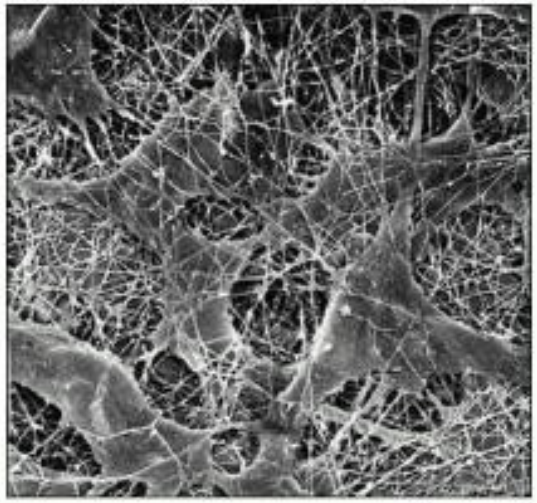
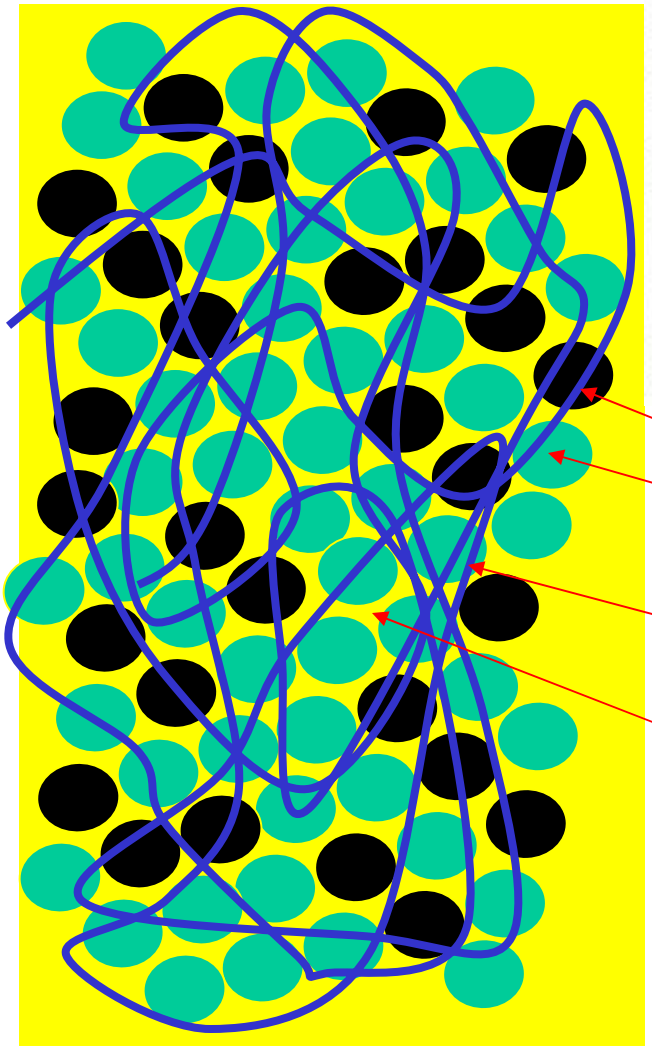
Mechanical Aspects of Tumour Growth

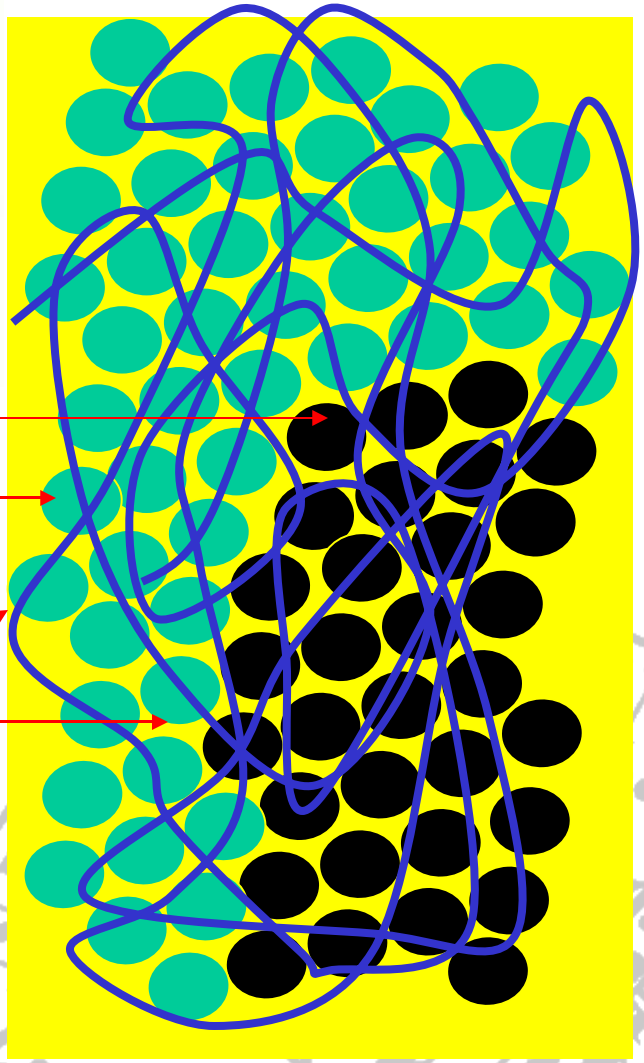
Aim: Are tumors solids or liquids?

Are viscoelastic and plastic effects important?

Multiphase model







tumour cells

host cells

deformable and degradable ECM

extracellular liquid

Multiphase models

volume ratios ϕ_t ϕ_h m ℓ

tumor cells, host cells, ECM, liquid

with $\phi_t + \phi_h + m + \ell = 1$.

$$\frac{\partial \phi_t}{\partial t} + \nabla \cdot (\phi_t \mathbf{v}_t) = \Gamma_t \,, \qquad -\phi_t \nabla P + \nabla \cdot (\phi_t \mathbf{T}_t) + \mathbf{m}_t = \mathbf{0} \,,$$

$$\frac{\partial \phi_h}{\partial t} + \nabla \cdot (\phi_h \mathbf{v}_h) = \Gamma_h \,, \qquad -\phi_h \nabla P + \nabla \cdot (\phi_h \mathbf{T}_h) + \mathbf{m}_h = \mathbf{0} \,,$$

$$\frac{\partial m}{\partial t} + \nabla \cdot (m \mathbf{v}_m) = \Gamma_m \,, \qquad -m \nabla P + \nabla \cdot (m \mathbf{T}_m) + \mathbf{m}_m = \mathbf{0} \,,$$

$$\frac{\partial \ell}{\partial t} + \nabla \cdot (\ell \mathbf{v}_\ell) = \Gamma_\ell \,, \qquad -\ell \nabla P + \mathbf{m}_\ell = \mathbf{0} \,,$$

Interaction of the constituents with the liquid

$$-\ell \nabla P + \mathbf{m}_\ell = \mathbf{0}\,,$$

$$\mathbf{m}_{\ell\alpha} = -\mathbf{M}_\alpha(\mathbf{v}_\ell - \mathbf{v}_\alpha)\,, \qquad \text{for} \quad \alpha = t, h, m$$

$$-\phi_t \nabla P + \nabla \cdot (\phi_t \mathbf{T}_t) + \mathbf{m}_t = \mathbf{0}\,,$$

Observation:
The interactions involving the liquid phase are much smaller than those between cells and ECM

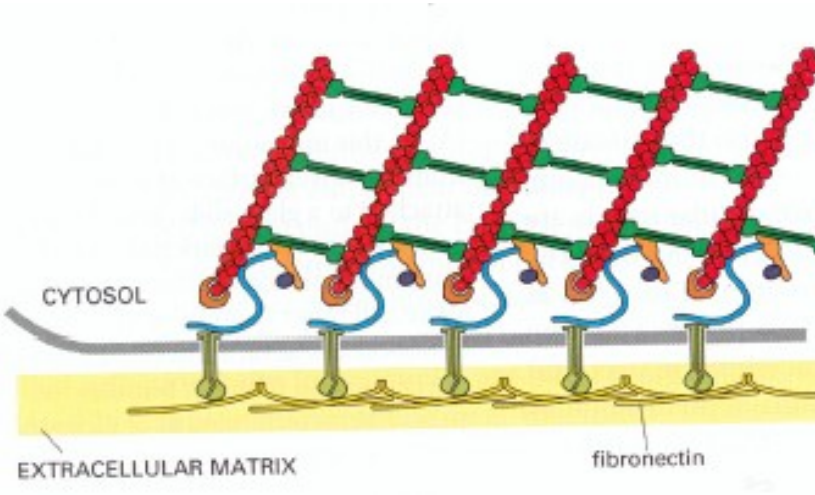
$$\nabla \cdot (\phi_t \mathbf{T}_t) + \mathbf{m}_{th} + \mathbf{m}_{tm} = \mathbf{0}$$

Interaction of the constituents with the liquid

$$\nabla \cdot (\phi_t \mathbf{T}_t) + \mathbf{m}_{th} + \mathbf{m}_{tm} = \mathbf{0}\,,$$

$$\nabla \cdot (\phi_h \mathbf{T}_h) - \mathbf{m}_{th} + \mathbf{m}_{hm} = \mathbf{0}\,,$$

$$\nabla \cdot (m\mathbf{T}_m) - \mathbf{m}_{tm} - \mathbf{m}_{hm} = \mathbf{0}\,.$$

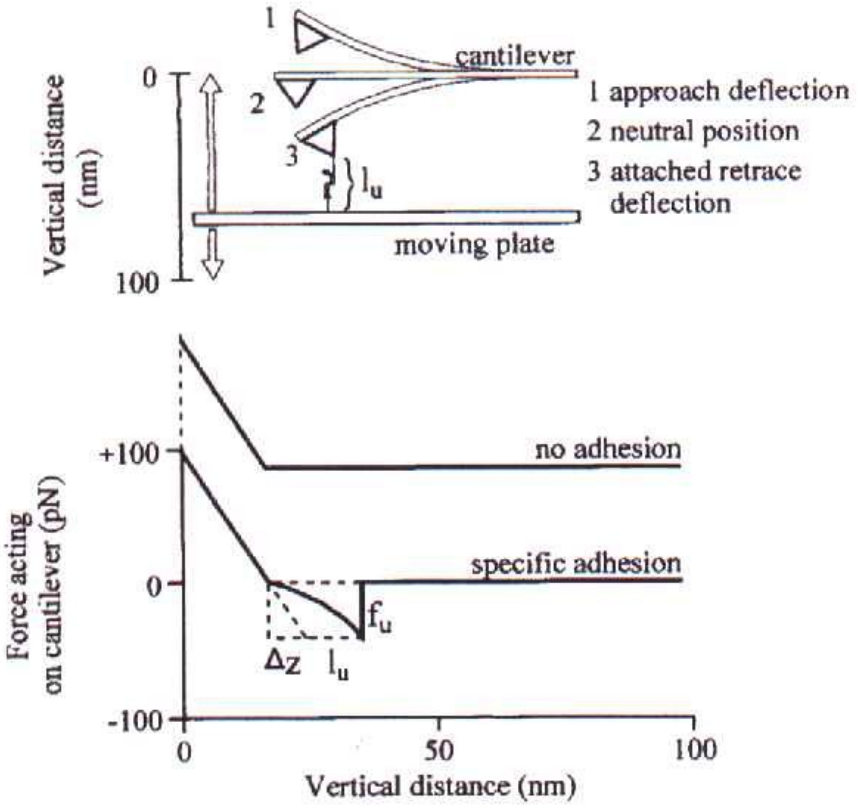


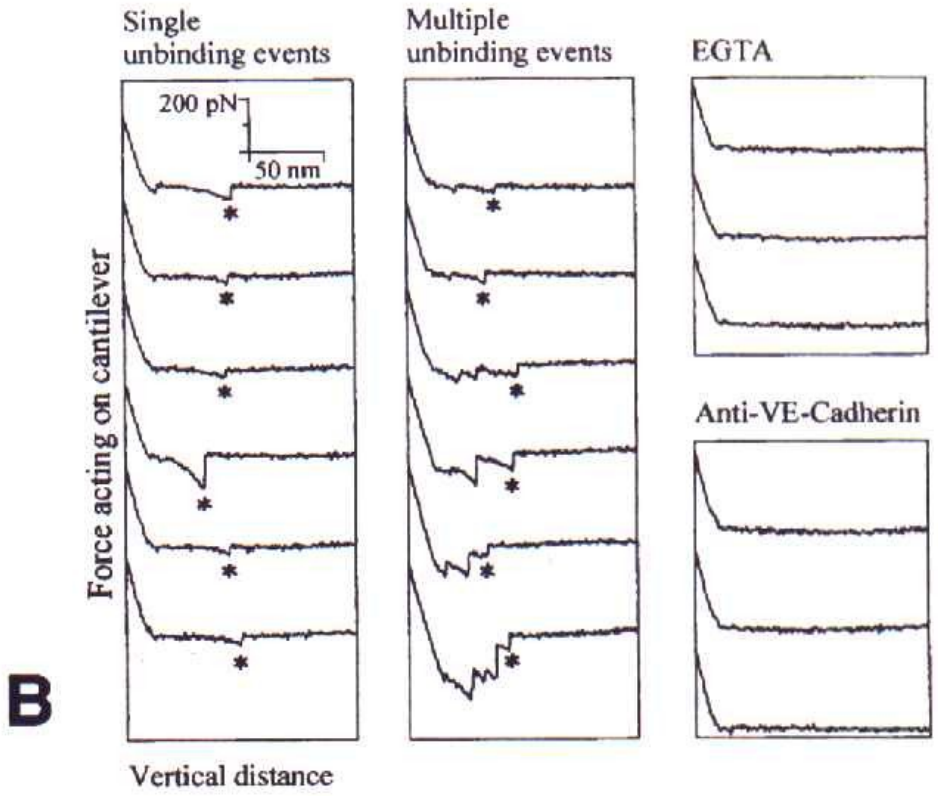
$$\nabla \cdot (\ell^2 \mathbf{M}^{-1} \nabla P_\ell) = \nabla \cdot \left[\sum_{\alpha=t,h,m} (\phi_\alpha \mathbf{I} + \ell \mathbf{M}^{-1} \mathbf{M}_\alpha) \mathbf{v}_\alpha \right]$$

$$\mathbf{v}_\ell = \mathbf{M}^{-1} \left(\sum_{\alpha=t,h,m} \mathbf{M}_\alpha \mathbf{v}_\alpha - \ell \nabla P_\ell \right)\,.$$

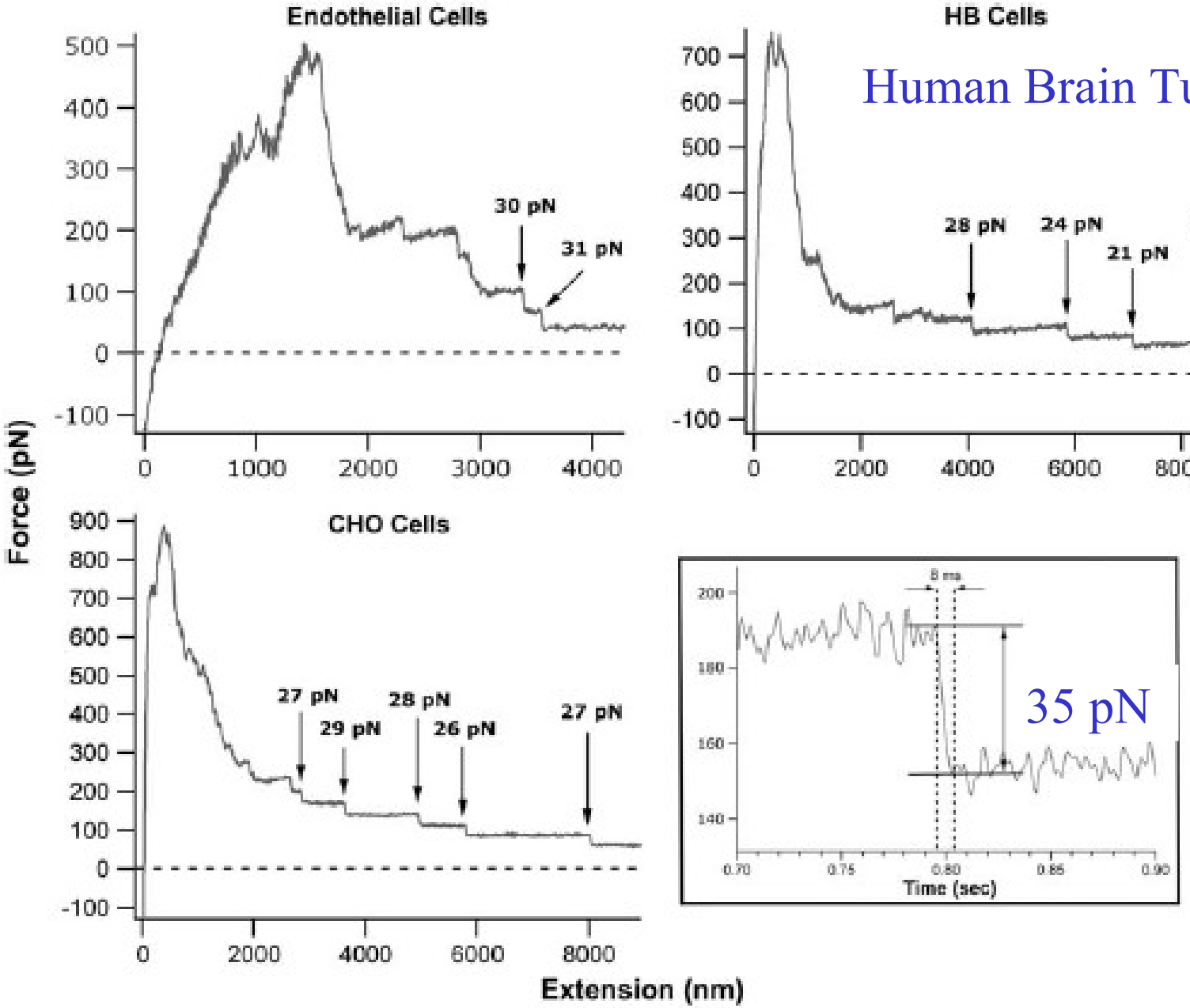
where $\mathbf{M} = \sum_{\alpha=t,h,m} \mathbf{M}_\alpha$

Adhesion forces





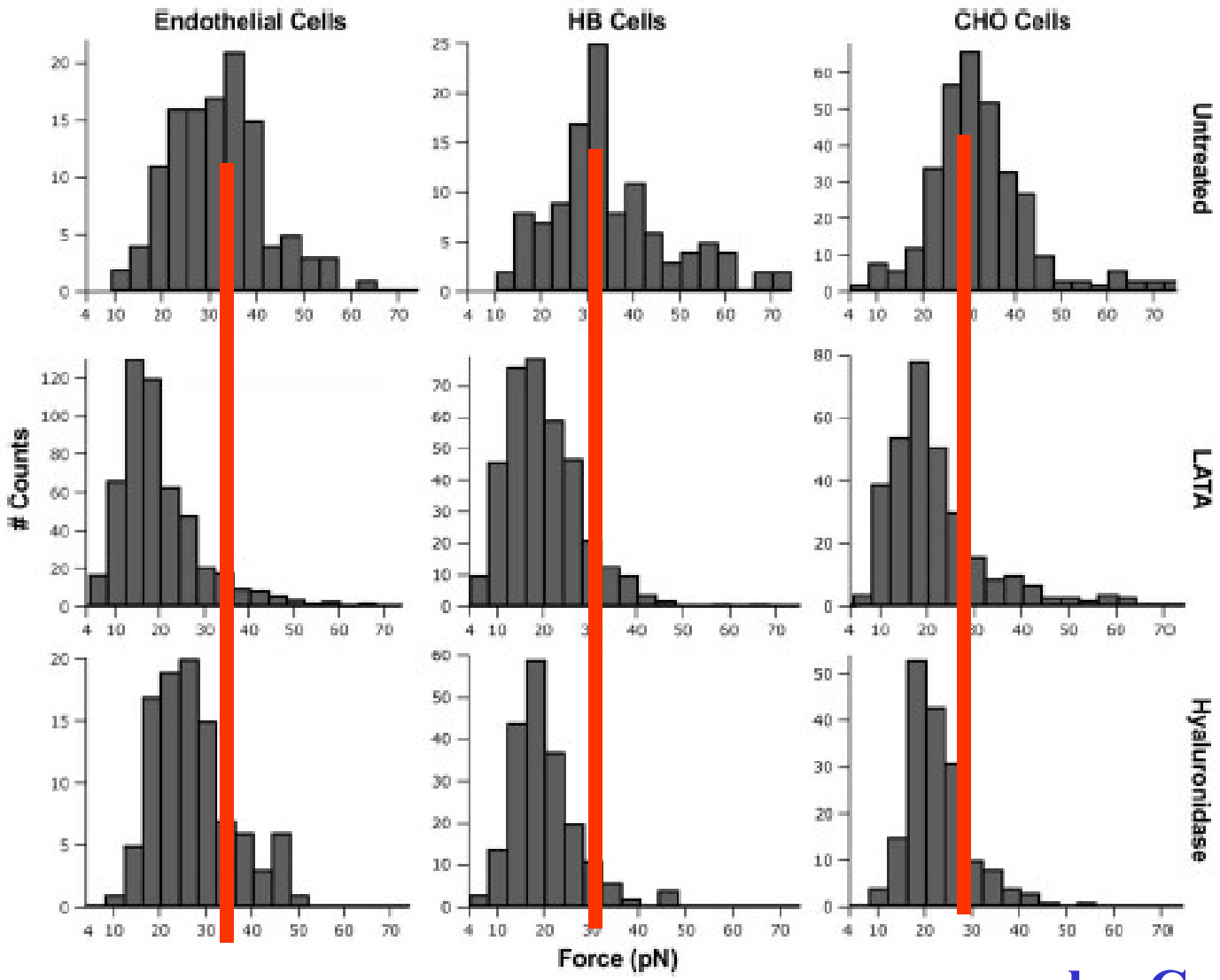
- Baumgartner et al., *PNAS* **97** (2000)



Sun et al.
Biophys J.
89 (2005)

FIGURE 3 Typical retraction-force curves as a function of cantilever extension for three cell lines. Numbers on the graphs denote the values of the individual force steps between consecutive plateaus. Note the very similar force drops in the quasi-constant force elongation regime, and that zero force is not reached at the end of the retractions, indicating tethers are still attached. Inset shows timescale for a typical force drop.

Interfering with the adhesion mechanisms



Disrupts actin cytoskeleton

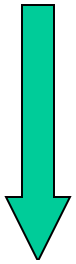
removes hyaluronan backbone from membrane

see also Canetta et al. (2004)

Modelling the interaction between cells and ECM

$$\mathbf{v}_\alpha = \mathbf{v}_m\,, \qquad \text{if} \quad |\mathbf{m}_{\alpha m}| \le \sigma_{\alpha m}\,, \qquad \alpha = t, h$$

$$\mathbf{m}_{\alpha m} - \sigma_{\alpha m}\frac{\mathbf{m}_{\alpha m}}{|\mathbf{m}_{\alpha m}|} = \mathbf{M}_{\alpha m}(\mathbf{v}_m - \mathbf{v}_\alpha)\,, \qquad \text{if} \quad |\mathbf{m}_{\alpha m}| > \sigma_{\alpha m}$$



$$\mathbf{v}_m - \mathbf{v}_\alpha = \mathbf{M}_{\alpha m}^{-1}\left(1 - \frac{\sigma_{\alpha m}}{|\mathbf{m}_{\alpha m}|}\right)_+ \mathbf{m}_{\alpha m}$$

Modelling the interaction between cells and ECM

Using force balance $\mathbf{m}_{\alpha m} = -(\phi_\alpha/\phi)\nabla\cdot(\phi\mathbf{T}_\phi)$

$$\mathbf{v}_\alpha - \mathbf{v}_m = \left(\frac{\phi_\alpha}{\phi} - \frac{\sigma_{\alpha m}}{|\nabla\cdot(\phi\mathbf{T}_\phi)|}\right)_+ \mathbf{M}_{\alpha m}^{-1}\nabla\cdot(\phi\mathbf{T}_\phi)$$

i.e., if cells are pulled strong enough they move relative to the ECM
if not they stick to the ECM

Summary

$$\frac{\partial \phi_t}{\partial t} + \nabla \cdot (\phi_t \mathbf{v}_m) = \nabla \cdot \left[\phi_t \mathbf{M}_{tm}^{-1} \left(\frac{\phi_t}{\phi} - \frac{\sigma_{tm}}{|\nabla \cdot (\phi \mathbf{T}_\phi)|} \right)_+ \nabla \cdot (\phi \mathbf{T}_\phi) \right] + \Gamma_t \,,$$

$$\frac{\partial \phi_h}{\partial t} + \nabla \cdot (\phi_h \mathbf{v}_m) = \nabla \cdot \left[\phi_h \mathbf{M}_{hm}^{-1} \left(\frac{\phi_h}{\phi} - \frac{\sigma_{hm}}{|\nabla \cdot (\phi \mathbf{T}_\phi)|} \right)_+ \nabla \cdot (\phi \mathbf{T}_\phi) \right] + \Gamma_h \,,$$

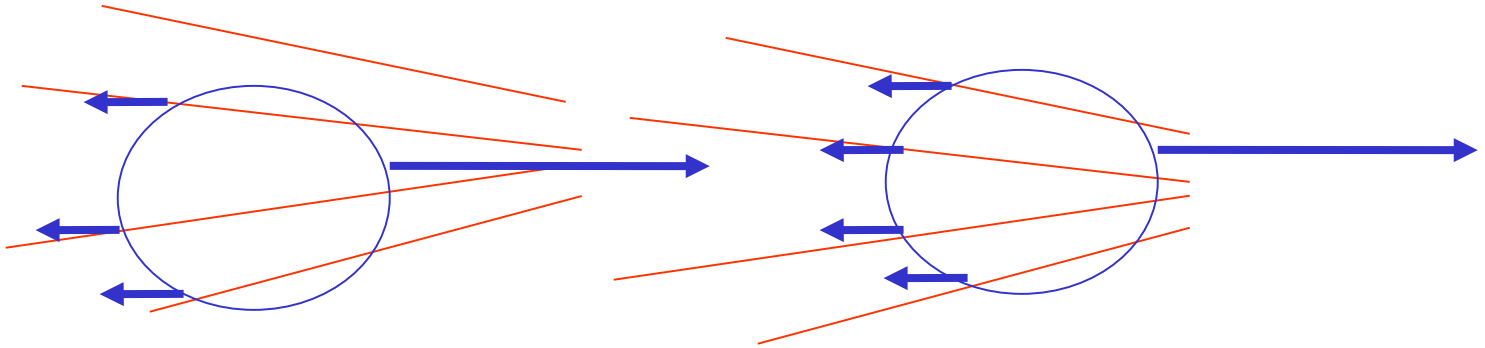
$$\frac{\partial m}{\partial t} + \nabla \cdot (m \mathbf{v}_m) = \Gamma_m \,,$$

$$\nabla \cdot (\phi \mathbf{T}_\phi + m \mathbf{T}_m) = \mathbf{0} \,.$$

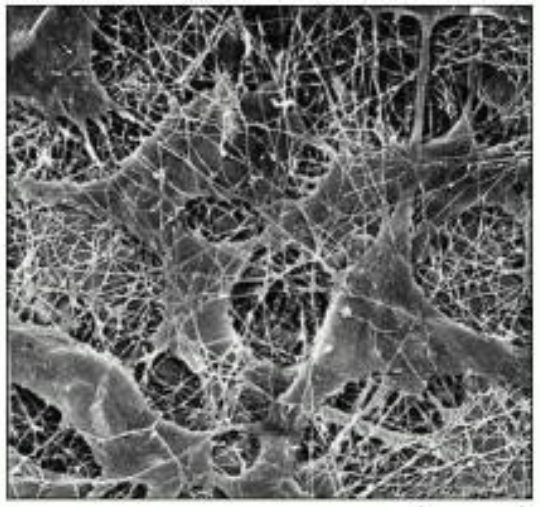
e.g., different clones have different σ

Modelling the interaction between cells and ECM

– **Adhesion depends on the amount of ECM, e.g.** $\sigma_{cm} = \dfrac{\hat{\sigma}_{cm}\phi_c m}{m_* - m}$



moves ➡ slows down ➡ stops



– **Different clones have different σ**

⬇

Different invasiveness

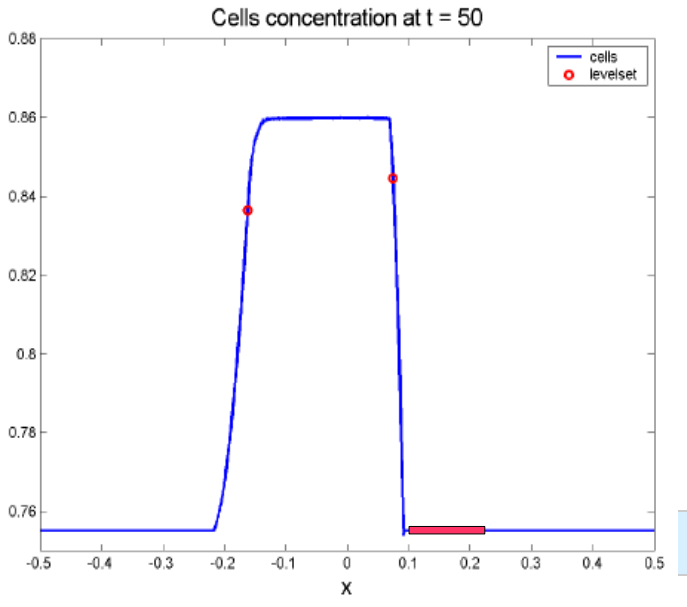
Modelling the interaction between cells and ECM

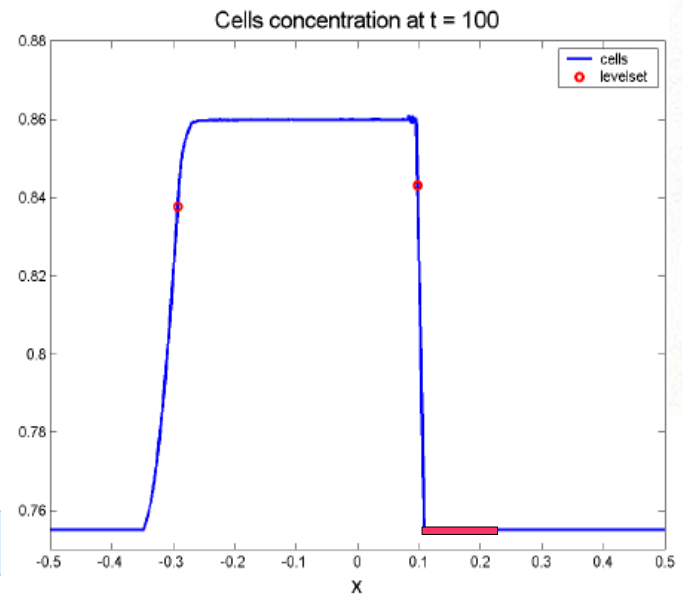
$$\frac{\partial \phi_t}{\partial t} + \nabla \cdot (\phi_t \mathbf{v}_m) = \nabla \cdot \left[\phi_t \mathbf{M}_{tm}^{-1} \left(\frac{\phi_t}{\phi} - \frac{\sigma_{tm}}{|\nabla \cdot (\phi \mathbf{T}_\phi)|} \right)_+ \nabla \cdot (\phi \mathbf{T}_\phi) \right] + \Gamma_t \,,$$

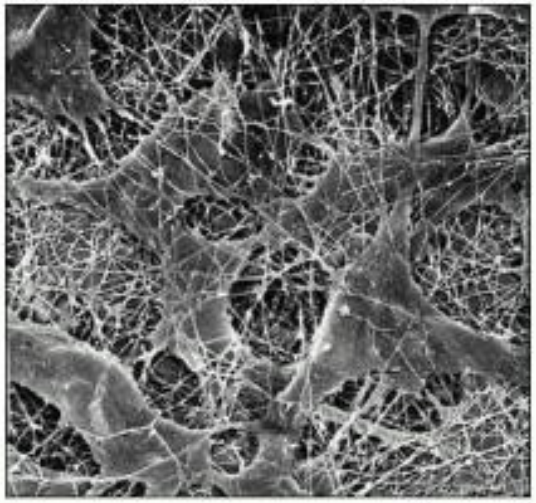
$$\frac{\partial \phi_h}{\partial t} + \nabla \cdot (\phi_h \mathbf{v}_m) = \nabla \cdot \left[\phi_h \mathbf{M}_{hm}^{-1} \left(\frac{\phi_h}{\phi} - \frac{\sigma_{hm}}{|\nabla \cdot (\phi \mathbf{T}_\phi)|} \right)_+ \nabla \cdot (\phi \mathbf{T}_\phi) \right] + \Gamma_h \,,$$

$$\frac{\partial m}{\partial t} + \nabla \cdot (m \mathbf{v}_m) = \Gamma_m \,,$$

$$\nabla \cdot (\phi \mathbf{T}_\phi + m \mathbf{T}_m) = \mathbf{0} \,.$$







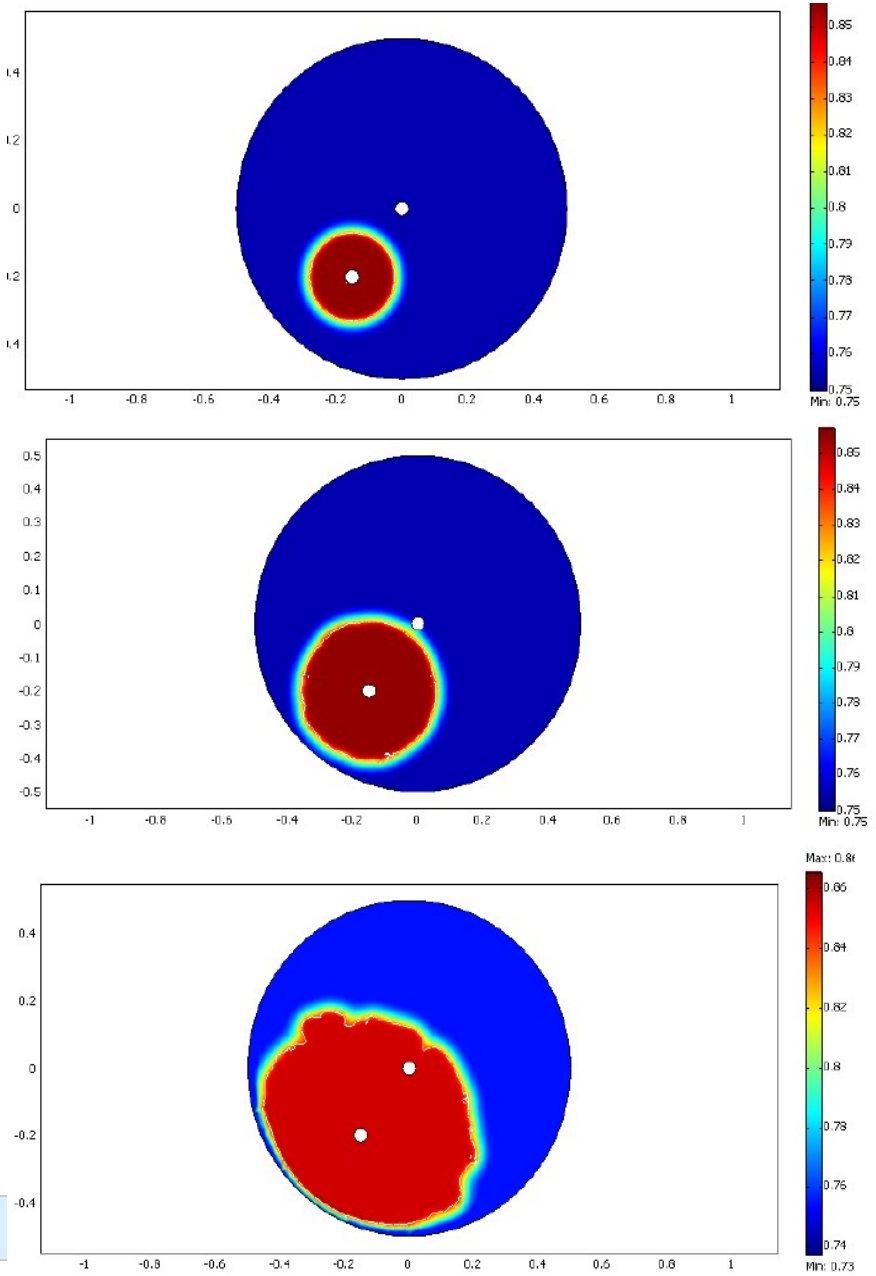
Modelling the interaction between cells and ECM

Islets of Langerhans

- **Non-remodelling ECM**
- **Growth by loss of contact inhibition mechanisms**
- **Cell ensembles as elastic fluids**

$$\mathbb{T}_\phi = -\Sigma(\phi)\mathbb{I},$$

$$\frac{\partial \phi_t}{\partial t} = \nabla \cdot \left[\phi_t \mathbf{M}_{tm}^{-1} \left(1 - \frac{\sigma_{tm}(m)}{|\nabla \tilde{\Sigma}(\phi_t)|} \right)_+ \nabla \tilde{\Sigma}(\phi_t) \right] + \Gamma_t$$

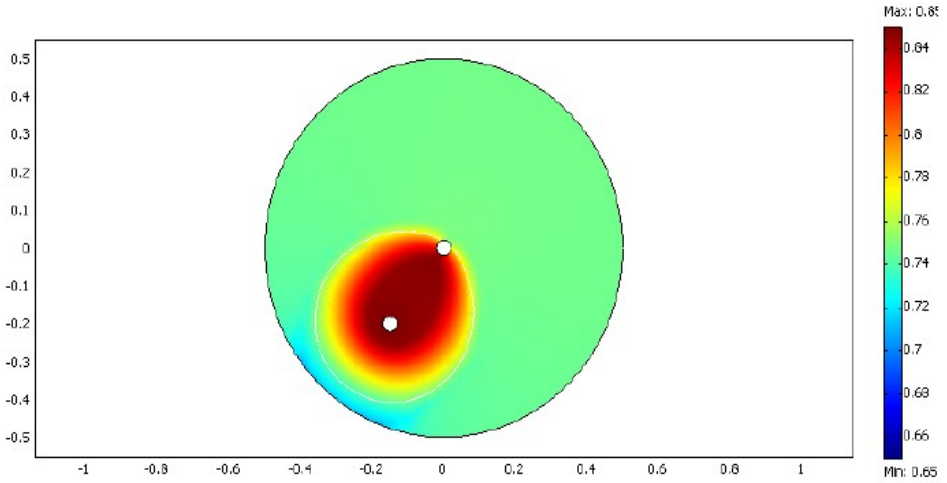


Modelling the interaction between cells and ECM

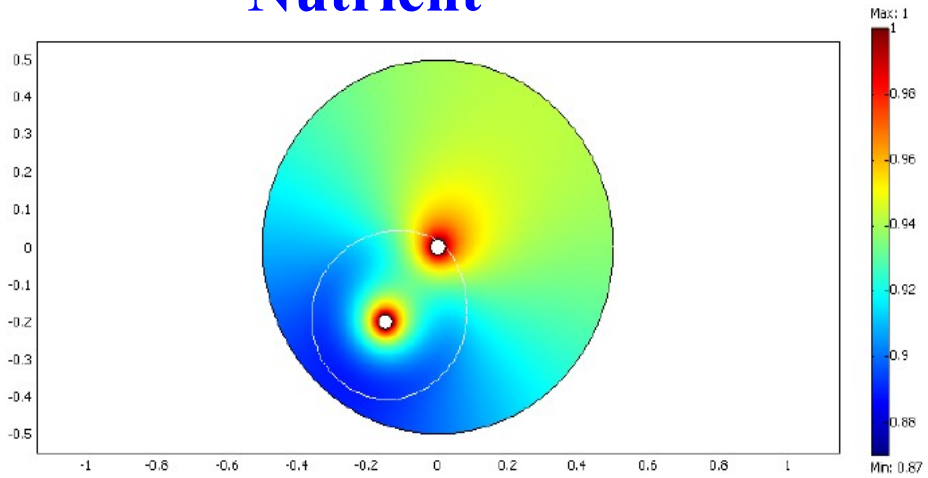
Islets of Langerhans

- Non-remodelling EC
- Growth by loss of contact inhibition mechanisms
- Cell ensembles as elastic fluids
- Vascularised case

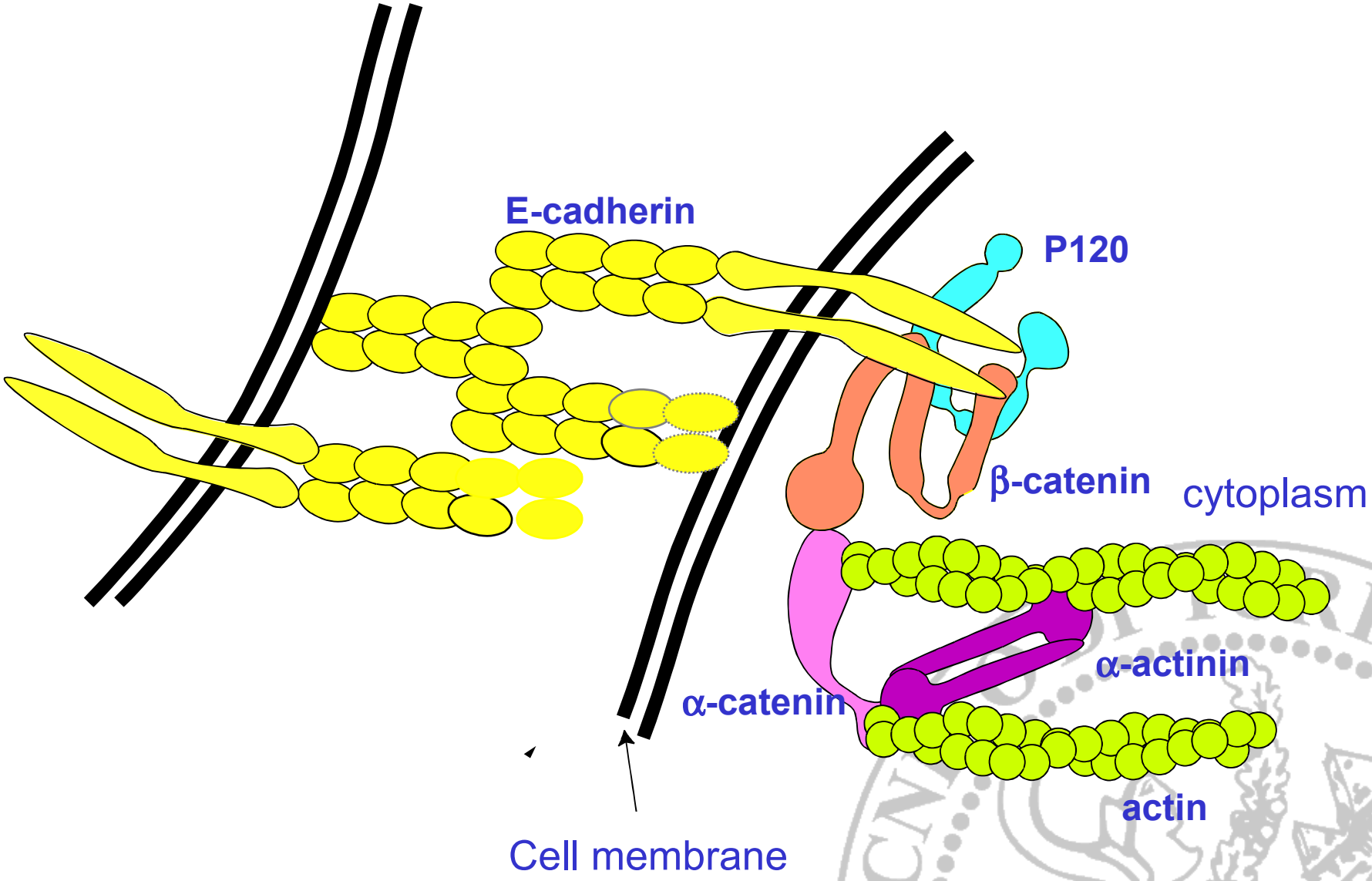
Cell volume ratio



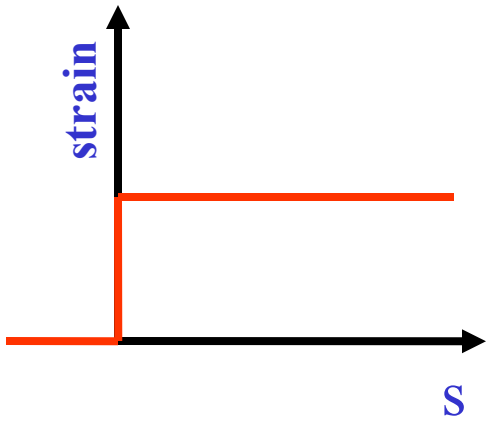
Nutrient

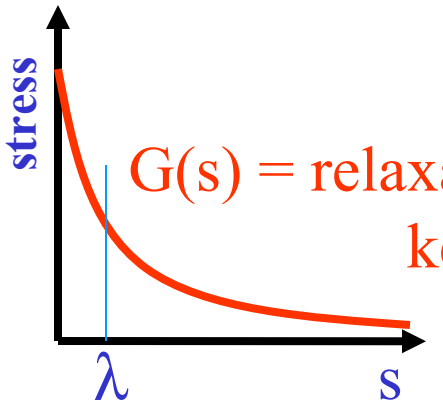


Cell-cell interactions

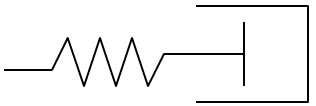


Stress relaxation in a liquid





G(s) = relaxation kernel



$$\mathbf{T}(t) = 2\mu \int_{-\infty}^{t} G(t-\tau)\mathbf{D}(\tau)\,d\tau = 2\mu \int_{0}^{+\infty} G(s)\mathbf{D}(t-s)\,ds$$

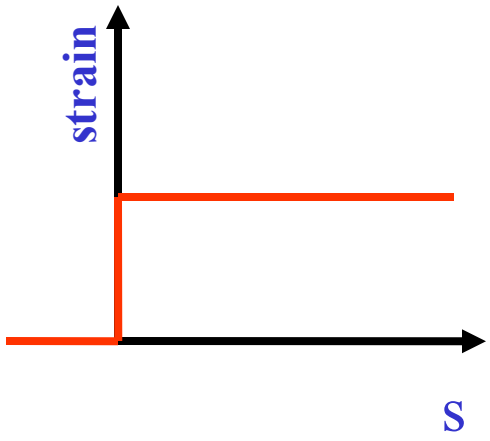
If $G(s) = G_0 e^{-s/\lambda}$

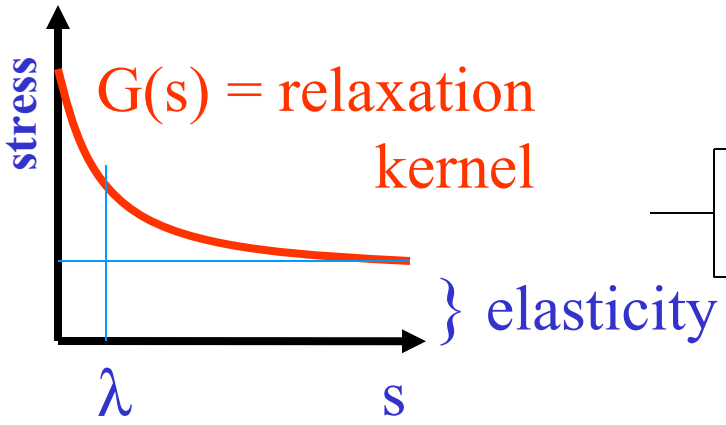
$$\lambda \frac{\mathcal{D}\mathbf{T}}{\mathcal{D}t} + \mathbf{T} = 2\mu\mathbf{D}$$

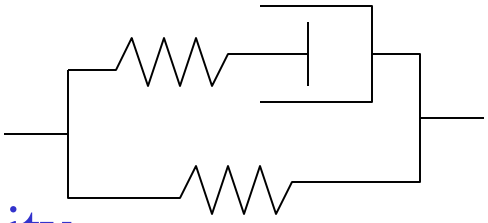
Remark: If $\mathbf{D} \approx \dot{\mathbf{E}}$ ⟹ $\lambda\dot{\mathbf{T}} + \mathbf{T} = 2\mu\dot{\mathbf{E}}$

~~$\lambda \frac{\mathcal{D}\mathbf{T}}{\mathcal{D}t} + \mathbf{T} = 2\mu \frac{\mathcal{D}\mathbf{E}}{\mathcal{D}t}$~~

Stress relaxation in a solid

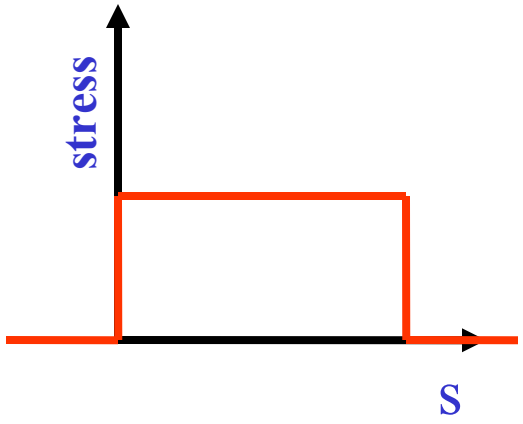


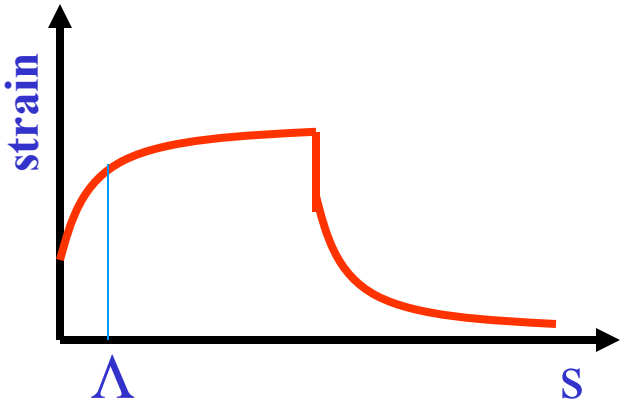




$$G(s) = E + (G_0 - E)e^{-s/\lambda} \Longrightarrow \lambda \dot{\mathbf{T}} + \mathbf{T} = E\left(\Lambda \dot{\mathbf{E}} + \mathbf{E}\right)$$

Creep



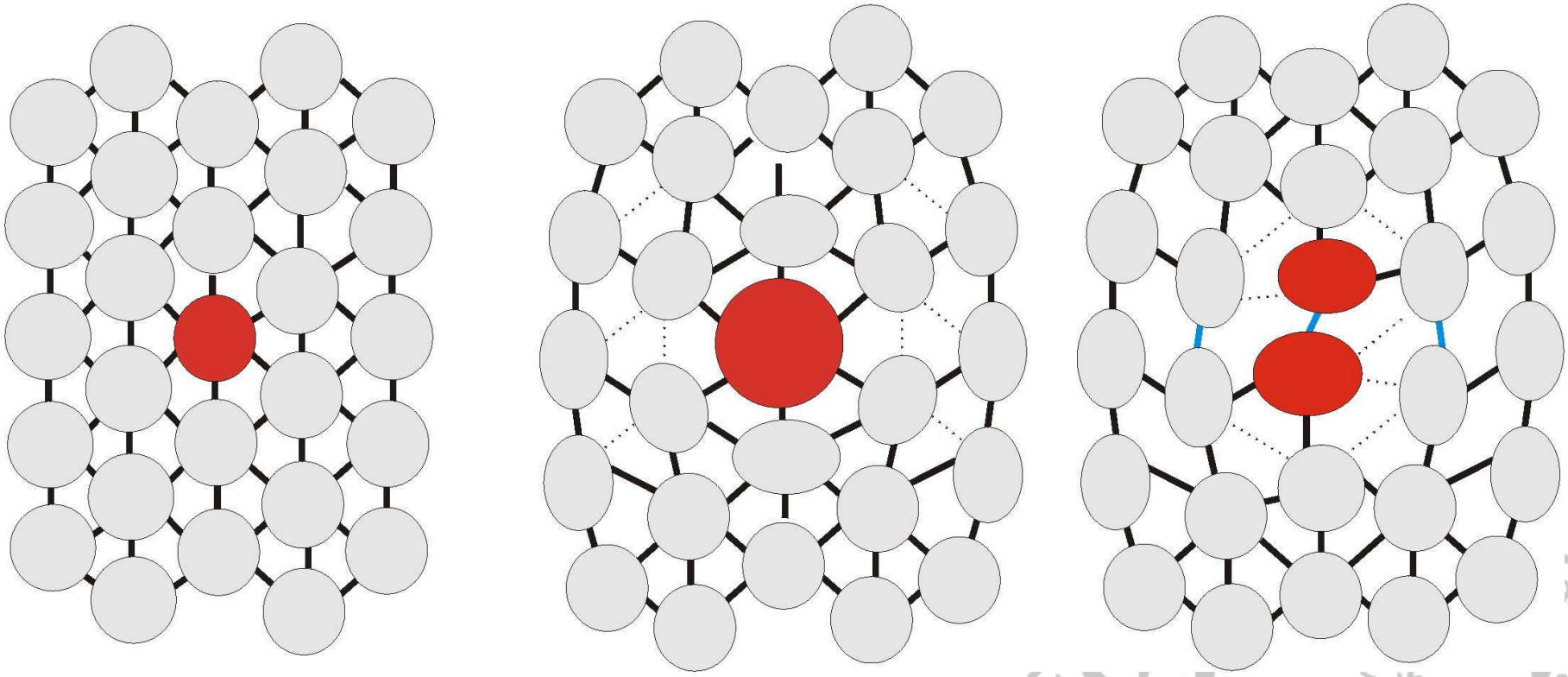


$$\mathbf{T}(t) = E\mathbf{E} + \int_{-\infty}^{t} G(t-\tau)\dot{\mathbf{E}}(\tau)\,d\tau = E\mathbf{E} + \int_{0}^{+\infty} G(s)\dot{\mathbf{E}}(t-s)\,ds$$

$$G(s) = E + (G_0 - E)e^{-s/\lambda} \Rightarrow \lambda\dot{\mathbf{T}} + \mathbf{T} = E\left(\Lambda\dot{\mathbf{E}} + \mathbf{E}\right)$$

Voigt-Kelvin solid $\Rightarrow$ $\mathbf{T} = E\left(\Lambda\dot{\mathbf{E}} + \mathbf{E}\right)$

Plastic re-organisation during growth



Cell re-organisation

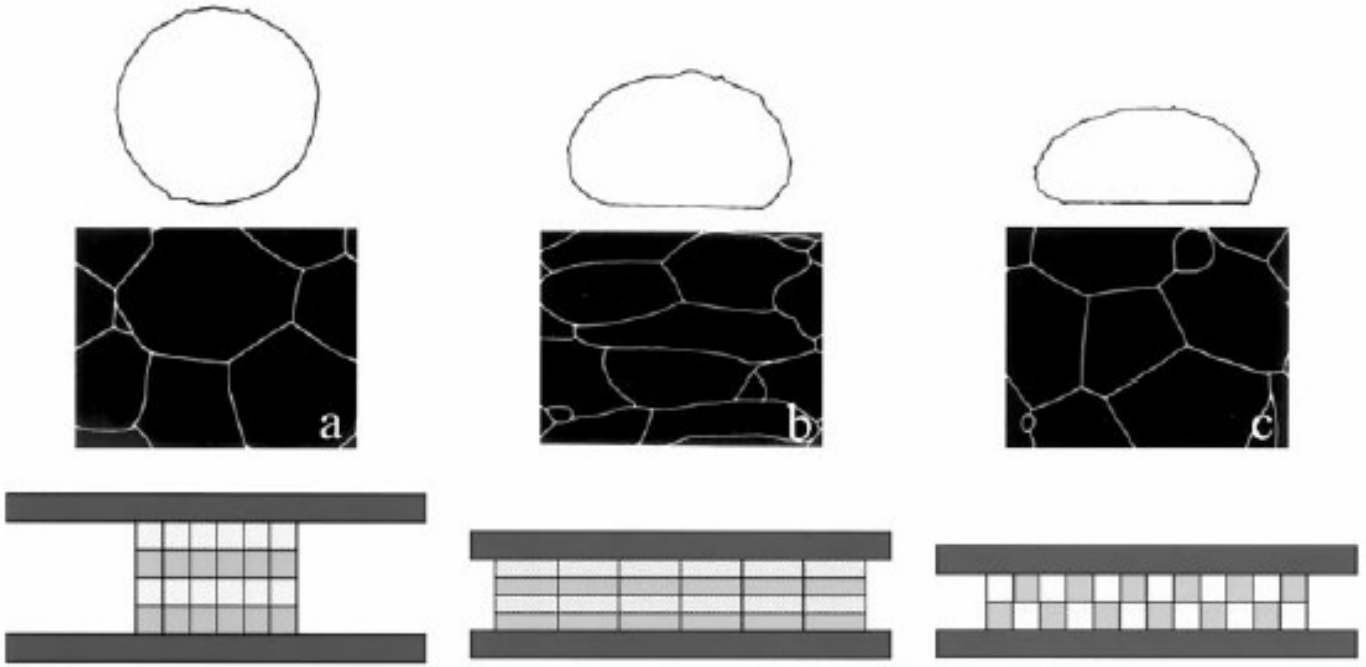
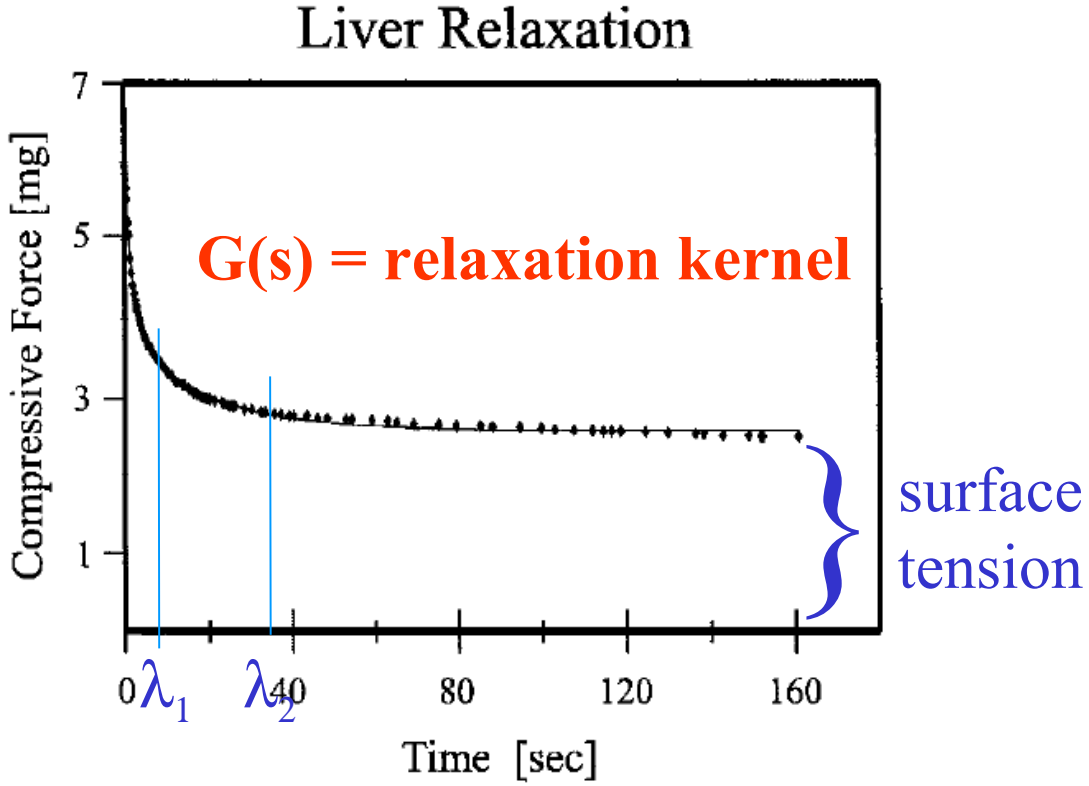


FIGURE 7 The bimodal relaxation process. *Bottom*: Schematic representation using cuboidal cells and aggregates. *Middle*: Cell perimeters traced from electron micrographic horizontal sections taken just below the widest point of the chick embryonic liver aggregates profiled above (Phillips et al., 1977). (*a*) Spherical aggregate before centrifugation, showing isodiametric cells. (*b*) Aggregate fixed under centrifugation at 2000 × *g*, applied for 5 min, showing internal cells under tension during the rapidly relaxing, more elastic phase. (*c*) Aggregate fixed under centrifugation at 2000 × *g*, applied for 36 hr, showing the final equilibrium state. Although the aggregate is much more flattened than at 5 min, the cells within it have fully relaxed and rearranged as diagrammed below.

- Forgacs et al., *Biophys. J.* **74**: 2227–2234 .(1998)

Stress relaxation



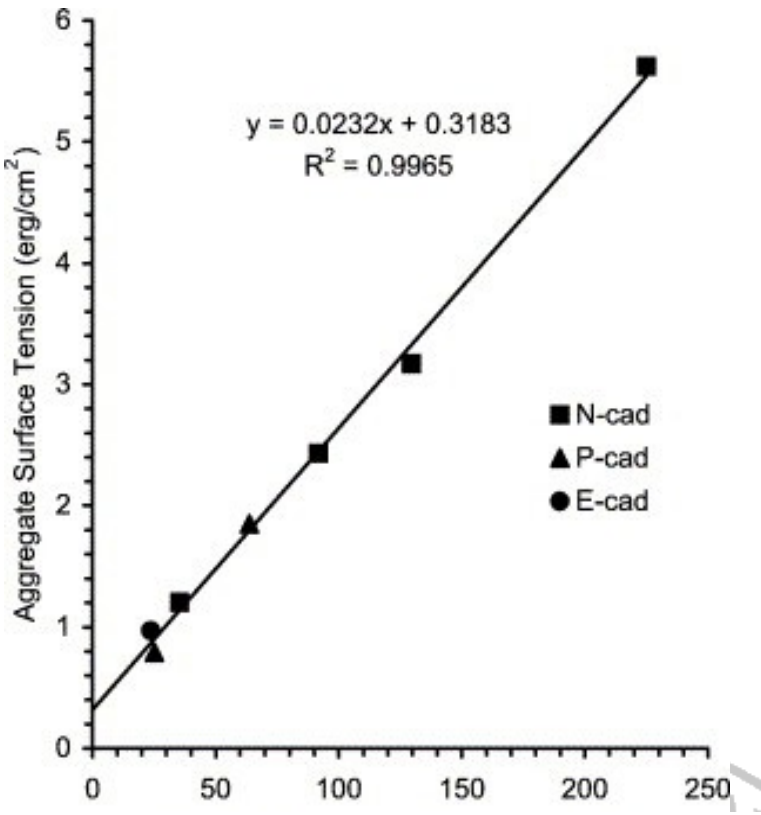


TABLE II – ASSESSMENT OF LIQUID *VS.* ELASTIC BEHAVIOR OF AGGREGATES OF LN-229 CELLS

	σ_1 (dynes/cm ± SEM)	σ_2 (dynes/cm ± SEM)	*t*-test σ_1 *vs.* σ_2 ($p < 0.05$)	σ_2/σ_1	F_2/F_1	*t*-test σ_2/σ_1 *vs.* F_2/F_1 ($p < 0.05$)
LN-229 TE	8.2±0.9	12.4±0.9	S	1.6	1.6	NS
LN-229 TE/C	10.3±0.3	10.0±0.4	NS	1.0	1.5	S

Cells were detached from tissue culture plates using either trypsin-EDTA alone (LN-229 TE) or with a mixture of trypsin-EDTA and collagenase type IV (LN-229 TE/C). Aggregates of LN-229 TE cells behaved elastically, since σ_1 was found to be statistically different from σ_2. Moreover, such aggregates obey Hooke's Law, since the ratio of F_2/F_1 was found to be identical to σ_2/σ_1, indicating that stress was equal to strain. In contrast, LN-229 TE/C aggregates behaved in a liquid-like manner, since σ_1 and σ_2 were statistically similar (unpaired *t*-test, $p = 0.44$). Further, the ratio of F_2/F_1 was significantly greater than σ_2/σ_1 (unpaired *t*-test, $p < 0.05$), also confirming that these aggregates do not obey Hooke's law and behave as liquid systems and not as elastic solids. S, significant difference; NS, no significant difference between sample means.

Cell re-organisation

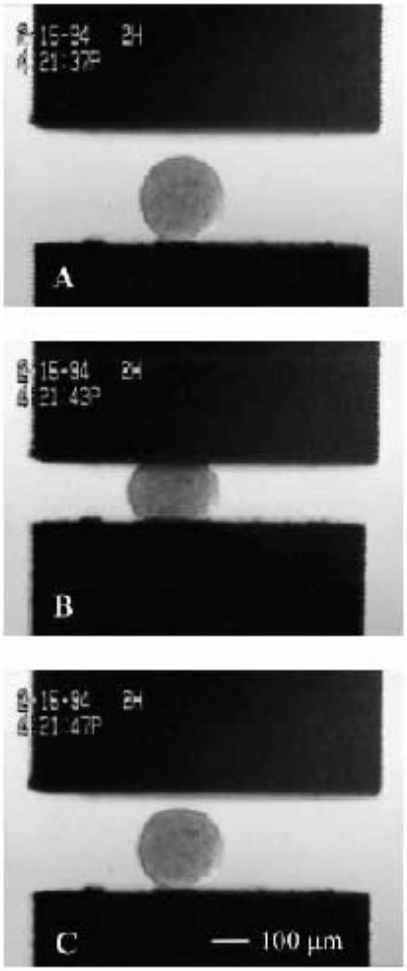
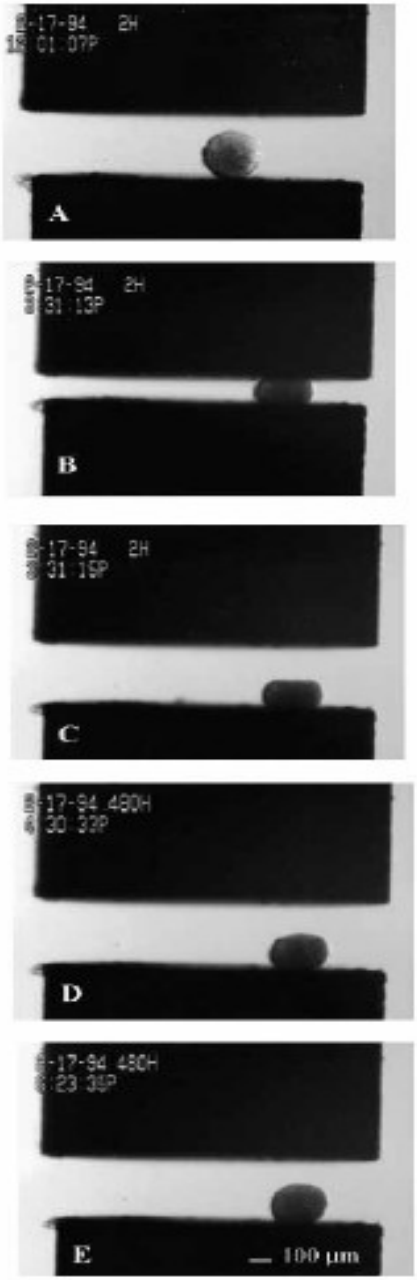


Fig. 4. A spherical heart aggregate on the lower compression plate
(A) before compression,
(B) after initiation of compression and
(C) released from compression after a few seconds behaves as an elastic solid, springing back to its original, spherical shape.



• Foty et al., *PRL* **72**: 2298-2301 (1996)

Fig. 5. A spherical heart aggregate on the lower compression plate
(A), compressed for 3.5 hours
(B), and then released
(C), temporarily retains flat upper and lower surfaces. Behaving as a viscous liquid, it slowly rounds up again (D,E) when incubated for an additional few hours.

Stress relaxation

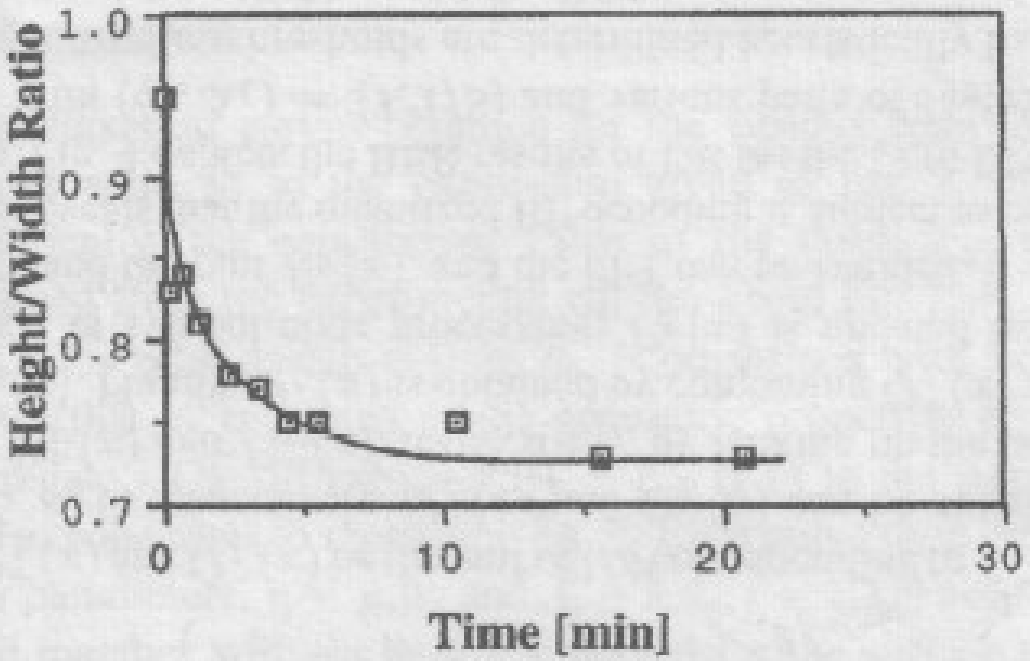
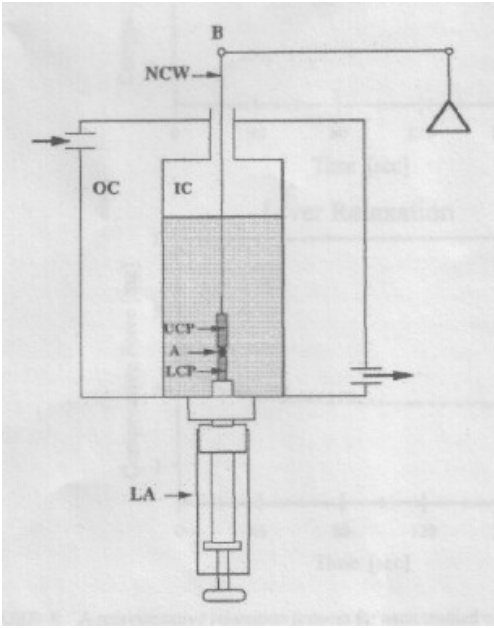
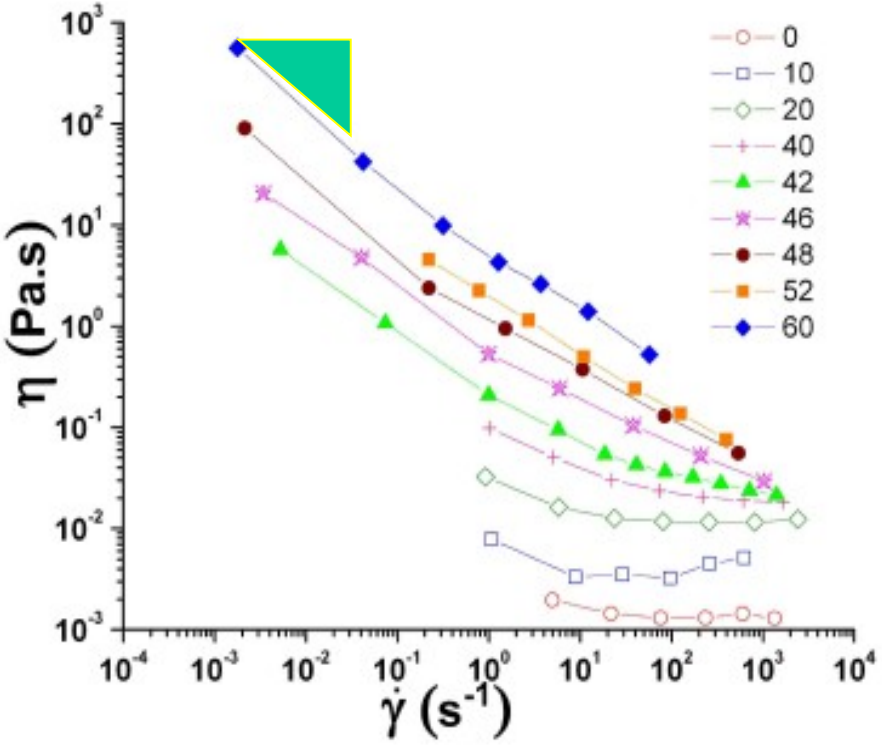


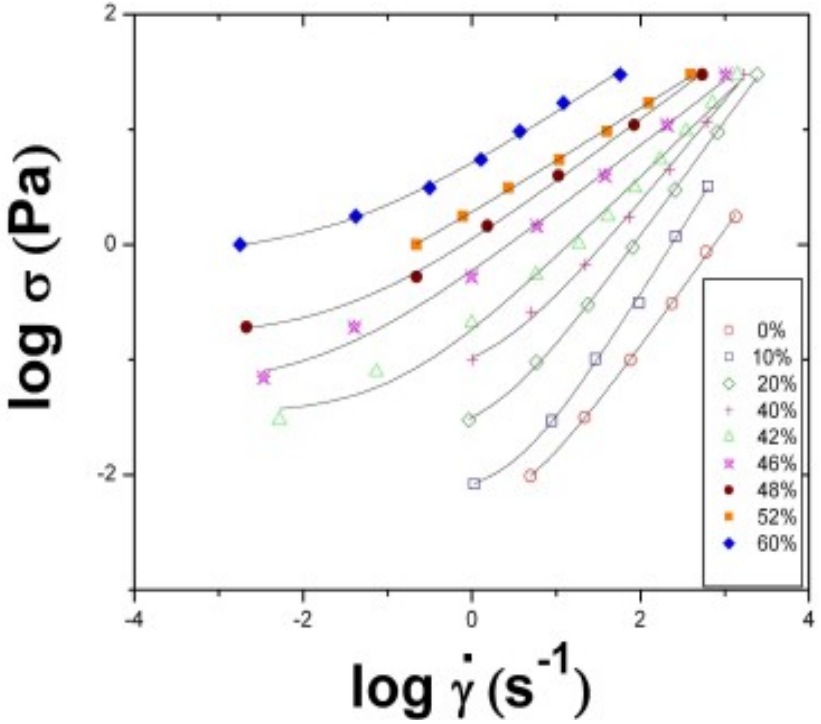
FIGURE 5 Liquid component of liver aggregate relaxation. An almost spherical chick embryonic liver aggregate was compressed under culture conditions between the parallel plates at a fixed separation distance and its profile shape video recorded. At intervals, the compression plates were separated for 11 s, allowing the aggregate to relax, after which compression was resumed. This process was reiterated until the upper and lower surfaces of the aggregate remained planar (shape equilibrium) after release from compression. **Squares** denote data points and the curve is drawn to lead the eye.



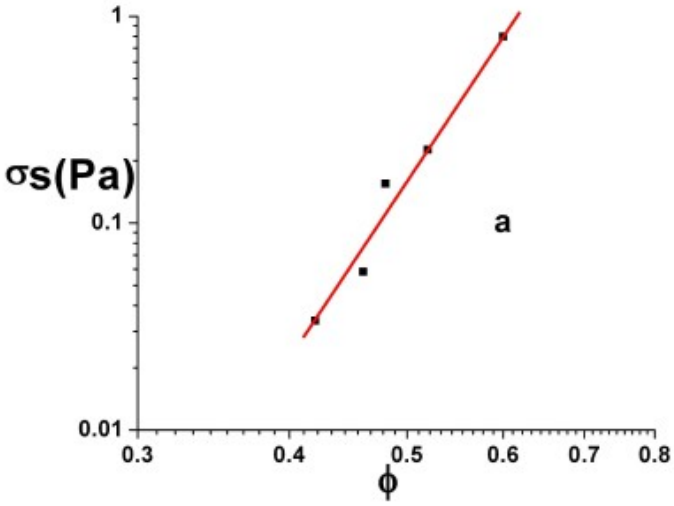
Forgacz et al. (1998)

Spheroids are Viscoplastic



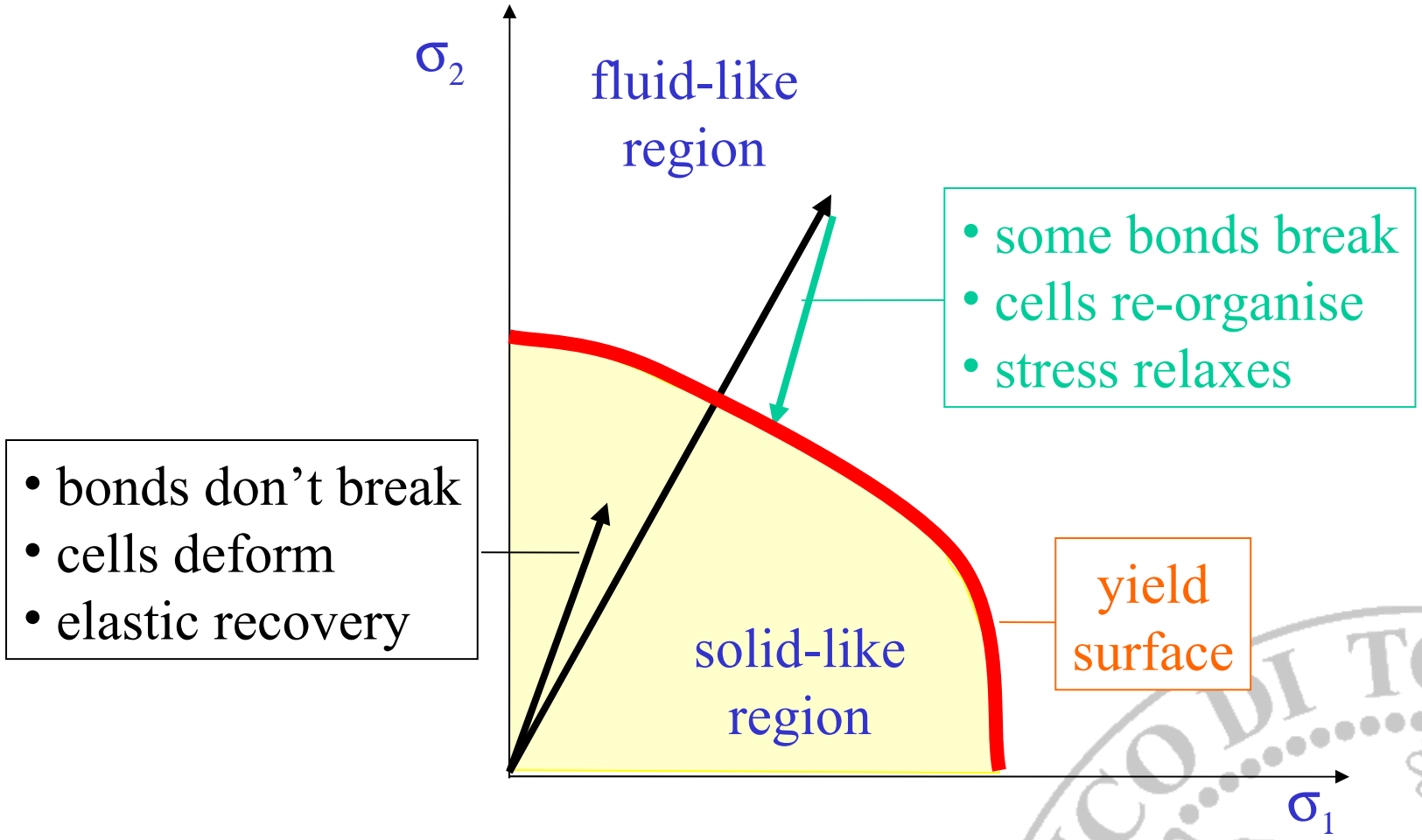


Yield stress using Herschel–Bulkley's model

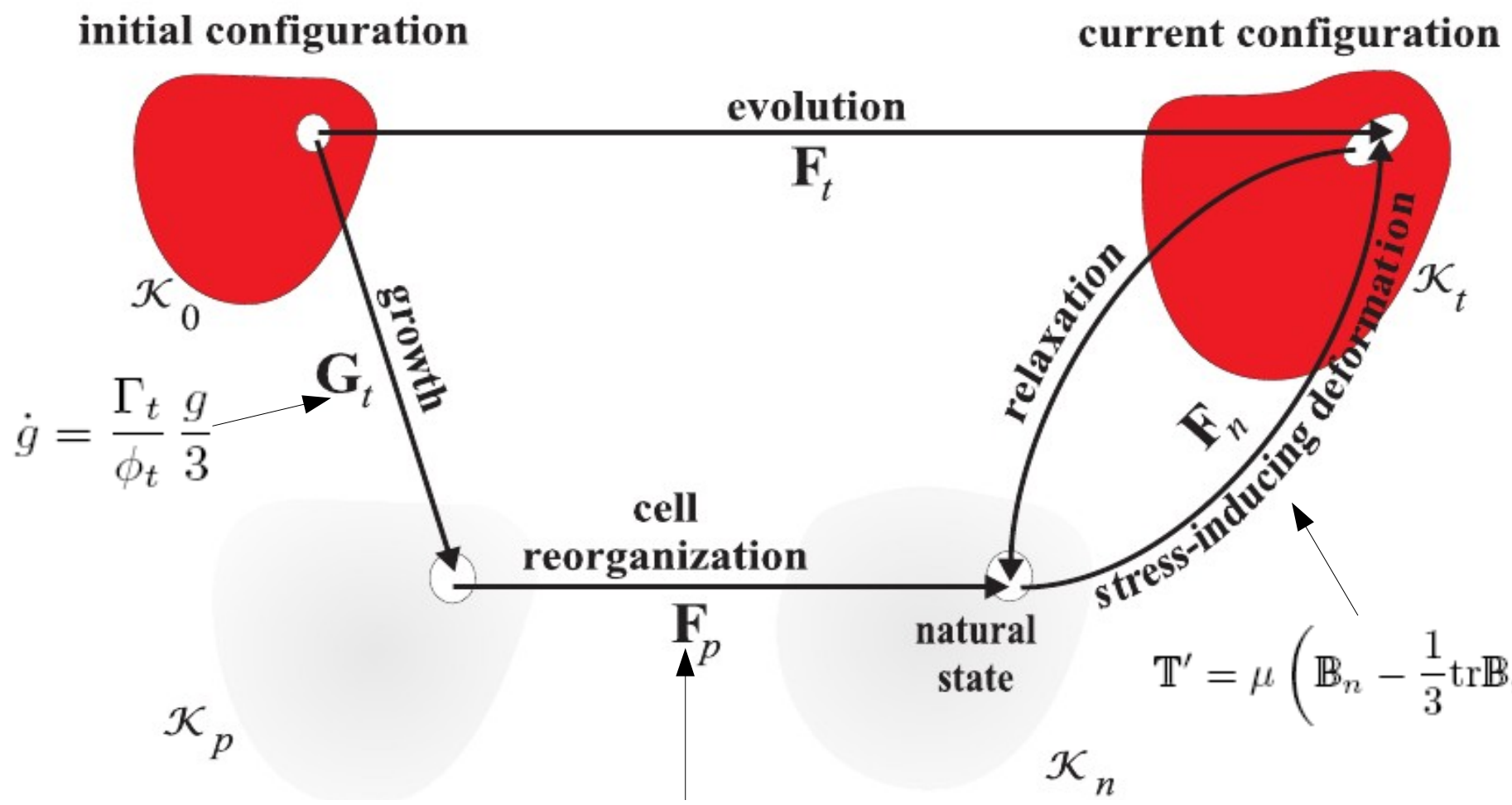


- Iordan, Duperray, Verdier, *Phys. Rev. E* **77,** 011911 (2008)

Cell re-organisation



Multiple Natural Configurations



$$\dot{\mathbb{F}}_p = \frac{\mu}{\tilde{\eta}}\left[1 - \frac{1}{\mu\tilde{f}\left(\mathbb{B}_n - \frac{1}{3}(\mathrm{tr}\mathbb{B}_n)\mathbb{I}\right)}\right]_+ \mathbb{F}_n^{-1}\left(\mathbb{B}_n - \frac{1}{3}(\mathrm{tr}\mathbb{B}_n)\mathbb{I}\right)\mathbb{F}$$

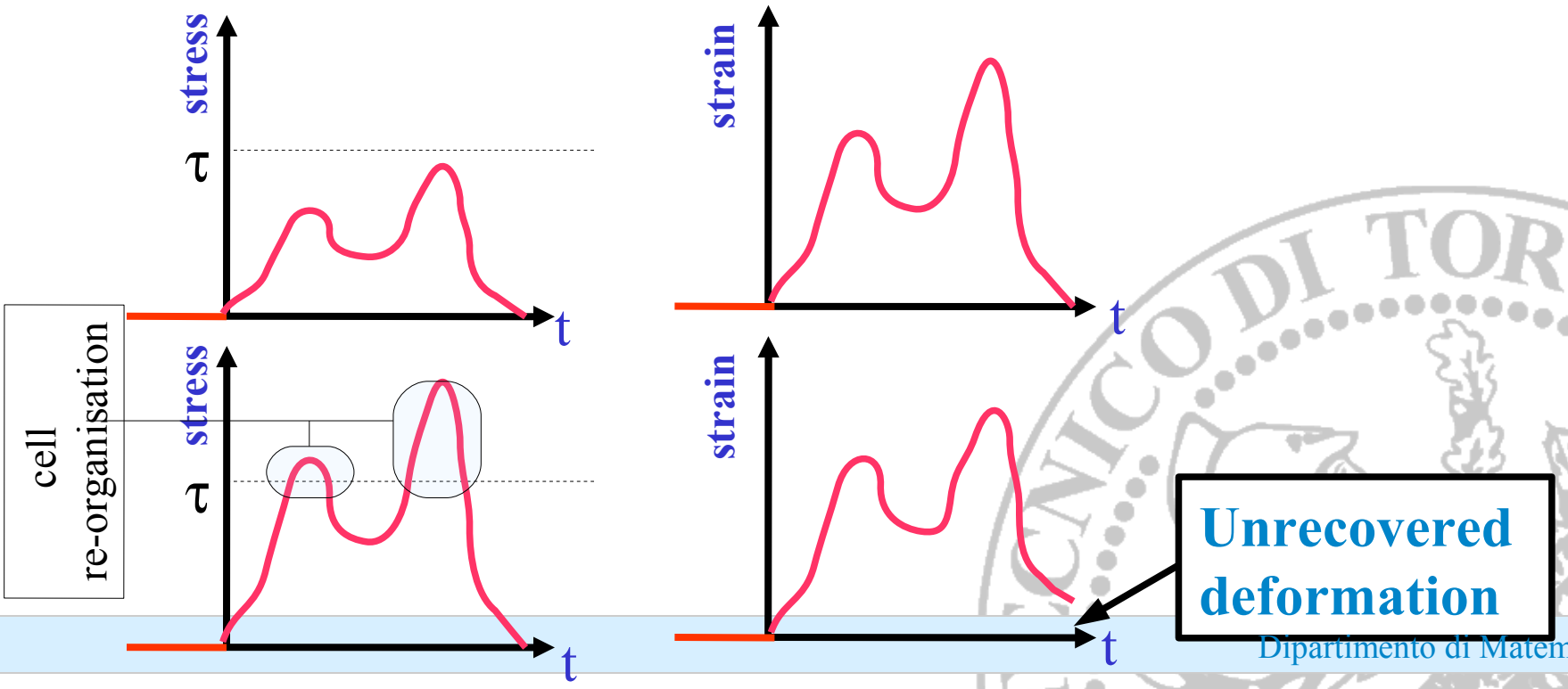
Invariant measure of the stress (maximum shear stress)

Limit cases: small elastic deformation

Small elastic deformations

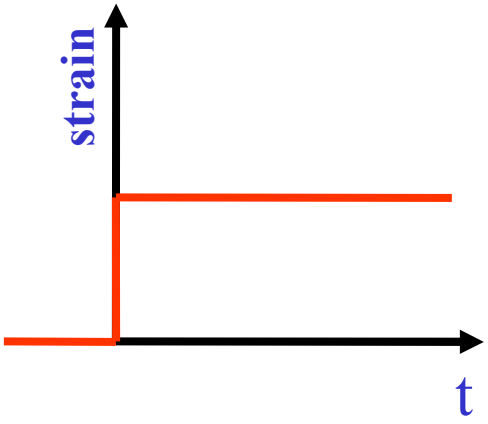
$$\dot{\mathbf{T}}'_t + \frac{\mu_t}{\eta_p}\left[1 - \frac{\phi_n \tau_0}{f(\mathbf{T}'_t)}\right]_+ \mathbf{T}'_t = 2\mu_t\left(\phi_n \mathbf{D}_t - \frac{\Gamma_t}{3}\mathbf{I}\right)$$

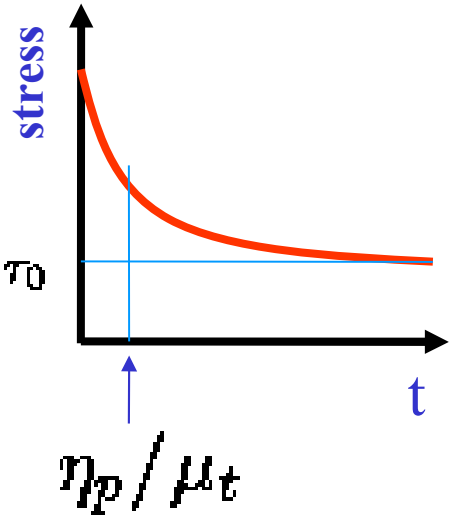
η_p / μ_t = characteristic time to relax the stress to the yield value



Standard tests

- Stress relaxation



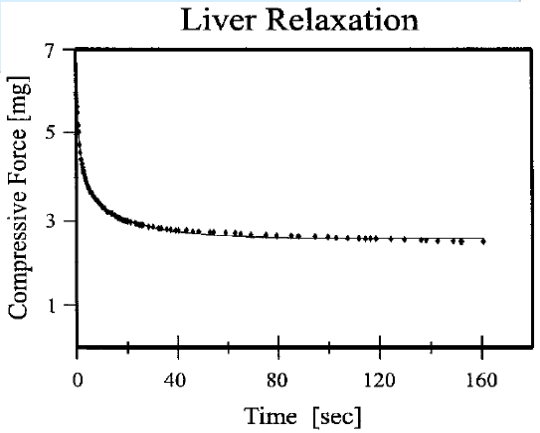


$f(T_t) = \phi_t \tau_0$

η_p / μ_t

} yield stress

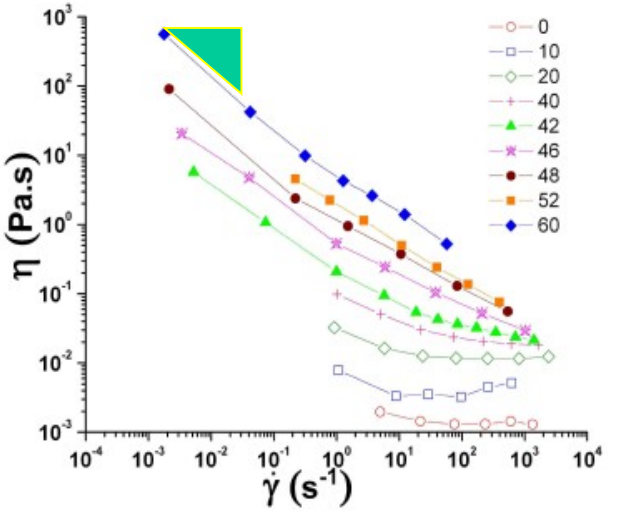
regardless of imposed strain



- Steady shear rate

$$T(t) \rightarrow \tau + \eta\,\gamma$$

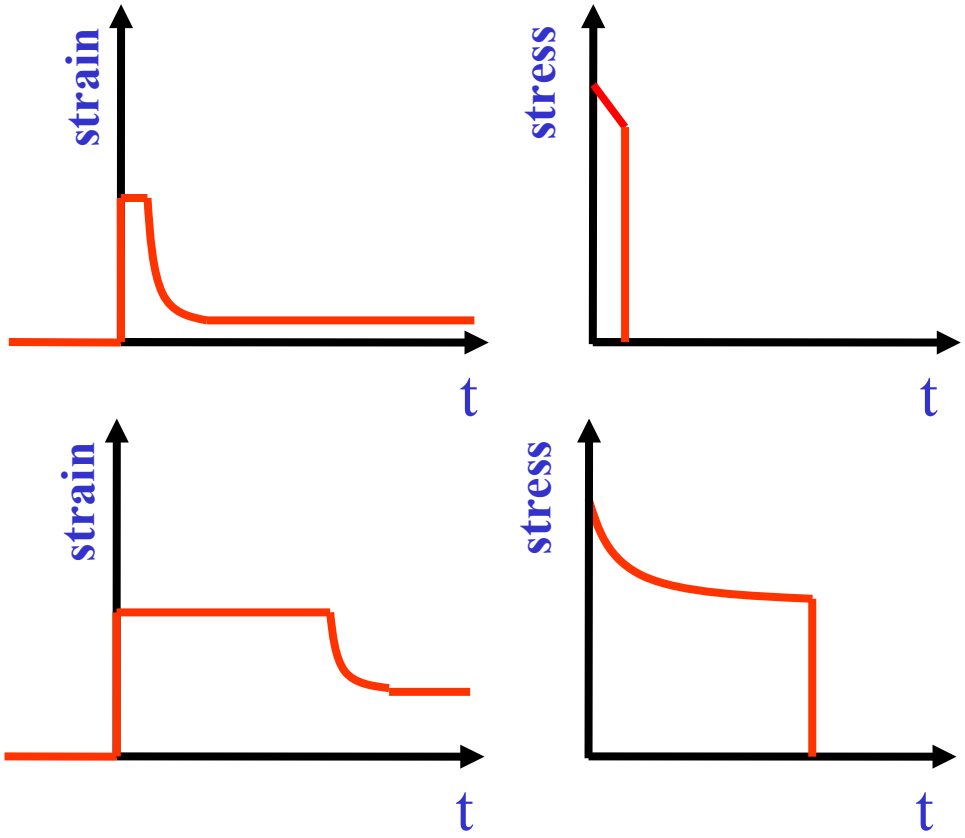
viscosity goes like γ^{-1}

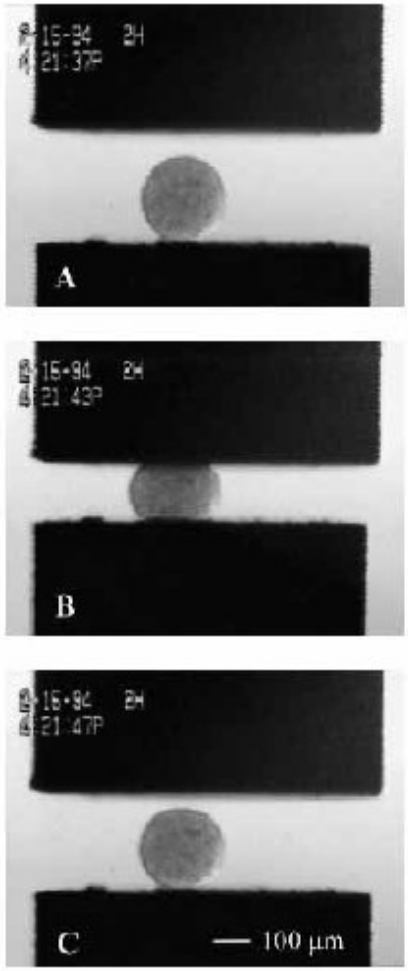


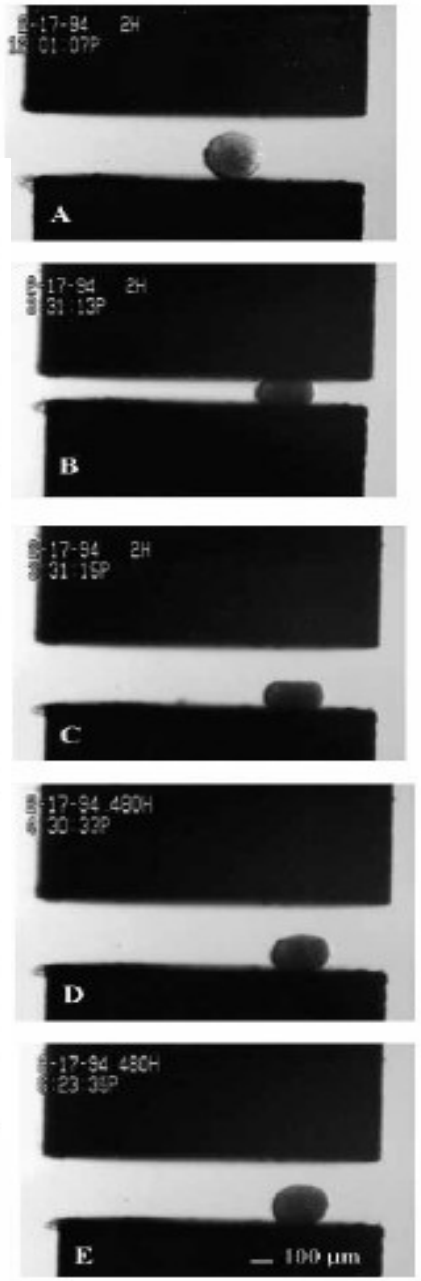
Foty's cell reorganisation test

- Imposing a deformation and then releasing the stress

$$\gamma = \left(\gamma_0 - \frac{\tau}{\mu}\right)\left(1 - e^{-t_{compr}/\lambda}\right)$$







Limit cases: small elastic deformation

Small elastic deformations

$$\dot{\mathbf{T}}_t' + \frac{\mu_t}{\eta_p}\left[1 - \frac{\phi_n \tau_0}{f(\mathbf{T}_t')}\right]_+ \mathbf{T}_t' = 2\mu_t\left(\phi_n \mathbf{D}_t - \cancel{\frac{\Gamma_t}{3}\mathbf{I}}\right)$$

η_p / μ_t = characteristic time to relax the stress to the yield value

Recall

$$\begin{cases} \mathbf{T} = E\,\mathbf{E} \\ \lambda\dot{\mathbf{T}} + \mathbf{T} = 2\mu\mathbf{D} \\ \lambda\dot{\mathbf{T}} + \mathbf{T} = E\left(\Lambda\dot{\mathbf{E}} + \mathbf{E}\right) \end{cases}$$

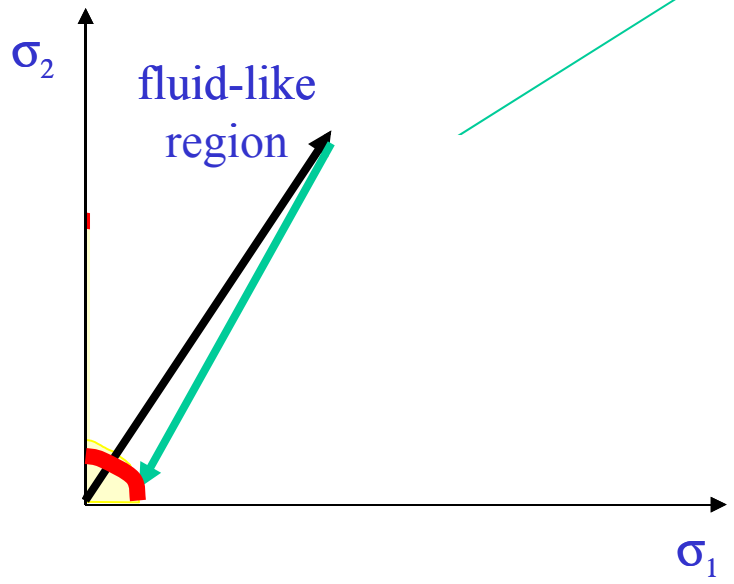
Elastic solid

Maxwell fluid

Standard linear solid

Limit cases: comparison with previous models

η_p / μ_t = characteristic time to relax the stress to the yield value



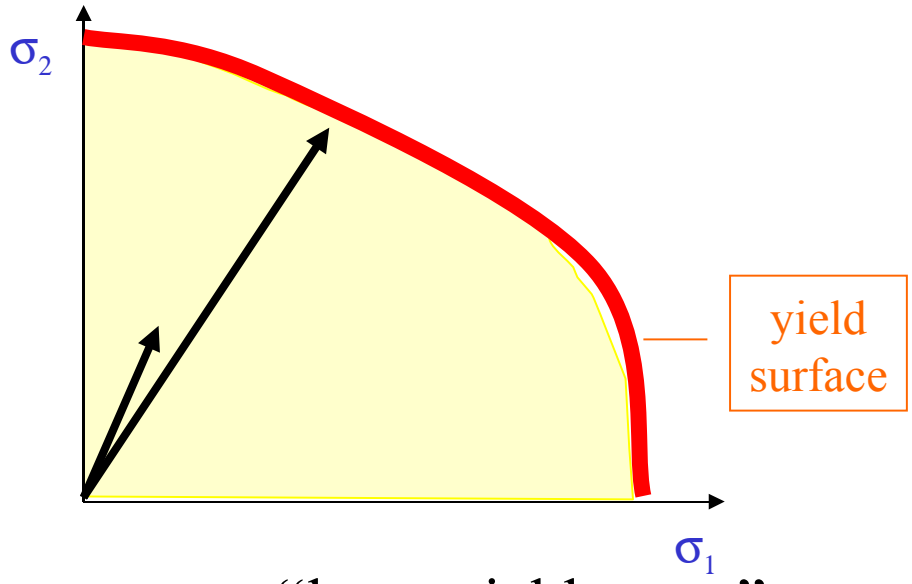
$\eta_p \ll \mu_t$

$\tau_0 \longrightarrow 0$

(negligible yield stress) ⟹ viscous models (e.g., Byrne-Preziosi, Chaplain et al., King et al.)

Limit cases: comparison with previous models

η_p / μ_t = characteristic time to relax the stress to the yield value



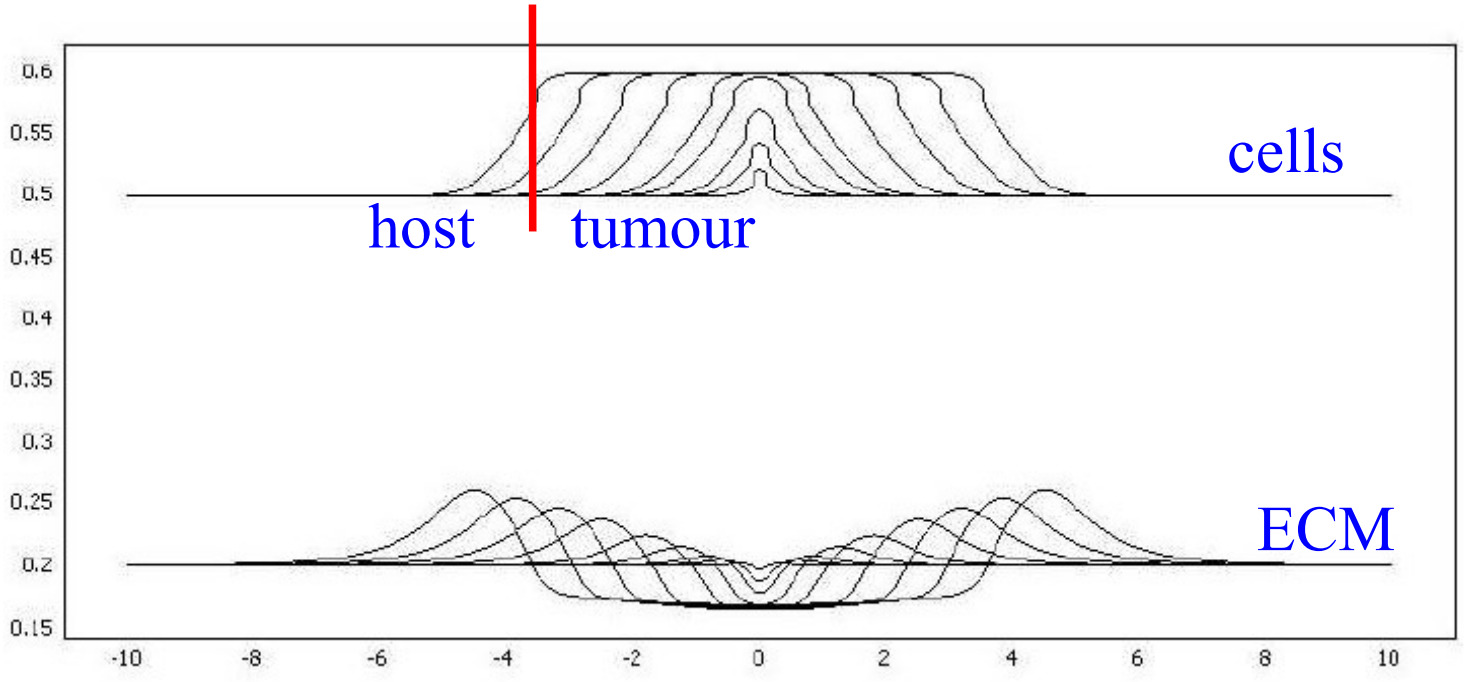
"large yield stress"
(till yield surface is reached)

"elastic models"
(e.g., Araujo et al.)

$\eta_p \gg \mu_t$ incompatible with small strain hypothesis
(large deformations will accumulate due to growth)

Example: Growth in a Duct

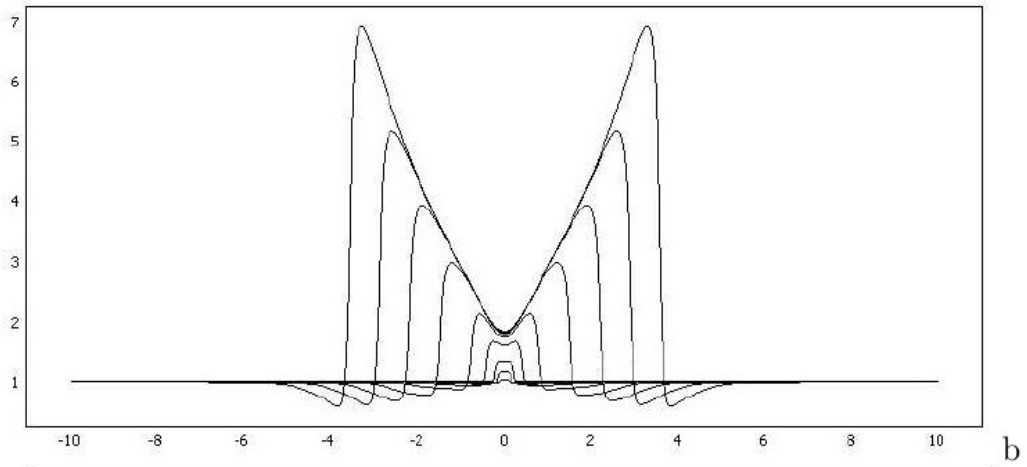
- $K = K_0 / K = 0.1$, ratio between the interaction force between tumour cells and the liquid flowing around it and the one between tumour cells and the ECM.
- $\mu = \mu_0 / \mu_t = 0.1$, ratio between the elastic moduli
- $\tau = \tau / \mu_t = 0.01$, ratio between yield stress and Young modulus
- $\eta_p = \nu\eta_p / \mu_t = 0.01$, ratio between the characteristic stress relaxation time due to cell reorganisation and the duplication time.
- $\delta = \delta/\gamma = 0.1$, ratio between the apoptotic and the growth rate.



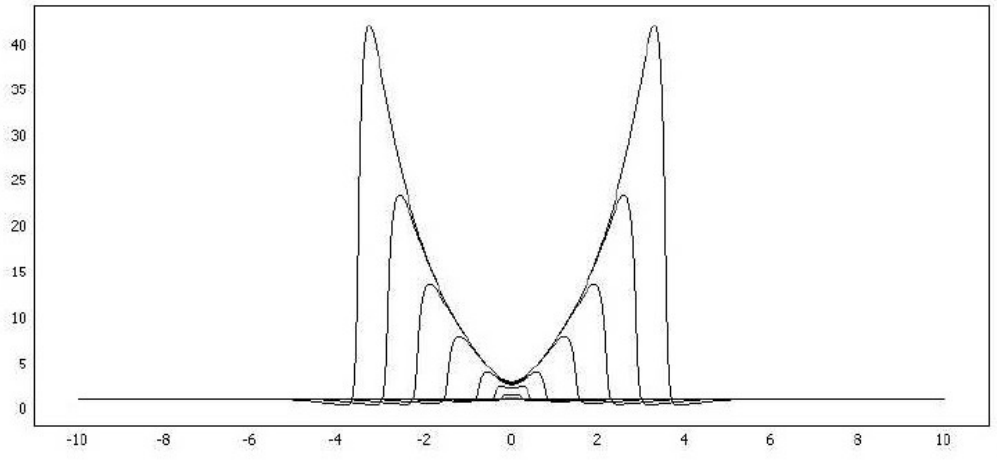
plastic deformation

growth

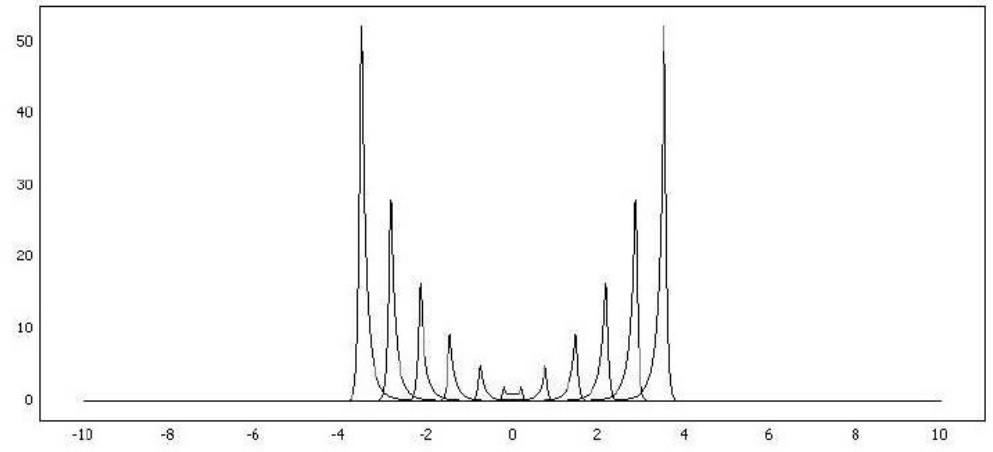
evolution of natural configuration



b



c



d

Example: Growth in a Duct