Adhesion, Mechanosensing, Mechanotransduction

Vesicles



only surface energy | surf energy + solid elast. | surf en bending energy | surf. en. bend + stretch energy

Young-Laplace equation $\Delta p = -\gamma H = -\gamma\left(\frac{1}{R_1} + \frac{1}{R_2}\right)$ → mean curvature

Surface energy $\gamma = \frac{W}{\Delta A}$ $\left(= \frac{F}{2L}\right.$ = surface tension$\left.\right)$

Youngs law: $\cos\theta = \frac{\gamma_{23} - \gamma_{12}}{\gamma_{13}}$



Force balance

Elastic deformation counteracts adhesion energy gain W:

contact radius a: $a^3 = \frac{9\pi(1-\nu^2)}{2E} R^2 W$ JKR theory

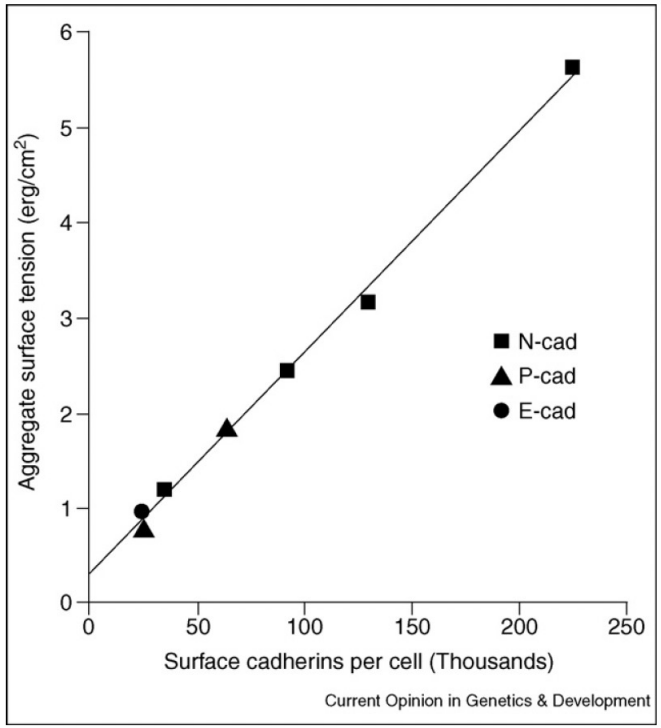
Bending energy $U_b = 2\kappa \int H^2 dA$ κ - bending rigidity

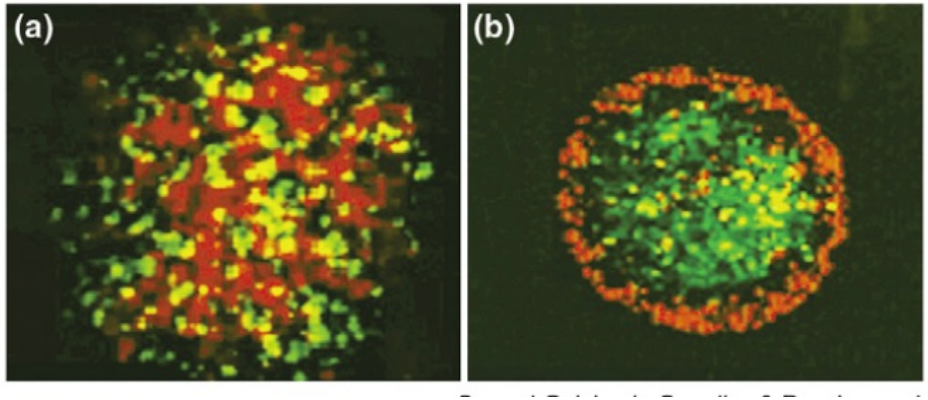
Biological bilipid membranes: $\kappa = 20kT$

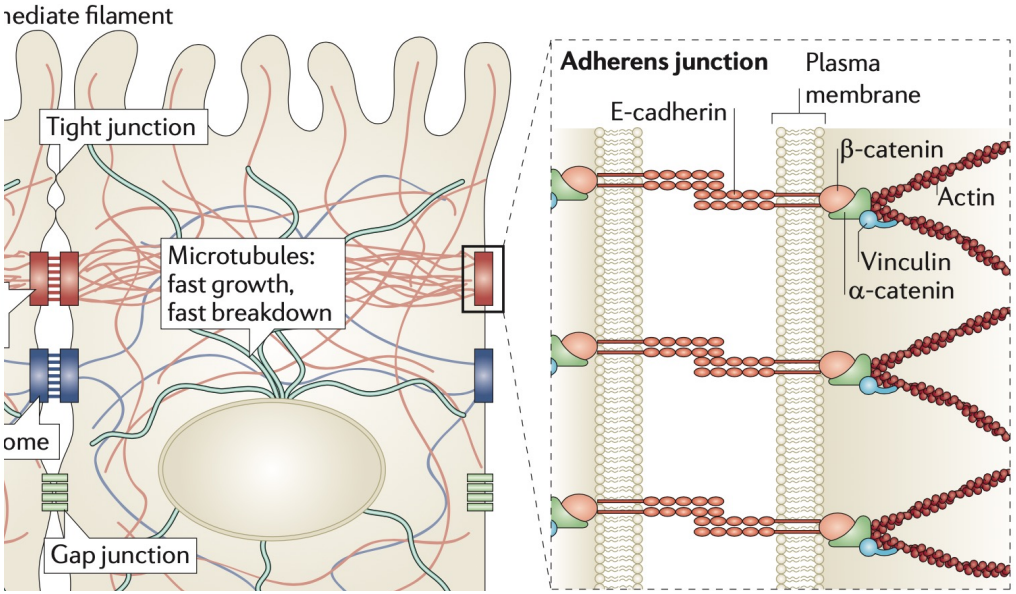
Differential adhesion

Steinberg2007:

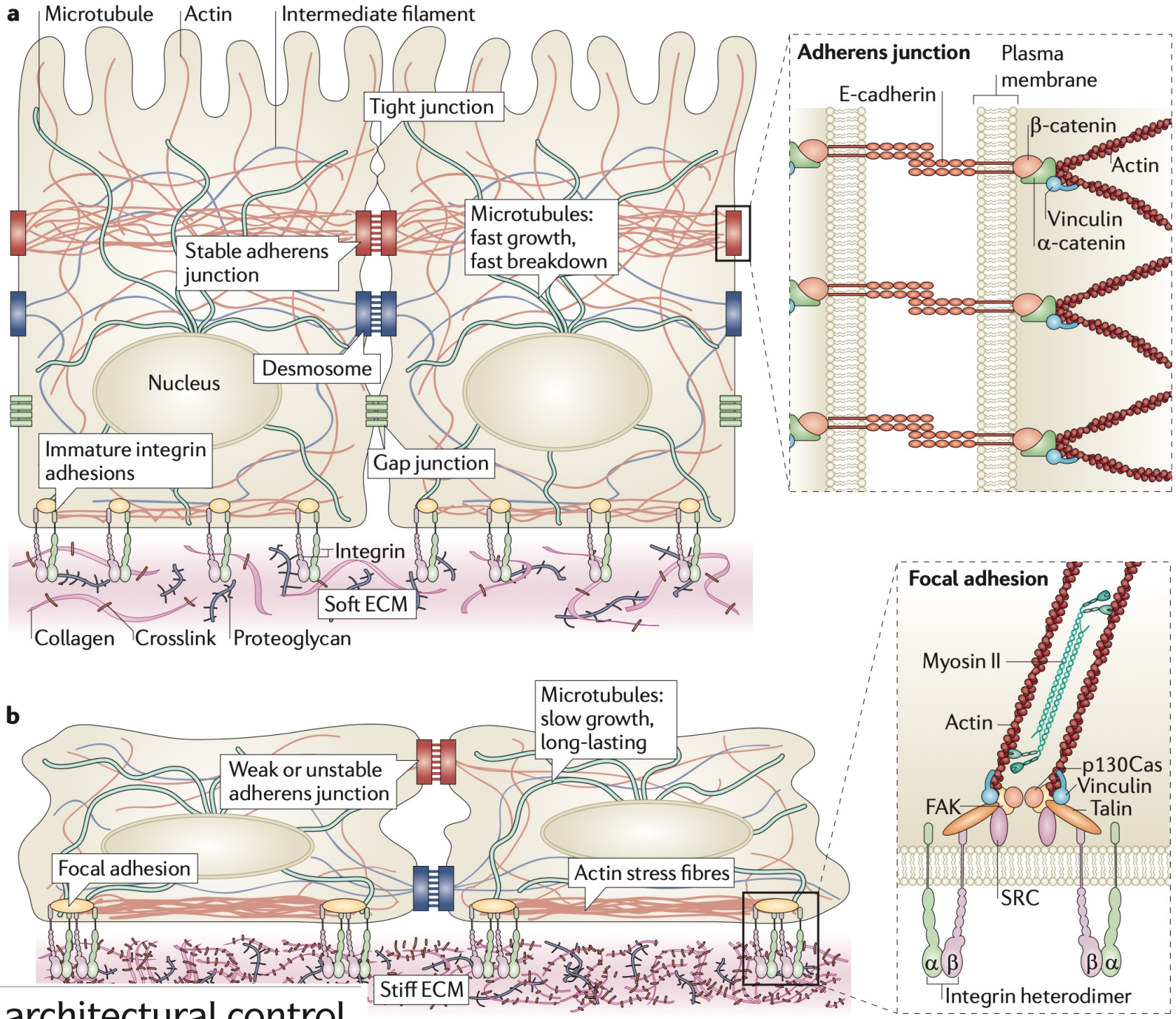
- Spreading of one embryonic tissue over another
- sorting of cells
- formation of intertissue boundaries







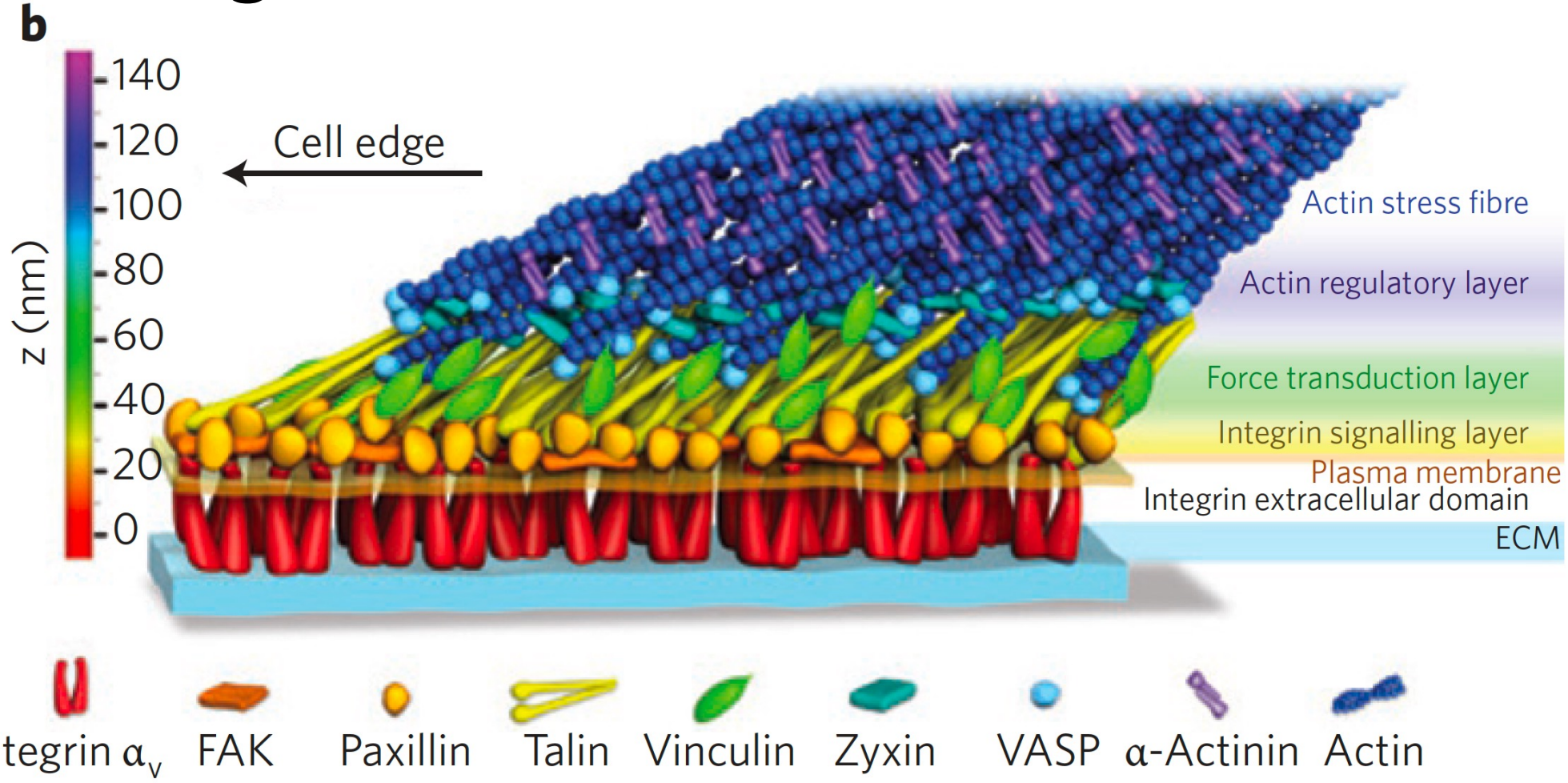
Mechanotransduction:
functional link between the sensing of mechanical cues and the subsequent biochemical response



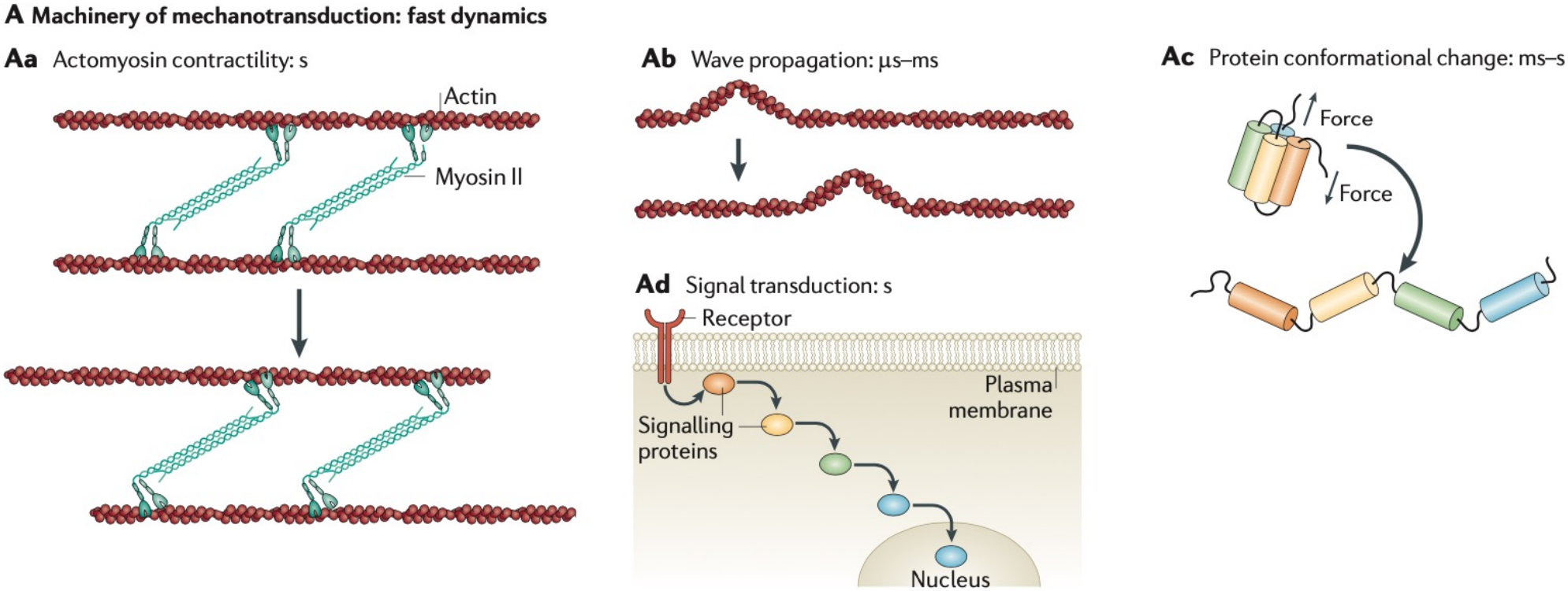
Balancing forces: architectural control of mechanotransduction

Christopher C. DuFort, Matthew J. Paszek* and Valerie M. Weaver*‡*

Length scales



Dalby, M. J., Riehle, M. O., Johnstone, H., Affrossman, S. & Curtis, A. S. Investigating the limits of filopodial sensing: a brief report using SEM to image the interaction between 10 nm high nano-topography and fibroblast filopodia. *Cell Biol. Int.* **28,** 229–236 (2004).



Balancing forces: architectural control of mechanotransduction

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Protein folding

Science Contents News Careers Journals

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Reversible Unfolding of Single RNA Molecules by Mechanical Force

Jan Liphardt[1,*], Bibiana Onoa[1], Steven B. Smith[2], Ignacio Tinoco Jr.[1], Carlos Bustamante[1,2,*]

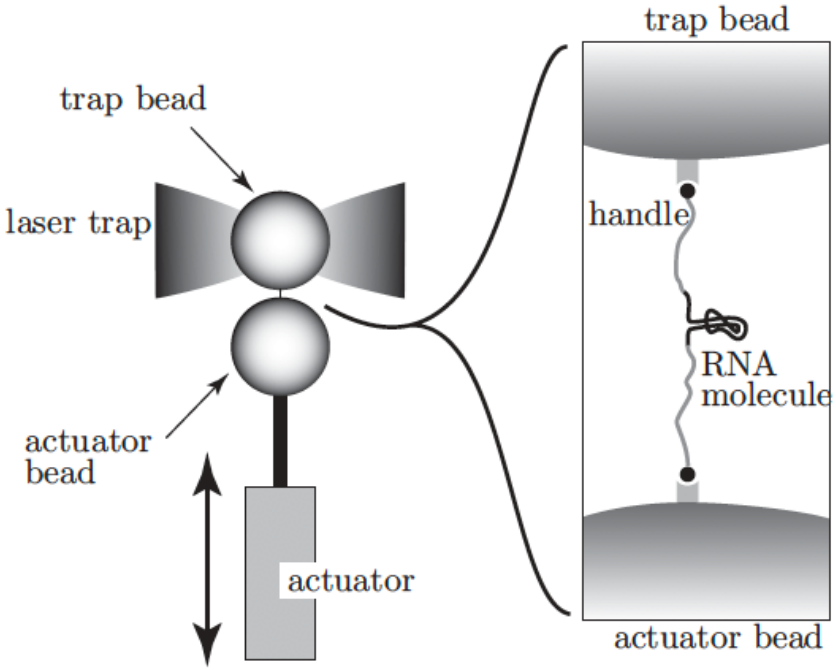
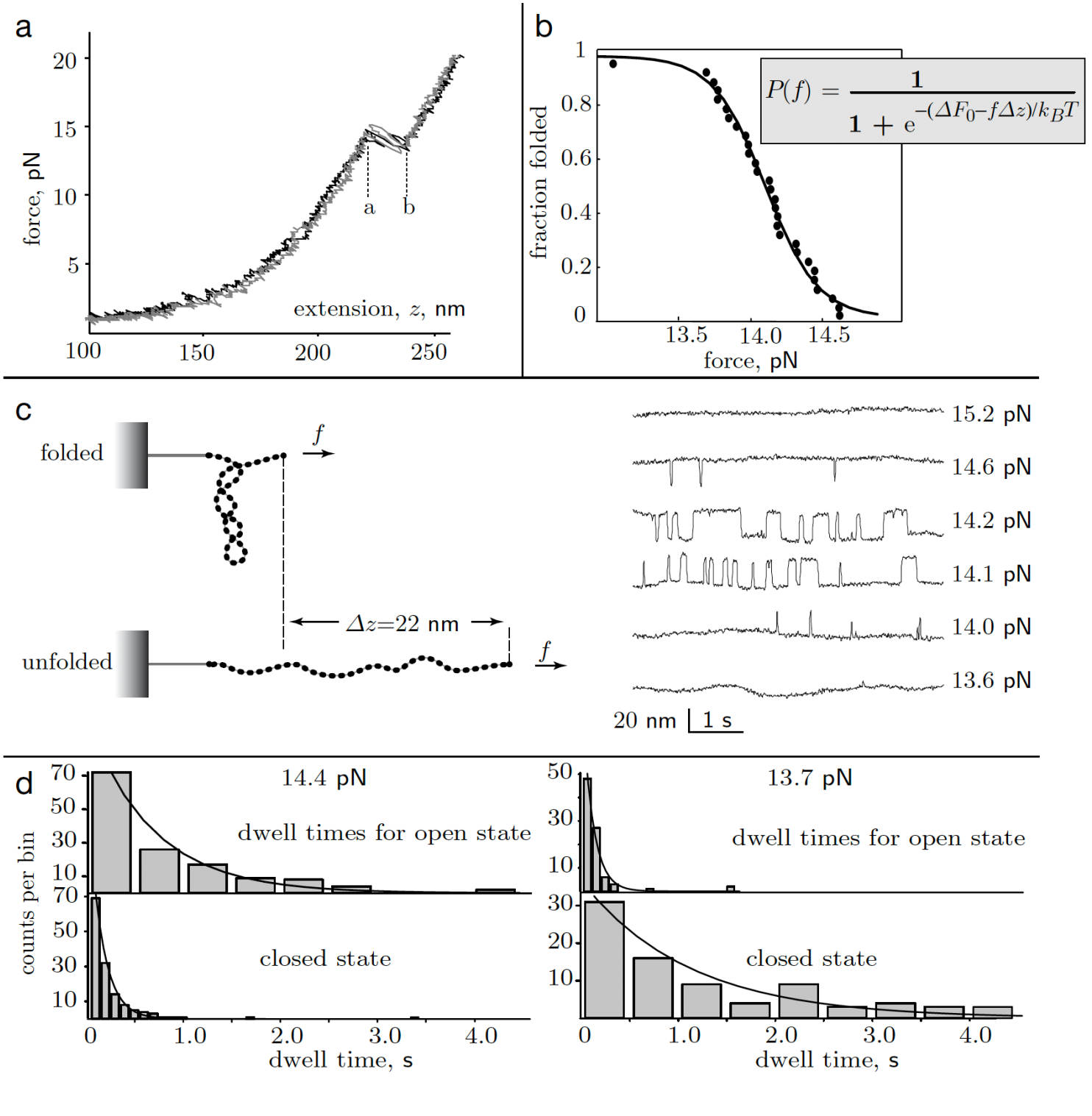
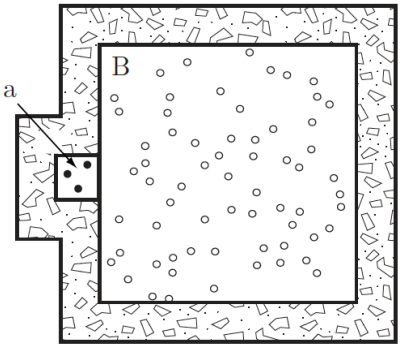
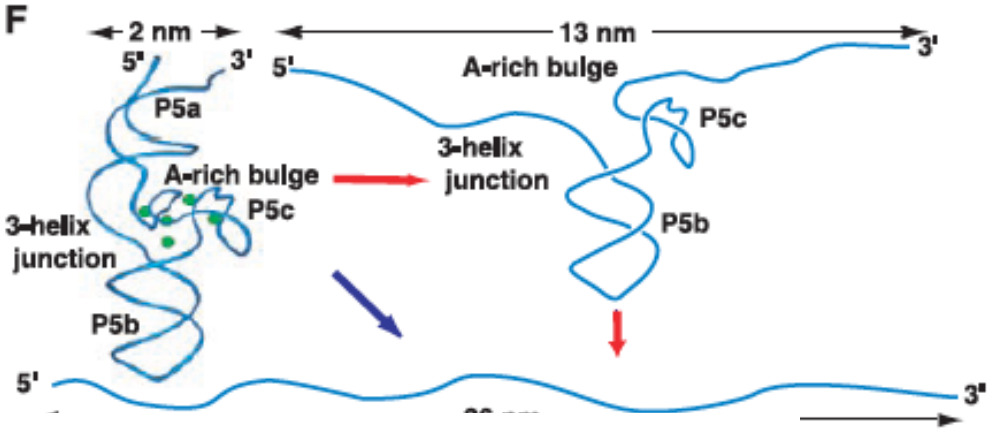


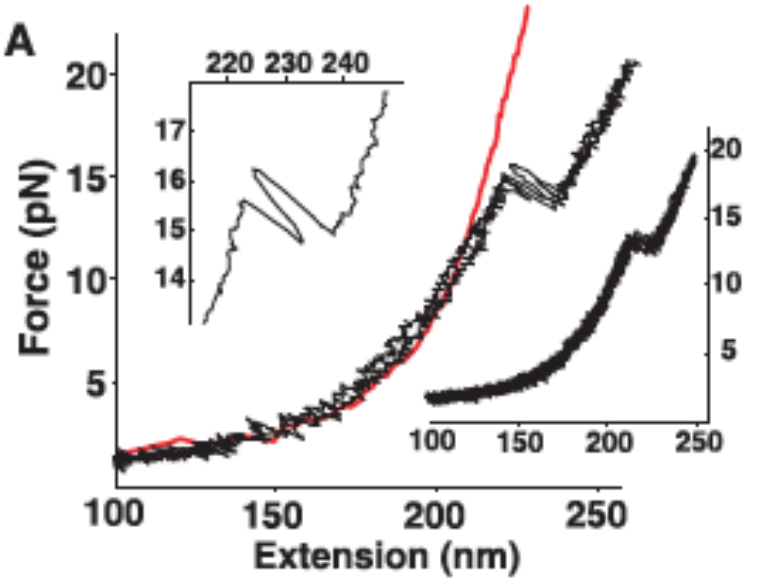
Figure 6.9: (Schematic.) Optical tweezer apparatus. A piezo-electric actuator controls the position of the bottom bead. The top bead is captured in an optical trap formed by two opposing lasers, and the force exterted on the polymer connecting the two beads is measured from the change in momentum of light that exits the optical trap. Molecules are stretched by moving the bottom bead vertically. The end-to-end length of the molecule is obtained as the difference of the position of the bottom bead and the top bead. *Inset:* The RNA molecule of interest is coupled to the two beads via molecular "handles." The handles end in chemical groups that stick to complementary groups on the bead. Compared to the diameter of the beads ($\approx 3000\,\mathrm{nm}$), the RNA is tiny ($\approx 20\,\mathrm{nm}$). [Figure kindly supplied by J. Liphardt.]

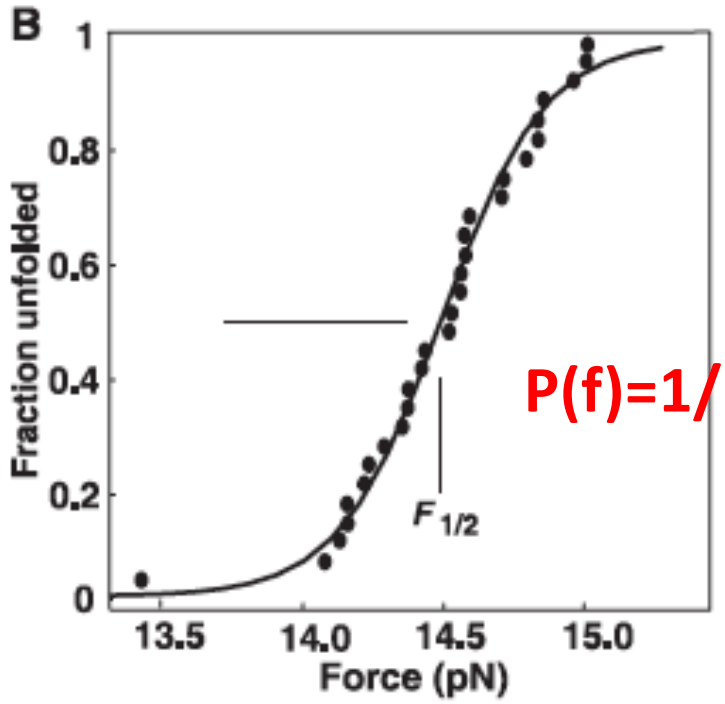




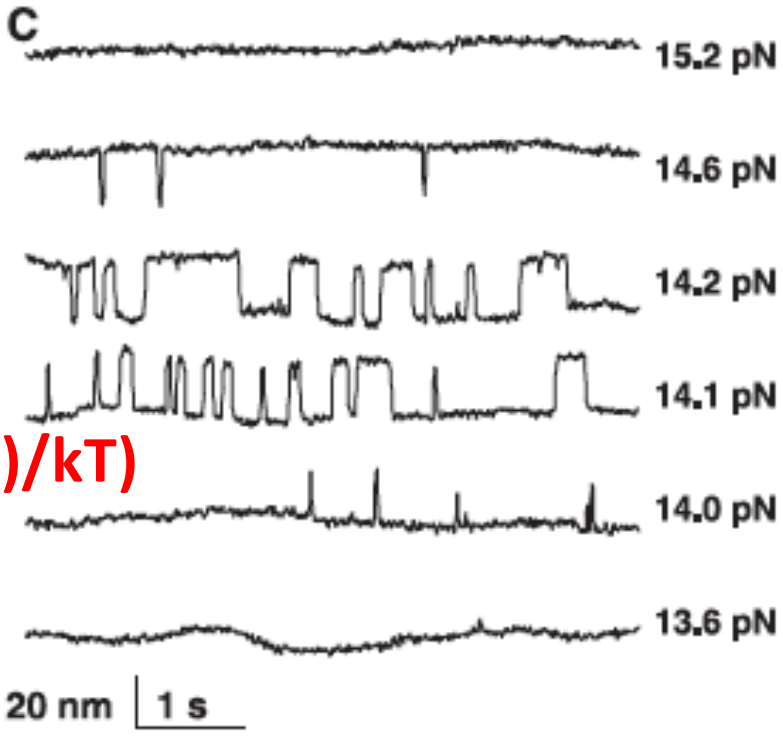
small system in thermal equilibrium with large
⇒ (NVT) => F







$$P(f)=1/(1+\exp(\Delta E-f\Delta z)/kT)$$



Detecting stiffness

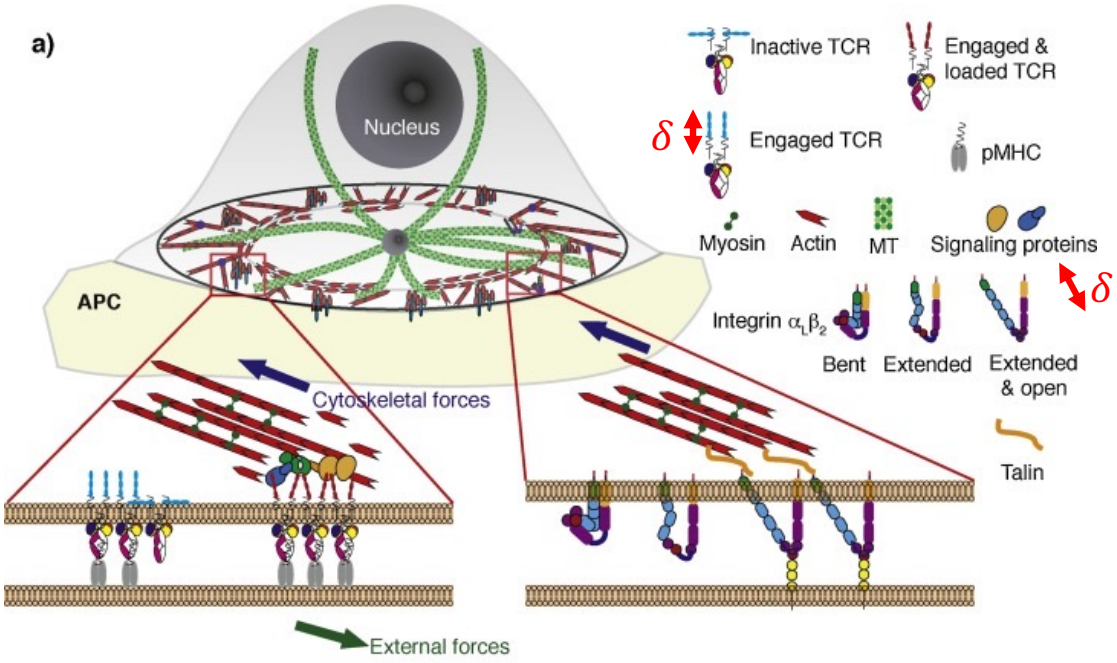
important unknown factors are the time it takes a cell to detect substrate stiffness and the distance over which the cell makes its rheological measurement, that is, determining any deformation as a result of applied force. Understanding these parameters can help define the molecular mechanisms by which stiffness sensing occurs. For example, if micron-scale deformations are needed to detect stiffness, then single nanometer-scale proteins are probably not sufficient by themselves to accomplish this function and larger complexes, such as focal adhesions or actin bundles, need to be assembled for this purpose.

Distance over which mechanosensing occurs

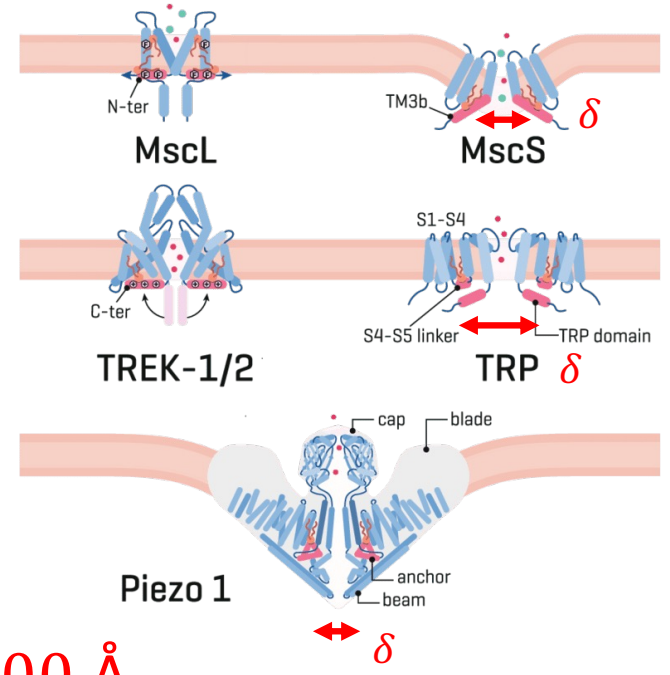
One hypothesis for the distance over which stiffness is sensed considers a role for single proteins at cell–substrate adhesion sites, where, when stressed by molecular motors, individual proteins partially unfold to either relieve autoinhibition of their enzymatic activity or expose new substrate-binding sites (Brown and Discher, 2009). Examples of proteins implicated in force or substrate stiffness responses are talin (del Rio et al., 2009), vinculin (Ezzell et al., 1997; Grashoff et al., 2010) and filamin (Byfield et al., 2009b; Gehler et al., 2009; Kasza et al., 2009), which all are flexible proteins that help link actin filaments to membrane adhesion sites. The size of individual proteins is of the order of a few nanometers and the complexes required to link the cytoskeleton to the membrane are smaller than a micrometer, suggesting that mechanosensing requires only very small movements and that substrate stiffness can be probed with submicrometer resolution. Other models of mechanosensing suggest that the sensor involves transmembrane ion channels that are linked mechanically to the adhesion sites (Glogauer et al., 1997; Koivusalo et al., 2009) and, therefore, the size of the integrated sensor is likely to be considerably lager than nanometer scale. Alternative models suggest a delocalized distribution of stresses throughout the cytoskeleton or the presence of sites within the actin stress fiber, possibly distant from the membrane adhesion complexes, that can act as mechanosensors.

Mekanosensorer

Proteiner som strekkes

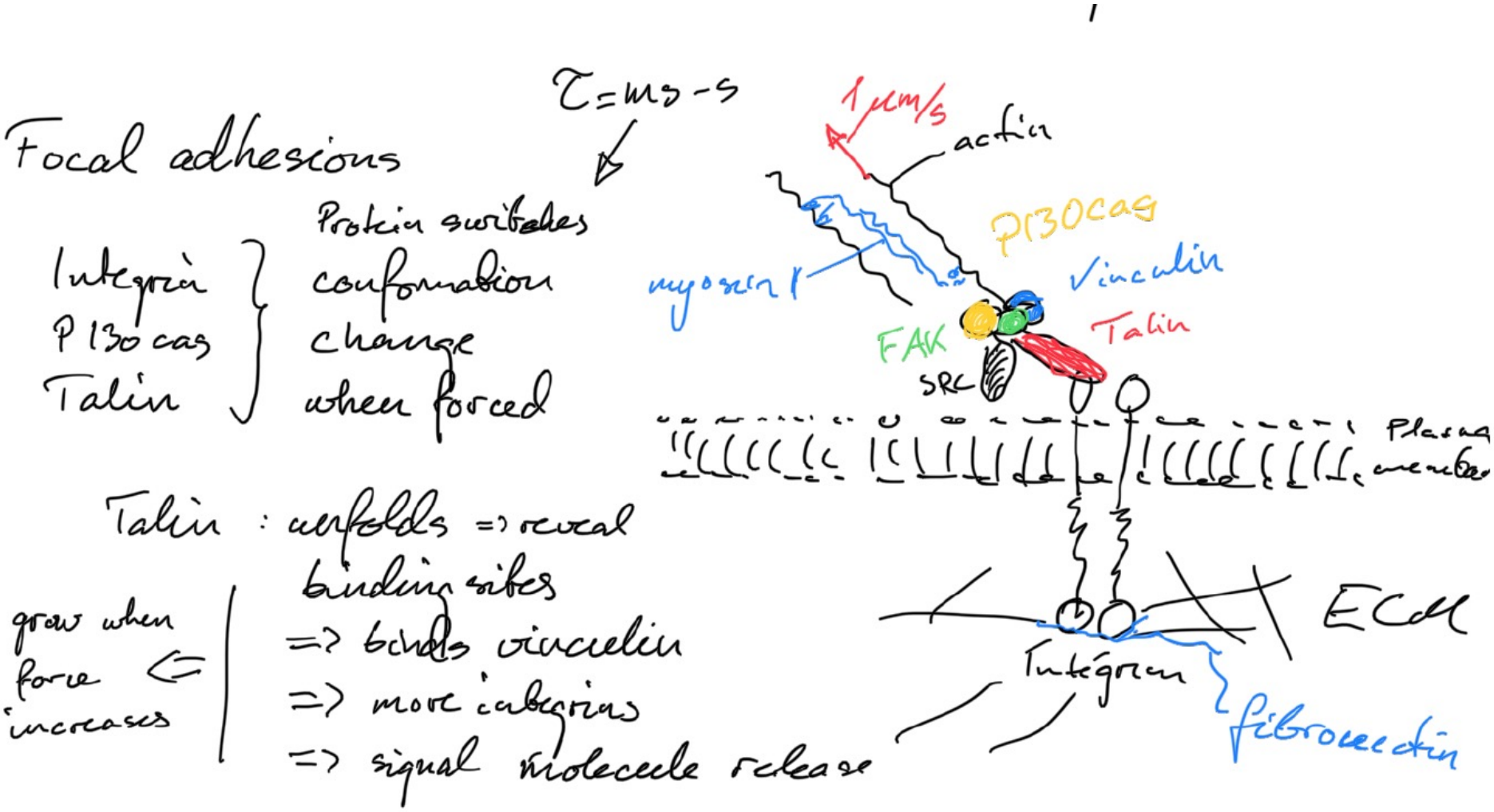


Ionekanaler



Alle sensorene må strekkes: $\delta > 100$ Å

Timescales

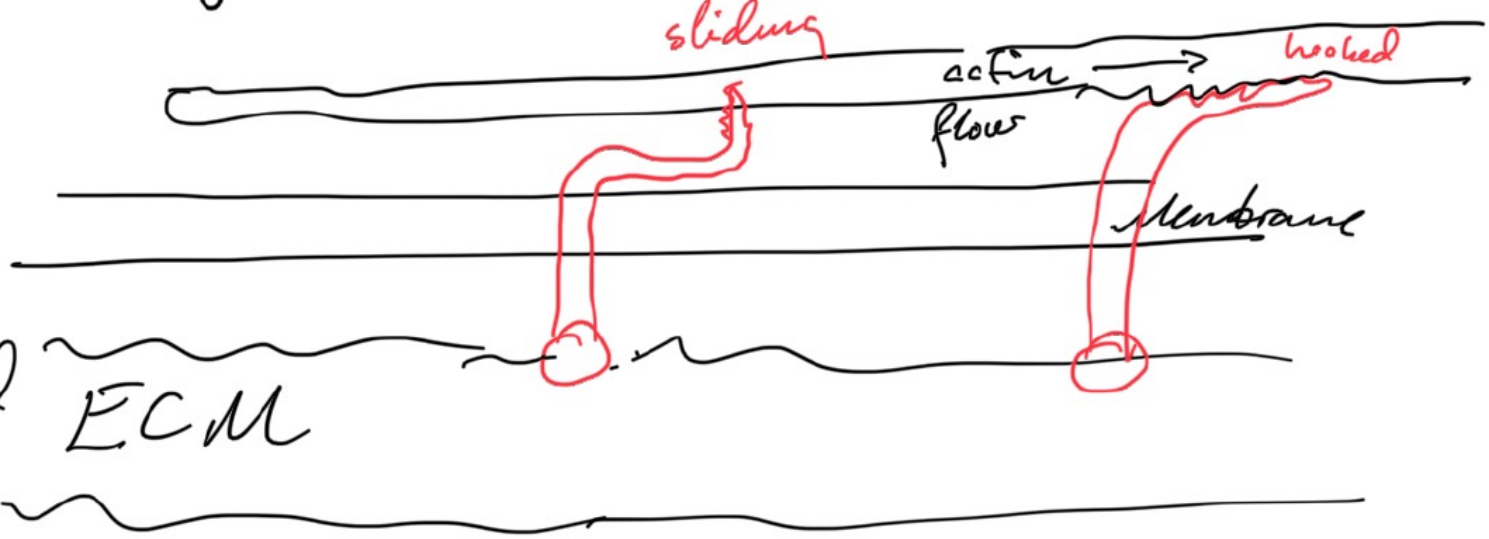

Focal adhesions
τ = ms - s
Protein switches
Integrin
P130cas
Talin
conformation change when forced
Talin : unfolds => reveal binding sites
grow when force increases
=> binds vinculin
=> more integrins
=> signal molecule release
1 μm/s
actin
myosin
P130cas
Vinculin
Talin
FAK
SRC
Plasma membrane
ECM
Integrin
fibronectin

Other mechanisms

Forces → changed intermolecular distances → altered cellular function

Ref to Bershadsky, Kozlov, Geiger 2006 (400 citing articles)

Two state protein unit



stress-induced flip

$$\Rightarrow \quad P = \frac{1}{1 + e^{-(F - f\Delta z)/kT}}$$

There is still a Δz !

Force generation

- ATP-driven motors:
  - myosin
  - dynein
  - kinesin
- Thermal ratchet

