} = \dot{\varepsilon}_d + \dot{\varepsilon}_s = \frac{F}{C_\eta} + \frac{\dot{F}}{C}$

$\Rightarrow \dot{F} + \frac{1}{\tau} F = C \dot{\varepsilon}$

"Relaxation exp.": RHS given, calculate F

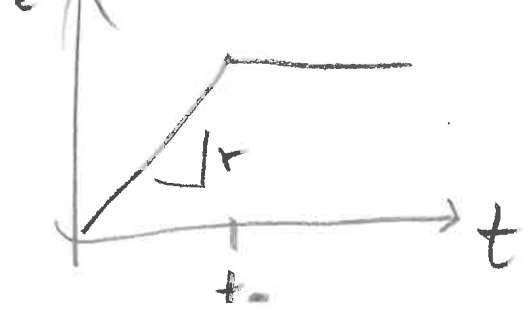
Opposite case: "creep exp."

ODE $F = F_{hom} + F_{part}$ $\qquad F_{hom} = F_0 e^{-t/\tau}$

$F_{part} = F_0(t) e^{-t/\tau} \Rightarrow \dot{F}_0 = C \dot{\varepsilon} e^{t/\tau} \Rightarrow F_0 = C \int_0^t dt' e^{t'/\tau} \dot{\varepsilon}$

$\Rightarrow F_{part} = C \int_0^t dt' e^{-(t-t')/\tau} \dot{\varepsilon}$

Example strain ramp:



up to time t_0, driven by external force

$F = 0$ for $t < 0$

$\Rightarrow F_{hom} = 0 \Rightarrow F = F_{part}$

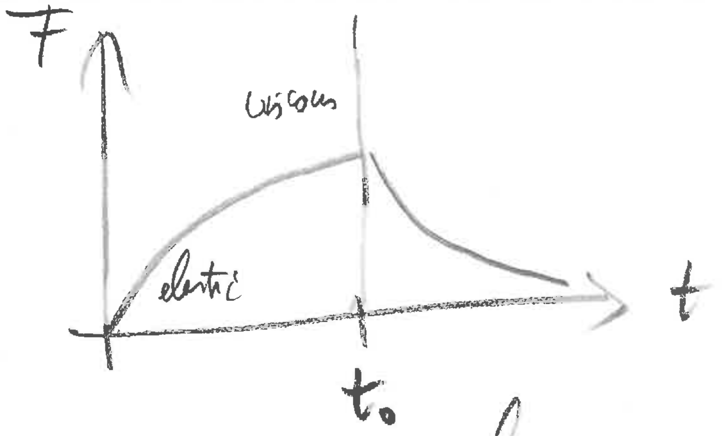
$t \le t_0$

$$F(t) = C r e^{-t/\tau} \underbrace{\int_0^t dt' \, e^{t'/\tau}}_{\tau[e^{t/\tau}-1]}$$

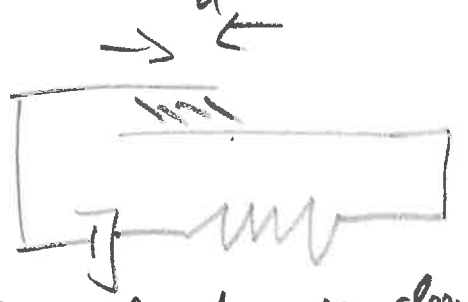
$$= C_\eta r \cdot (1-e^{-t/\tau})$$

$$\approx \begin{cases} C r t & t \ll \tau \quad \text{elastic} \\ C_\eta r & t \gg \tau \quad \text{viscous} \end{cases}$$

$t \ge t_0$ $\quad \dot{\varepsilon} = 0 \Rightarrow F = F_0 e^{-(t-t_0)/\tau}$



The area under the curve is dissipated as heat.



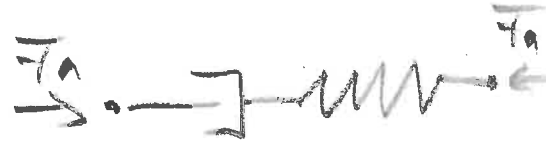
Example active force

Now the force comes from the inside, but the situation is equivalent to a compression force from the outside.

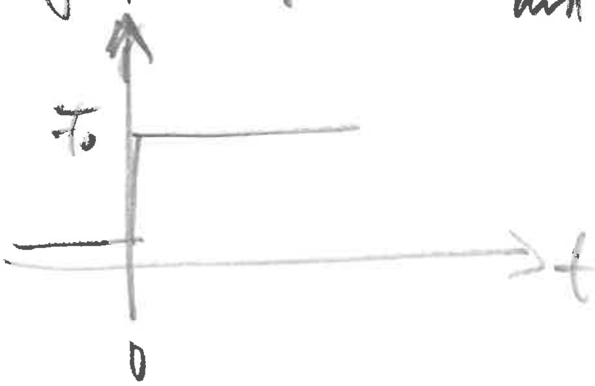
This is a creep experiment.

same equation as above

$$\tau \dot{F} + F = C\tau\dot{\varepsilon}$$



The creep function is defined for a force jump. We introduce two times $t=0^-$ and $t=0^+$ left and right of $t=0$



$$\frac{F(0^-)+F(0^+)}{2} + \tau \frac{F(0^+)-F(0^-)}{\Delta t} = C\tau \frac{\varepsilon(0^+)+\varepsilon(0^-)}{\Delta t}$$

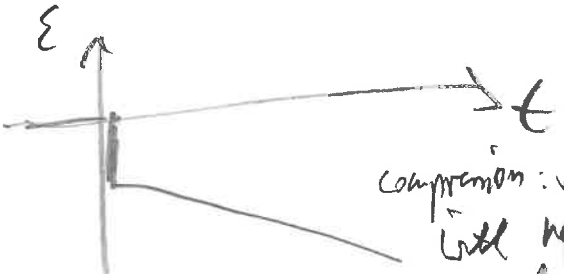
Multiplying with Δt and taking the limit $\Delta t \to 0$:

$$F(0^+) = F_0 = C\,\varepsilon(0^+) \Rightarrow \text{elastic jump}$$

From here on the spring does not change anymore and we pull length out of the dashpot. Relaxation function

$$J = \frac{\varepsilon}{F_0} = \frac{1}{C} + \frac{t}{C_\eta}$$

extension



compression: same with negative values

This shows that a Maxwell model can be problematic under constant contractility! It has no stable state under force

For compression, material would disappear all the time.

(2) Viscoelastic Solid → Kelvin-Voigt model

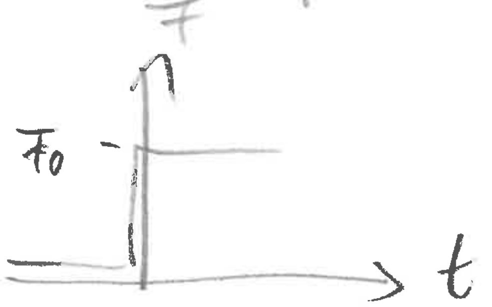
Now forces add up $F = F_s + F_d = C\varepsilon + C_\eta \dot{\varepsilon}$

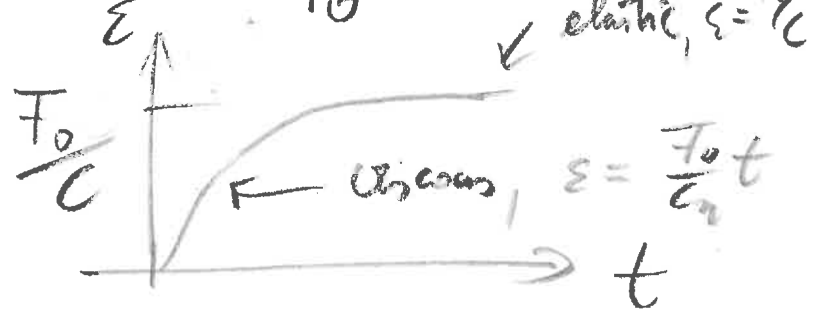
Similar eq. like for Maxwell-model, but F and ε exchanged

$$\Rightarrow \quad \varepsilon(t) = \frac{1}{C_\eta}\int_0^t dt' \, e^{-(t-t')/\tau} \, F(t')$$

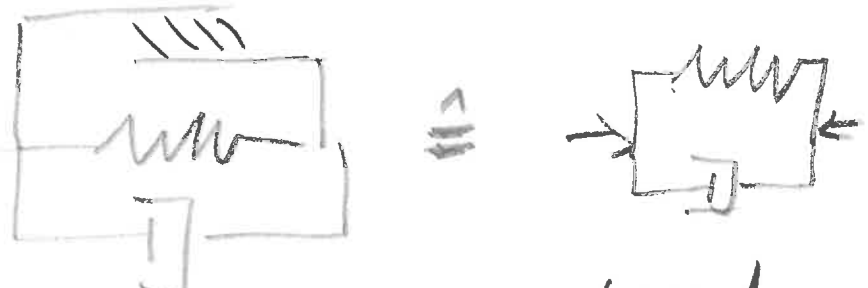
memory kernel

The natural analysis therefore is a creep exp. with creep function $J(t) \doteq \dfrac{\varepsilon(t)}{F_0} = \dfrac{1}{C}\left(1 - e^{-t/\tau}\right)$



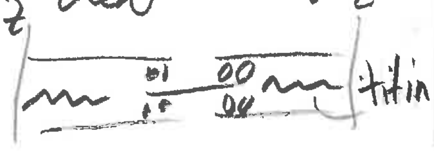


Now we see that an active KV-model is stable:

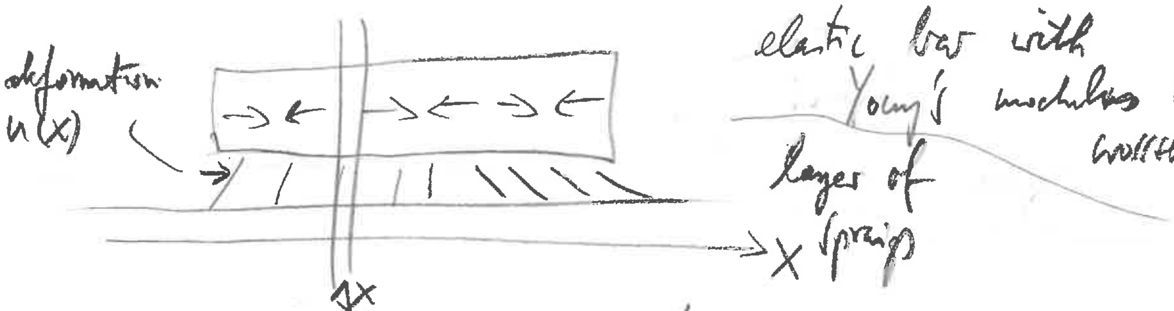


compressed KV-element

However, the catch here is that it is not clear how polymers can resist compression. Muscle: use titin



Spatial models: cells as contractile bars on an elastic foundation



We consider the normal force $N(x)$ on a slice of width Δx:

$$N(x) = N(x+\Delta x) - k\, u(x) \quad \text{force balance}$$

$$\Rightarrow \quad \frac{dN(x)}{dx} = \varsigma\, u(x) \qquad \varsigma \text{ spring constant density}$$

stress $\sigma = \dfrac{N(x)}{A(x)}$

strain $\varepsilon(x) = \dfrac{u(x+\Delta x) - u(x)}{\Delta x} = \dfrac{du(x)}{dx}$

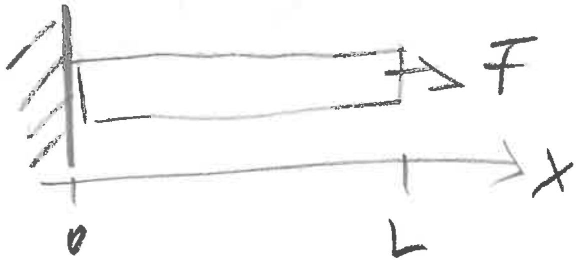
Material law: $\sigma(x) = E(x)\, \varepsilon(x)$

$$\Rightarrow \quad \frac{dN}{dx} \overset{\mathrm{M}}{=} \frac{d}{dx}(\sigma A) \overset{\text{material law}}{=} \frac{d}{dx}(\underbrace{EA}_{=C}\, \varepsilon) \overset{\text{strain def.}}{=} \frac{d}{dx}\left(C(x) \frac{du}{dx}\right)$$

$$\overset{\text{force balance}}{=} \varsigma\, u(x)$$

$$C(x) = \text{const} \quad \Rightarrow \quad \boxed{C u'' - \varsigma u = 0}$$

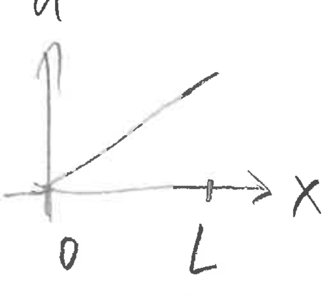
(1) bar without springs pulled at right by force F:



$\varsigma = 0 \qquad u''(x) = 0$

$F = N(L) = C\, u'(L)$ BC

$\Rightarrow u = \dfrac{F}{C} x$



(2) Now with the springs: $C u'' - \rho u = 0$

$\Rightarrow \quad \ell^2 u'' - u = 0 \quad$ with $\ell = \sqrt{\frac{C}{\rho}}$ ← cell stiffness, ← substrate stiffness

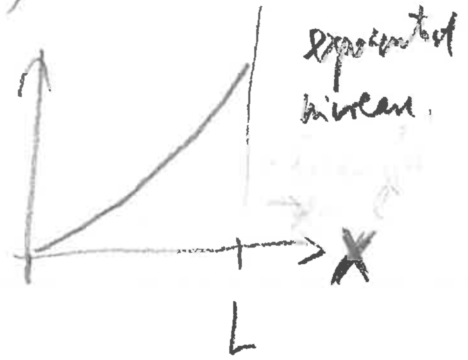
"localization length"

$\Rightarrow \quad u = A e^{x/\ell} + B e^{-x/\ell}$

$u(0) = 0 \Rightarrow B = -A \Rightarrow u = 2A \sinh\left(\frac{x}{\ell}\right)$

BC: $F = C u'(L) = \frac{2AC}{\ell} \cosh\left(\frac{L}{\ell}\right)$

$$\Rightarrow \boxed{u(x) = \frac{F\ell}{C} \frac{\sinh(x/\ell)}{\cosh(L/\ell)}}$$



Traction force on foundation $F_t = k \cdot u$

$\Rightarrow$ most force at boundary, exponential decrease on scale ℓ

(3) Now we do not pull from outside, but let the bar be contractile

$N = Cu' + P$ ← active stress, corresponds to a force dipole density

$P > 0$

$\Rightarrow \quad \ell^2 u'' - u = -\frac{P'}{\rho}$

For $P = $ const, the RHS vanishes.

$\Rightarrow \quad u = 2A \sinh\left(\frac{x}{\ell}\right)$ like before

However, the boundary condition is different:

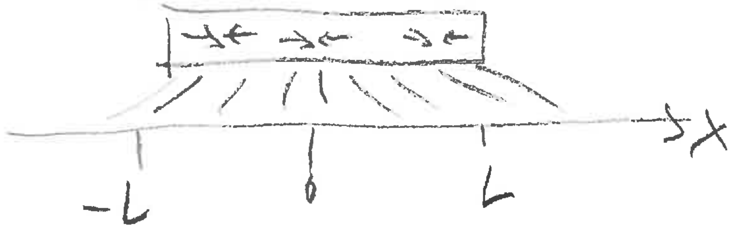
$N(L) = 0$ "free" or "zero stress" BC

$$\Rightarrow \quad C u'(L) + P = 0 \Rightarrow -\frac{P}{C} = \frac{2A}{\ell}\cosh\left(\frac{L}{\ell}\right)$$

$$\Rightarrow \quad \boxed{u(x) = -\frac{P\ell}{C}\,\frac{\sinh(x/\ell)}{\cosh(L/\ell)}}$$

We double the system as a model for cells.

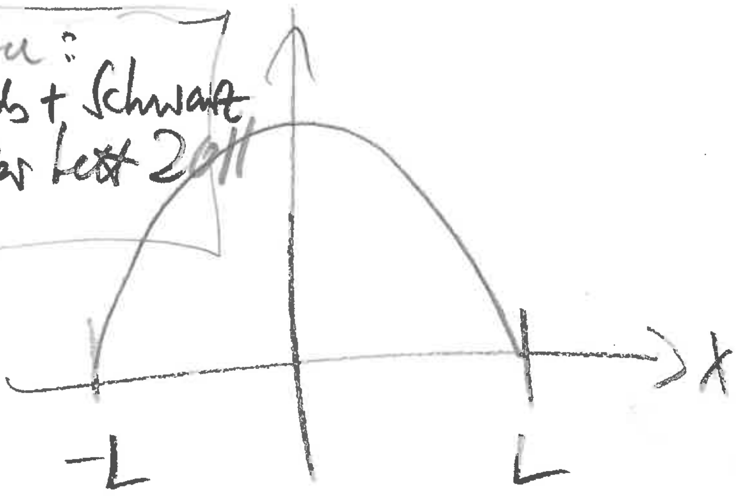
$u(0) = 0$ due to symmetry reasons



Again force is localized at periphery on scale ℓ, as known for cells and cell clusters.

Internal stress $N(x) = Cu' + P = P\left(1 - \frac{\cosh(x/\ell)}{\cosh(L/\ell)}\right)$

Reference: Edwards + Schwarz Phys Rev Lett 2011



parabolic stress profile, measured by Xavier Trepat for healing wound away