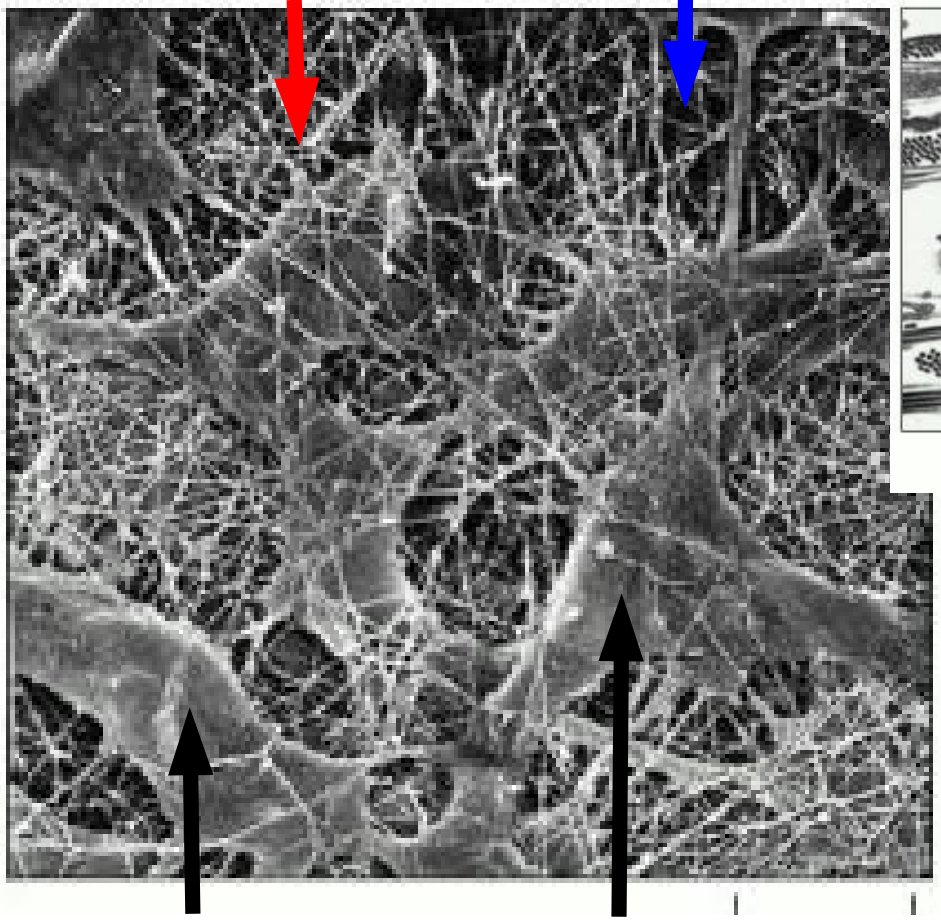
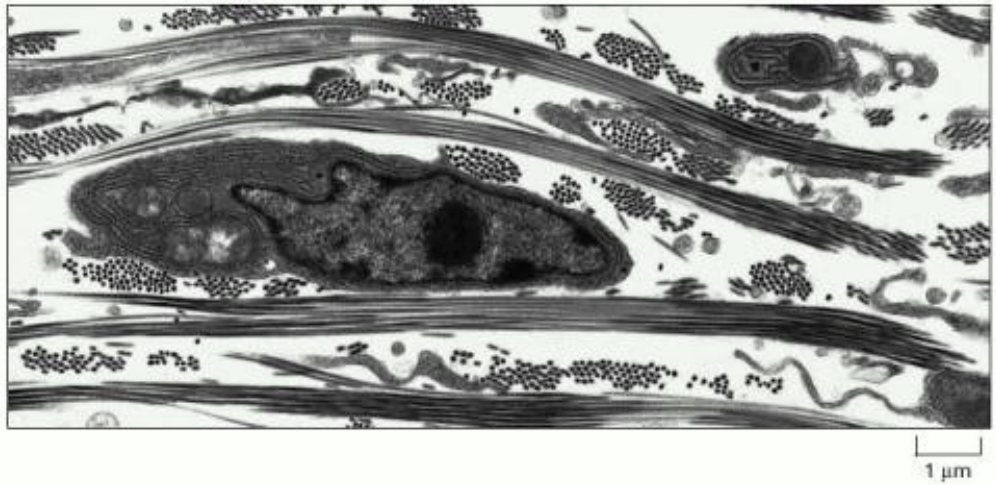
Tumours as Multiphase Systems

deformable and degradable ECM

extracellular liquid



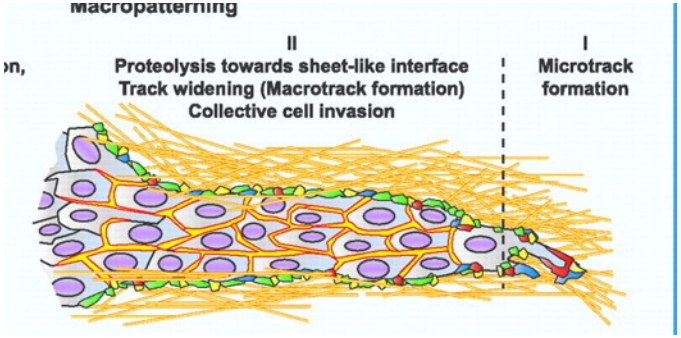


host cells and tumour cells

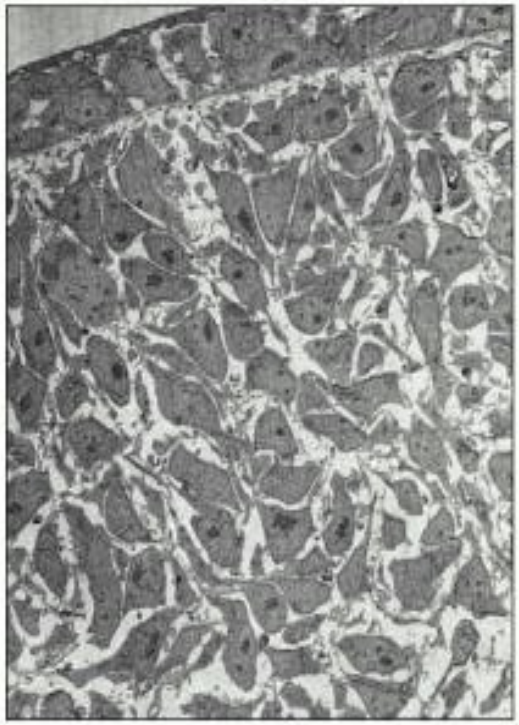
(P. Friedl, K. Wolf)

http://jcb.rupress.org/cgi/content/full/jcb.200209006/DC1

Tumours as Multiphase Systems



Friedl, P. et al. Cancer Res 2008;68:7247-7249



- **Growing ensemble of glioma cells**

  (T. Demuth, M. Berens)

  jcs.biologists.org/cgi/content/abstract/116/21/4409

- **Cell-cell interaction (neutrophil chasing a bacterium)**

  (D. Rogers)

  www.biochemweb.org/neutrophil.shtml

- **Collective cell motion**

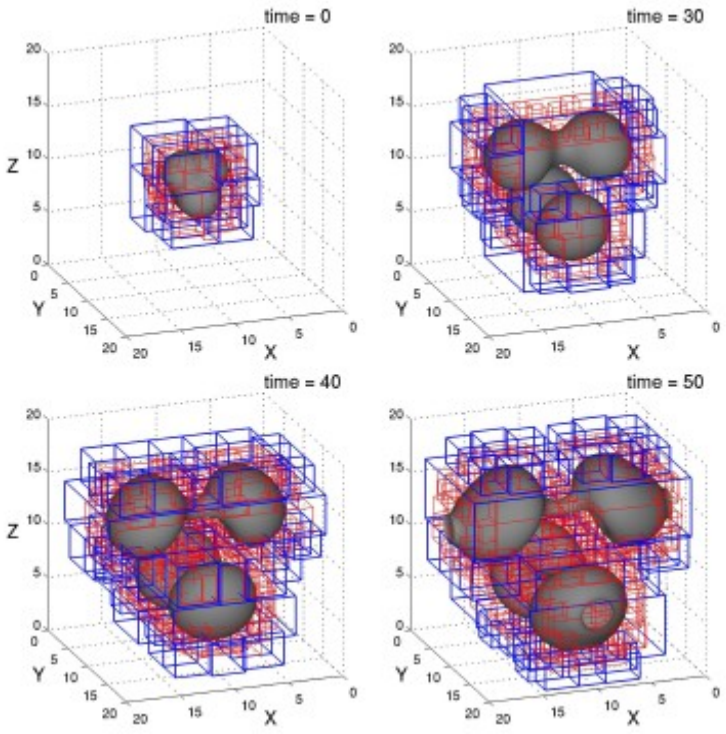
  (P. Friedl, K. Wolf)

Tumours as Monocomponent Tissues

Liquid in empty environment

With angiogenesis

Tumour Development

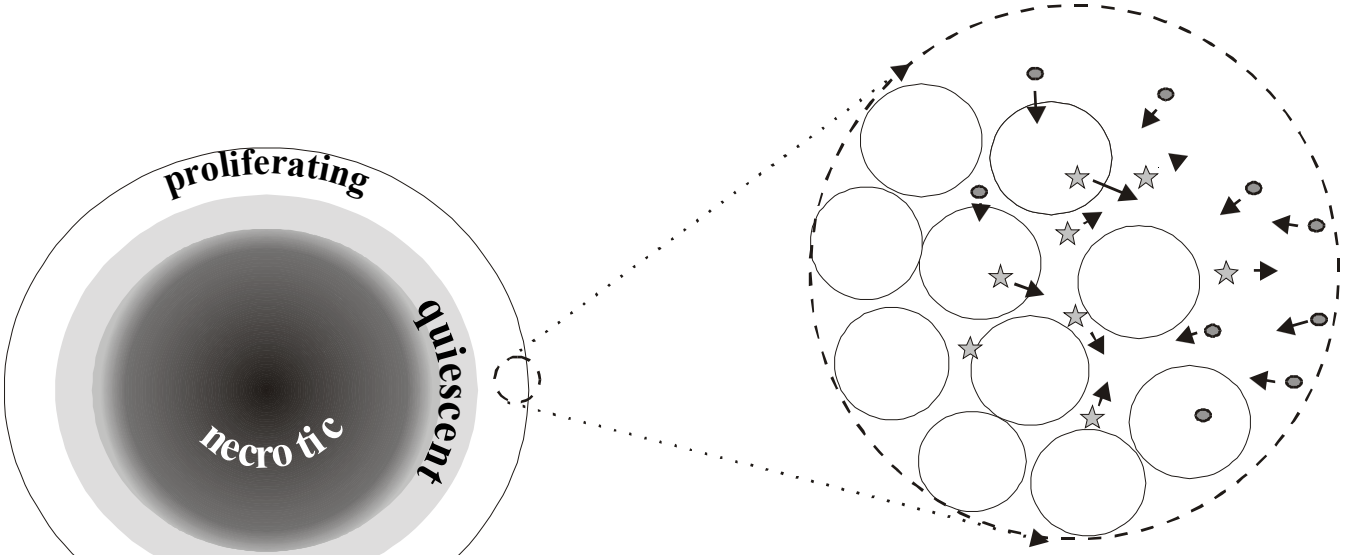


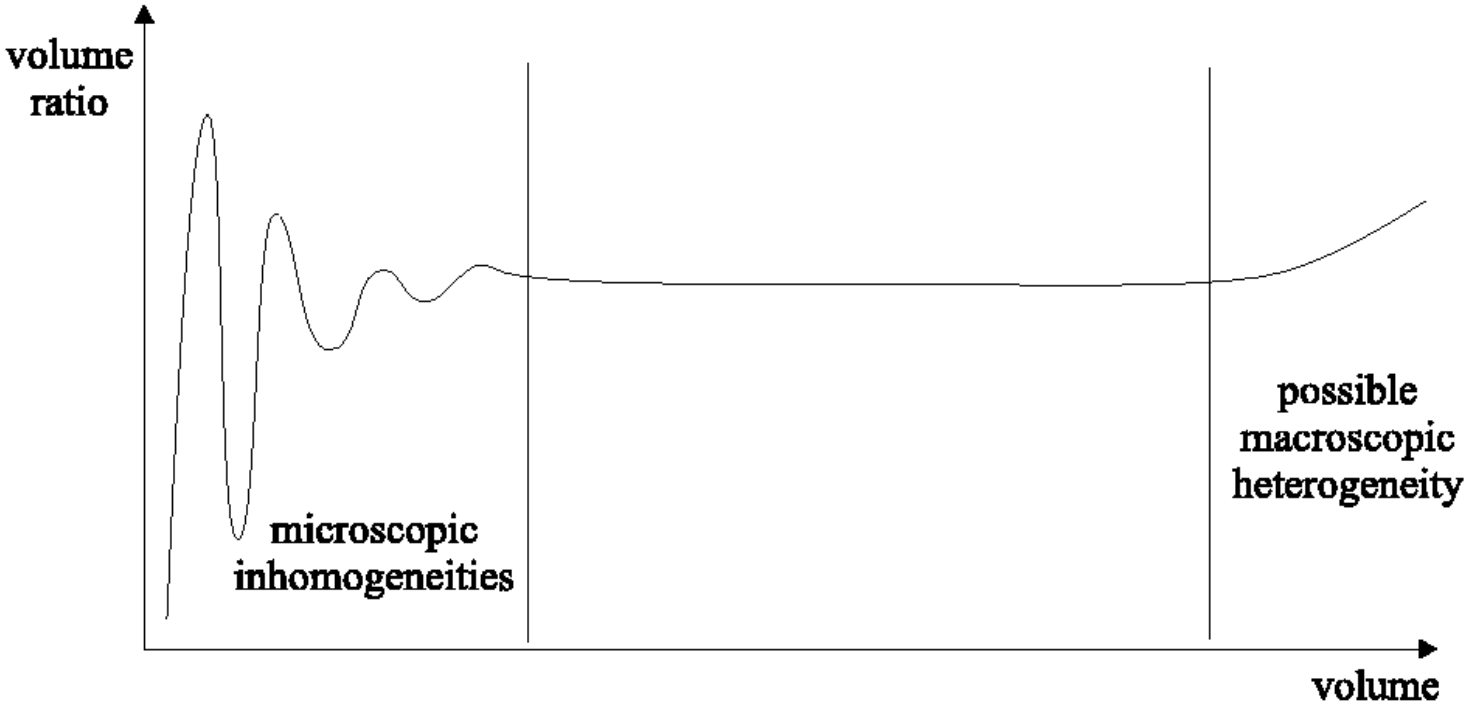
$$\nabla \cdot \mathbf{v} = \Gamma_T$$

$$\mathbf{v} = \nabla \Psi$$

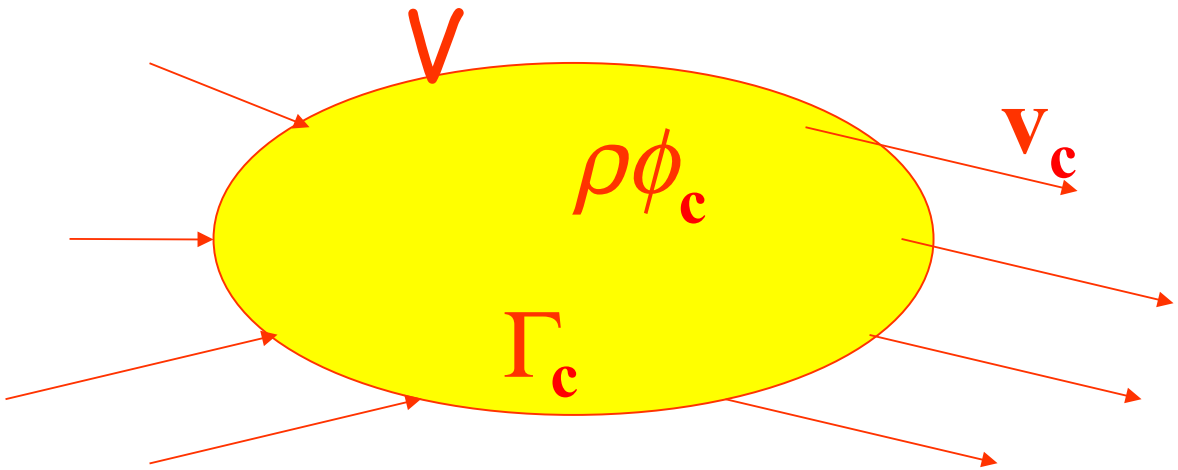
Macklin & Lowengrub, *J. Theor. Biol.* (2008)

Original movies at
biomathematics.shis.uth.tmc.edu/Multimedia.php


proliferating
quiescent
necrotic


volume ratio
microscopic inhomogeneities
possible macroscopic heterogeneity
volume

Mass Balance Equations



$$\frac{d}{dt}\int_{\mathcal{V}} \rho\phi_c \, dV = -\int_{\partial\mathcal{V}} \rho\phi_c \mathbf{v}_c \cdot \mathbf{n} \, d\Sigma + \int_{\mathcal{V}} \rho\Gamma_c \, dV$$

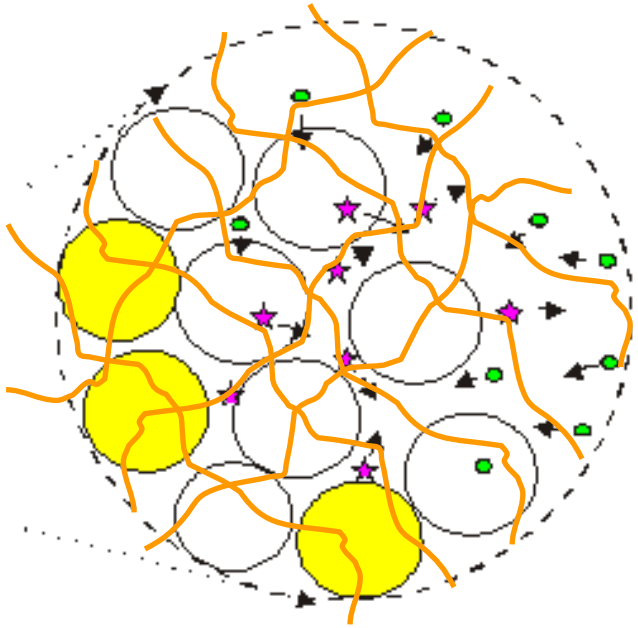
$$\frac{\partial}{\partial t}(\rho\phi_c) + \nabla \cdot (\rho\phi_c \mathbf{v}_c) = \rho\Gamma_c$$

$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha \quad \xrightarrow{\text{saturation}} \quad \nabla \cdot \sum_{\alpha=c,m,\ell,v} (\phi_\alpha \mathbf{v}_\alpha) = \sum_{\alpha=c,m,\ell,v} \Gamma_\alpha$$

$$\Gamma_\alpha = 0$$

Tumours as Multiphase Systems

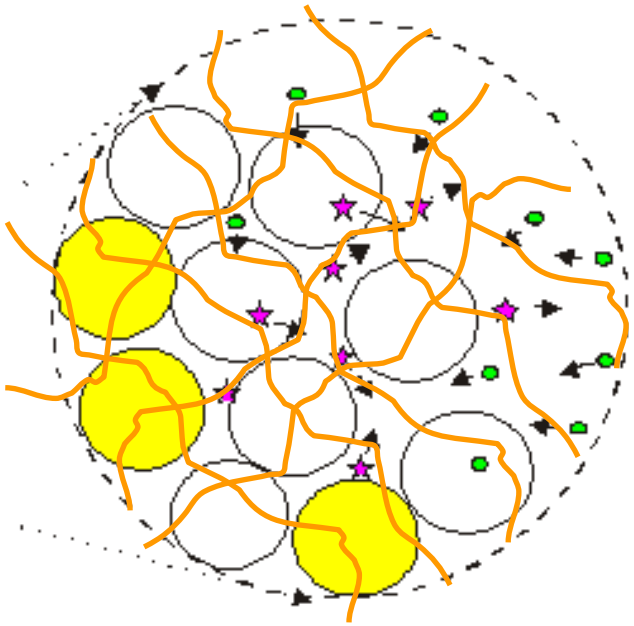
$$\frac{d}{dt}\int_{\mathrm{V}} \rho\phi_c \mathbf{v}_c \, dV = -\int_{\partial \mathrm{V}} \rho\phi_c \mathbf{v}_c (\mathbf{v}_c \cdot \mathbf{n}) \, d\Sigma + \int_{\partial \mathrm{V}} \widetilde{\mathbf{T}}_c^T \mathbf{n} \, d\Sigma$$
$$+ \int_{\mathrm{V}} \widetilde{\mathbf{m}}_c \, dV + \int_{\mathrm{V}} \rho\Gamma_c \mathbf{v}_c \, dV + \int_{\mathrm{V}} \rho\phi_c \mathbf{b}_c \, dV \,,$$



$$\rho\phi_c \left(\frac{\partial \mathbf{v}_c}{\partial t} + \mathbf{v}_c \cdot \nabla \mathbf{v}_c \right) = \nabla \cdot \widetilde{\mathbf{T}}_c + \rho\phi_c \mathbf{b}_c + \widetilde{\mathbf{m}}_c \,.$$

Tumours as Multiphase Systems

$$\begin{cases} \rho_j \left[\dfrac{\partial \phi_j}{\partial t} + \nabla \cdot (\phi_j \mathbf{v}_j) \right] = \rho_j \Gamma_j \\ \rho_j \phi_j \left(\dfrac{\partial \mathbf{v}_j}{\partial t} + \mathbf{v}_j \cdot \nabla \mathbf{v}_j \right) = \nabla \cdot \mathbf{T}_j + \mathbf{m}_j + \rho_j \phi_j \mathbf{b}_j \end{cases}$$



+ saturation $\displaystyle\sum_{j=1}^{n} \phi_j = 1,$

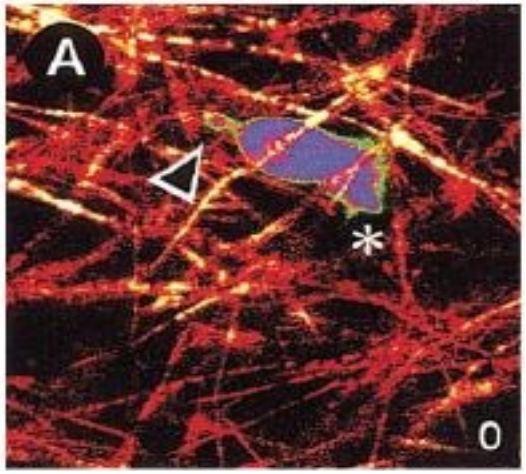
+ diffusion of nutrients
& chemical factors

- D. Ambrosi & L.P., *Math. Models Methods Appl. Sci.* **12**, 737-754 (2002)
- H. Byrne & L.P., *Math. Med. Biol.* **20**, 341-366 (2004)

Tumour Growth in a Rigid ECM

$$\rho\phi\left(\frac{\partial \mathbf{v}}{\partial t}+\mathbf{v}\cdot\nabla\mathbf{v}\right)=\nabla\cdot\mathbf{T}+\mathbf{m}+\rho\phi\mathbf{b}$$

$$-\Sigma(\phi)\mathbf{I} \qquad -\frac{1}{K}\mathbf{v}$$



(P. Friedl)

$$\mathbf{v}=K[-\nabla\Sigma+\rho\phi\mathbf{b}]=-K\Sigma'(\phi)\nabla\phi+\rho K\phi\mathbf{b}$$

$$\rho\left[\frac{\partial\phi}{\partial t}+\nabla\cdot(\phi\ \mathbf{v}\ )\right]=\Gamma_T$$

(degenerate parabolic eq.)

Tumour Growth in a Rigid ECM

$$\mathbf{v} = K[-\nabla\Sigma + \rho\phi\mathbf{b}] = -K\Sigma'(\phi)\nabla\phi + \rho K\phi\mathbf{b}$$

$$\rho\left[\frac{\partial\phi}{\partial t} + \nabla\cdot(\phi\ \mathbf{v}\ )\right] = \Gamma_T \quad \overset{?}{\Longleftrightarrow} \quad \nabla^2\Psi = \frac{\Gamma - \Delta}{\rho_0} = \Gamma_T$$

$$\phi(\mathbf{x},t) = \phi_0 + \epsilon\phi_1(\mathbf{x},t)$$

$$\epsilon\frac{\partial\phi_1}{\partial t} = \nabla\cdot\left[(\phi K\Sigma')(\phi=\phi_0)\epsilon\nabla\phi_1\right] + \Gamma(\phi)$$

$1/\varepsilon$

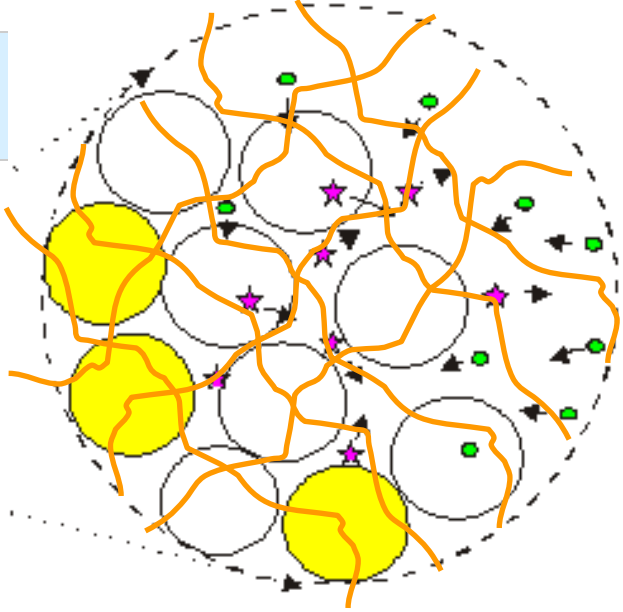
3 Phases

$$\frac{\partial \phi_0}{\partial t} + \nabla \cdot (\phi_0 \mathbf{v}_0) = \Gamma_0 ,$$

$$\frac{\partial \phi_T}{\partial t} + \nabla \cdot (\phi_T \mathbf{v}_T) = \Gamma_T ,$$

$$\frac{\partial \phi_\ell}{\partial t} + \nabla \cdot (\phi_\ell \mathbf{v}_\ell) = \Gamma_\ell ,$$

Growth terms



$$\rho \phi_0 \left(\frac{\partial \mathbf{v}_0}{\partial t} + \mathbf{v}_0 \cdot \nabla \mathbf{v}_0 \right) = \nabla \cdot \mathbf{T}_0 + \mathbf{b}_0 + \mathbf{m}_0^\sigma ,$$

$$\rho \phi_T \left(\frac{\partial \mathbf{v}_T}{\partial t} + \mathbf{v}_T \cdot \nabla \mathbf{v}_T \right) = \nabla \cdot \mathbf{T}_T + \mathbf{b}_T + \mathbf{m}_T^\sigma ,$$

$$\rho \phi_\ell \left(\frac{\partial \mathbf{v}_\ell}{\partial t} + \mathbf{v}_\ell \cdot \nabla \mathbf{v}_\ell \right) = \nabla \cdot \mathbf{T}_\ell + \mathbf{b}_\ell + \mathbf{m}_\ell^\sigma ,$$

Interaction forces exchanged with other constituents

Partial stresses

At least three phases

(rigid ECM)

$$\begin{cases} \frac{\partial}{\partial t}\phi_0 = \Gamma_0\,, \\ \frac{\partial}{\partial t}\phi_T + \nabla\cdot(\phi_T \mathbf{v}_T) = \Gamma_T\,, \\ \nabla\cdot(\phi_T \mathbf{v}_T + \phi_\ell \mathbf{v}_\ell) = 0\,, \\ \mathbf{v}_\ell - \mathbf{v}_T = -K\nabla P\,, \\ \mathbf{v}_T = K_0\left[-(1-\phi_0)\nabla P + \nabla\cdot\hat{\mathbf{T}}_T + \mathbf{b}_T\right], \end{cases}$$

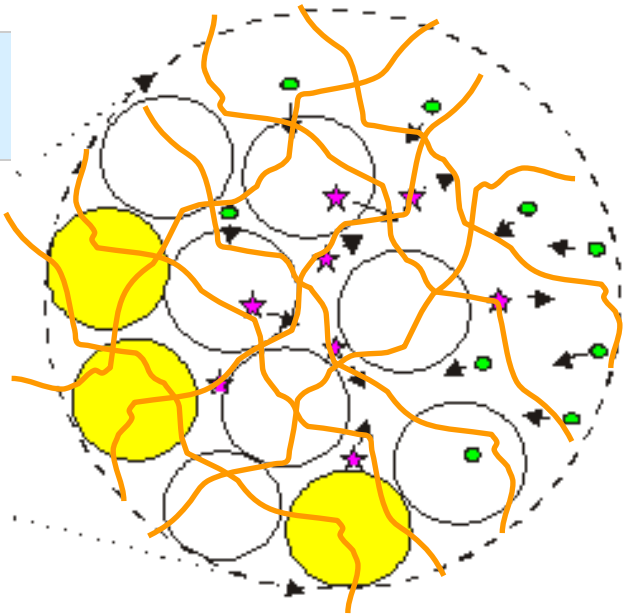
$\alpha(\phi_T)\nabla c$

$-\Sigma(\phi)\mathbf{I}$

Limit case: Neglecting interaction with the liquid +

$$\frac{\partial \phi_T}{\partial t} + \nabla\cdot(K_0\alpha(\phi_T)\phi_T\nabla c) = \nabla\cdot(K_0\Sigma'(\phi_T)\phi_T\nabla\phi_T) + \Gamma_T$$

3 Phases



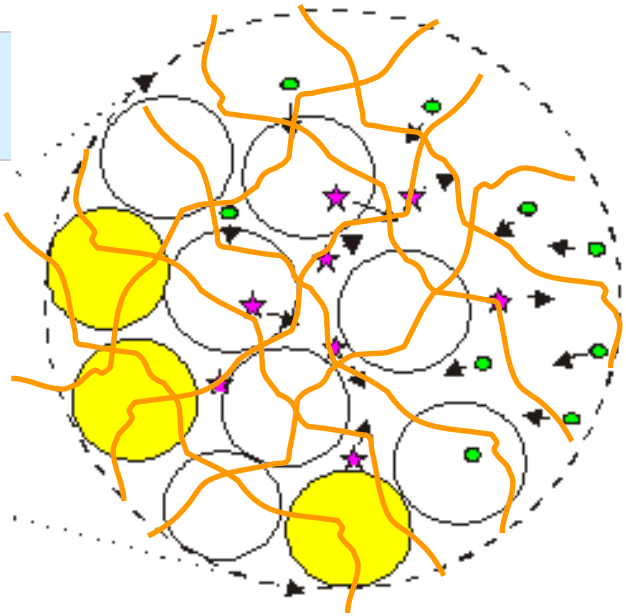
$$\frac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha \,, \qquad \text{for} \quad \alpha = c, m, \ell,$$

$$\begin{cases} -\phi_c \nabla P + \nabla \cdot (\phi_c \mathbf{T}_c) + \mathbf{m}_c + \rho \phi_c \mathbf{b}_c = \mathbf{0} \,, \\ -\phi_m \nabla P + \nabla \cdot (\phi_m \mathbf{T}_m) + \mathbf{m}_m = \mathbf{0} \,, \\ \mathbf{M}_m(\mathbf{v}_\ell - \mathbf{v}_m) + \mathbf{M}_c(\mathbf{v}_\ell - \mathbf{v}_c) = -\phi_\ell \nabla P \,, \end{cases} \Rightarrow \quad \mathbf{v}_\ell = \mathbf{M}^{-1} \left(\sum_{\alpha=c,m} \mathbf{M}_\alpha \mathbf{v}_\alpha - \phi_\ell \nabla P \right)$$

$$\nabla \cdot \left(\frac{\mathbf{K}}{\mu} \nabla P \right) = \nabla \cdot \left[\sum_{\alpha=c,m} \left(\phi_\alpha \mathbf{I} + \frac{\mathbf{K}}{\phi_\ell \mu} \mathbf{M}_\alpha \right) \mathbf{v}_\alpha \right] - \sum_{\alpha=c,m,\ell} \Gamma_\alpha$$

3 Phases

$$\begin{cases} \dfrac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha \,, \qquad \text{for} \quad \alpha = c, m \\ \nabla \cdot (\phi_c \mathbf{T}_c) + \mathbf{m}_{cm} + \rho \phi_c \mathbf{b}_c = \mathbf{0} \,, \\ \nabla \cdot (\phi_m \mathbf{T}_m) - \mathbf{m}_{cm} = \mathbf{0} \,. \end{cases}$$



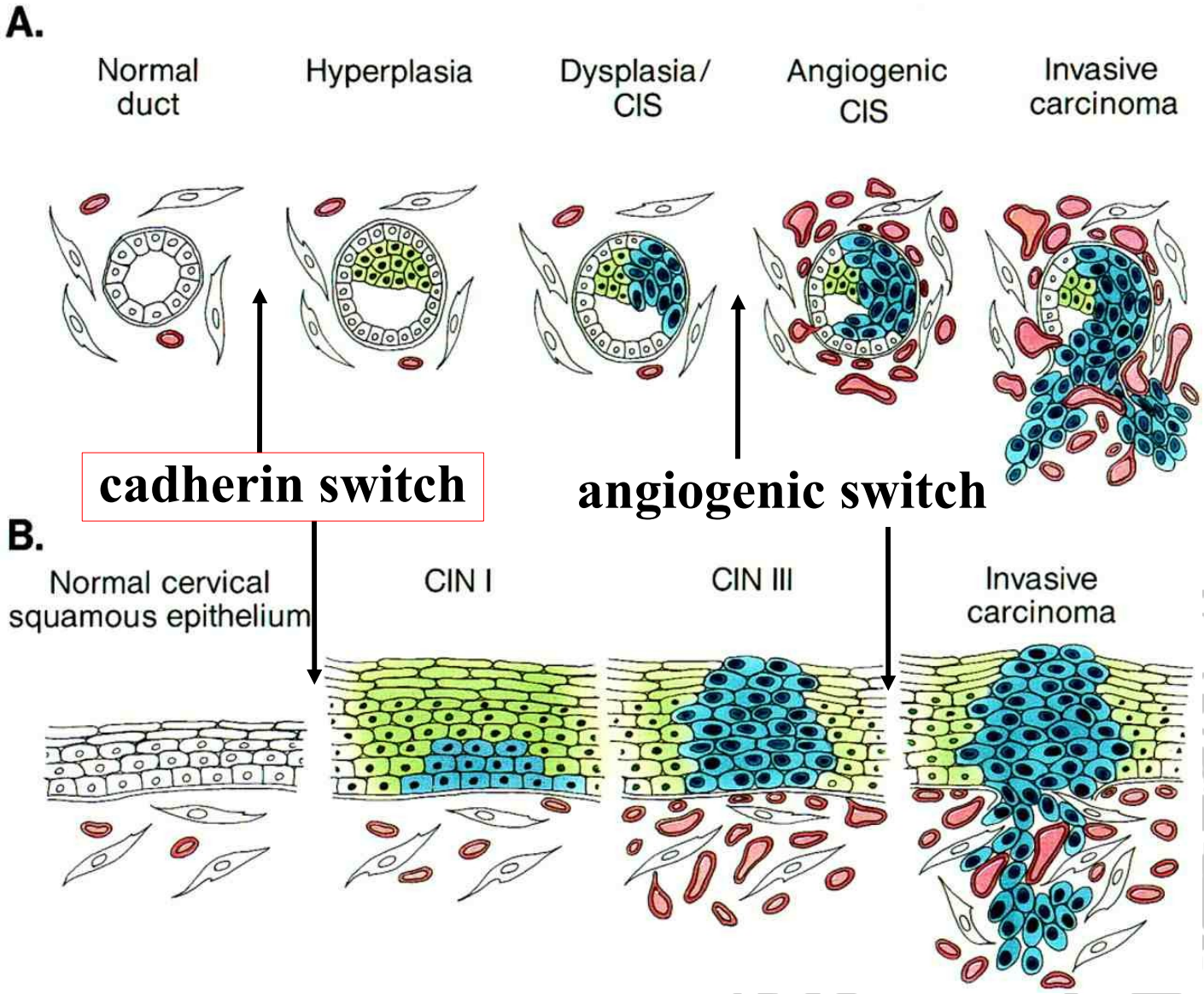
Mechanical effects in:

Growth

Stress **Interaction force**

$$\begin{cases} \mathbf{v}_\ell = \mathbf{M}^{-1} \left(\displaystyle\sum_{\alpha=c,m} \mathbf{M}_\alpha \mathbf{v}_\alpha - \phi_\ell \nabla P \right) \\ \nabla \cdot \left(\dfrac{\mathbf{K}}{\mu} \nabla P \right) = \nabla \cdot \left[\displaystyle\sum_{\alpha=c,m} \left(\phi_\alpha \mathbf{I} + \frac{\mathbf{K}}{\phi_\ell \mu} \mathbf{M}_\alpha \right) \mathbf{v}_\alpha \right] - \sum_{\alpha=c,m,\ell} \Gamma_\alpha \end{cases}$$

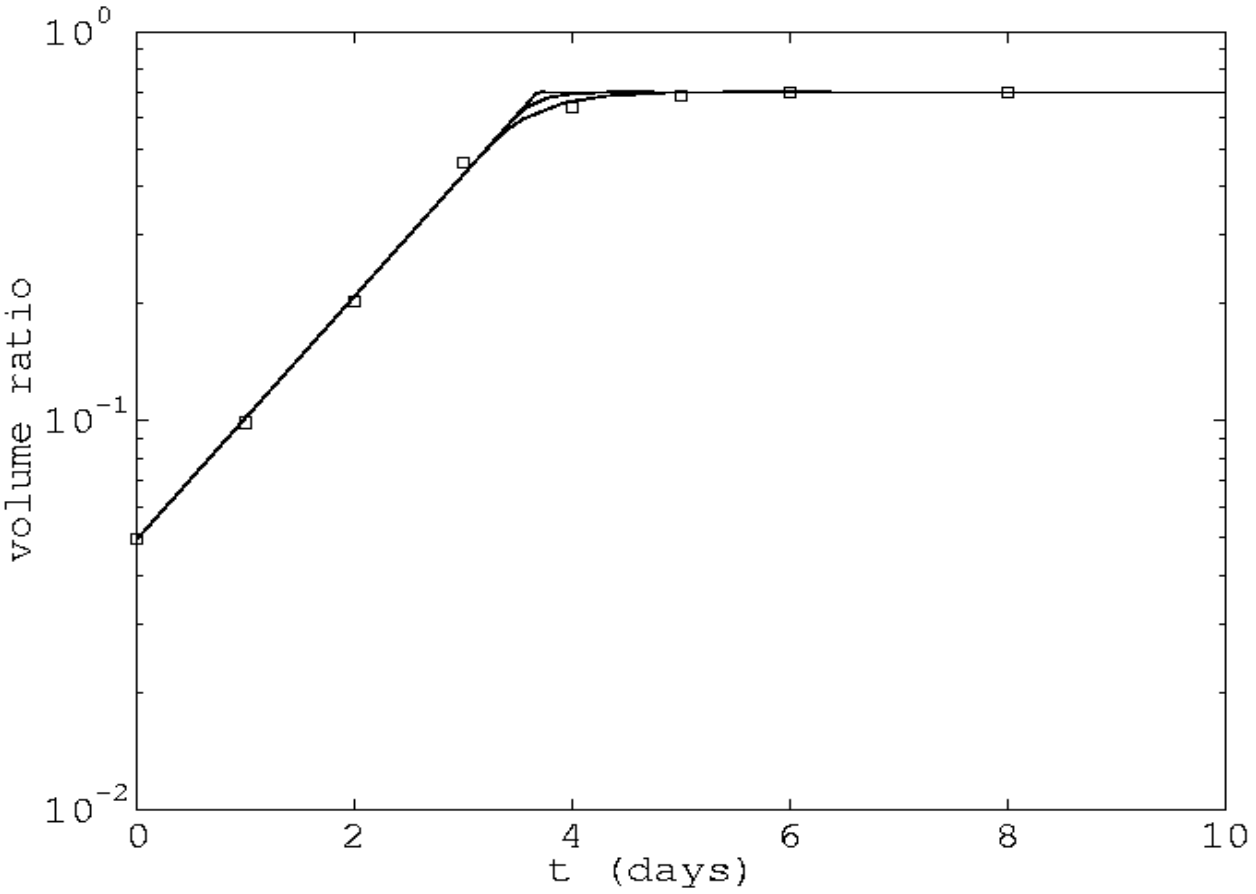
Contact inhibition of growth



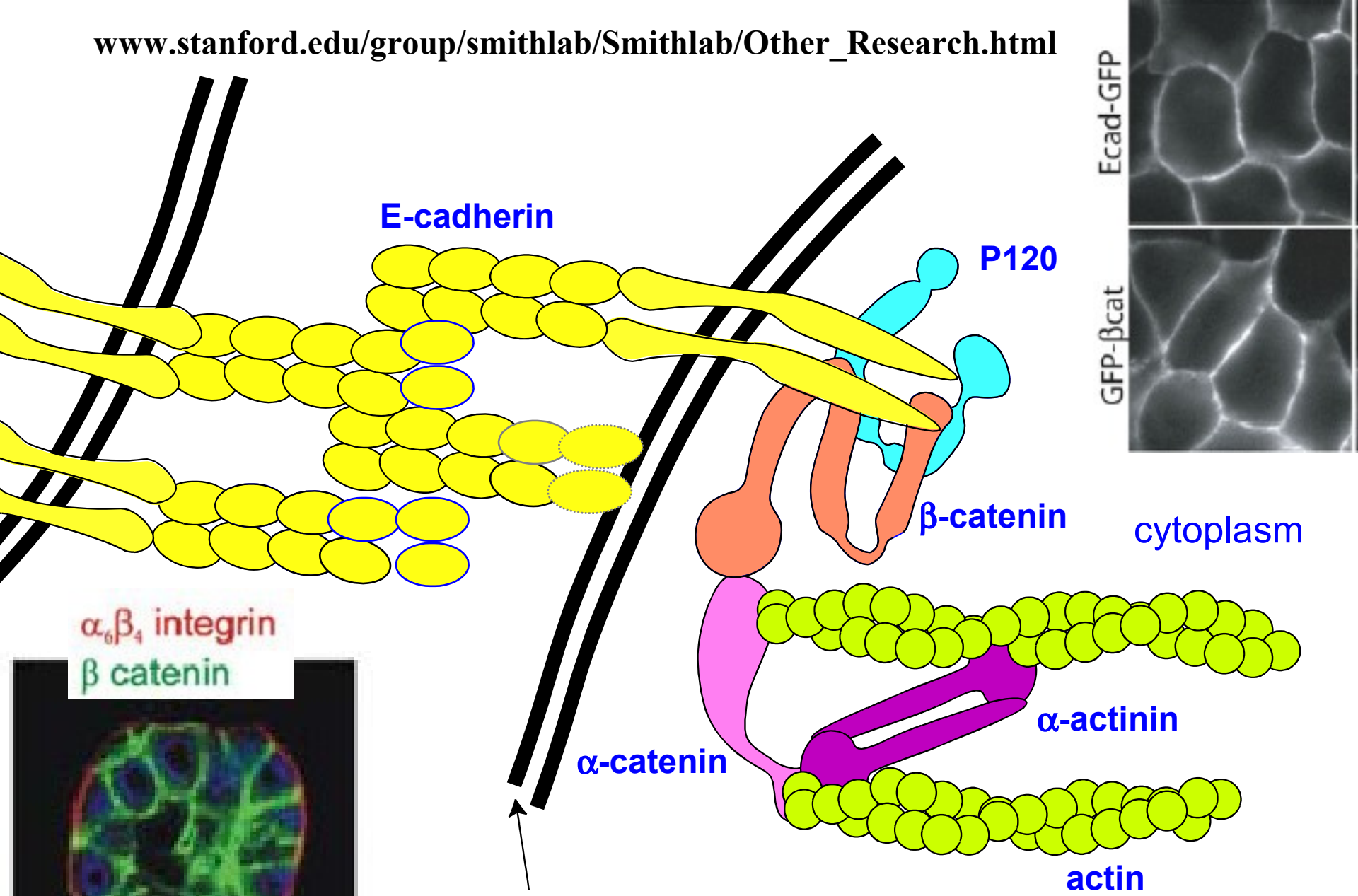
Contact inhibition of growth

Epithelial cells growing to confluence

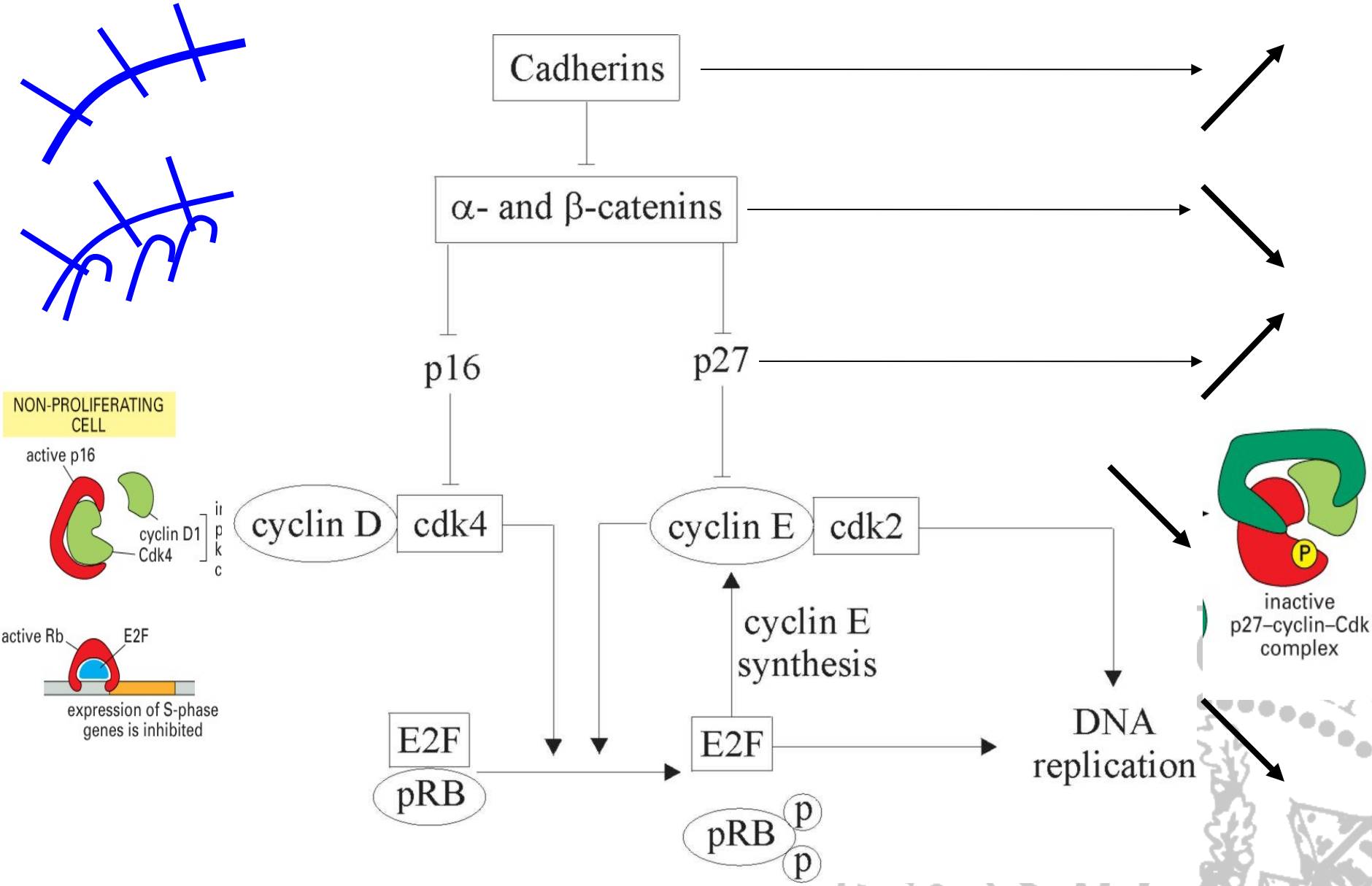
Tzukatani et al. (1997)



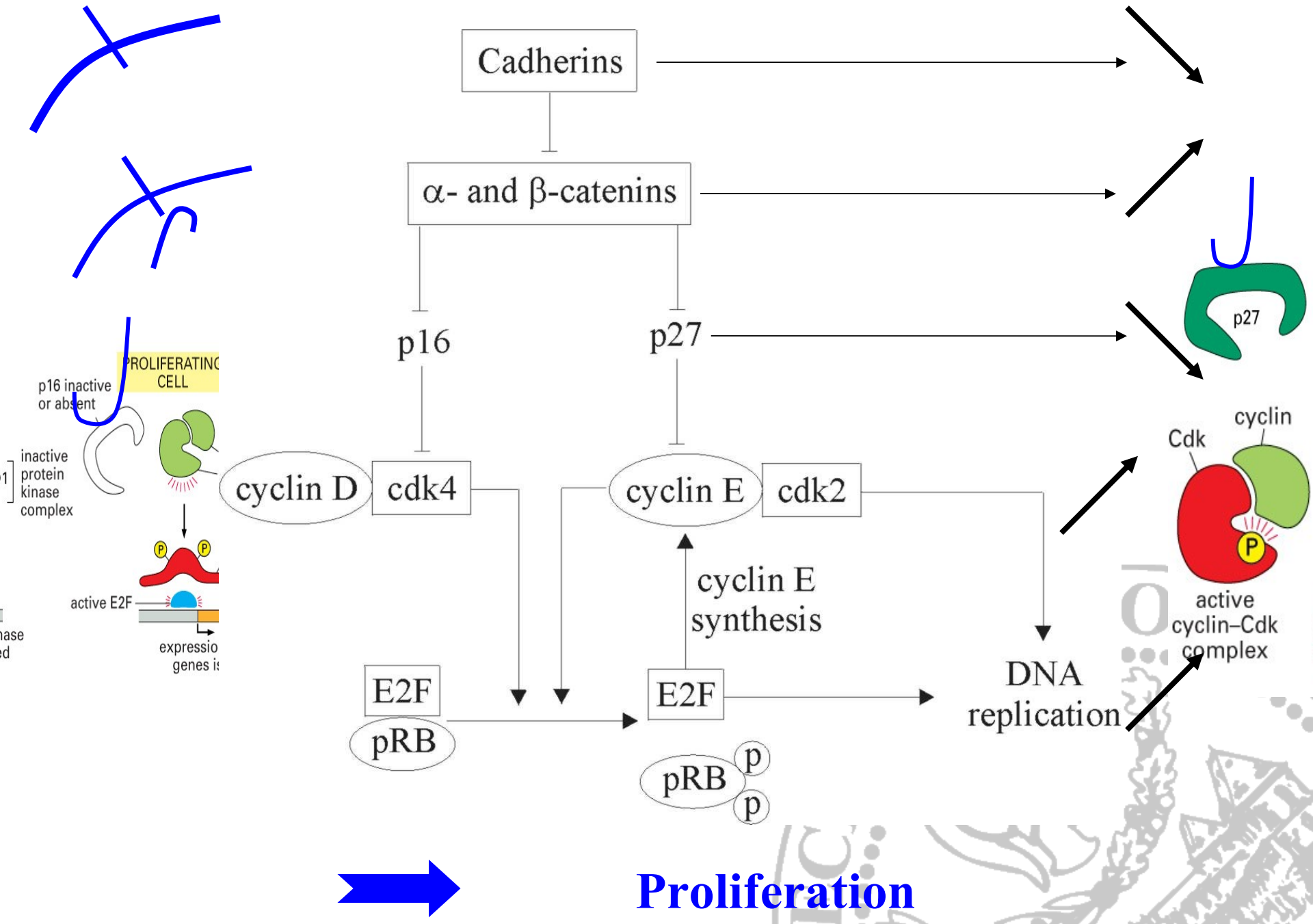
www.stanford.edu/group/smithlab/Smithlab/Other_Research.html

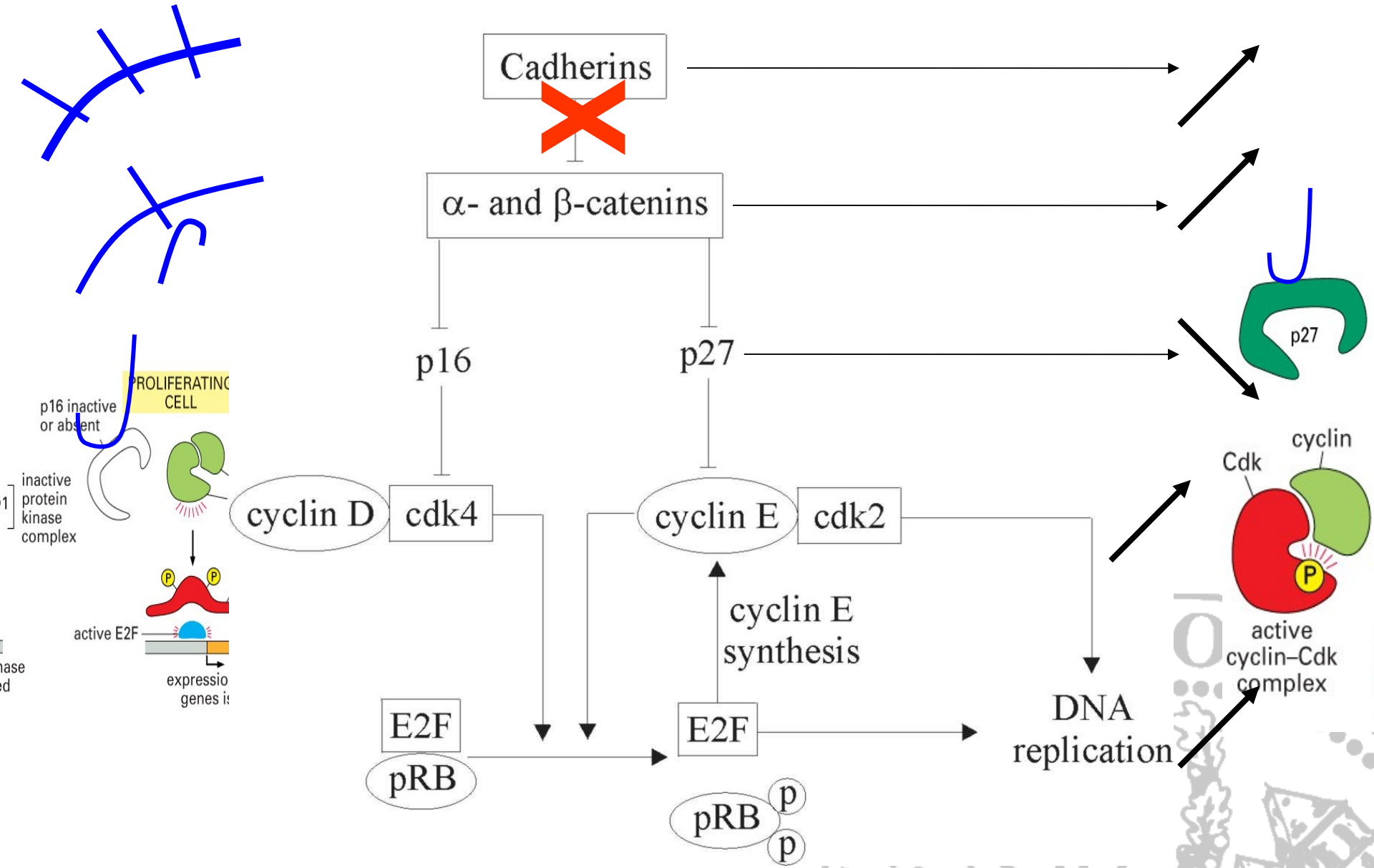


www.youtube.com/watch?v=pBUIb5jchVo&feature=related



Growth arrest in the G1 phase

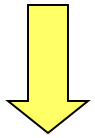

Cadherins
α- and β-catenins
p16
p27
p27
cyclin D
cdk4
cyclin E
cdk2
cyclin E synthesis
E2F
pRB
E2F
pRB
p
p
DNA replication
Cdk
cyclin
P
active cyclin–Cdk complex
p16 inactive or absent
inactive protein kinase complex
active E2F
P
P
Proliferation



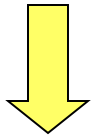
Over - proliferation

Growth Term

Feedback loops in protein cascades



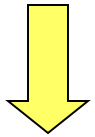
Bi-stability



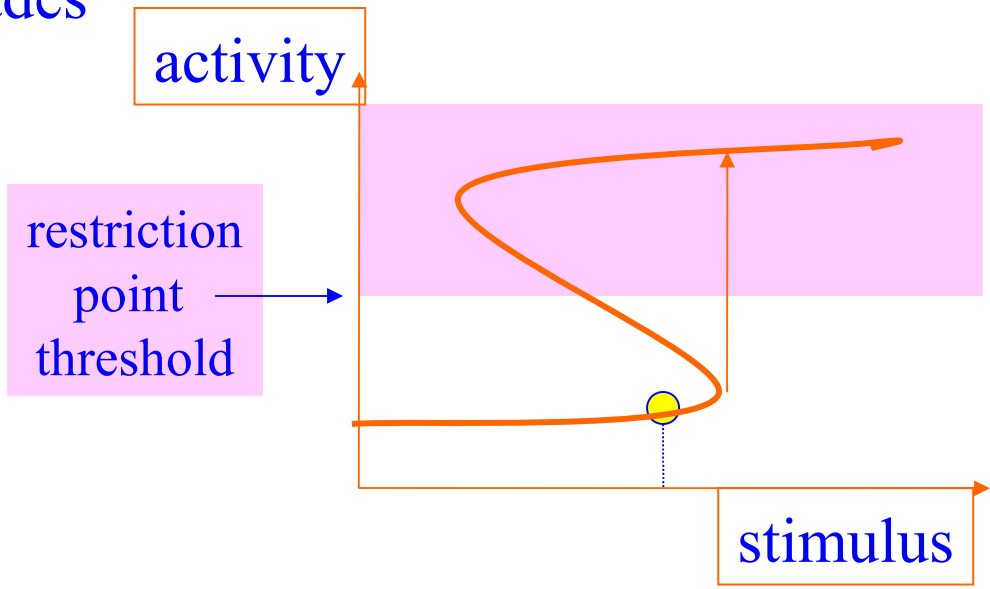
All-or-none response

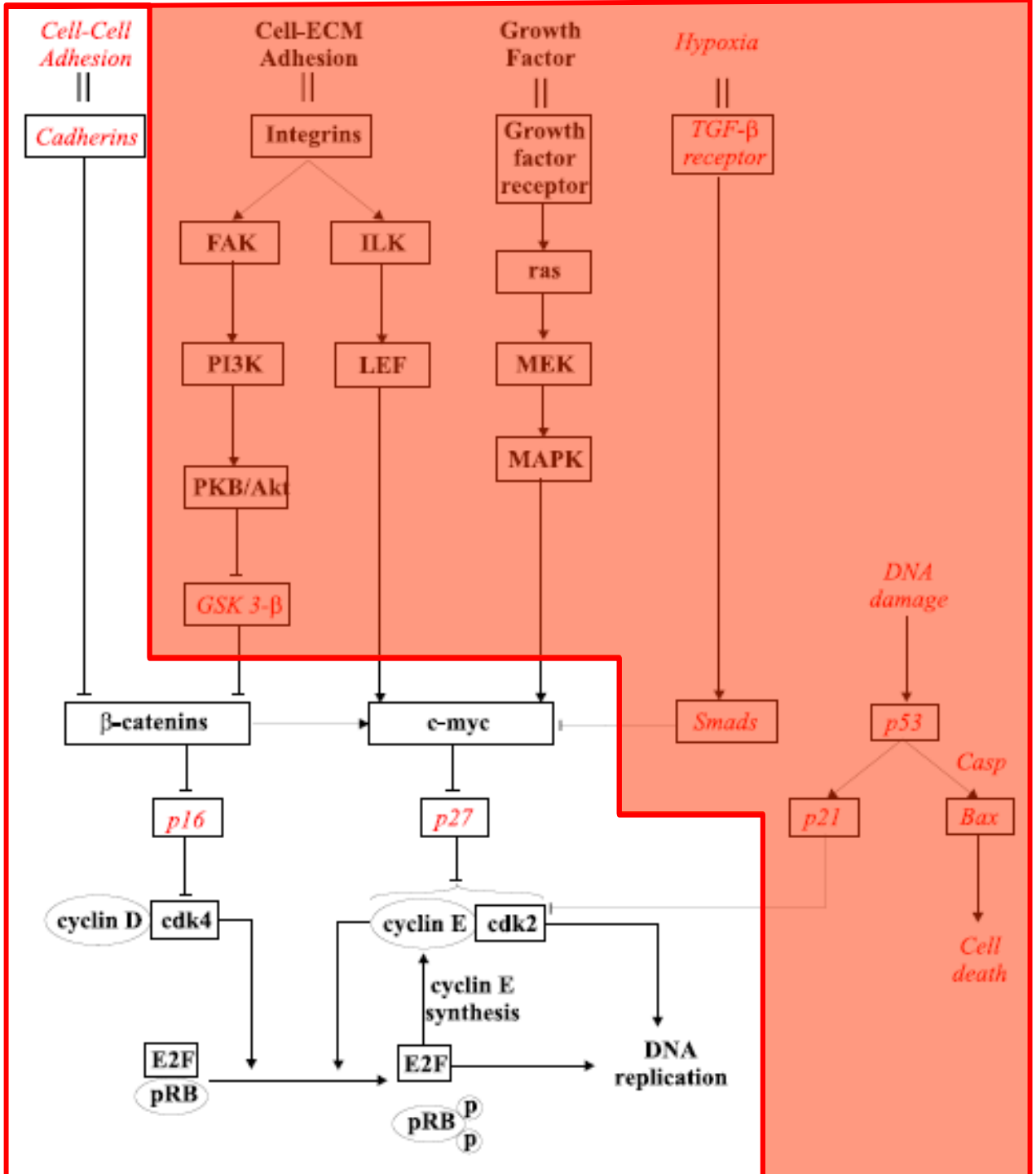
+

Stochastic effects



Growth term
mollifier of step function




Cell-Cell Adhesion
Cadherins
Cell-ECM Adhesion
Integrins
FAK
ILK
PI3K
LEF
PKB/Akt
GSK 3-β
Growth Factor
Growth factor receptor
ras
MEK
MAPK
Hypoxia
TGF-β receptor
Smads
DNA damage
p53
Casp
p21
Bax
Cell death
β-catenins
c-myc
p16
p27
cyclin D
cdk4
cyclin E
cdk2
cyclin E synthesis
E2F
pRB
E2F
pRB
p
p
DNA replication

Hypothesis

- **Cells replicate if they sense there is “sufficient space”**
- **If not, they enter a quiescent state ready to re-activate if, f.i., a neighboring cell dies**
- **Cells move preferentially toward regions with lower stress**
- **Cells constantly produce ECM and MDE**

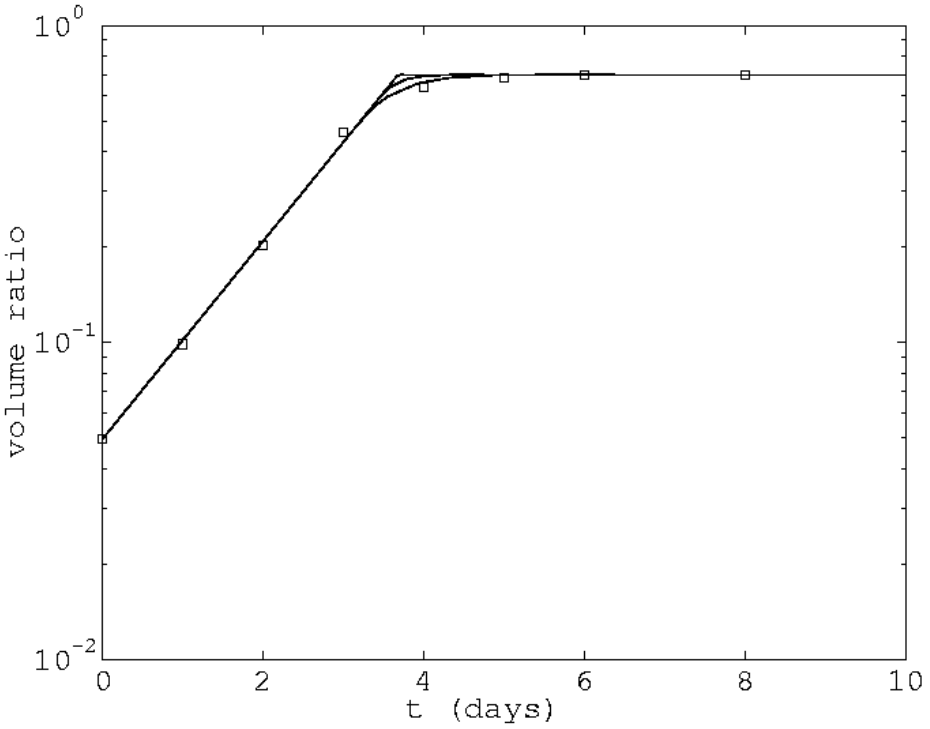
Misperception of stress → **hyperplasia tumour growth**

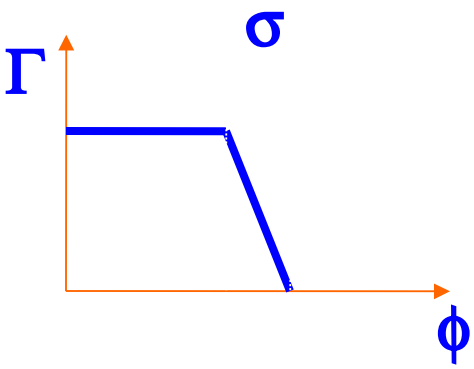
normal cells $$\frac{\partial n}{\partial t} = \nabla \cdot [nK\Sigma'(\psi)\nabla\psi] + [\gamma_n H_\sigma(\psi - \psi_n) - \delta_n]n\,,$$

tumour cells $$\frac{\partial a}{\partial t} = \nabla \cdot [aK\Sigma'(\psi)\nabla\psi] + [\gamma_a H_\sigma(\psi - \psi_a) - \delta_a]a\,.$$

overall volume ratio $$\psi = n + a + m_n + m_a$$

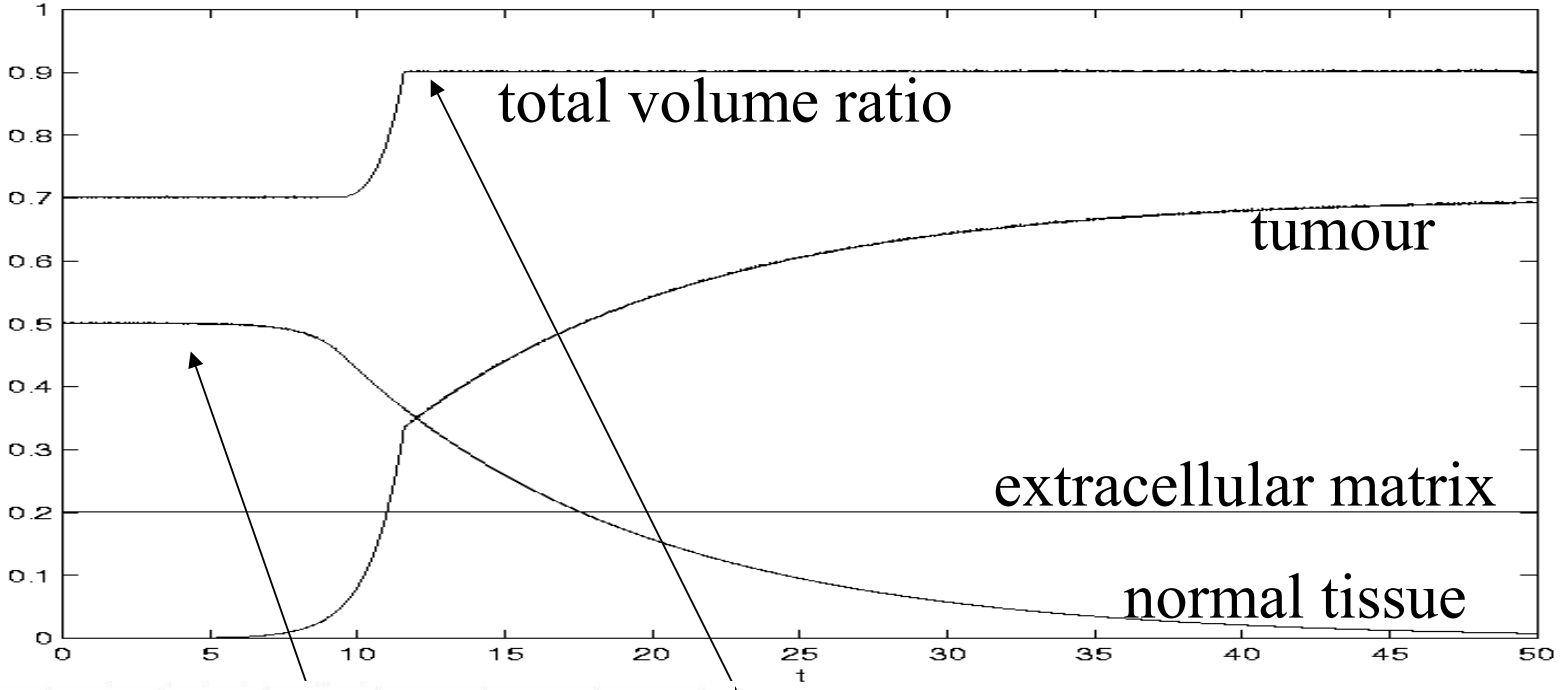
Growth to confluence in vitro

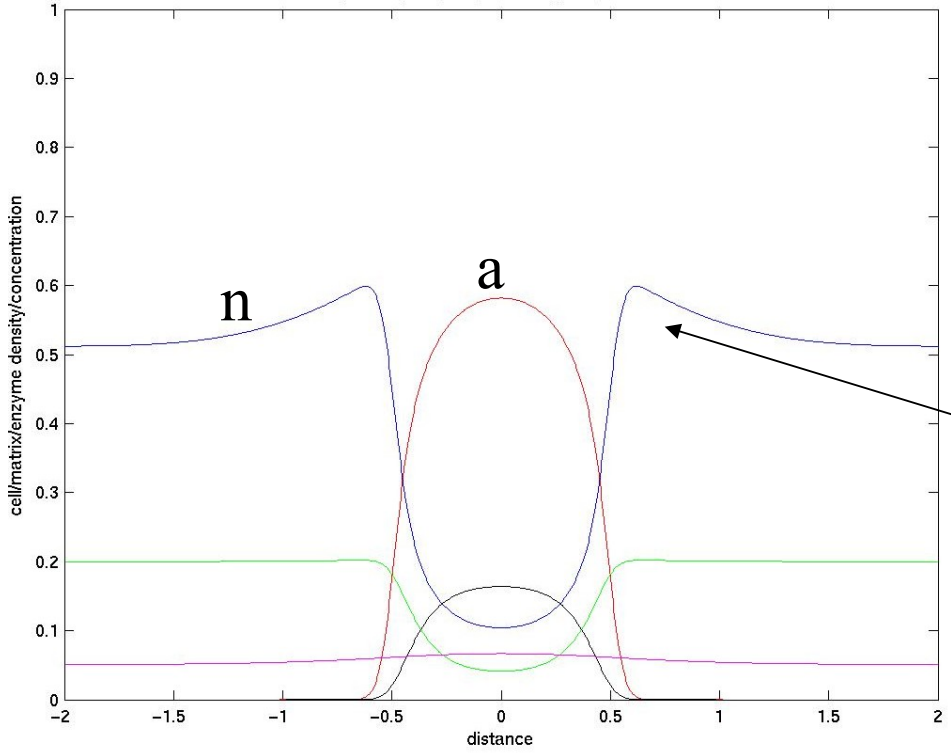


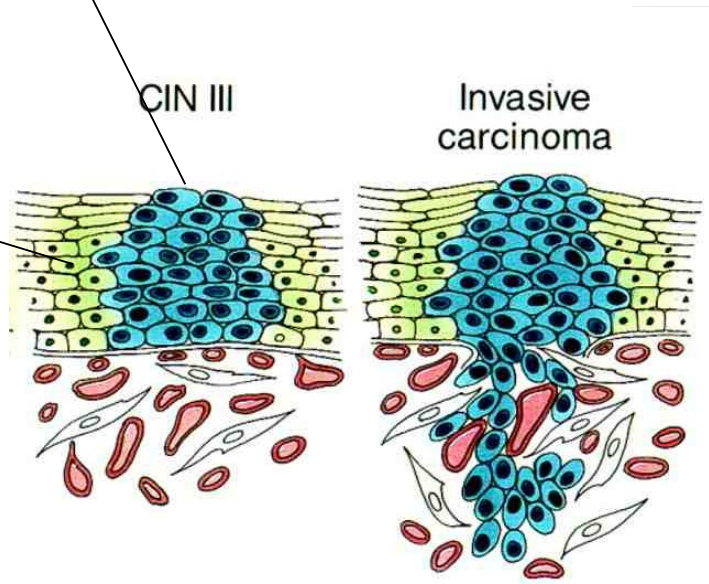


Human breast epithelial cells

Cell type	Duplication time (hours)	Growth rate ($days^{-1}$)
CHO	18–19	0.86–0.91
CHO	14–21	0.8–1.2
L929	10–12	1.4-1.6
Fibroblast	16.2	1.03
HBE	22.3	0.75
BPAEC	38–44	0.38–0.44


total volume ratio
tumour
extracellular matrix
normal tissue
t

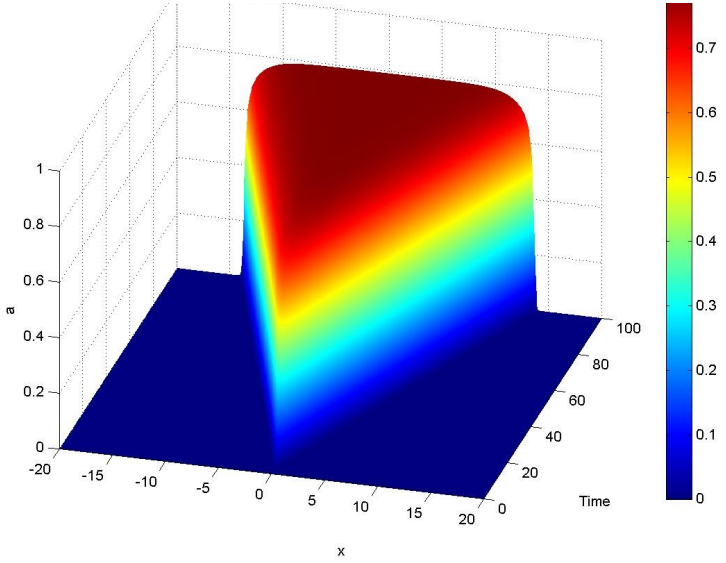

n
a
cell/matrix/enzyme density/concentration
distance


CIN III
Invasive carcinoma

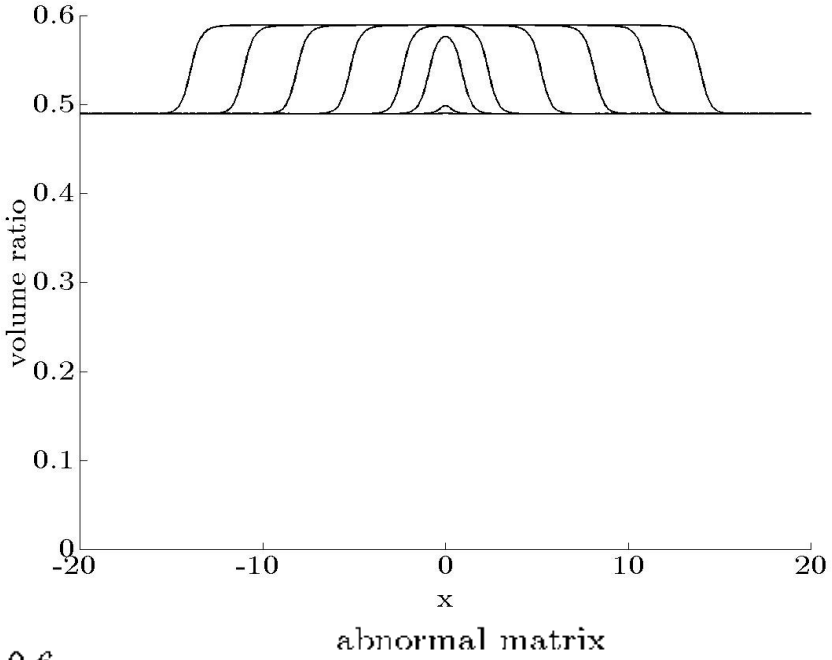
Tissue Invasion

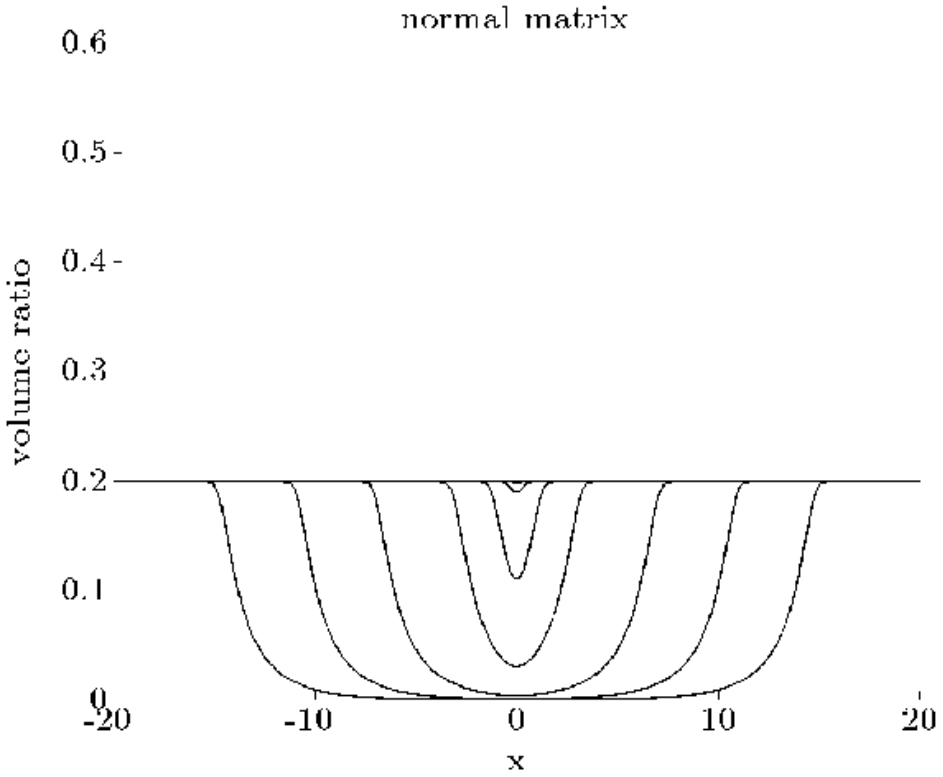
tumour cells

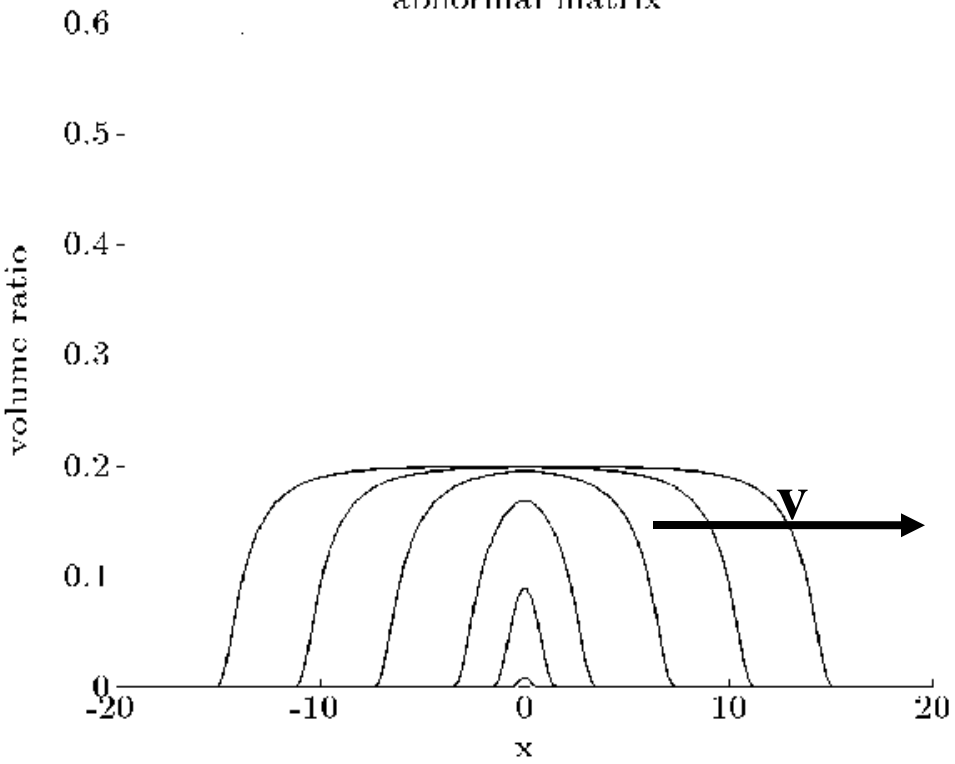
normal cells



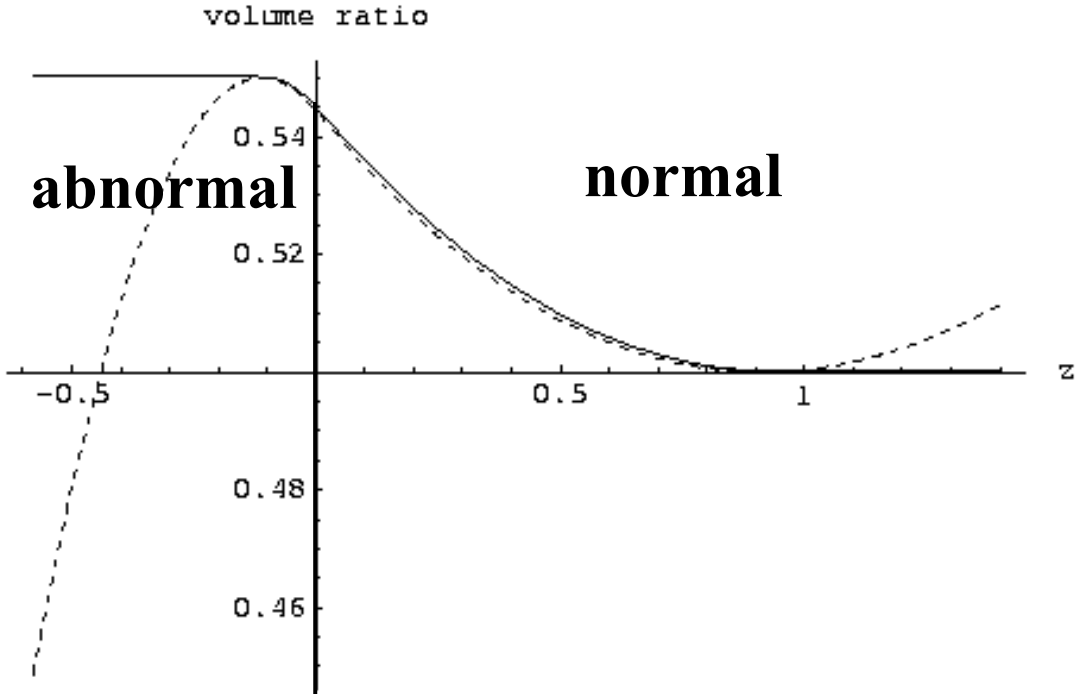
Tissue Invasion

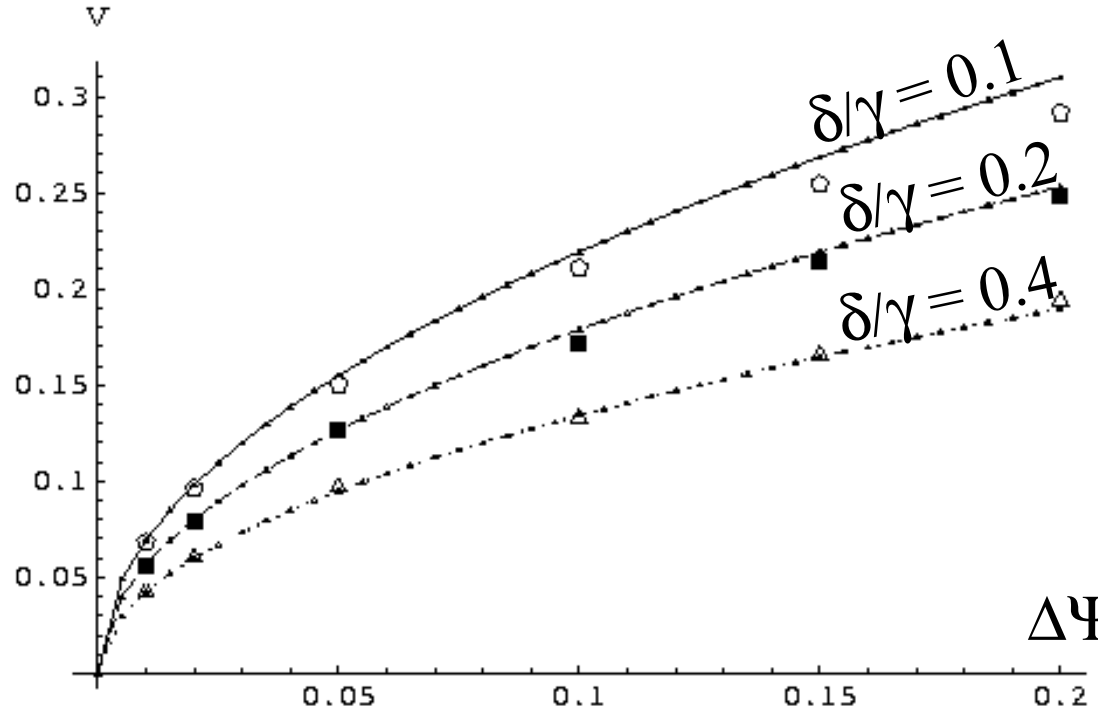






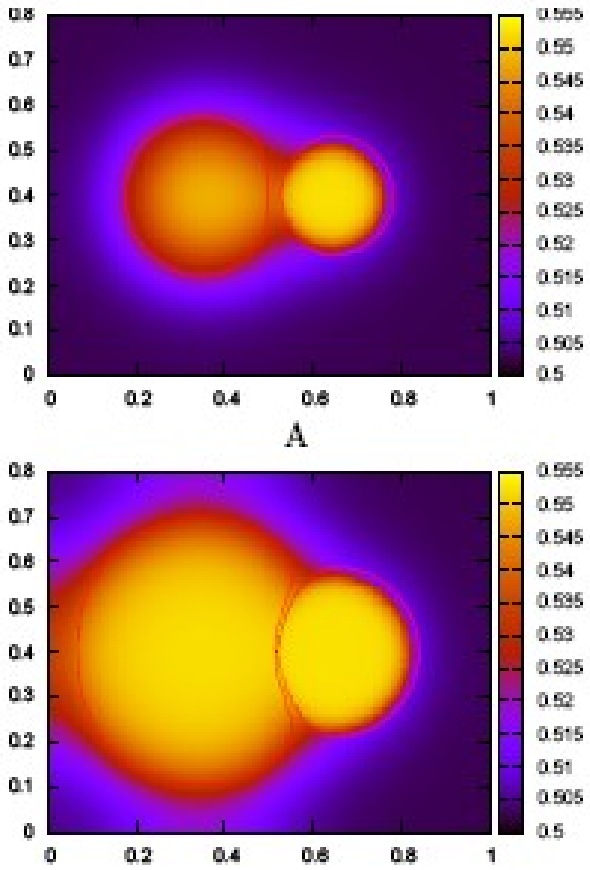
Travelling Wave



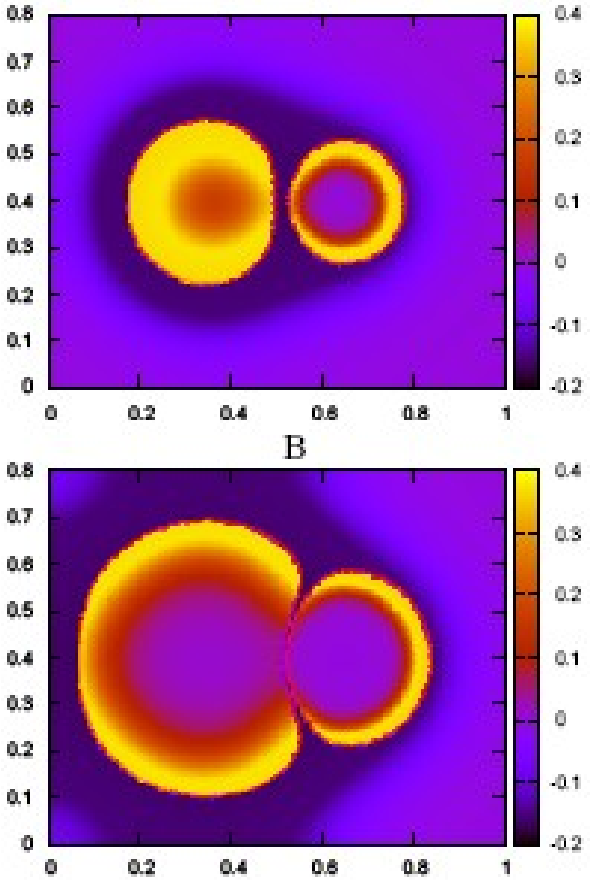


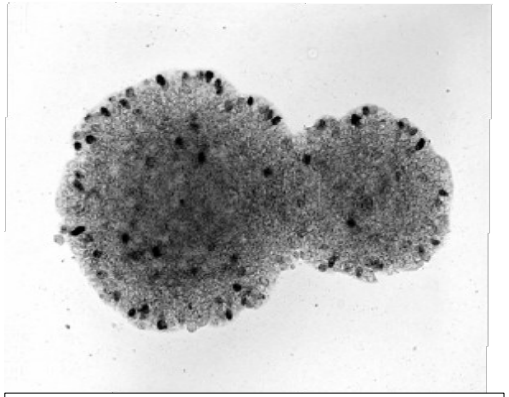
Growth of Widr Clones

Volume ratio



Growth rates

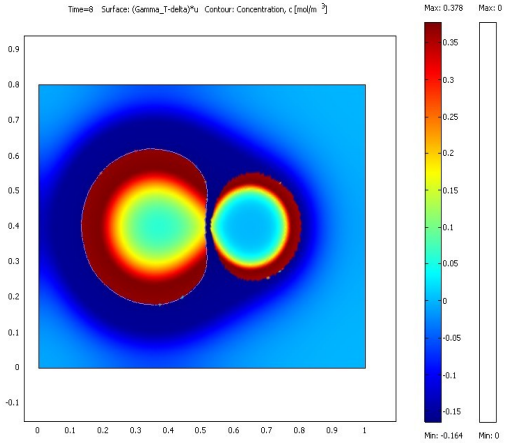


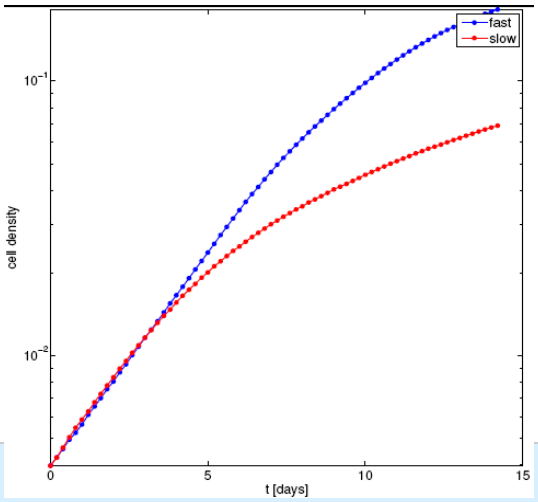


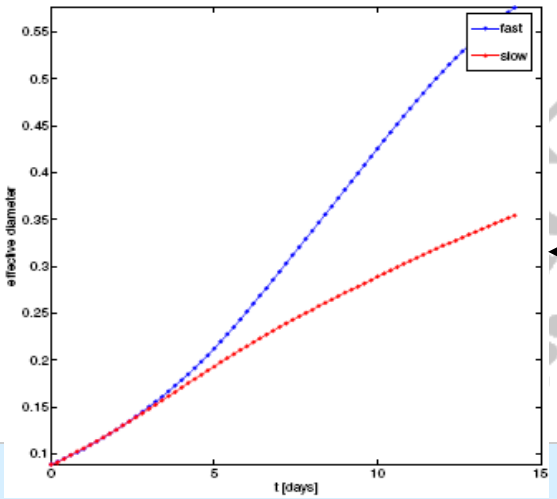
- J. Galle, & L. P. *Appl. Math. Letters*

Clones on the left are more motile → Faster stress relaxation

Growth of Widr Clones







Fibrosis

Host

$$\frac{\partial \phi_n}{\partial t} = \nabla \cdot [\phi_n K_m \nabla(\phi_n \Sigma(\psi))] + \gamma_n H_\sigma(\psi - \psi_n)\phi_n - \delta_n(\psi)\phi_n \,,$$

Tumour

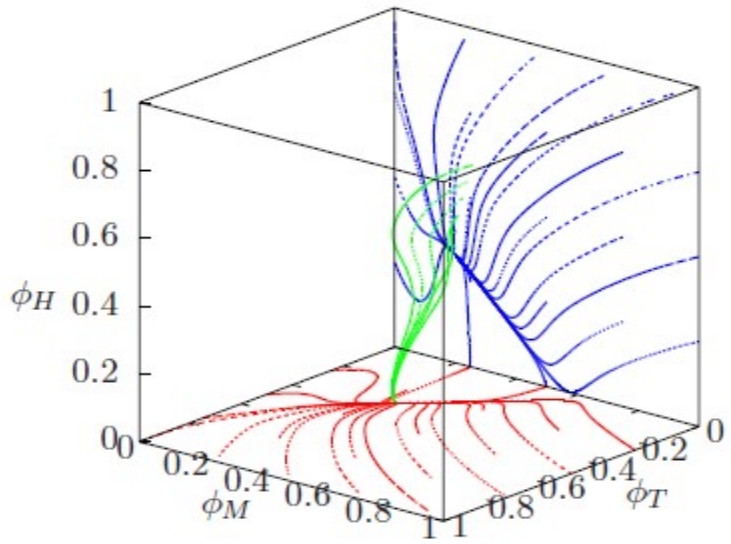
$$\frac{\partial \phi_t}{\partial t} = \nabla \cdot [\phi_t K_m \nabla(\phi_t \Sigma(\psi))] + \gamma_t H_\sigma(\psi - \psi_t)\phi_t - \delta_t(\psi)\phi_t \,,$$

ECM

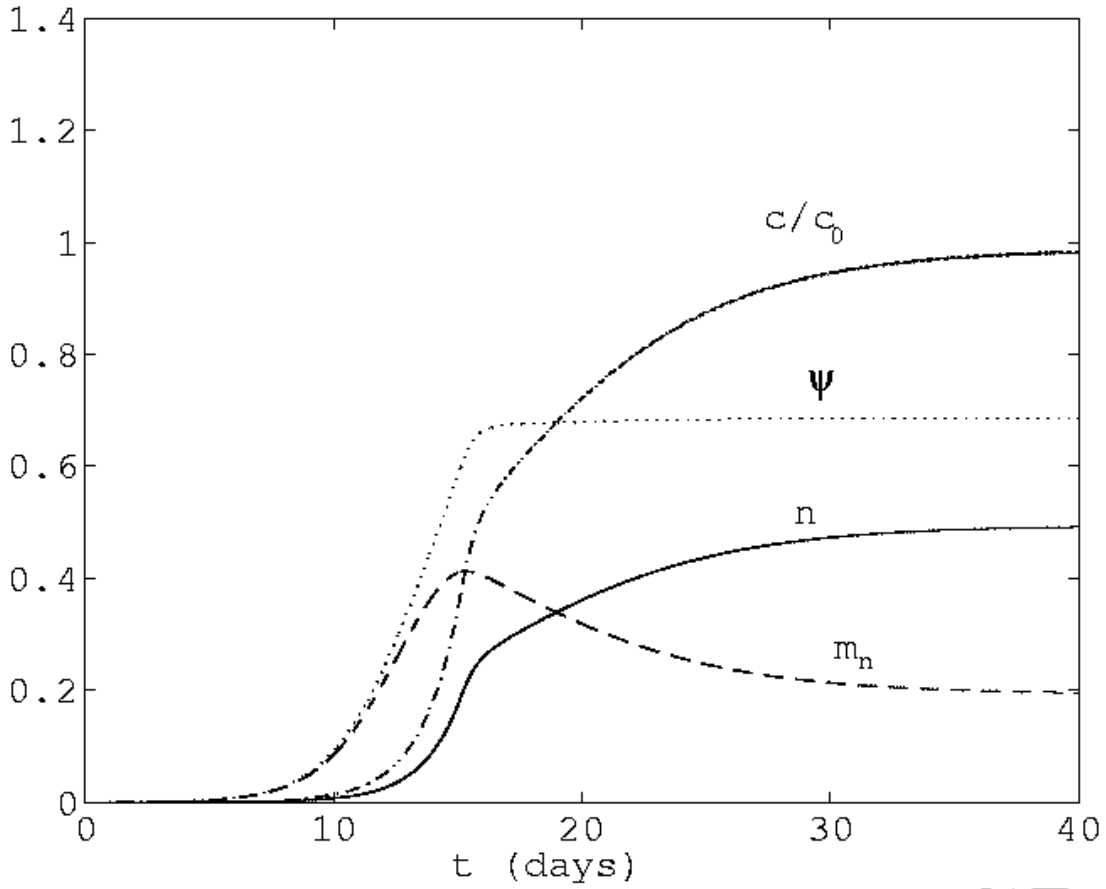
$$\frac{\partial m}{\partial t} = \mu_n(\Sigma)\phi_n + \mu_t(\Sigma)\phi_t - \nu c m \,,$$

MMP

$$\frac{\partial c}{\partial t} = \kappa \nabla^2 c + \pi_n(\Sigma)\phi_n + \pi_t(\Sigma)\phi_t - \frac{c}{\tau} \,.$$



Generation of normal tissue



Stationary values

$$c = \pi_n \tau \left(\hat{\psi}_n - M_n \right) .$$

$\hat{\psi}_n$

$$\pi = \hat{\psi}_n - M_n$$

$$\pi_n = M_n = \frac{\mu_n}{\nu \pi_n \tau} .$$

Parameter	Estimated value
δ	$0.1\ \text{days}^{-1}$
μ_n	$0.1 - 10\ \text{days}^{-1}$
ν	$10^{-5}\ \frac{\mu\text{m}^2}{\text{molecules days}}$
π_n	$10^6 - 10^7\ \frac{\text{molecules}}{\mu\text{m}^2\ \text{days}}$
τ	$\frac{1}{6}$ sec - 0.13 h
κ	$0.85 \times 10^{-6}\ \frac{\text{cm}^2}{\text{sec}}$

Fibrosis

Host

$$\frac{\partial \phi_n}{\partial t} = \nabla \cdot [\phi_n K_m \nabla(\phi_n \Sigma(\psi))] + \gamma_n H_\sigma(\psi - \psi_n)\phi_n - \delta_n(\psi)\phi_n \,,$$

Tumour

$$\frac{\partial \phi_t}{\partial t} = \nabla \cdot [\phi_t K_m \nabla(\phi_t \Sigma(\psi))] + \gamma_t H_\sigma(\psi - \psi_t)\phi_t - \delta_t(\psi)\phi_t \,,$$

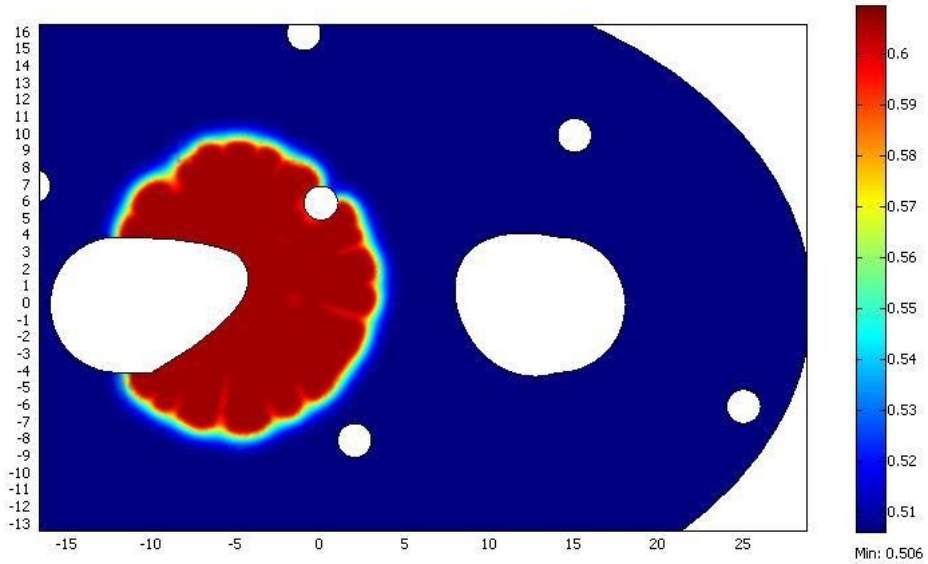
ECM

$$\frac{\partial m}{\partial t} = \mu_n(\Sigma)\phi_n + \mu_t(\Sigma)\phi_t - \nu c m \,,$$

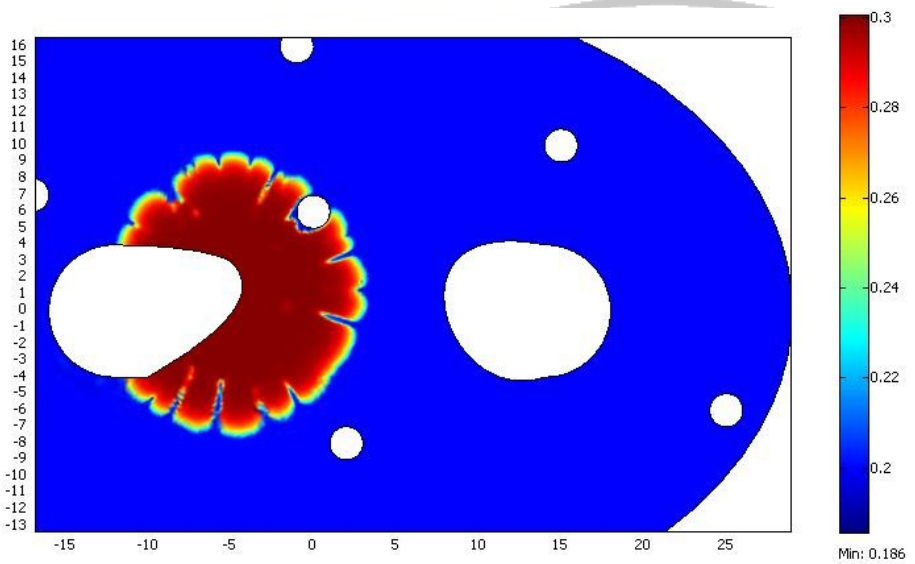
MMP

$$\frac{\partial c}{\partial t} = \kappa \nabla^2 c + \pi_n(\Sigma)\phi_n + \pi_t(\Sigma)\phi_t - \frac{c}{\tau} \,.$$

Cells



ECM



Hyper- / Hypo- } content of ECM

i.e. stiffer tissue

Tissue	Elastic modulus (Pa)
Normal mammary gland	167 ± 31
Average breast tumor	4049 ± 938
Stroma attached to tumor	916 ± 269
Reconstituted basement membrane	175 ± 37
Collagen (2.0 mg/ml)	328 ± 87
Collagen (4.0 mg/ml)	1589 ± 380

ECM content in prostate cancer: 7% - 26%

Hyper- / Hypo- } content of ECM

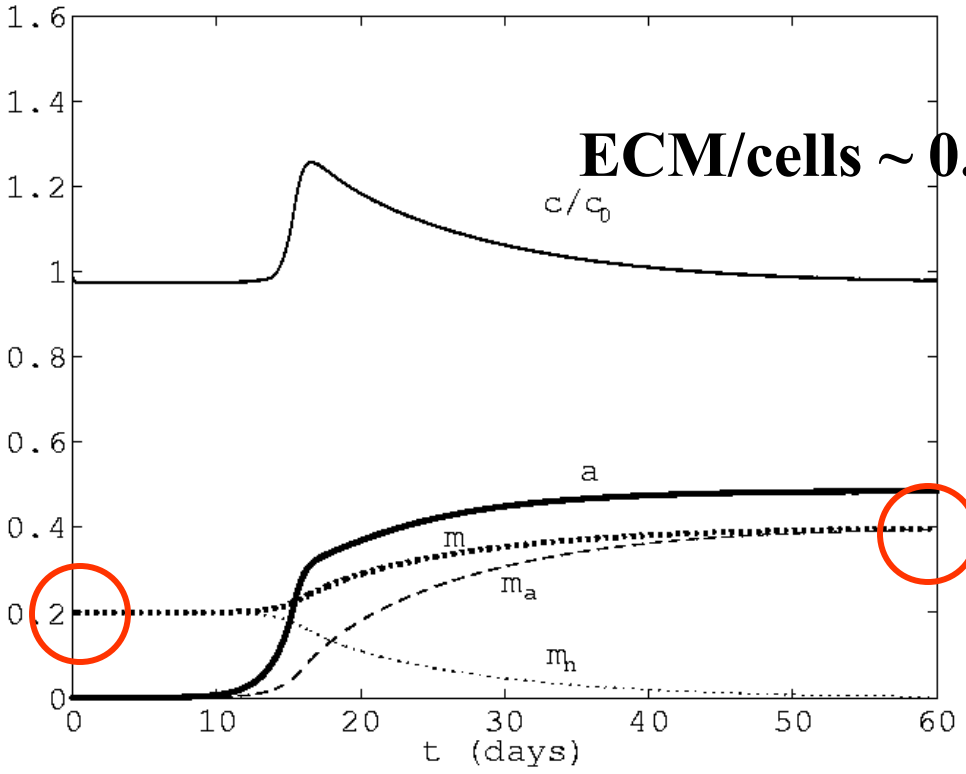
$$M_a = \frac{\mu_a}{\nu \pi_a \tau} :$$

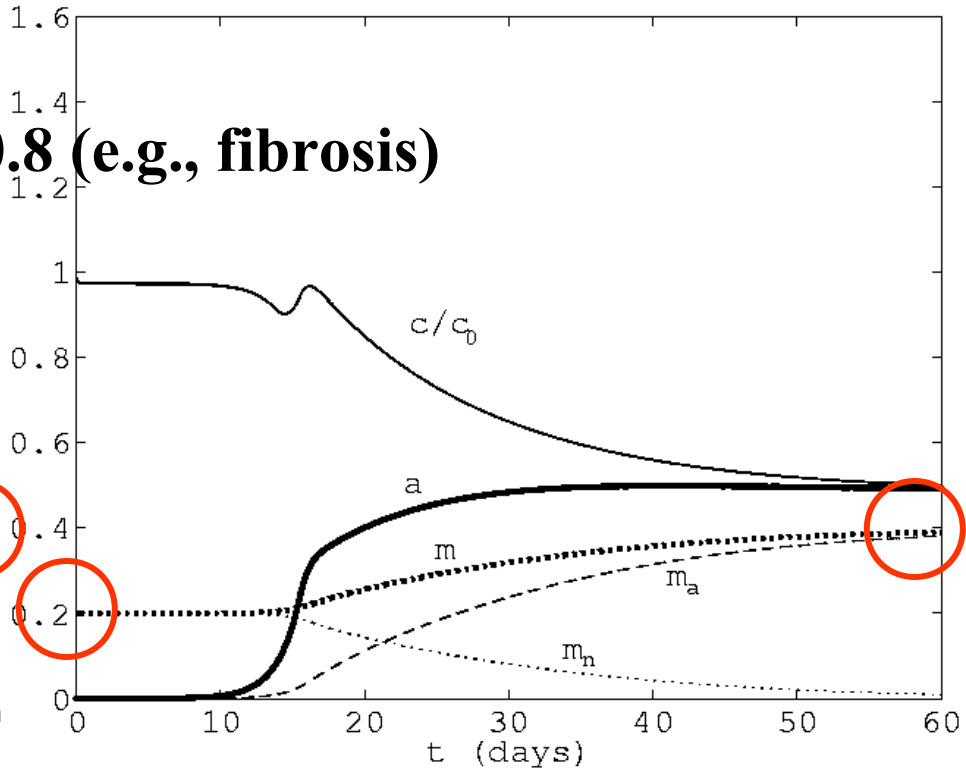
i.e. stiffer tissue

hyper-production of ECM

hypo-production of MDEs

ECM/cells ~ 0.8 (e.g., fibrosis)



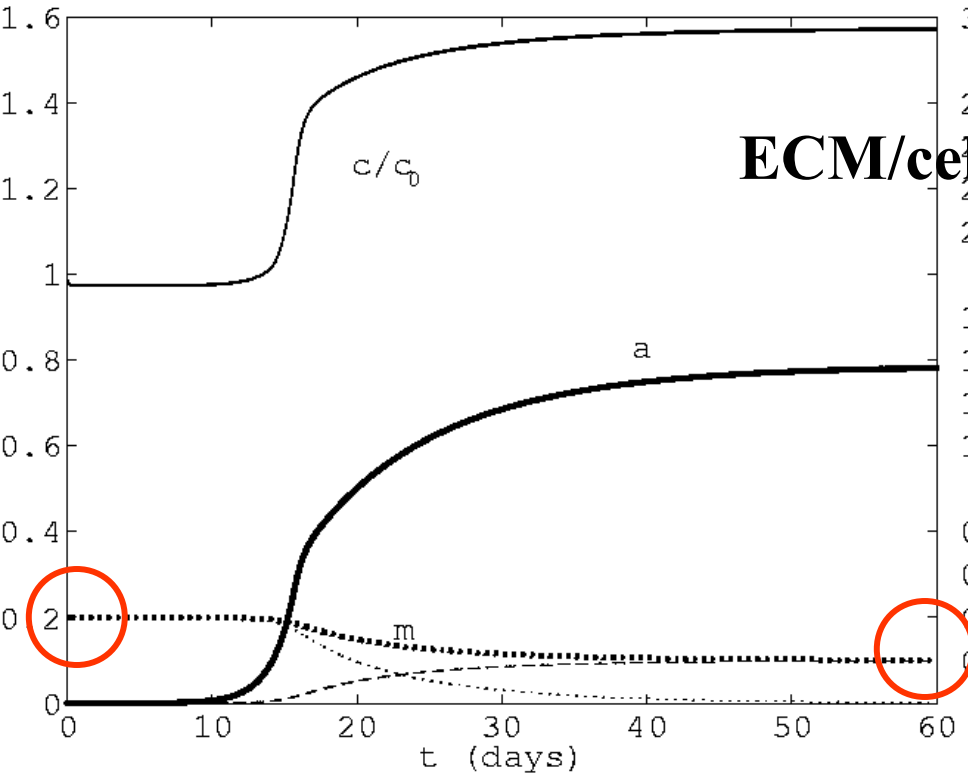


Hyper- / Hypo- } content of ECM

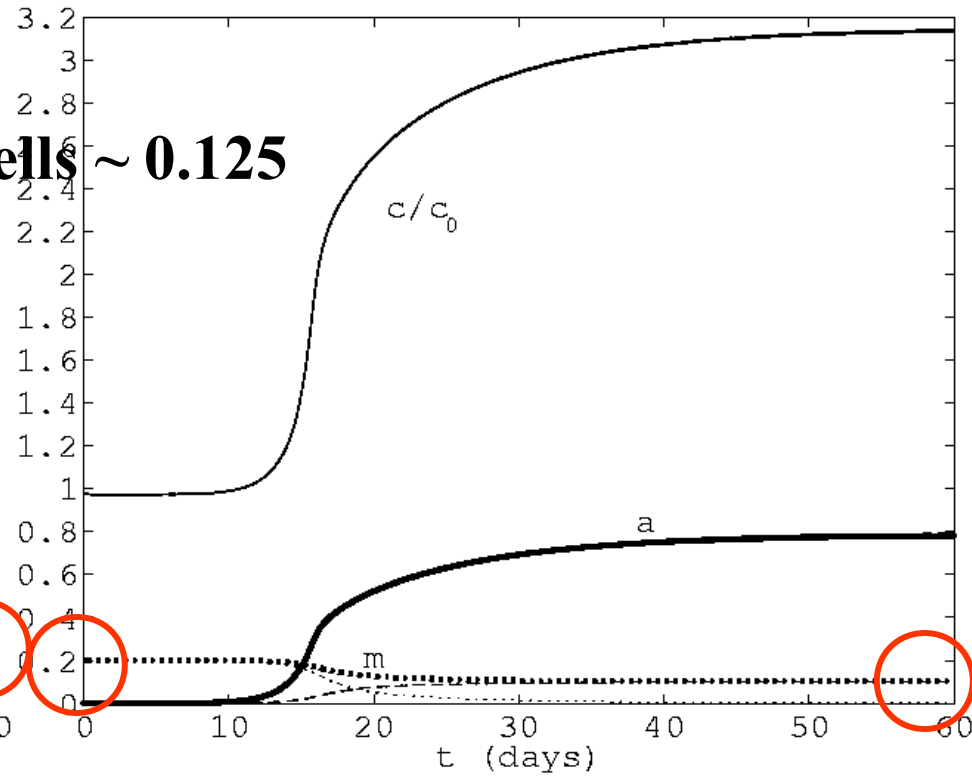
$$M_a = \frac{\mu_a}{\nu \pi_a \tau} ;$$

hypo-production of ECM

hyper-production of MDEs



ECM/cells ~ 0.125



Mechanics in Multiphase Models

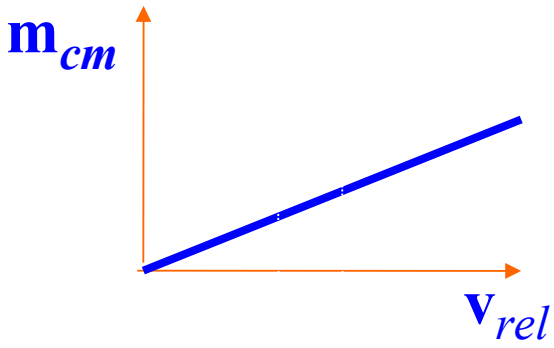
Mechanical effects in:

$$\begin{cases} \dfrac{\partial \phi_\alpha}{\partial t} + \nabla \cdot (\phi_\alpha \mathbf{v}_\alpha) = \Gamma_\alpha \,, \qquad \text{for} \quad \alpha = c, m \\ \nabla \cdot (\phi_c \mathbf{T}_c) + \mathbf{m}_{cm} + \rho \phi_c \mathbf{b}_c = \mathbf{0} \,, \\ \nabla \cdot (\phi_m \mathbf{T}_m) - \mathbf{m}_{cm} = \mathbf{0} \,. \end{cases}$$

Growth

Stress

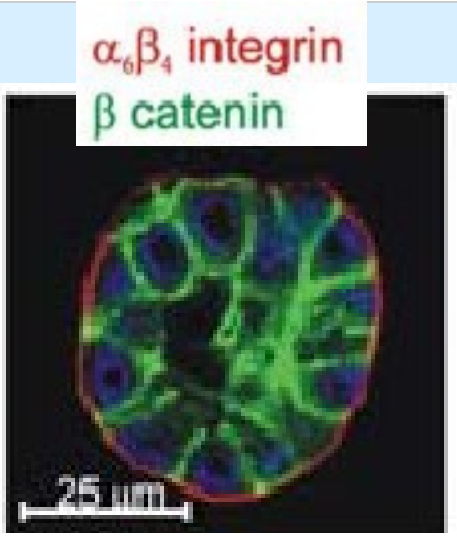
Interaction force



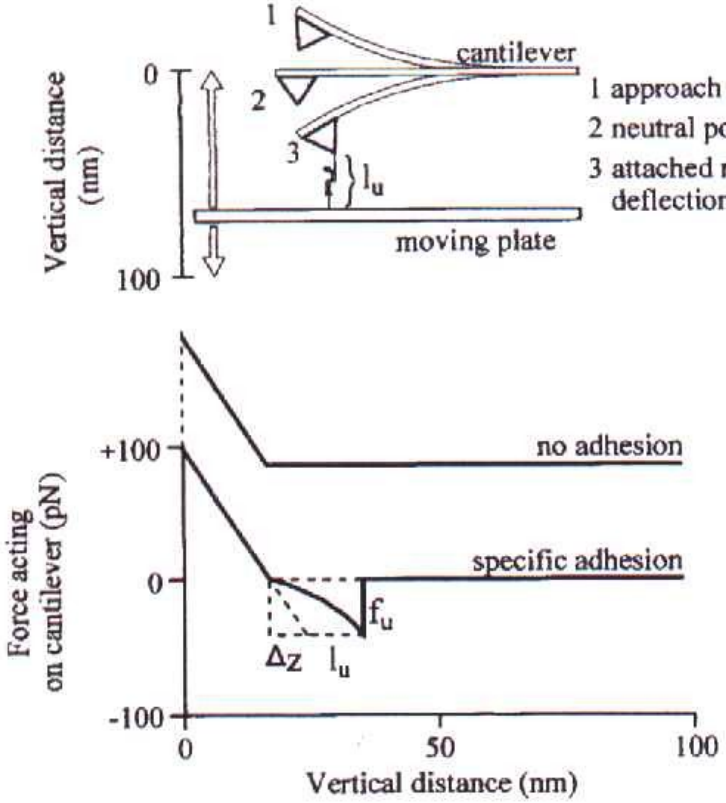
Darcy's-type law

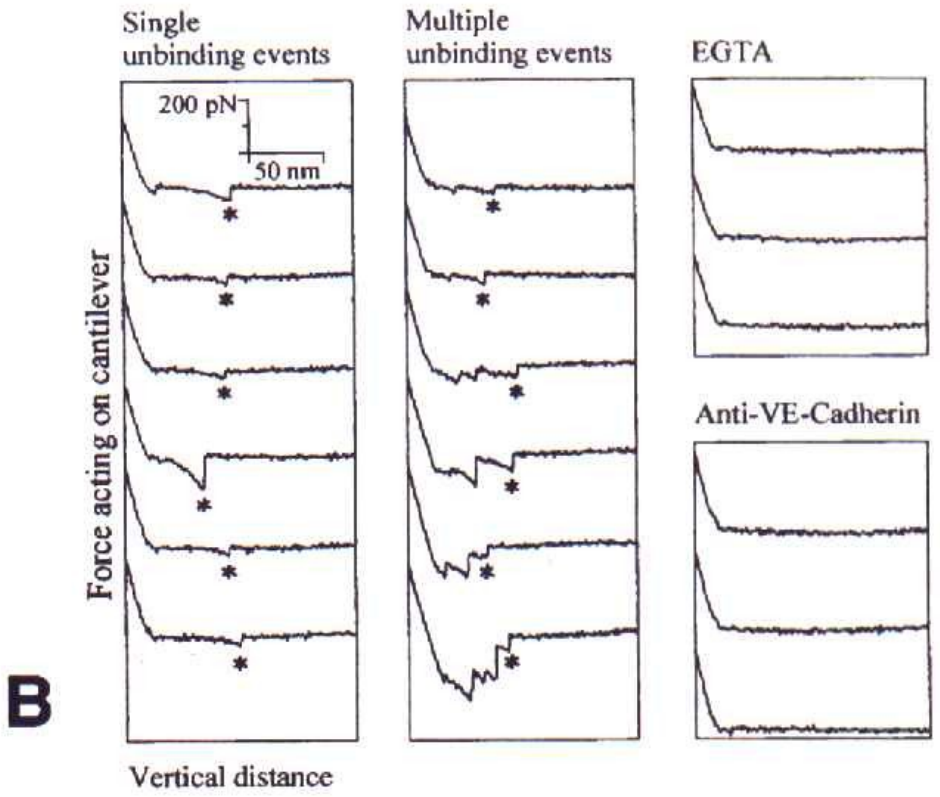
Cell aggregates as fluids (viscous or inviscid)

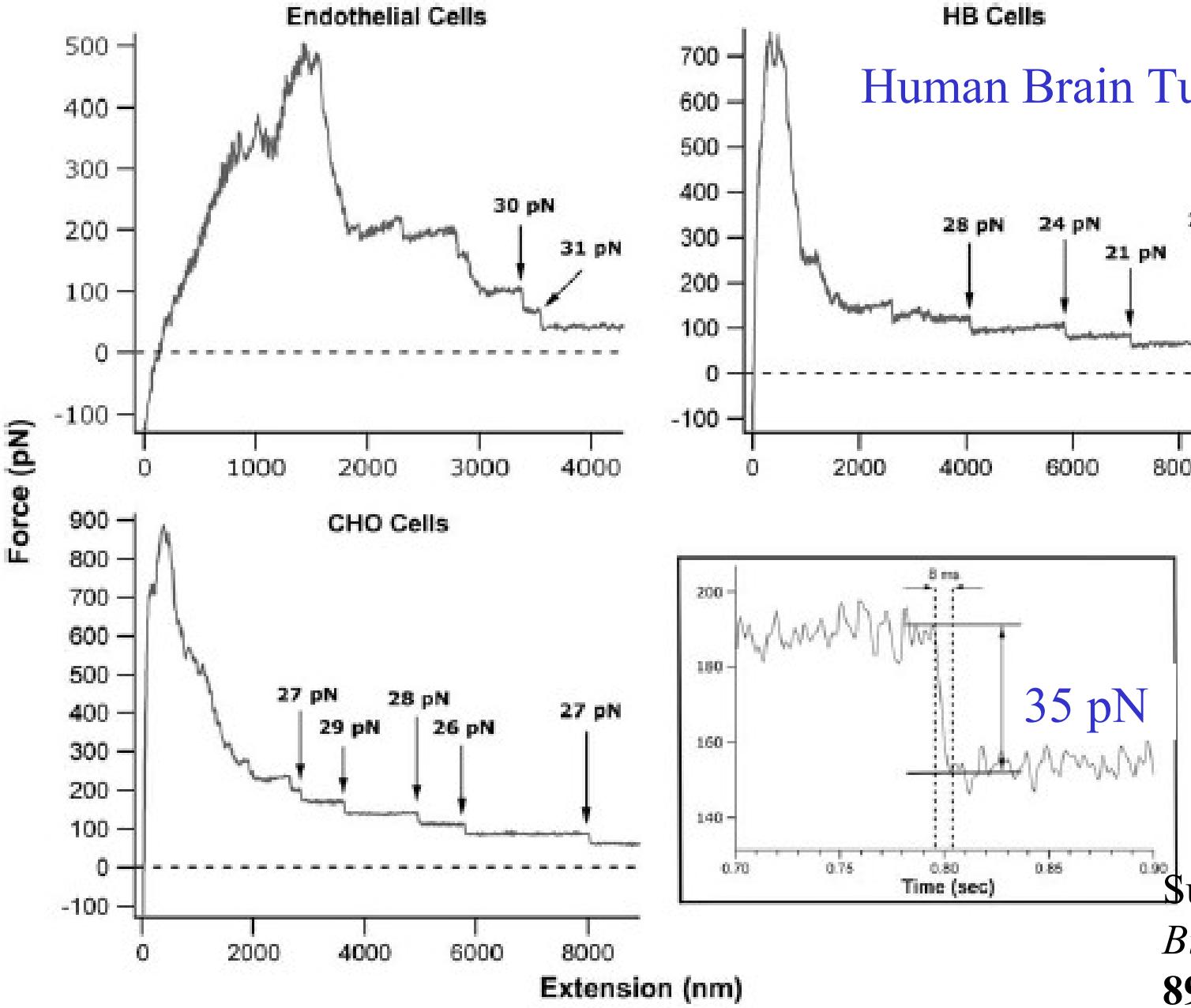
Cell-ECM interaction



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



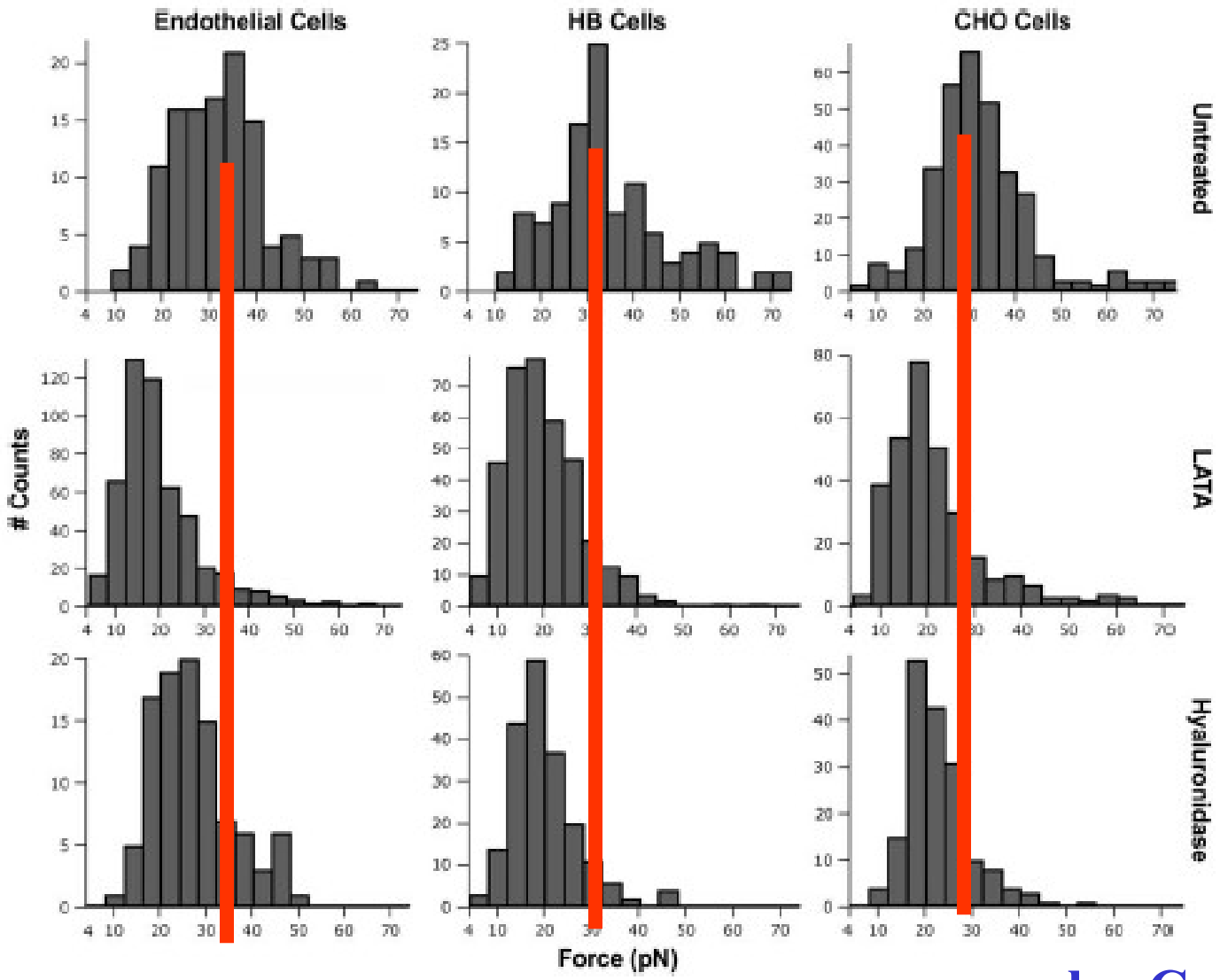




Sun et al.
Biophys J.
89 (2005)

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

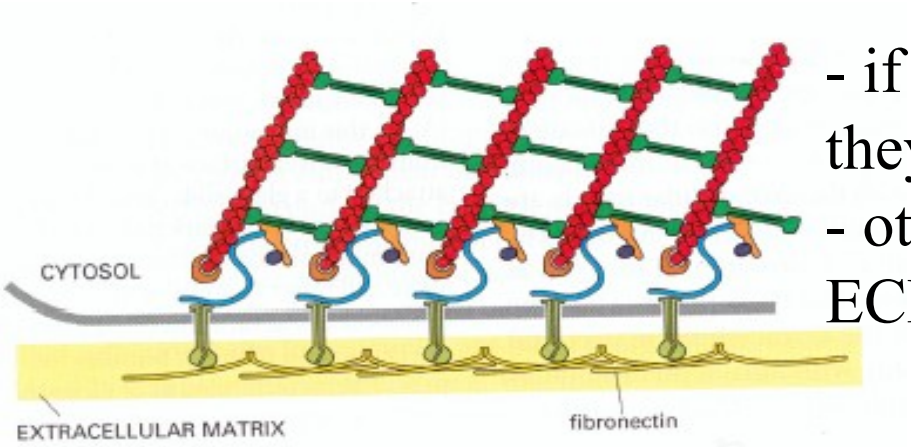


Disrupts actin cytoskeleton

removes hyaluronan backbone from membrane

see also Canetta et al. (2004)

Modelling the interaction between cells and ECM

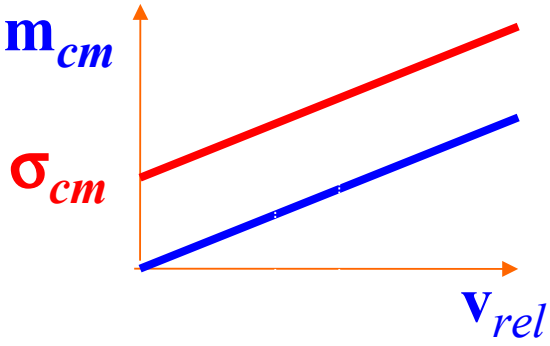


- if cells are not pulled strong enough they stick to the ECM
- otherwise they move relative to the ECM

Interaction force

Adhesion strength

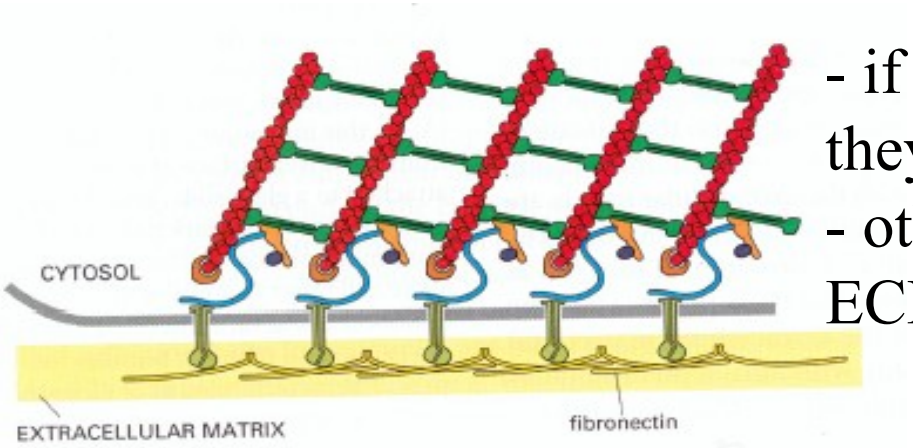
$$\mathbb{M}_{cm}(\mathbf{v}_m - \mathbf{v}_c) = \begin{cases} 0 & \text{if } |\mathbf{m}_{cm}| < \sigma_{cm} \\ (|\mathbf{m}_{cm}| - \sigma_{cm}) \dfrac{\mathbf{m}_{cm}}{|\mathbf{m}_{cm}|} & \text{if } |\mathbf{m}_{cm}| \geq \sigma_{cm} \end{cases}$$



← **Darcy's-type law**

• L.P. & A. Tosin, *J. Math. Biol.* **58**, 625-656, (2009)

Modelling the interaction between cells and ECM



- if cells are not pulled strong enough they they stick to the ECM
- otherwise they move relative to the ECM

Interaction force

Adhesion strength

$$\mathbb{M}_{cm}(\mathbf{v}_m - \mathbf{v}_c) = \begin{cases} 0 & \text{if } |\mathbf{m}_{cm}| < \sigma_{cm} \\ (|\mathbf{m}_{cm}| - \sigma_{cm}) \dfrac{\mathbf{m}_{cm}}{|\mathbf{m}_{cm}|} & \text{if } |\mathbf{m}_{cm}| \geq \sigma_{cm} \end{cases}$$

$$\mathbf{v}_c - \mathbf{v}_m = \left(1 - \frac{\sigma_{cm}}{|\nabla \cdot (\phi_c \mathbb{T}_c)|}\right)^+ \mathbb{K}_{cm} \nabla \cdot (\phi_c \mathbb{T}_c) \, .$$

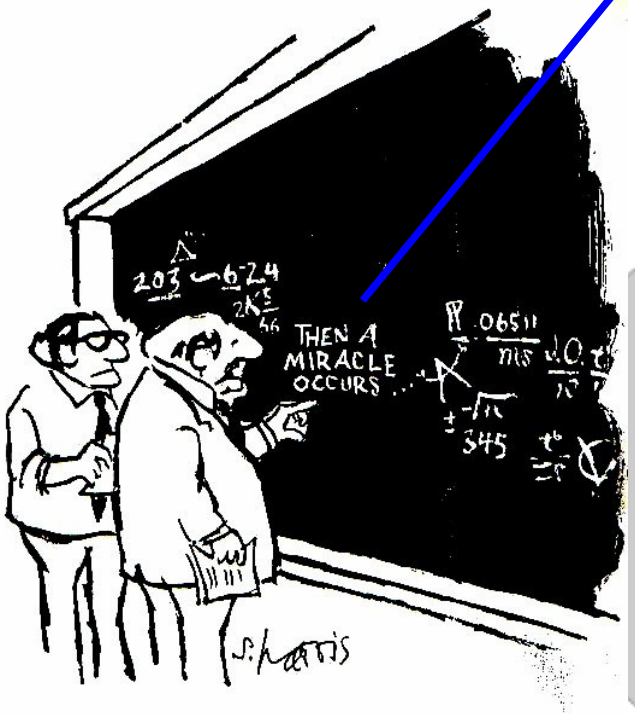
- L.P. & A. Tosin, *JMB,* (2008)

Modelling the interaction between cells and ECM

$$\mathbf{r}^{\alpha\beta}(\mathbf{X}^{\alpha},\mathbf{X}^{\beta},t)=\chi^{\alpha}(\mathbf{X}^{\alpha},t)-\chi^{\beta}(\chi^{\beta\,-1}(\chi^{\alpha}(\mathbf{X}^{\alpha},t-a),t-a),t)$$

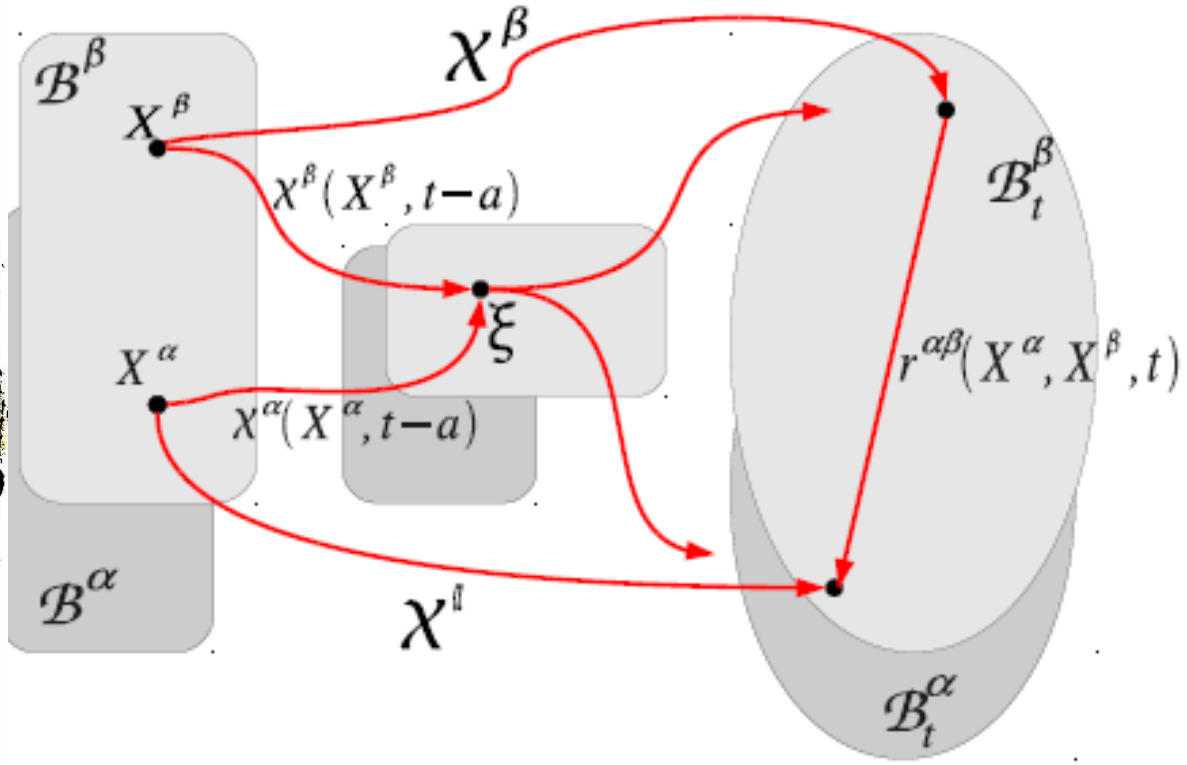
$$\simeq\ a\left(\mathbf{v}^{\alpha}(\mathbf{x},t)-\mathbf{v}^{\beta}(\mathbf{x},t)\right),\qquad a\to 0\,,$$

G. Vitale & L.P., *M3AS*, (2010)



"I THINK YOU SHOULD BE MORE EXPLICIT HERE IN STEP TWO."

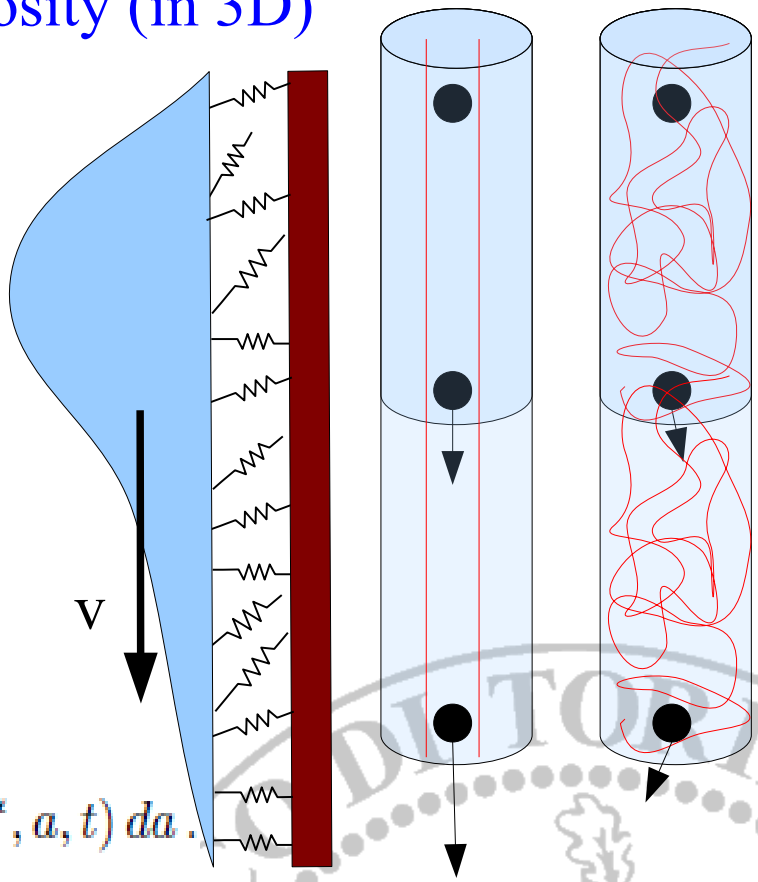
Figure 8. © 1975 by Sidney Harris – American Scientist magazine



Modelling the interaction between cells and ECM

Contribution due to porosity and tortuosity (in 3D)

$$\mathbf{m}_D^{\alpha\beta}(\mathbf{x},t) = -M(\mathbf{v}^\alpha(\mathbf{x},t) - \mathbf{v}^\beta(\mathbf{x},t))\,,$$



Contribution due to adhesion

$$N^{\alpha\beta}(\mathbf{X}^\alpha,t) = \int_0^{+\infty} f^{\alpha\beta}(\mathbf{X}^\alpha,a,t)\,da\,.$$

$$\mathbf{m}_{ad}^{\alpha\beta}(\mathbf{X}^\alpha,t) = -k_{mic}^{\alpha\beta}\int_0^{+\infty} \mathbf{r}^{\alpha\beta}(\mathbf{X}^\alpha,a,t) f^{\alpha\beta}(\mathbf{X}^\alpha,a,t)\,da\,.$$

Modelling the adhesive contribution

Evolution equation

$$\begin{cases} \dfrac{\partial f^{\alpha\beta}}{\partial t} + \dfrac{\partial f^{\alpha\beta}}{\partial a} = -\eta^{\alpha\beta} \\ \\ f(a=0,t) = \beta\left(N_{max} - N^{\alpha\beta}(t)\right) = \beta\left(N_{max} - \displaystyle\int_0^{+\infty} f(a,t)\,da\right) \end{cases}$$

In the limit:

bond age << travel time $\Longleftrightarrow$ Breaking length << cell diameter

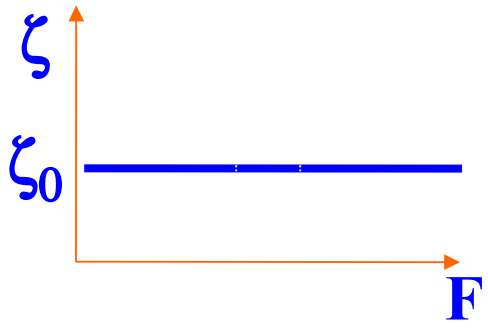
$$\begin{cases} \dfrac{\partial f}{\partial a}(a;t) = -\zeta(F_{mic}(a;t))f(a;t)\,, \\ \\ f(a=0;t) = \beta\left(N_{max} - \displaystyle\int_0^{+\infty} f(a;t)\,da\right). \end{cases}$$

$$f(a) = \frac{\beta N_{max} \exp\left[-\displaystyle\int_0^a \zeta(F_{mic}(\alpha))\,d\alpha\right]}{1+\beta\displaystyle\int_0^{+\infty} \exp\left[-\int_0^{\tilde{a}} \zeta(F_{mic}(\alpha))\,d\alpha\right]\,d\tilde{a}}$$

$$\Longrightarrow \quad \mathbf{m}_{ad}^{\alpha\beta} = \frac{\beta N_{max}\displaystyle\int_0^{+\infty} \mathbf{F}_{mic}(a)\exp\left[-\int_0^a \zeta(F_{mic}(\alpha))\,d\alpha\right]\,da}{1+\beta\displaystyle\int_0^{+\infty} \exp\left[-\int_0^a \zeta(F_{mic}(\alpha))\,d\alpha\right]\,da}$$

Modelling the adhesive contribution

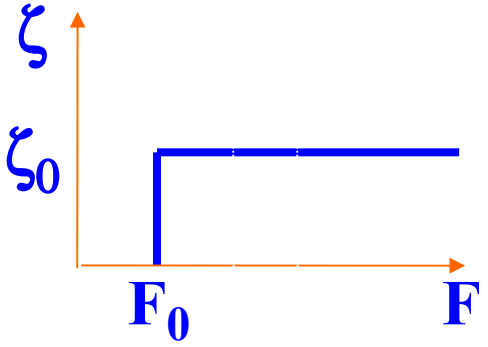
If



$$f(a) = \frac{\beta\zeta_0 N_{max}}{\beta + \zeta_0} e^{-\zeta_0 a},$$

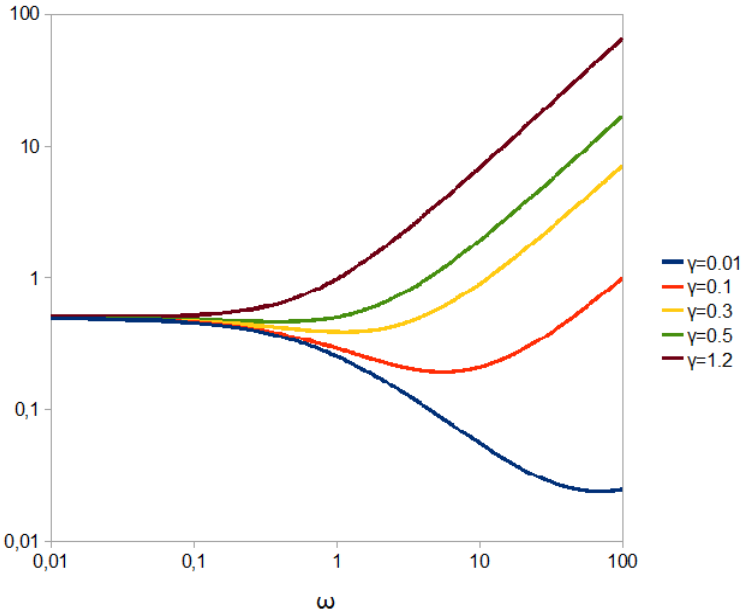
$$\frac{\mathbf{m}_{cm}^{ad}}{N_{max}} = -k_{cm}^{mic} \frac{\gamma}{\zeta_0(1+\gamma)} (\mathbf{v}_c - \mathbf{v}_m) \qquad \gamma = \frac{\beta}{\zeta_0}.$$

If

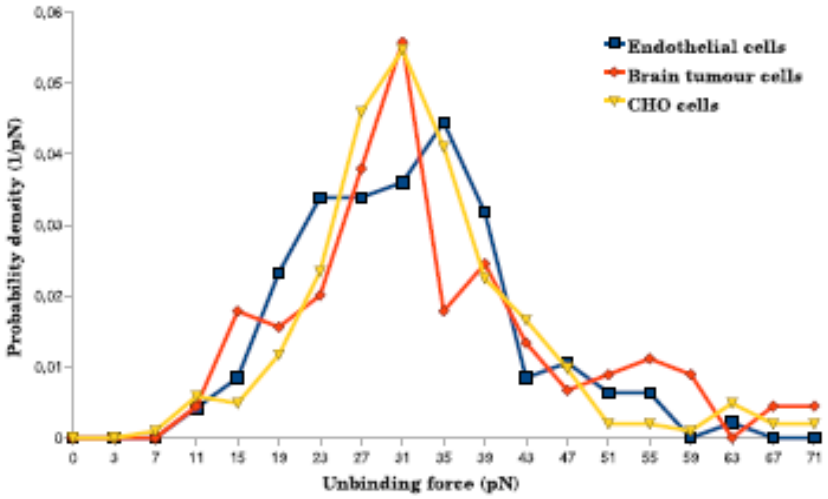


$$\frac{|\mathbf{m}_{cm}^{ad}|}{N_{max}} = F_0 \frac{\frac{1}{2} + \gamma\omega + \gamma^2\omega^2}{1 + (1+\gamma)\omega}$$

$$\omega = \frac{k_{cm}^{mic} v_{rel}}{\beta F_0}$$



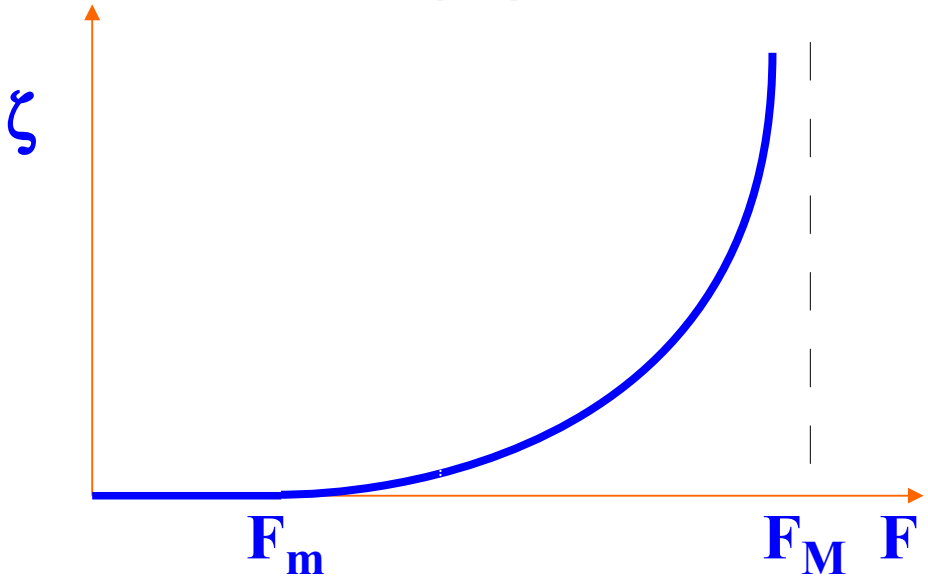
Modelling the adhesive contribution

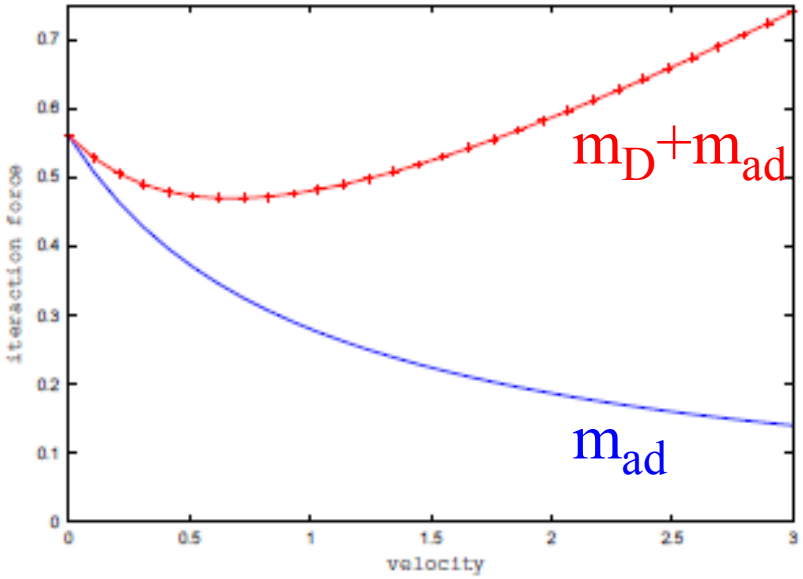


$$\zeta_r(F_{mic}(a)) = \frac{b(F_{mic}(a))}{B(F_{mic})}$$

$$B(F_{mic}) = \int_{F_{mic}}^{F_M} b(\phi)\, d\phi$$

$$\mathbf{m}^{\alpha\beta} = -N_{max}\frac{\sigma^2 + m_b^2}{2(W + m_b)}\frac{\mathbf{v}^\alpha - \mathbf{v}^\beta}{v_{rel}} - M(\mathbf{v}^\alpha - \mathbf{v}^\beta),$$

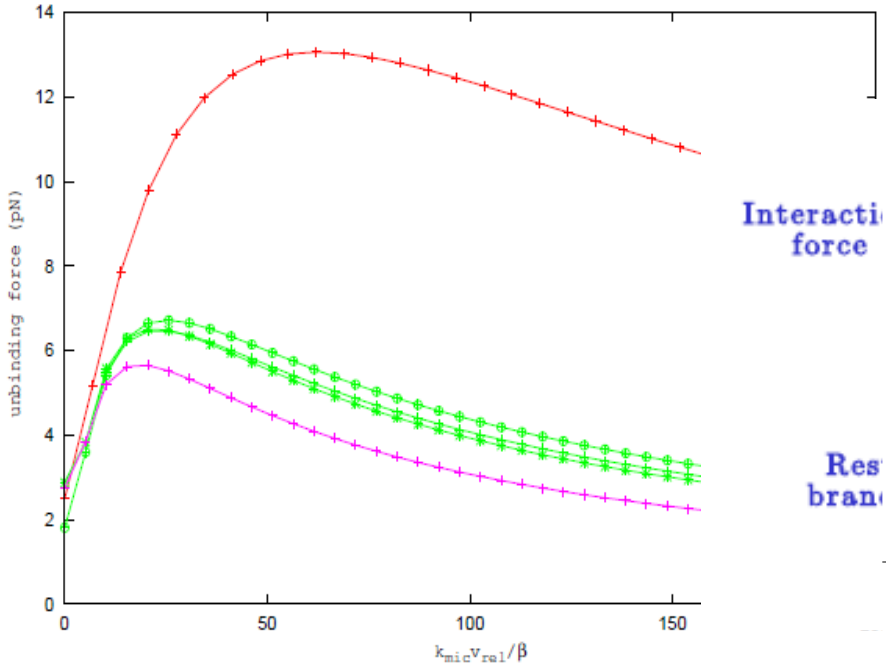


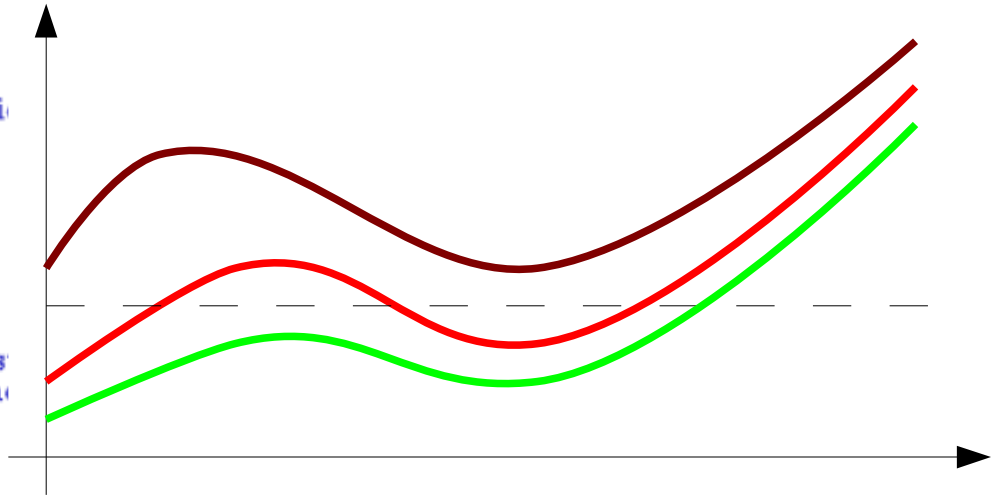


Modelling the interaction between cells and ECM

$$\zeta(F_{mic}(a)) = \zeta_0 H(F - F_0) + \zeta_r(F_{mic}(a))$$

$$\frac{|\mathbf{m}_{ad}^{\alpha\beta}|}{N_{max}} = \frac{\displaystyle\int_0^{F_m} F \exp\left[-\frac{(F-F_0)_+}{\hat{F}_0}\right] dF + \int_{F_m}^{F_M} F \exp\left[-\frac{(F-F_0)_+}{\hat{F}_0}\right] \frac{B(F)}{B(F_m)} dF}{W + \displaystyle\int_0^{F_m} \exp\left[-\frac{(F-F_0)_+}{\hat{F}_0}\right] dF + \int_{F_m}^{F_M} \exp\left[-\frac{(F-F_0)+}{\hat{F}_0}\right] \frac{B(F)}{B(F_m)} dF}$$



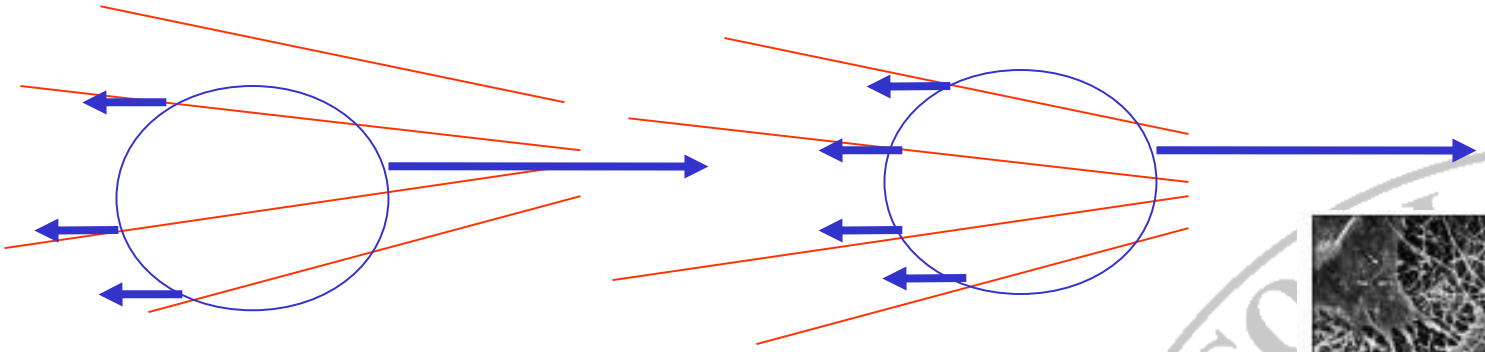


Modelling the interaction between cells and ECM

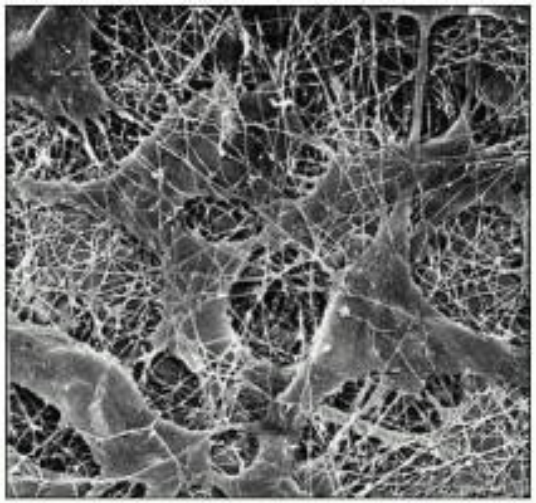
– Different clones have different thresholds

Different invasiveness

– Adhesion depends on the amount of ECM,

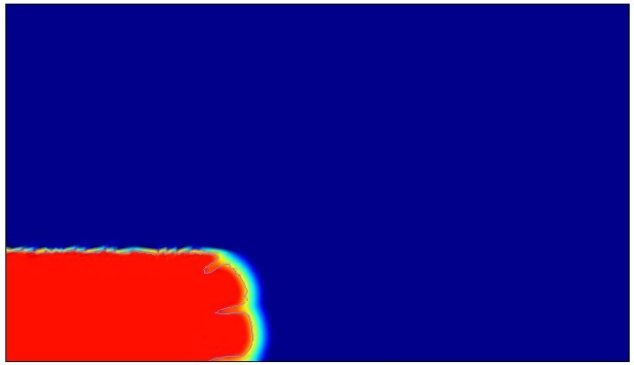


moves → slows down → stops

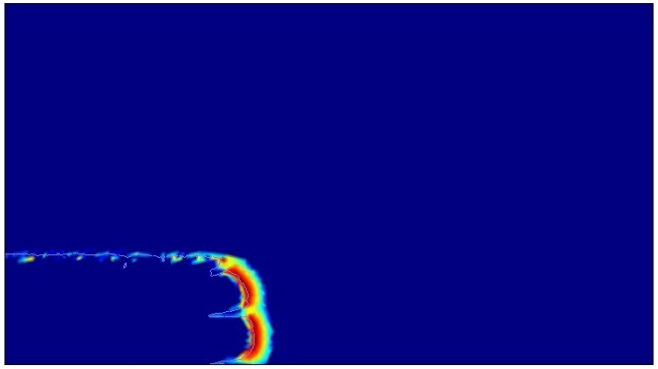


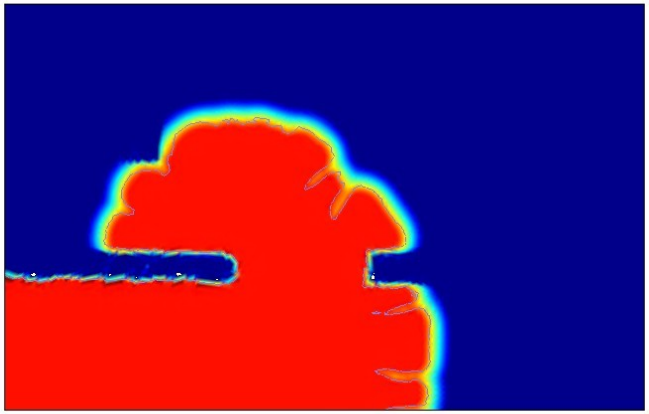
Modelling the interaction between cells and ECM

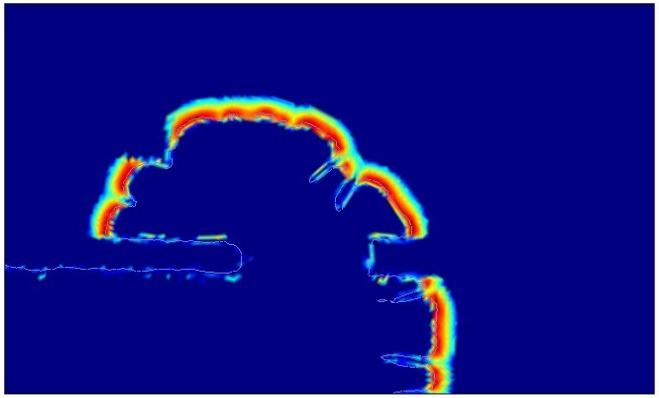
Volume ratio



Interfacial force







Modelling the interaction between cells and ECM