echanical properties of filamentous biopolymers

rks of filamentous biopolymers have unusual elastic properties:

elastic modulus at very low volume fraction (<0.1%)

at (very low) increasing strain

fects of substrate mechanics on cell function.

pe specific

o cells measure stiffness?

n and time scales?

vs non-linear elastic substrate

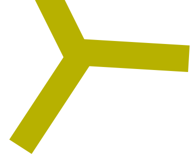
Qi Wen, Fitzroy Byfield, Ilya Levental, Shang Tee

Fred MacKintosh, Kees Storm, Tom Lubensky

Penn

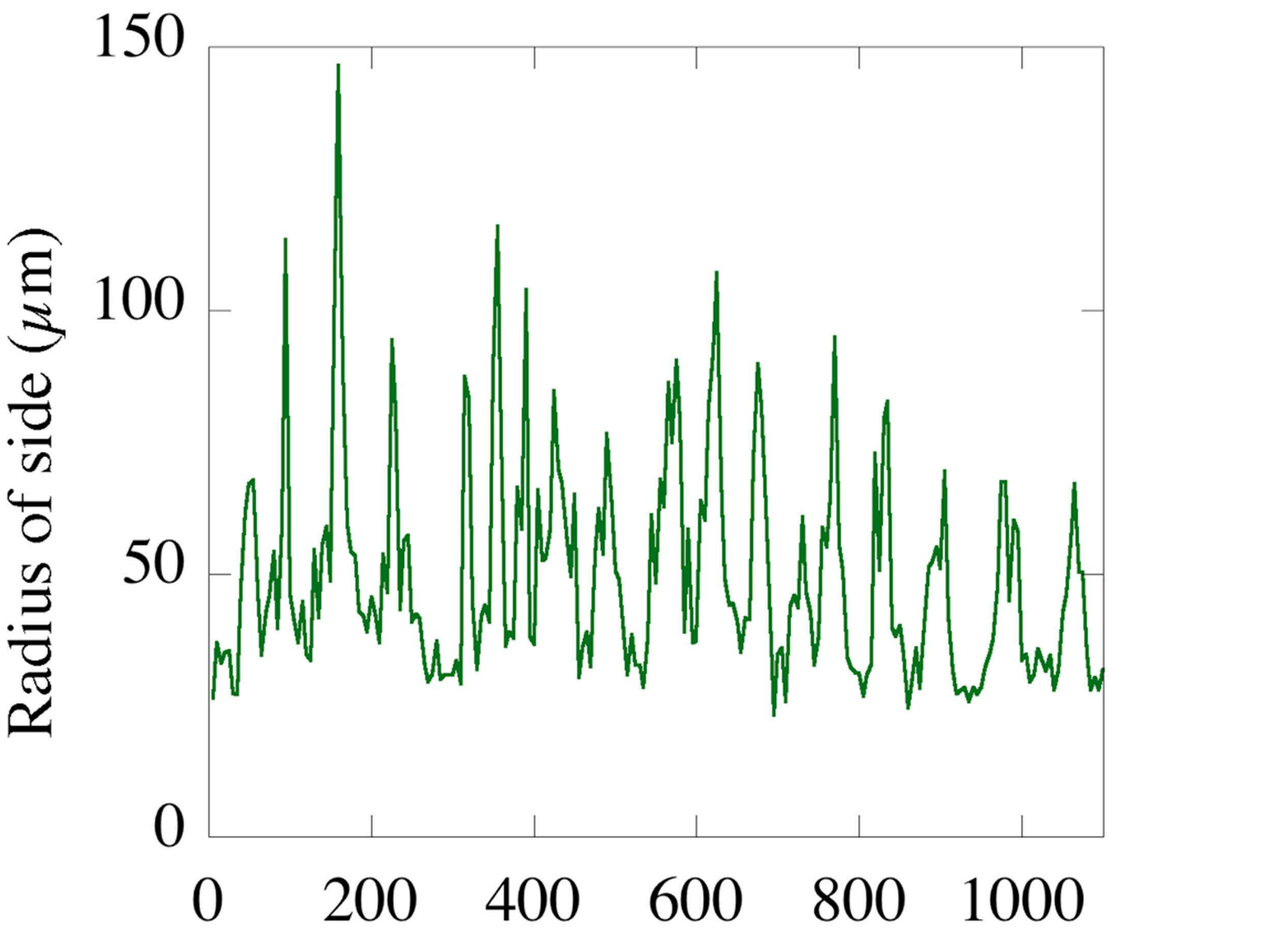
generating stress

adhesive
island

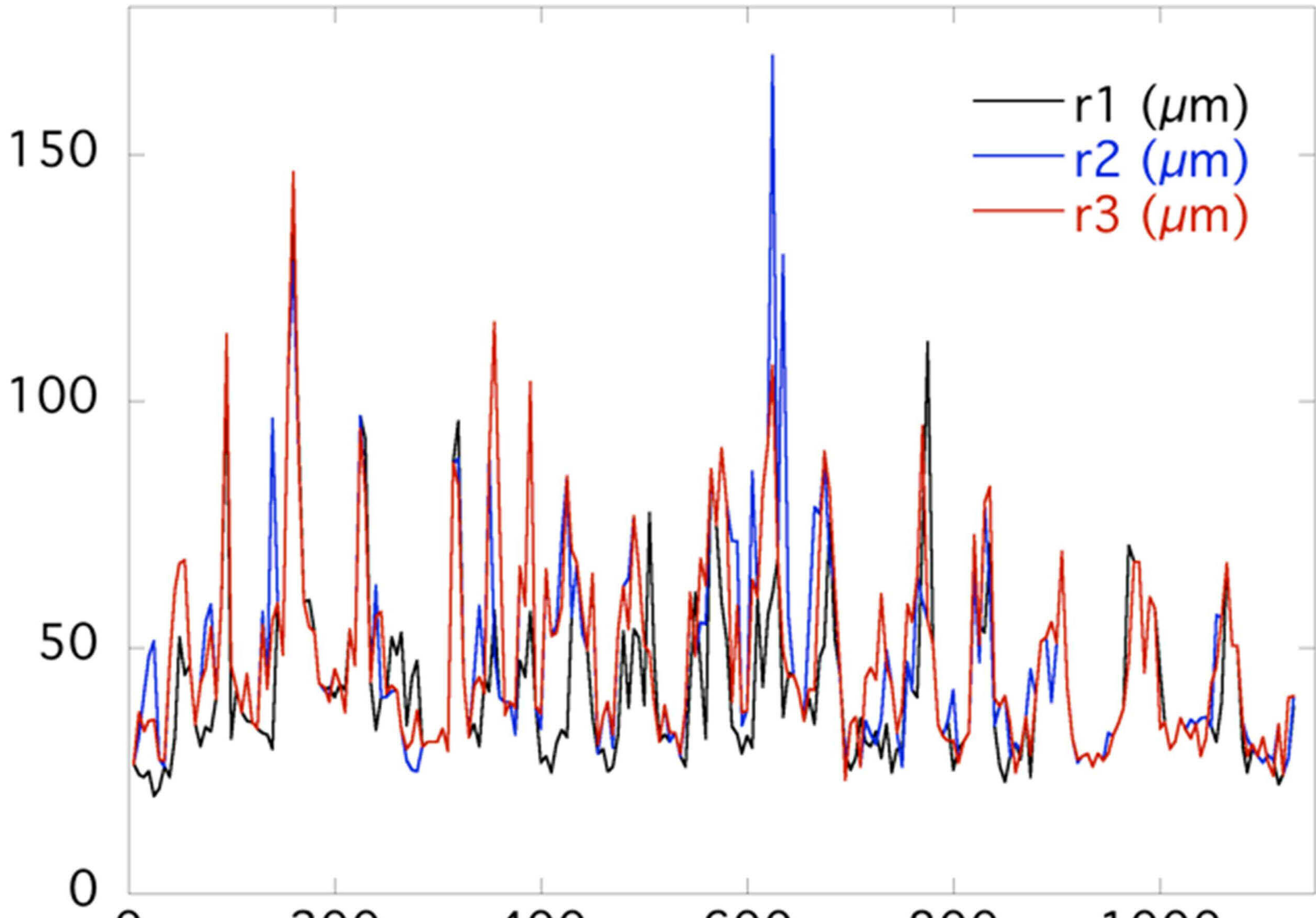


QuickTime and a
decompressor
are needed to see this picture.

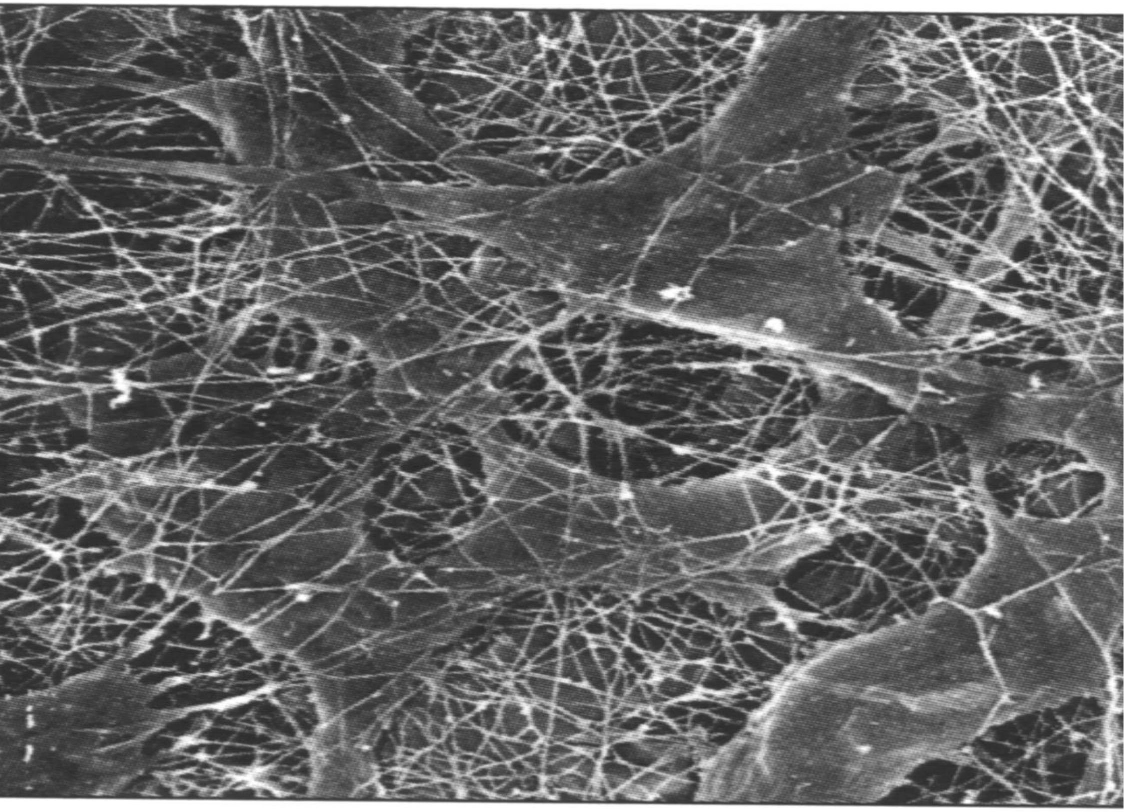
Cells can measure stiffness, because they are always pullin



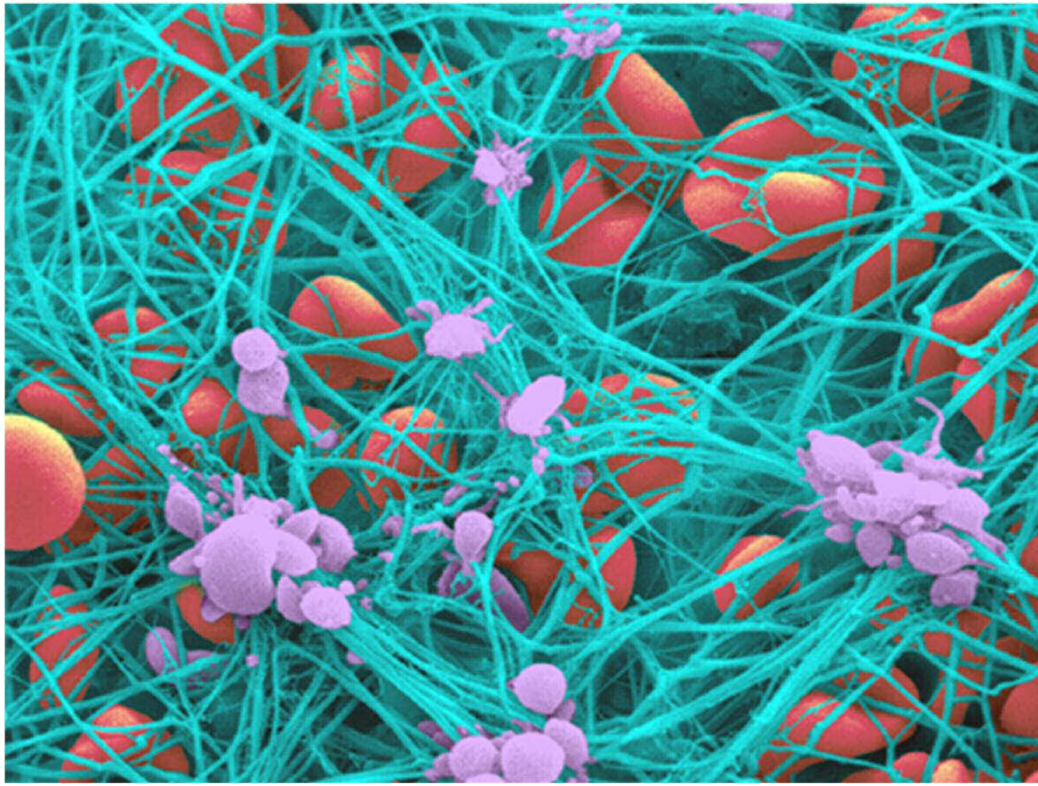
Radius of side (μm)
150
100
50
0
0
200
400
600
800
1000


r1 (μm)
r2 (μm)
r3 (μm)
150
100
50
0

E = 10 to 100,000 Pa) compared to plastic or glass (E>GPa)

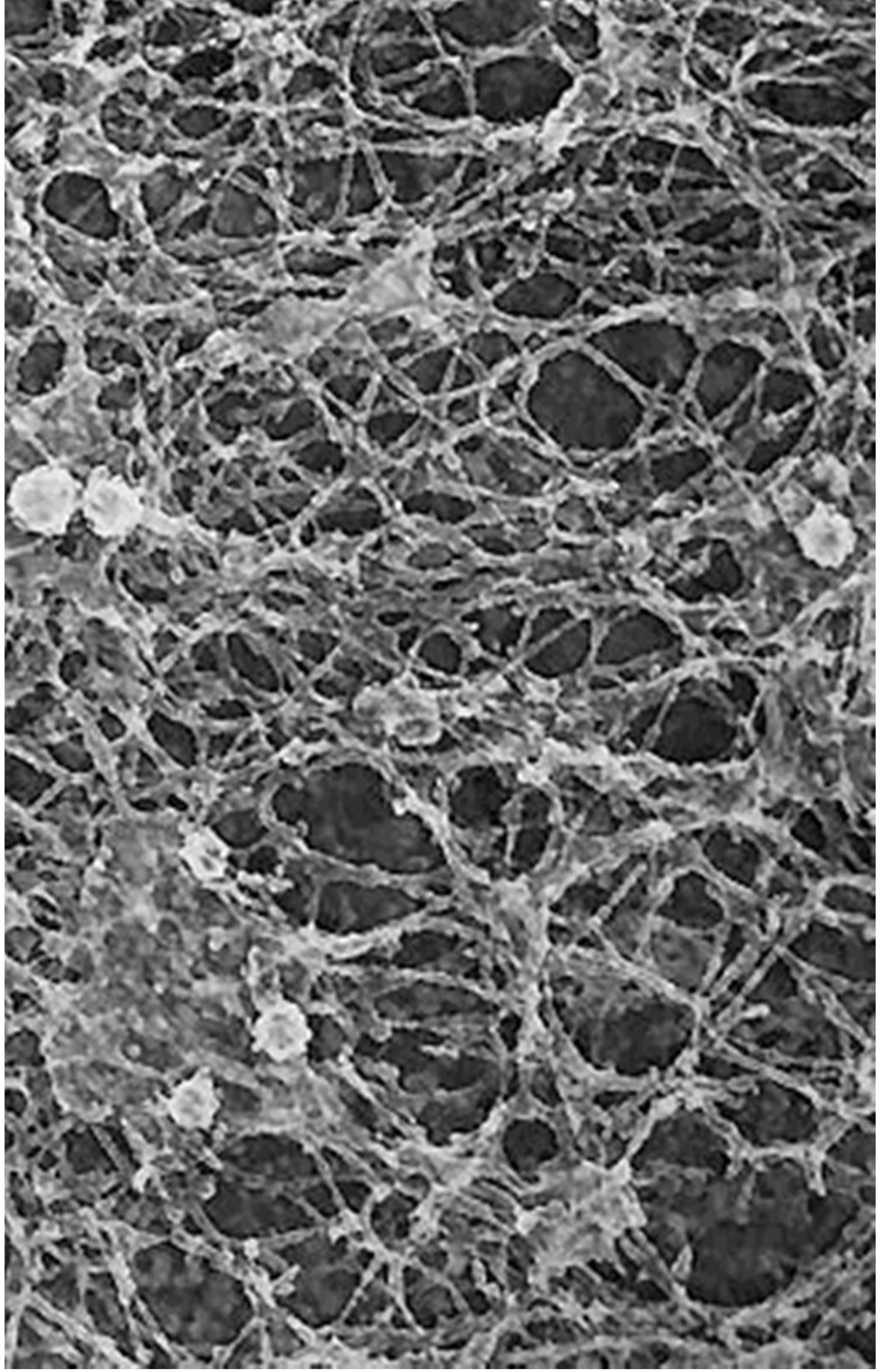


Fibroblasts in collagen ECM
(T. Nishida et al. Invest. Ophthalmol. Vis.)

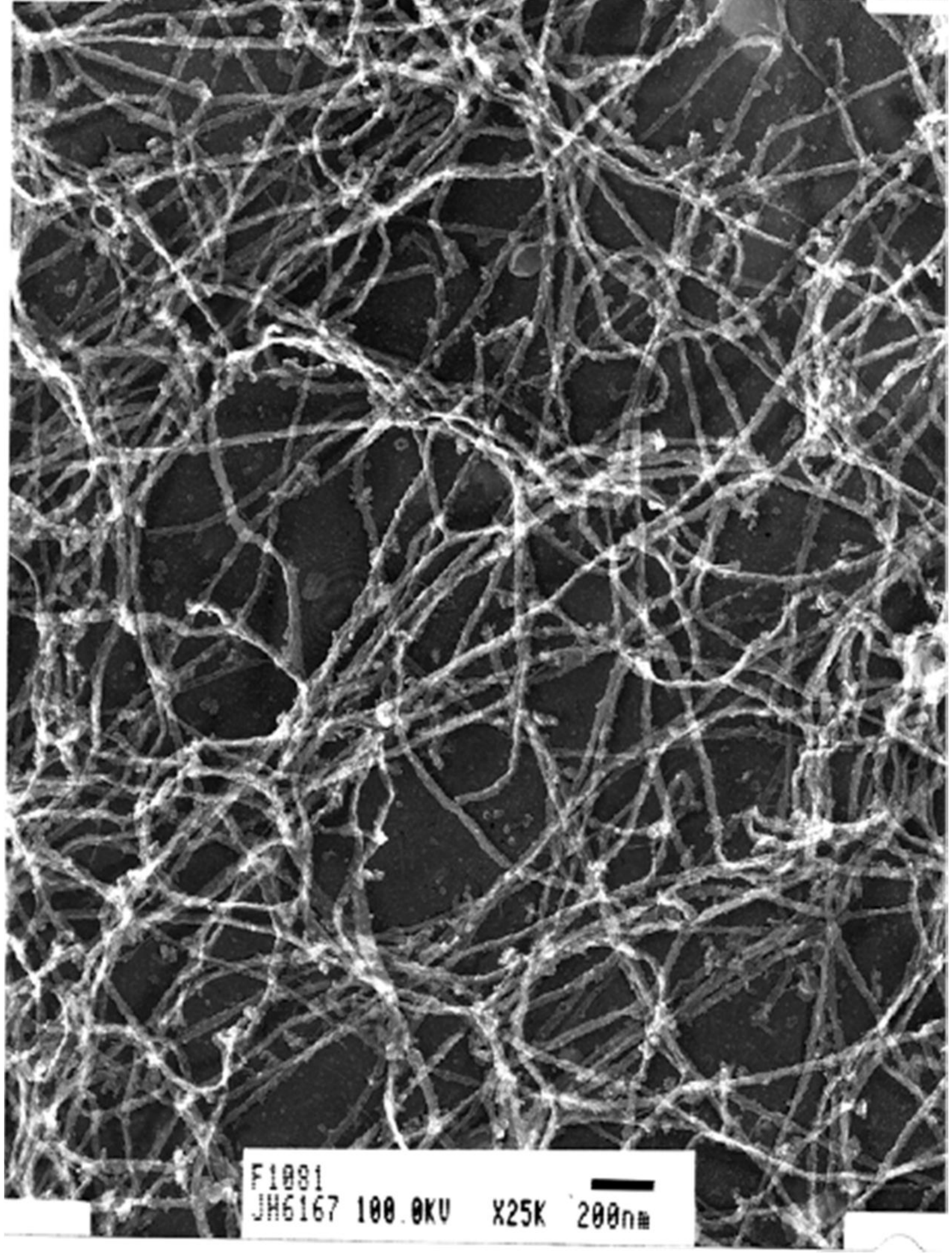


Red cells and **platelets** in blood clot. John Weisel- Penn

an rheology (stiffness) direct cell function and differentiation?
hat magnitude of stiffness do cells probe (what s hard or soft)



Cortical actin gel
JH Hartwig



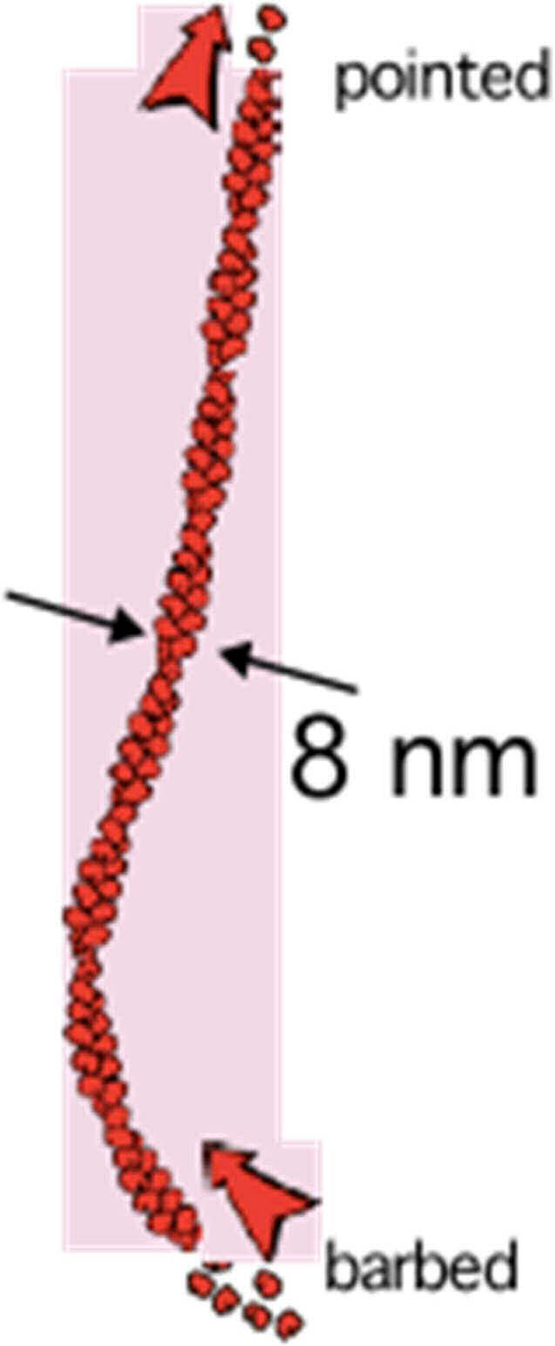
neurofilament network

Cytoskeletal and extracellular matrix filaments are all approximately semiflexible polymers

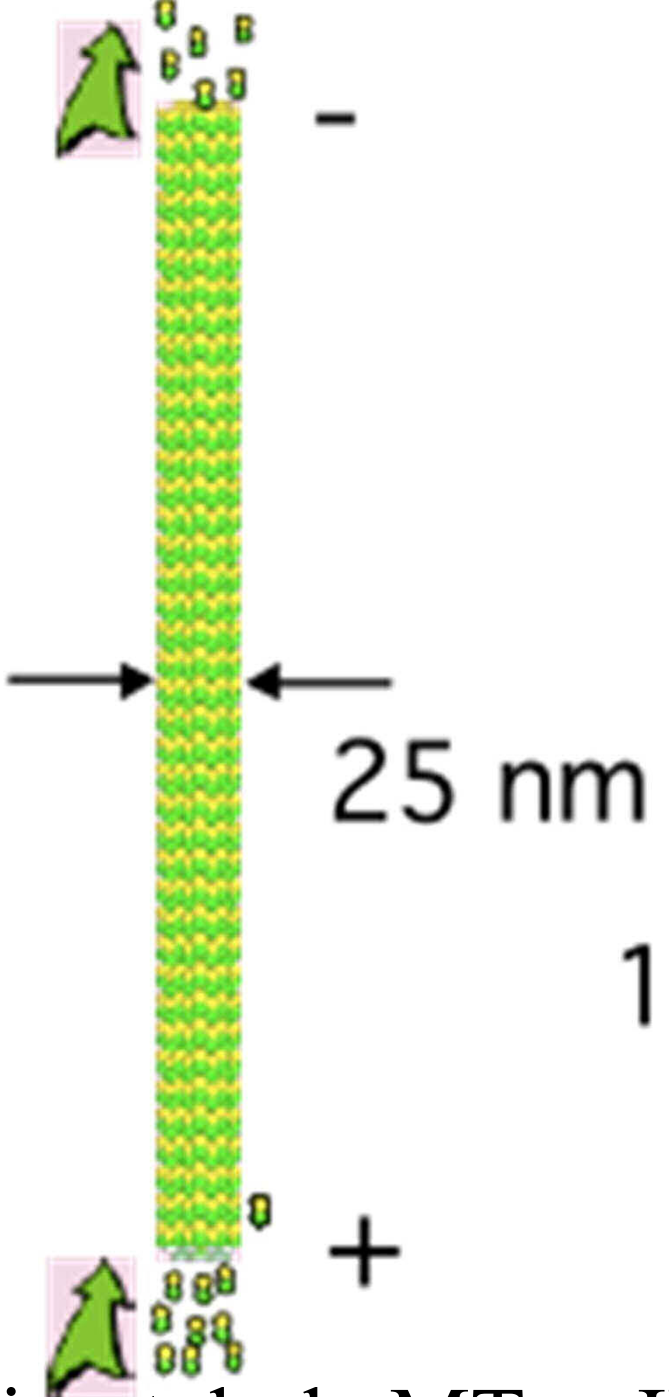
Filament contour is slightly curved:

countour length > but not >> end-to end distance, or distance between crosslinks

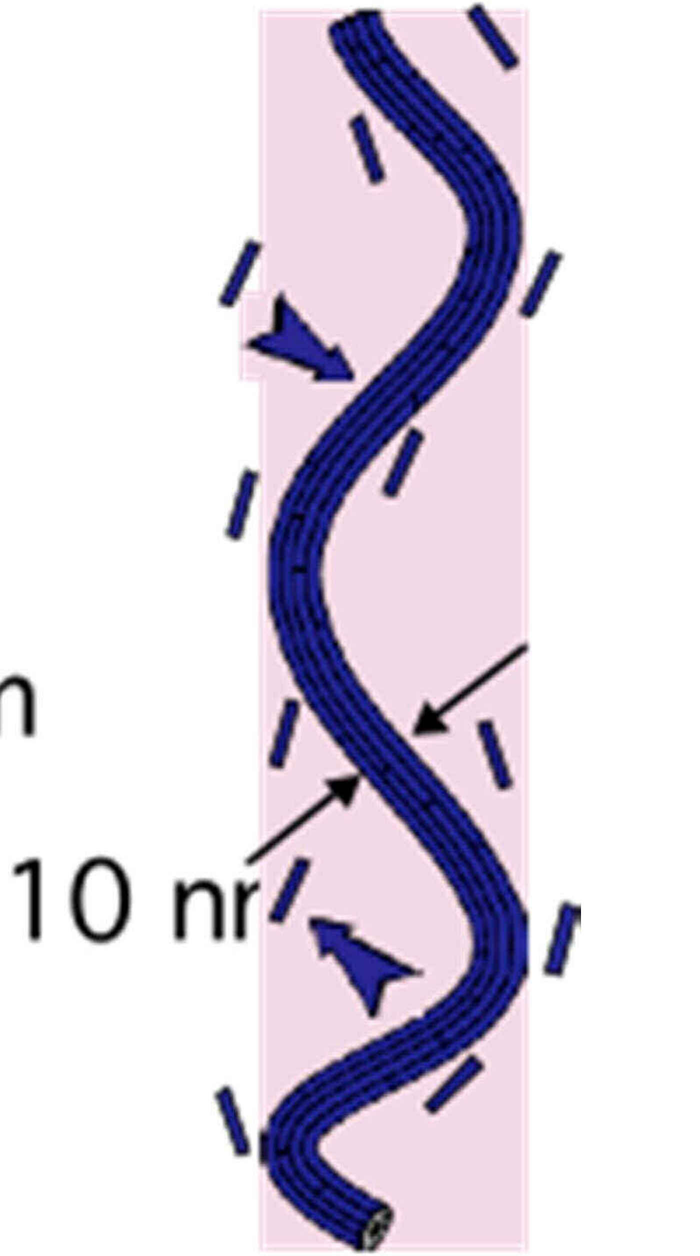
Thermal motions are sufficient to bend the filament at least a little.



F-actin



microtubule MT



IF (e.g. NF, vimen

3-16 > 1 200-500

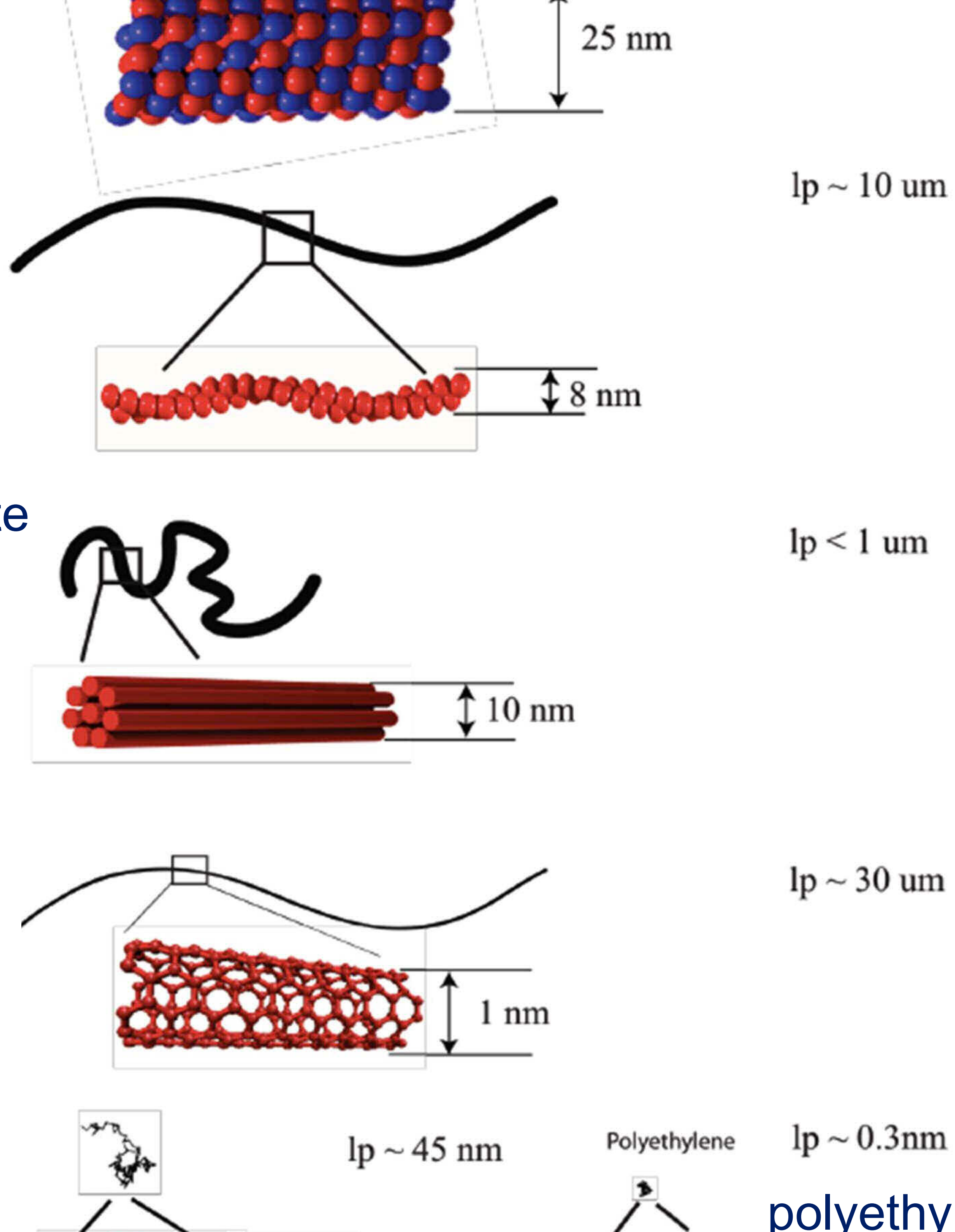
Uniquely extendec conformation of biopolymers determi their rheologic proper

tin

diate
nts

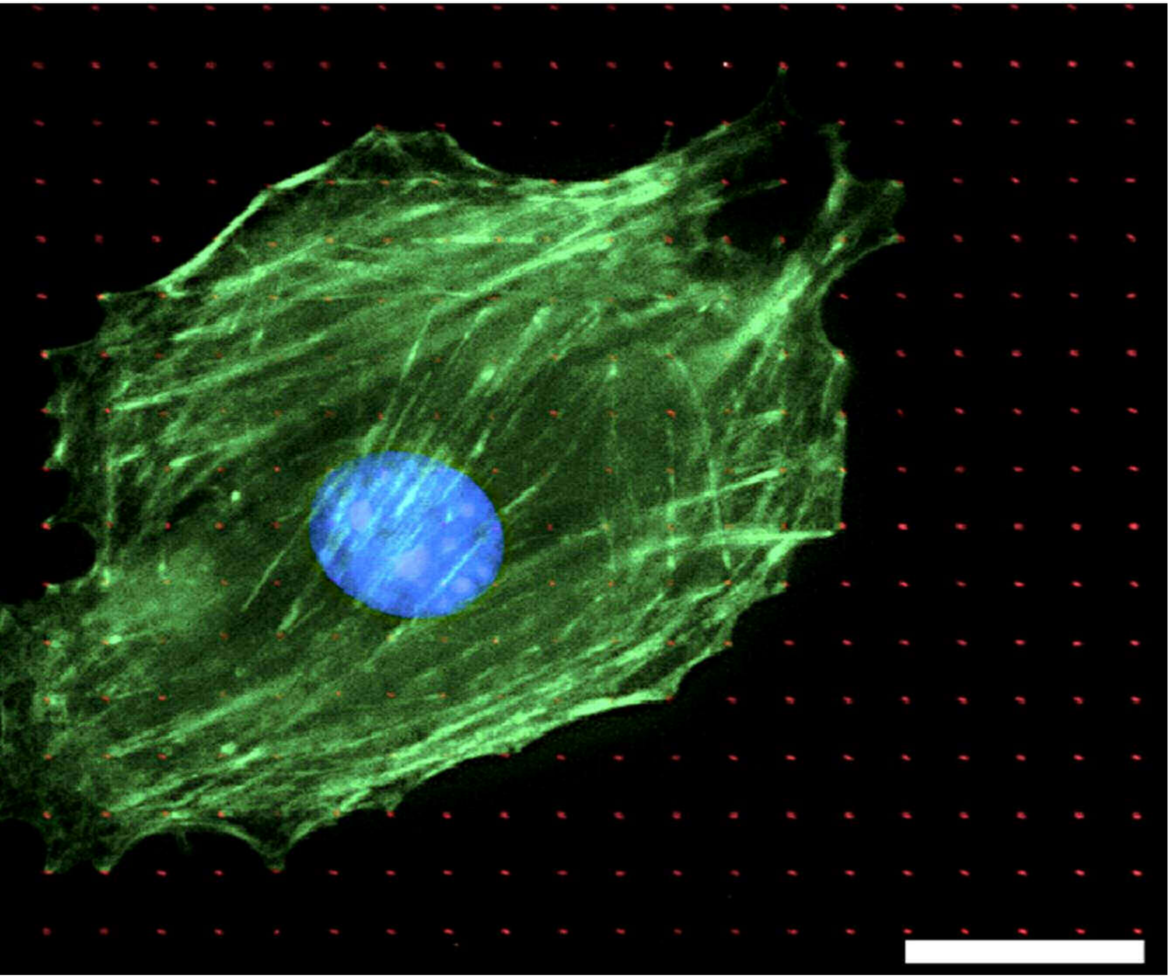
bon
bes

NA
e.g.

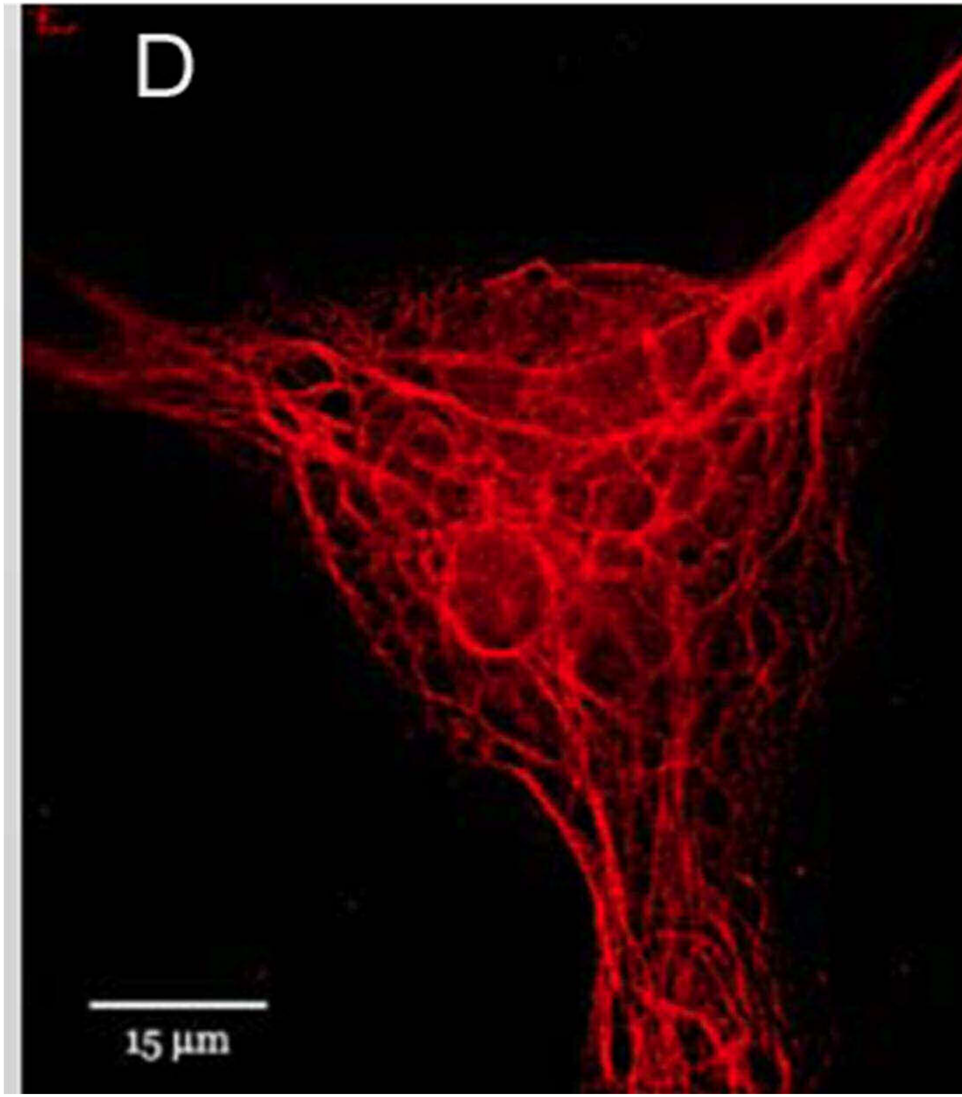


polyethylene

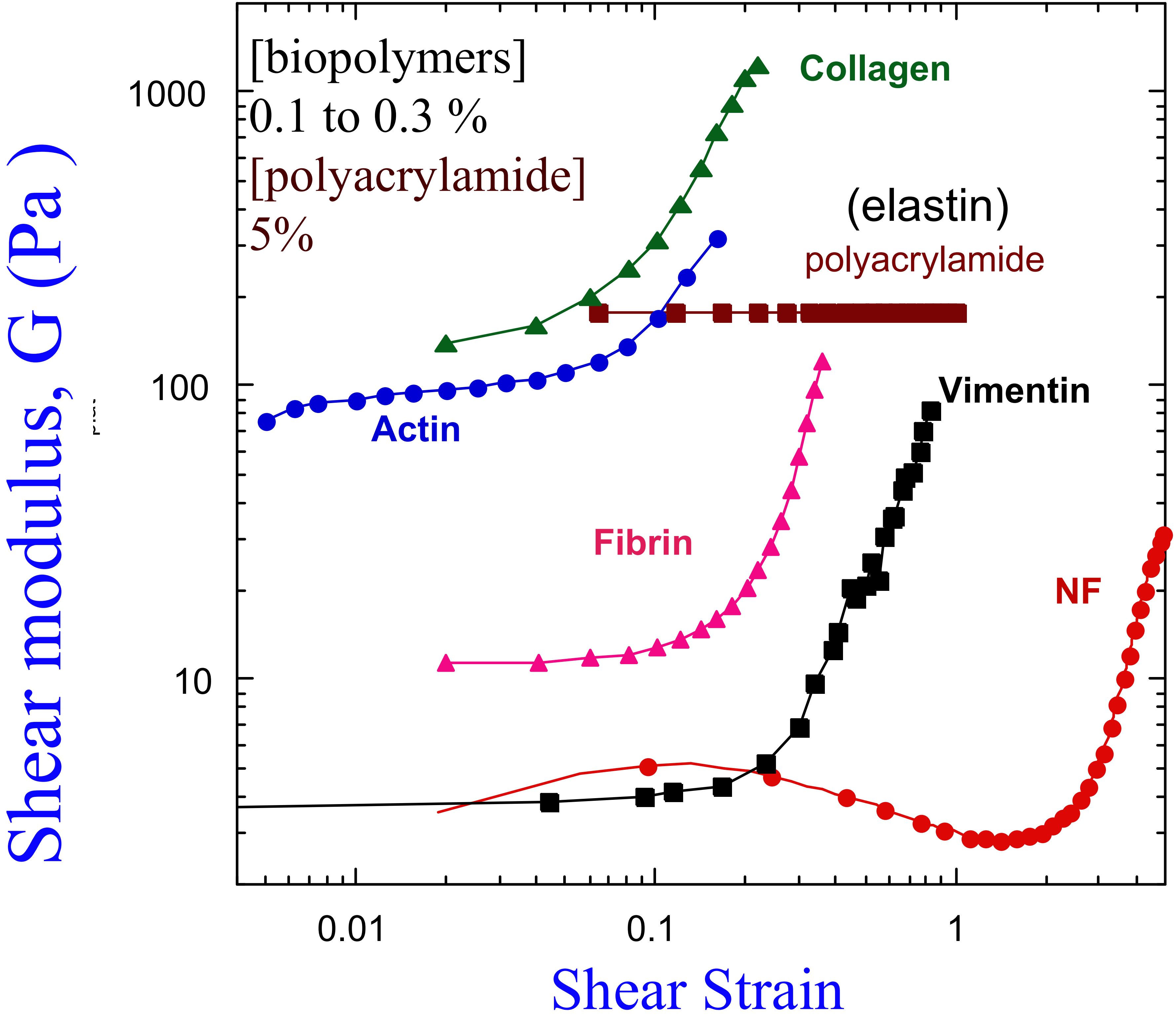
Wen et al, Curr. Opin. Coll. 2



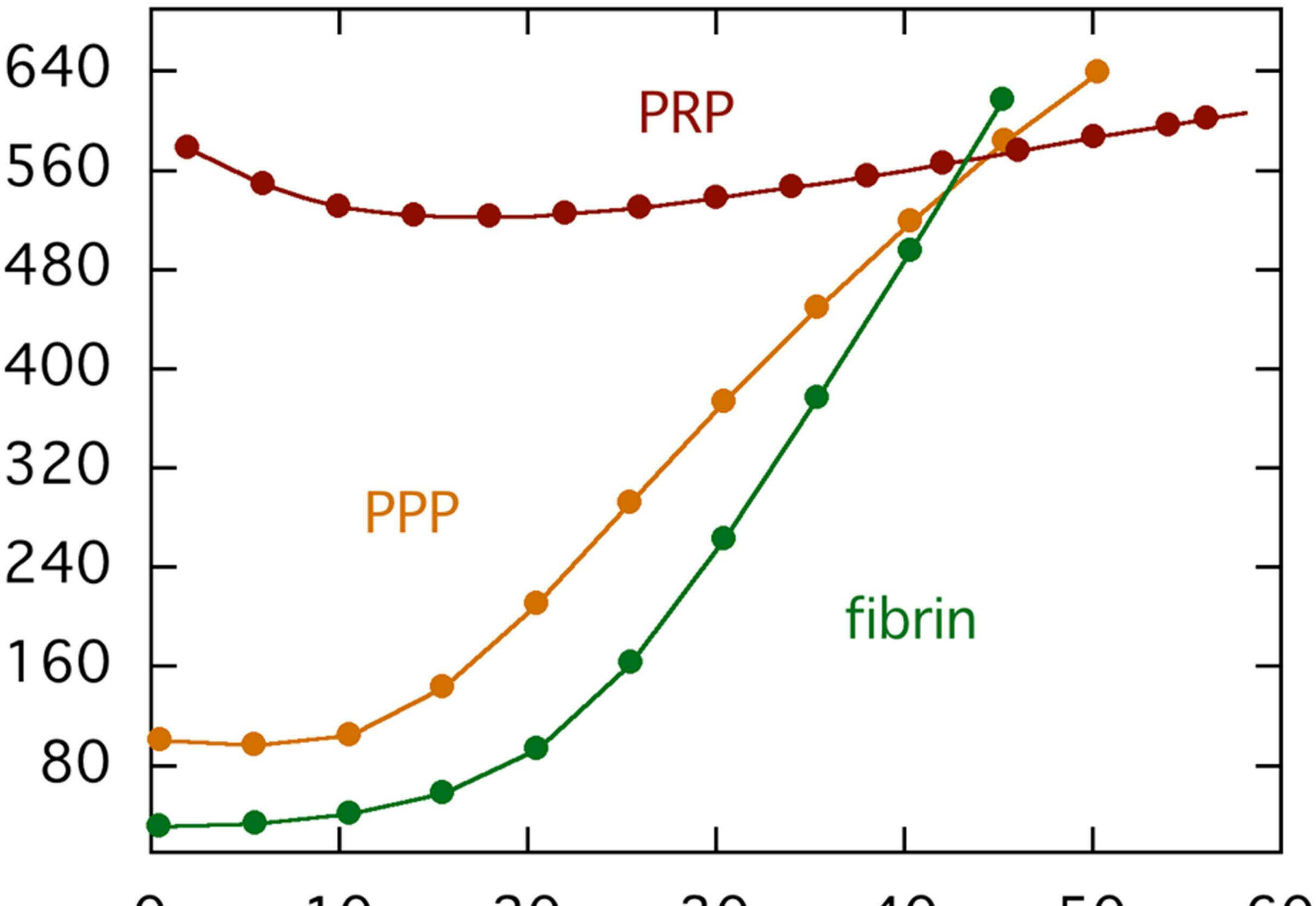
in filaments in a fibroblast



Intermediate filaments in an astr



Storm et
Nat. 2005
Gardel et
Sci 2005

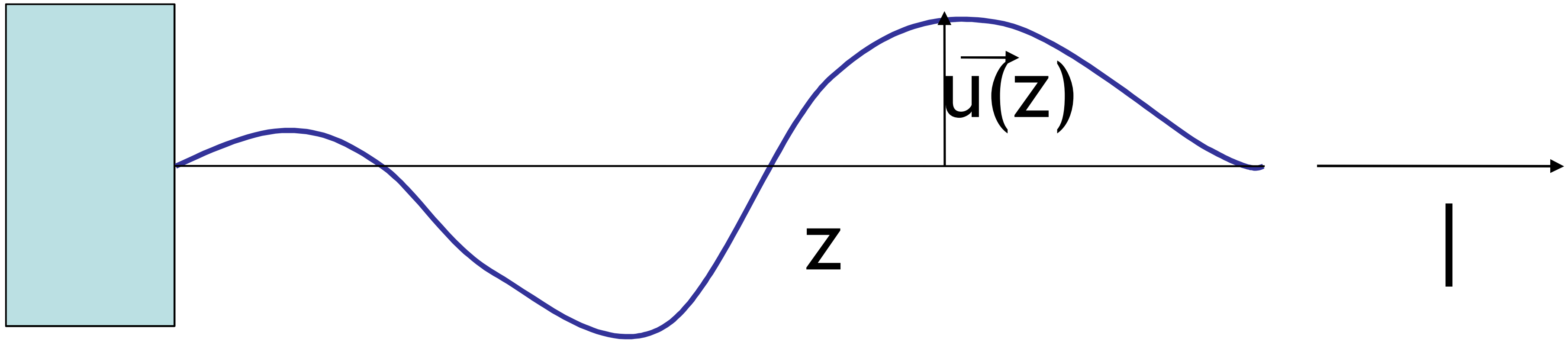


640
560
480
400
320
240
160
80
PRP
PPP
fibrin

Why are networks of biopolymers strain-stiffening?

1. Intrinsic non-linear force-extension relation of thermally fluctuating semi-flexible polymer
   entropic, affine

2. Orientition of stiff fibers in network under shear
   shift from bending to stretching
   enthalpic, non-affine,
   fiber need not have non-linear elasticity

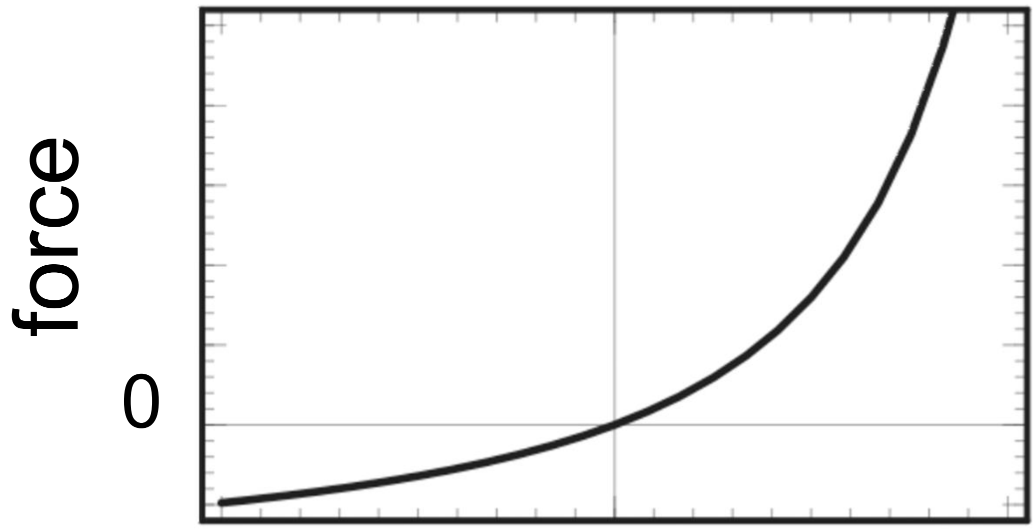


energy :

$$E = \int_0^L \mathrm{d}z \, \left\{ \frac{\kappa}{2} |\vec{u}''|^2 + \frac{\tau}{2} |\vec{u}'|^2 \right\}$$

force-extension :

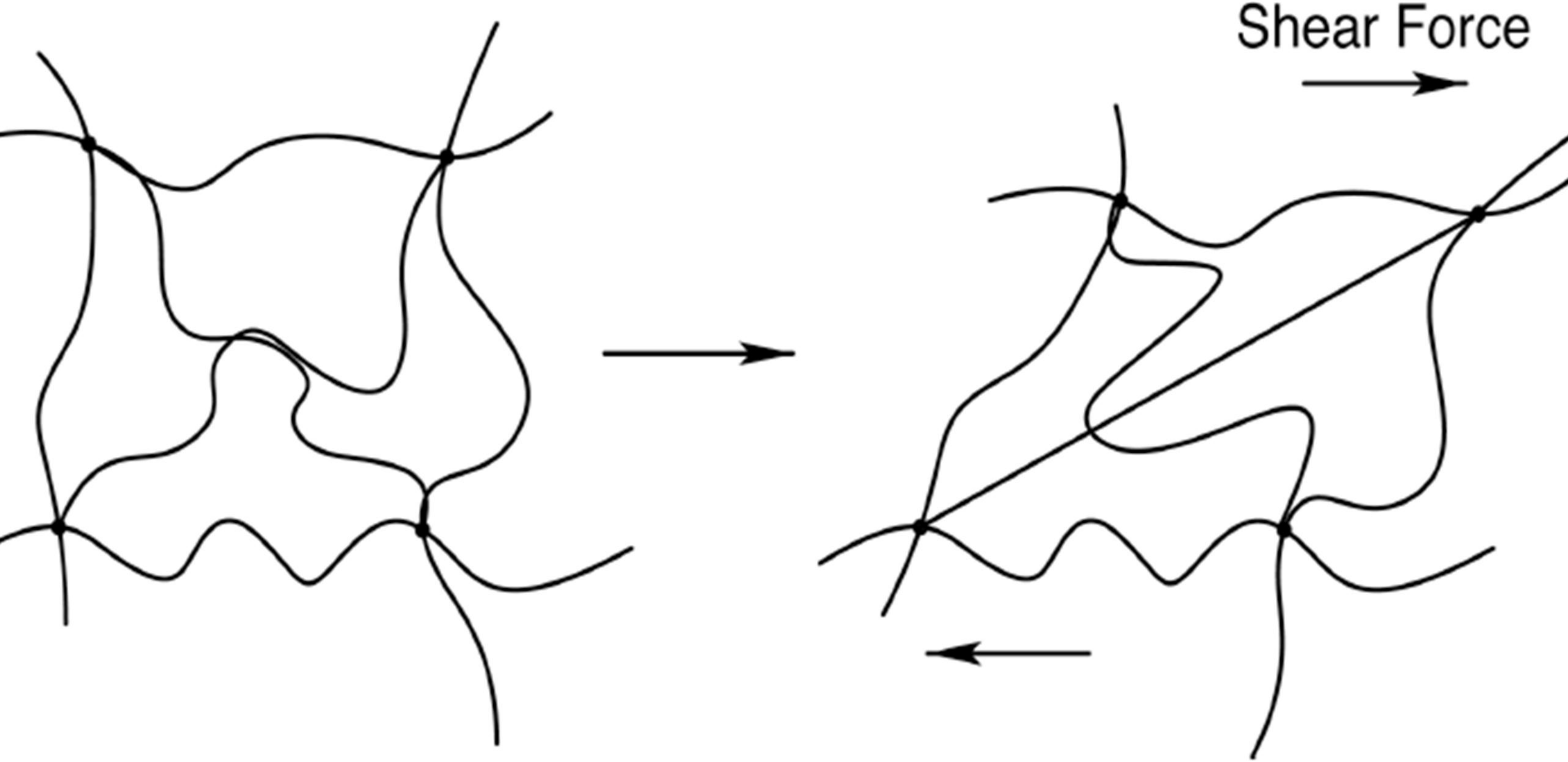
$$\langle \Delta L \rangle = L_c - r = \frac{L_c^2}{l_p \pi^2} \sum_n \frac{1}{\left(n^2 + \phi\right)}$$



ϕ = normalized force = $|L_c$

PRL, 1995;75:4425-8

ners predicts increasing stiffness with increasing str



odel needs as input: mesh size,bending stiffness
ssumes that network is isotropic and the persistence leng
similar to mesh size

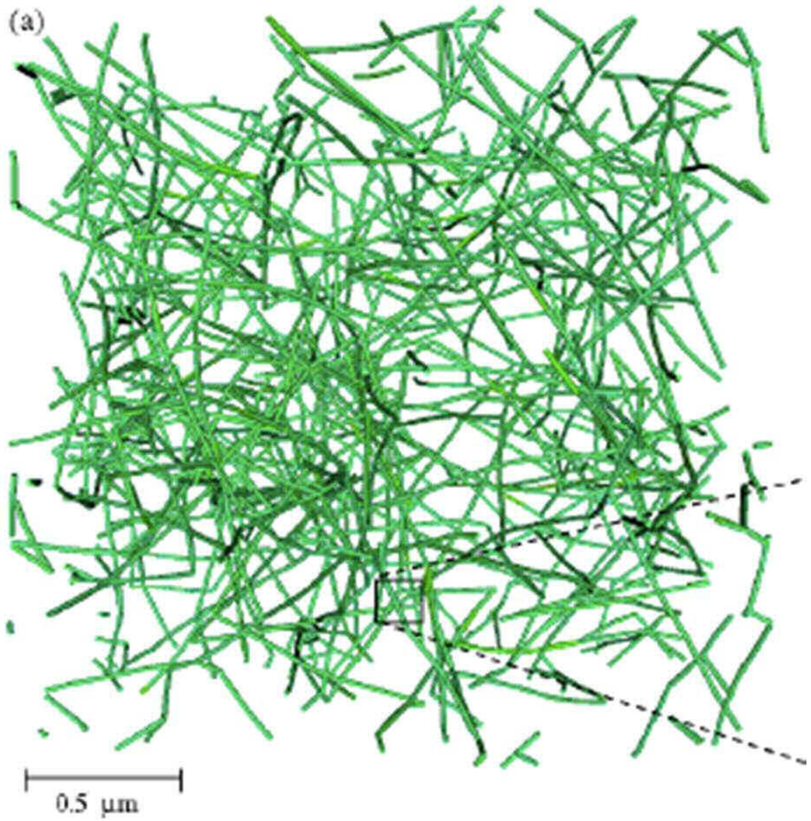
ent alignment, something contractile cells do very we

P. R. Onck, et al. PRL 95, 178102 (2005).

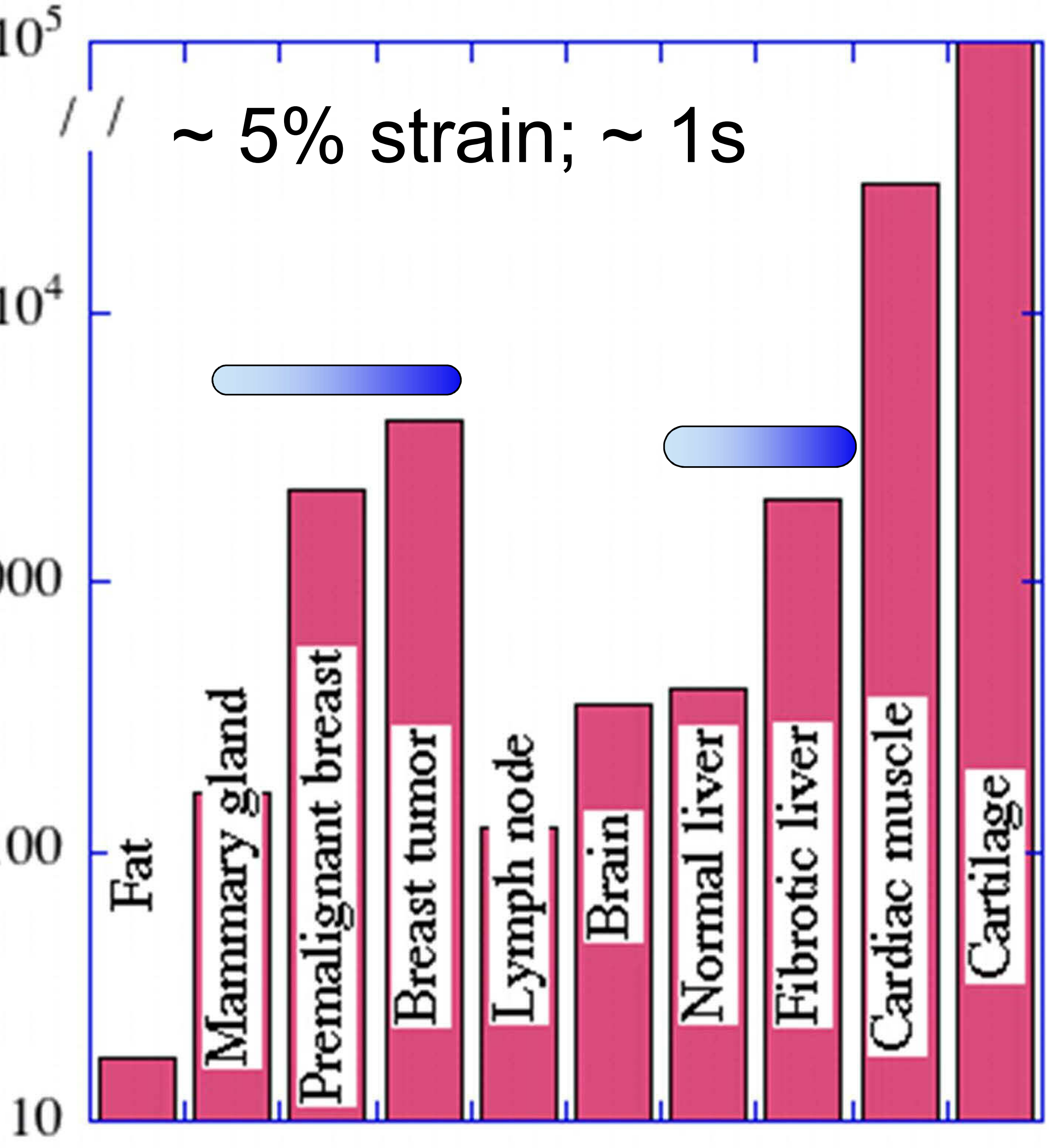
QuickTime and a
BMP decompressor
are needed to see this picture.

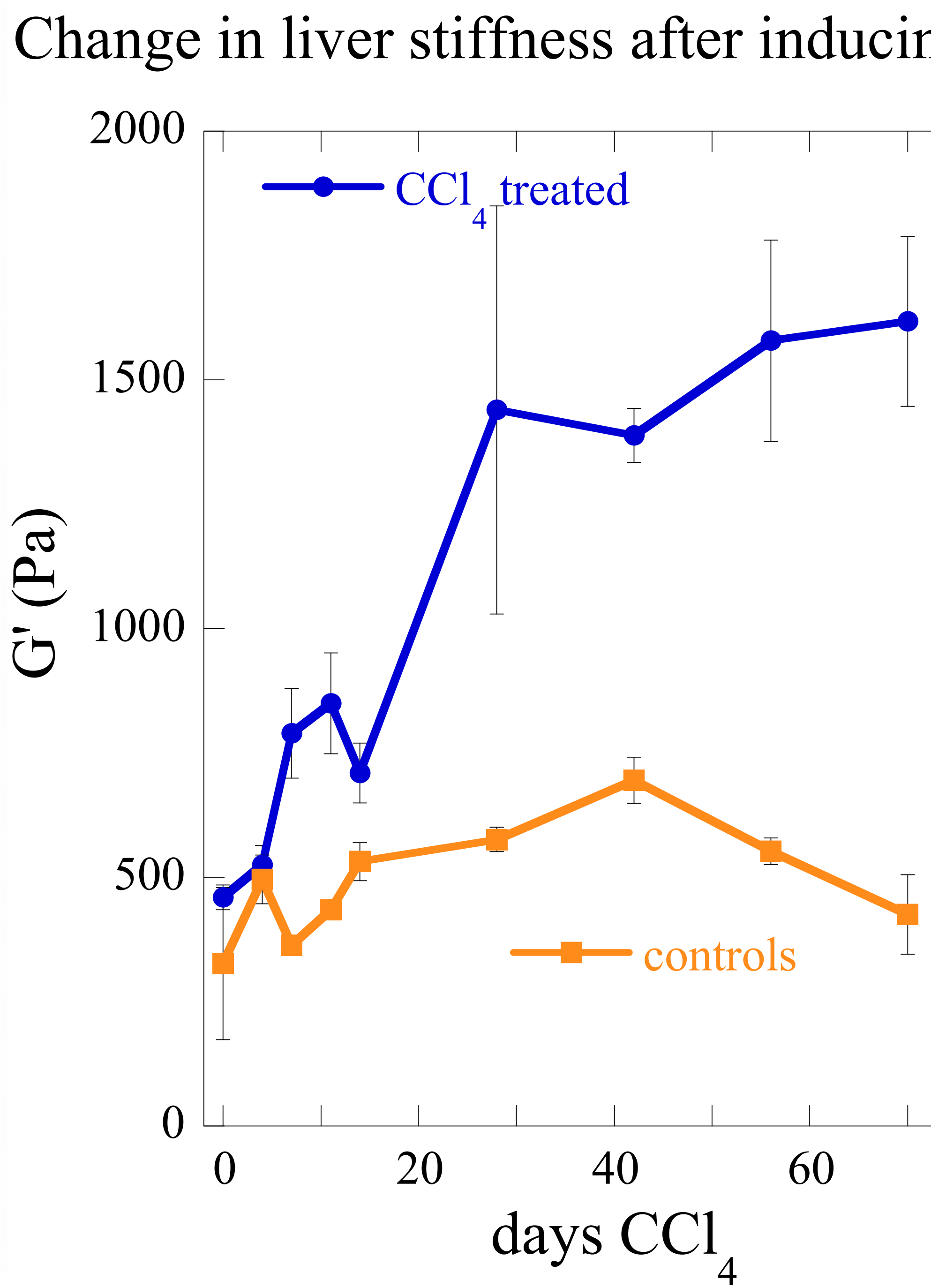
hree-Dimensional Cross-Linked F-Actin Networks: Relation between Network Architectur and Mechanical Behavior

E. M. Huisman, T. van Dillen, P. R. Onck, and E. Van der Giessen



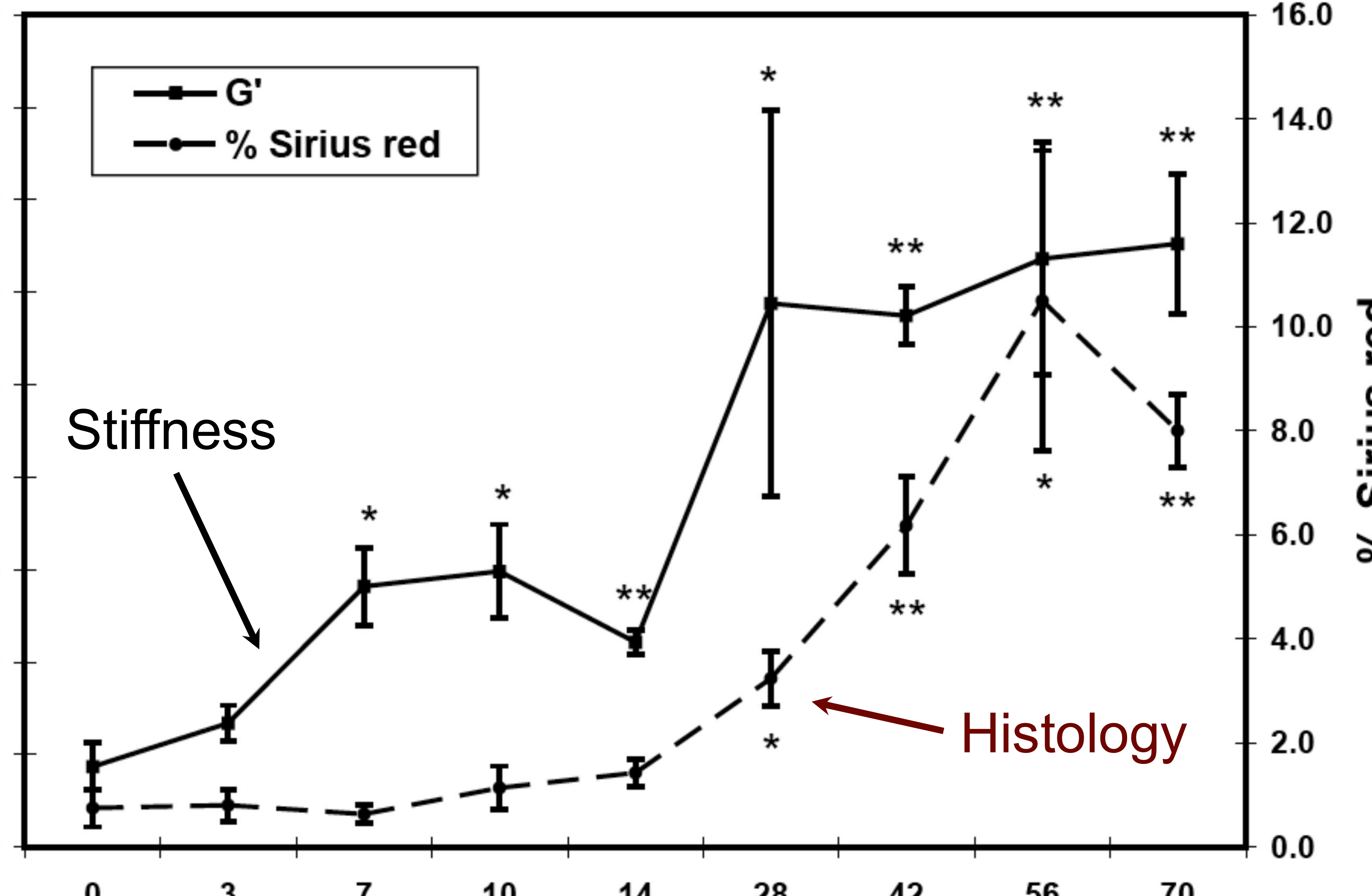
characterized by an elastic modulus*





Changes in organ stiffness often accompany diseas

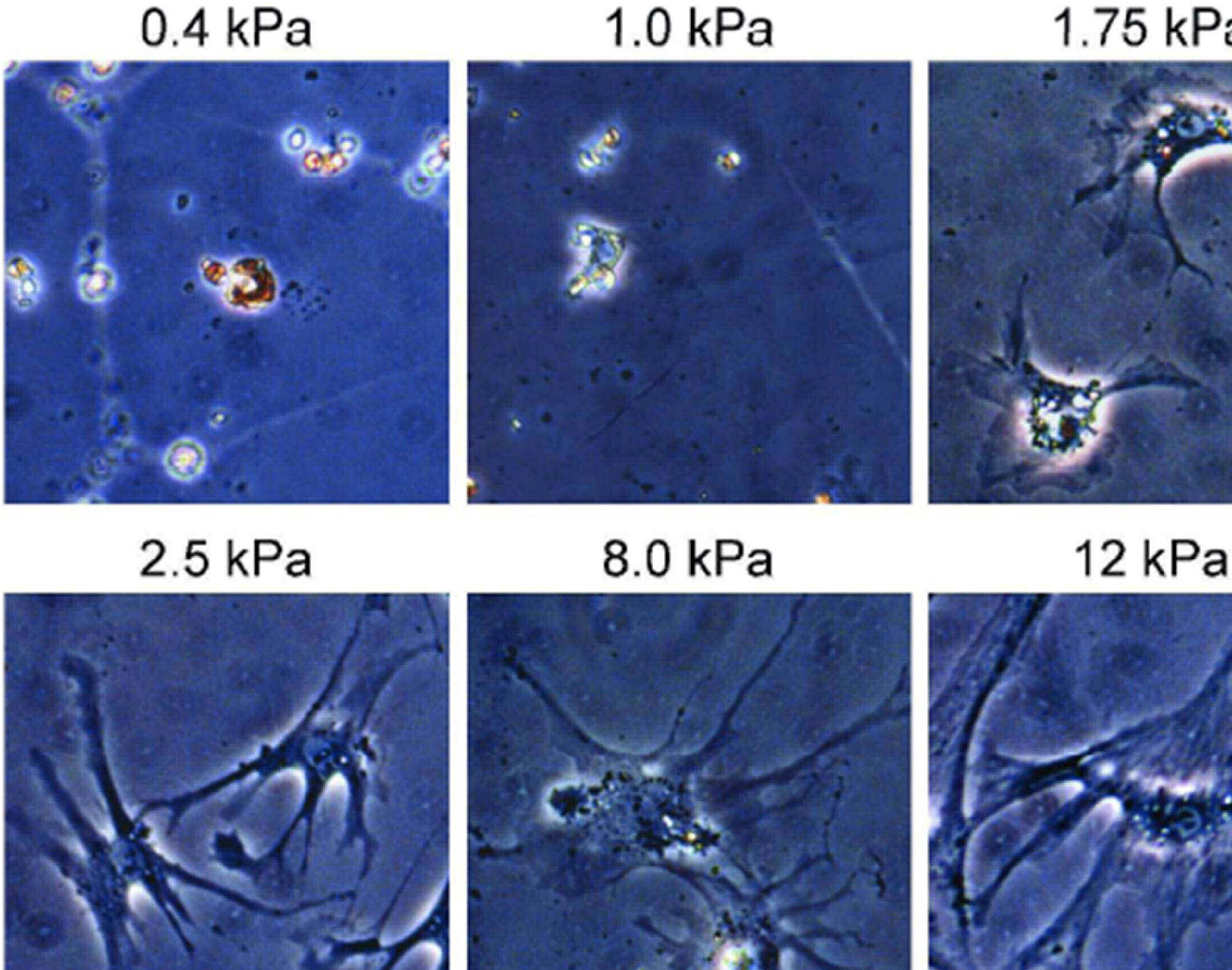
ological evidence of fibrosis occurs ***after*** liver stiffenin



thologically stiff substrates

ecca
s

et al,
Physiol.



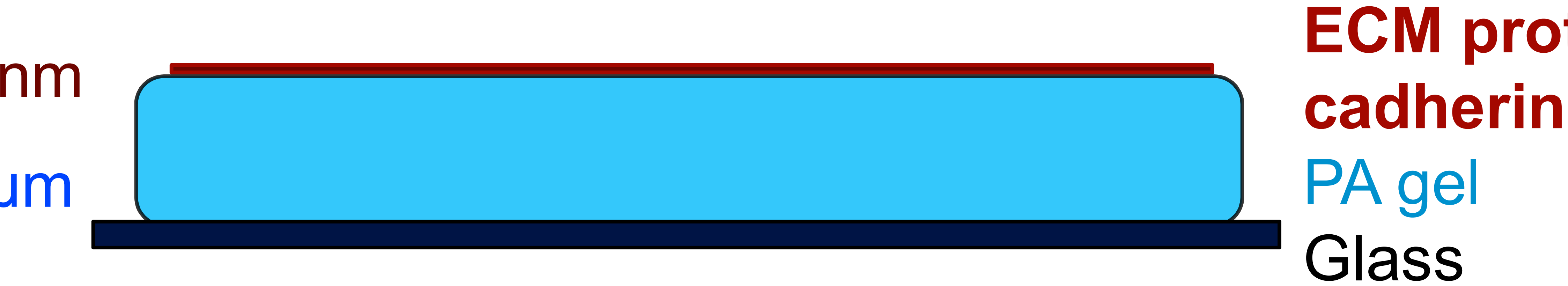
hat determines tissue stiffness?

xtracellular matrix
ytoskeleton

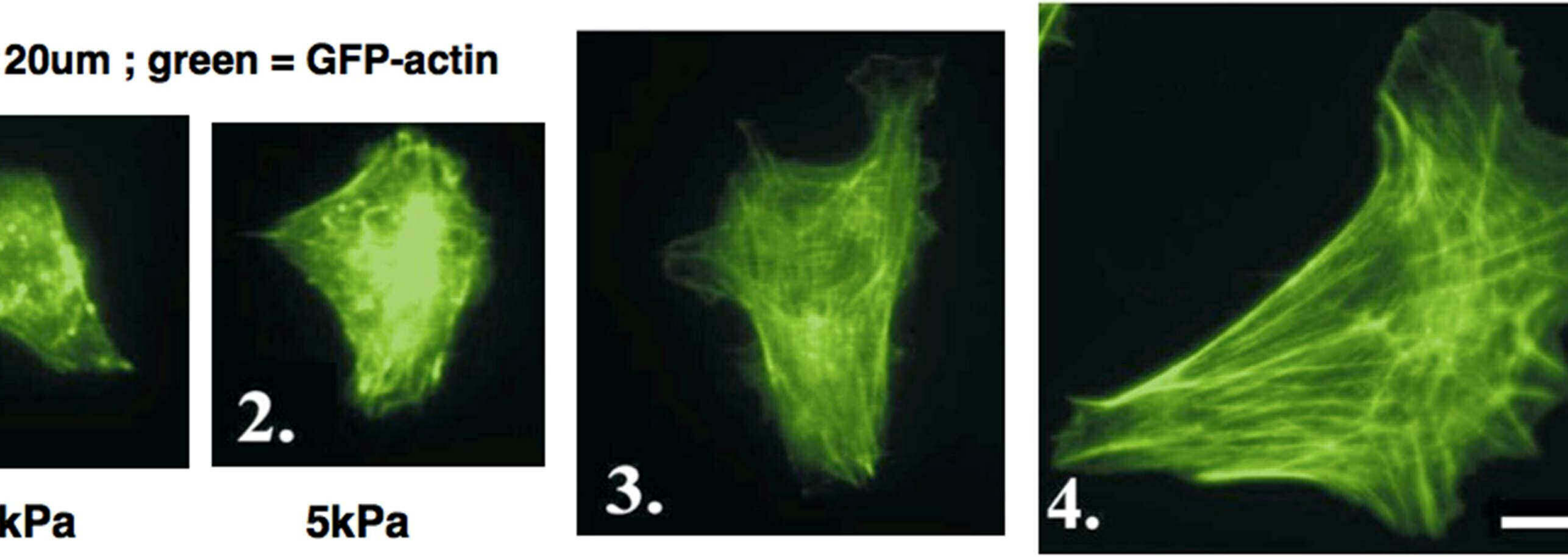
assive viscoelasticity or poroelasticity

ctive (motor driven) tension and non-thermal motions

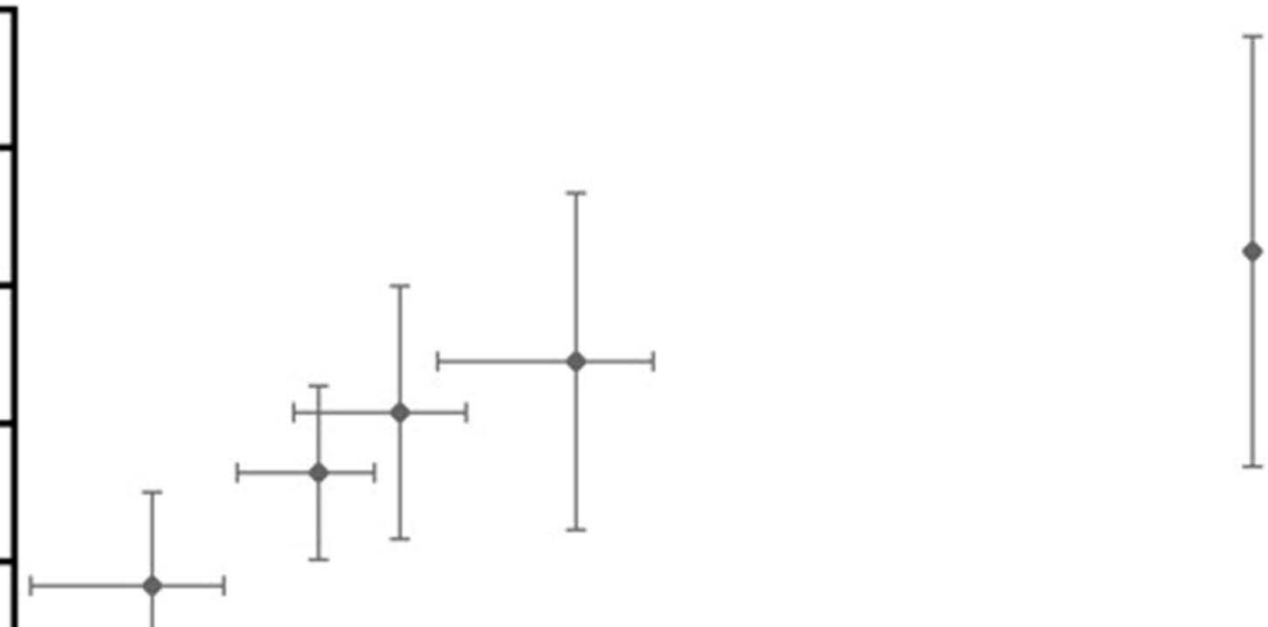
tracellular and intra-tissue pressures / water flow els and pillar arrays



20um ; green = GFP-actin



kPa 5kPa 10kPa Glass ~ GPa

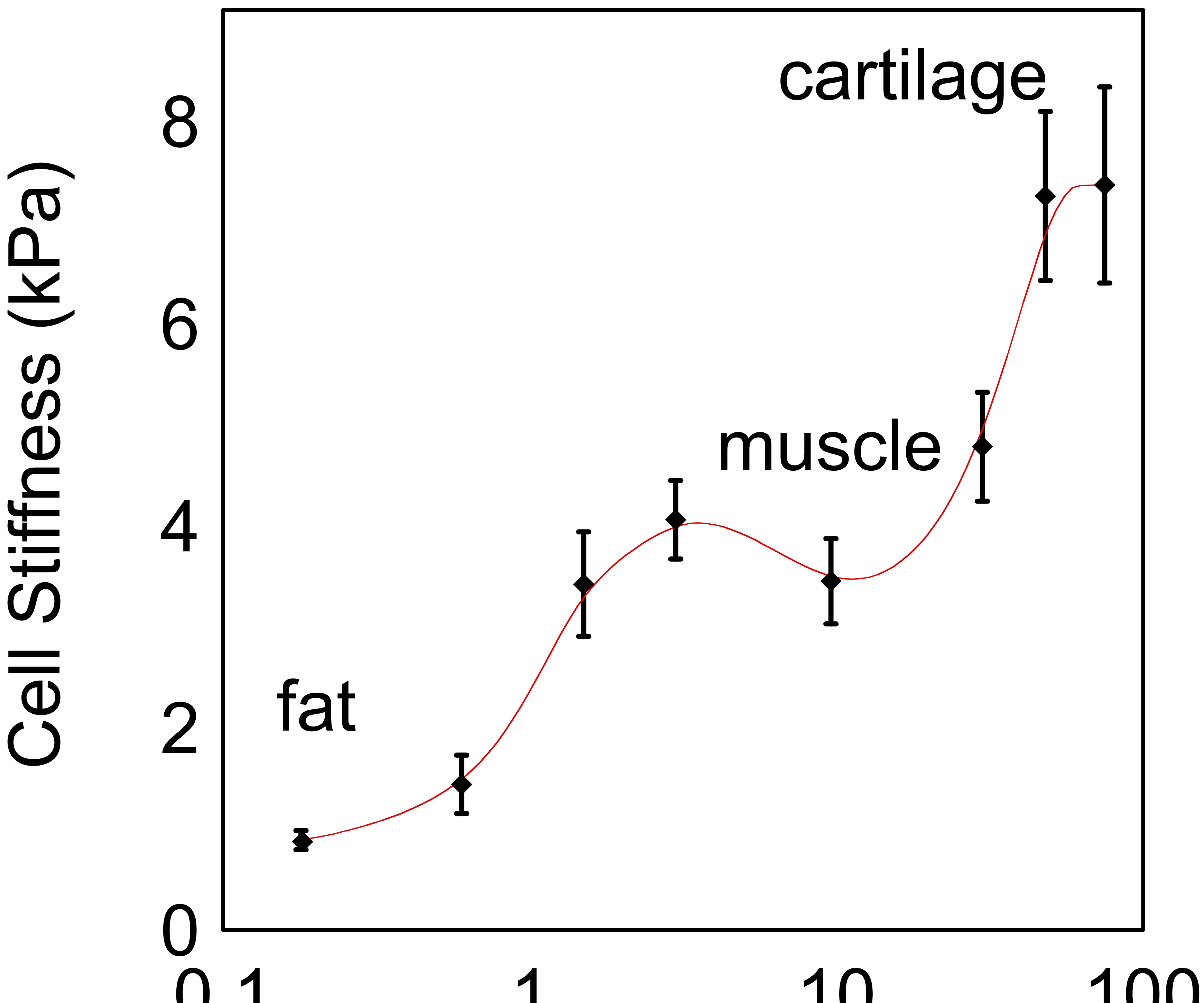


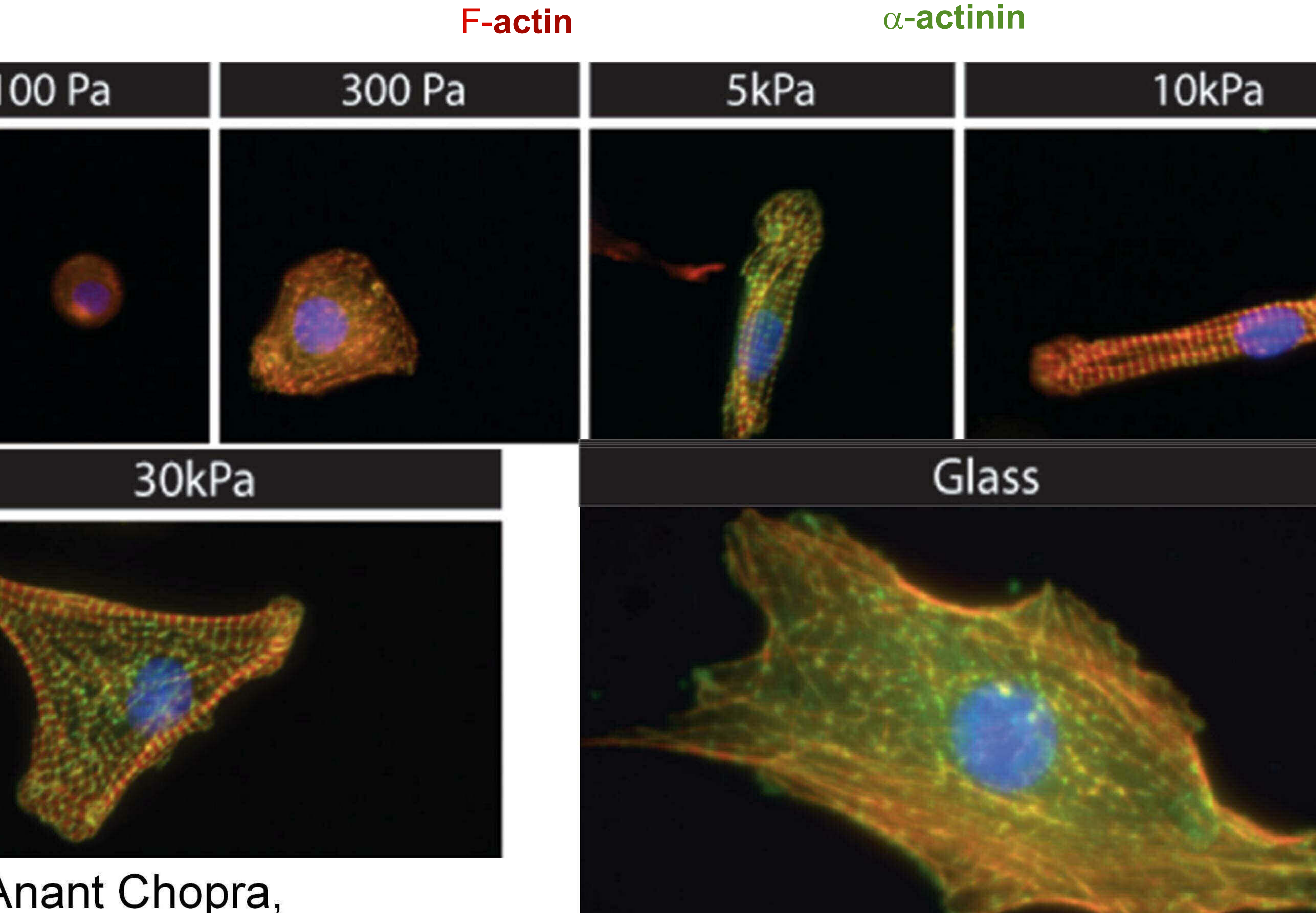
Pelham and Wang PNAS 1

Fibroblasts stiffen and increase adherent area on stiff subtrates

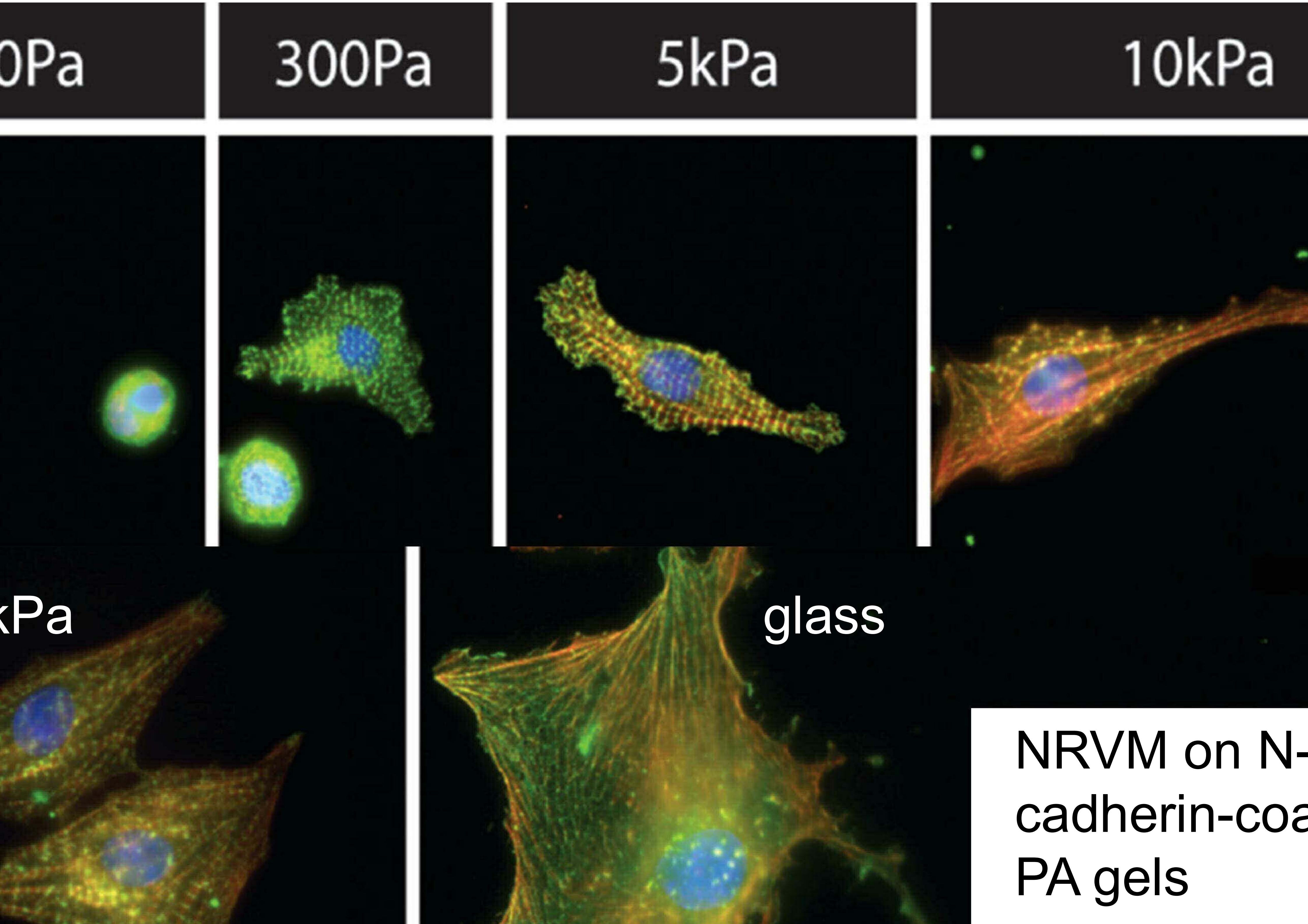
Solon et al. Biophys. J. 2007

Biphasic change in hMSC stiffness





Anant Chopra,


0Pa
300Pa
5kPa
10kPa
kPa
glass
NRVM on N-
cadherin-coa
PA gels

w do cells sense or respond to stiffness?

t is the range of stiffness that can be probed?

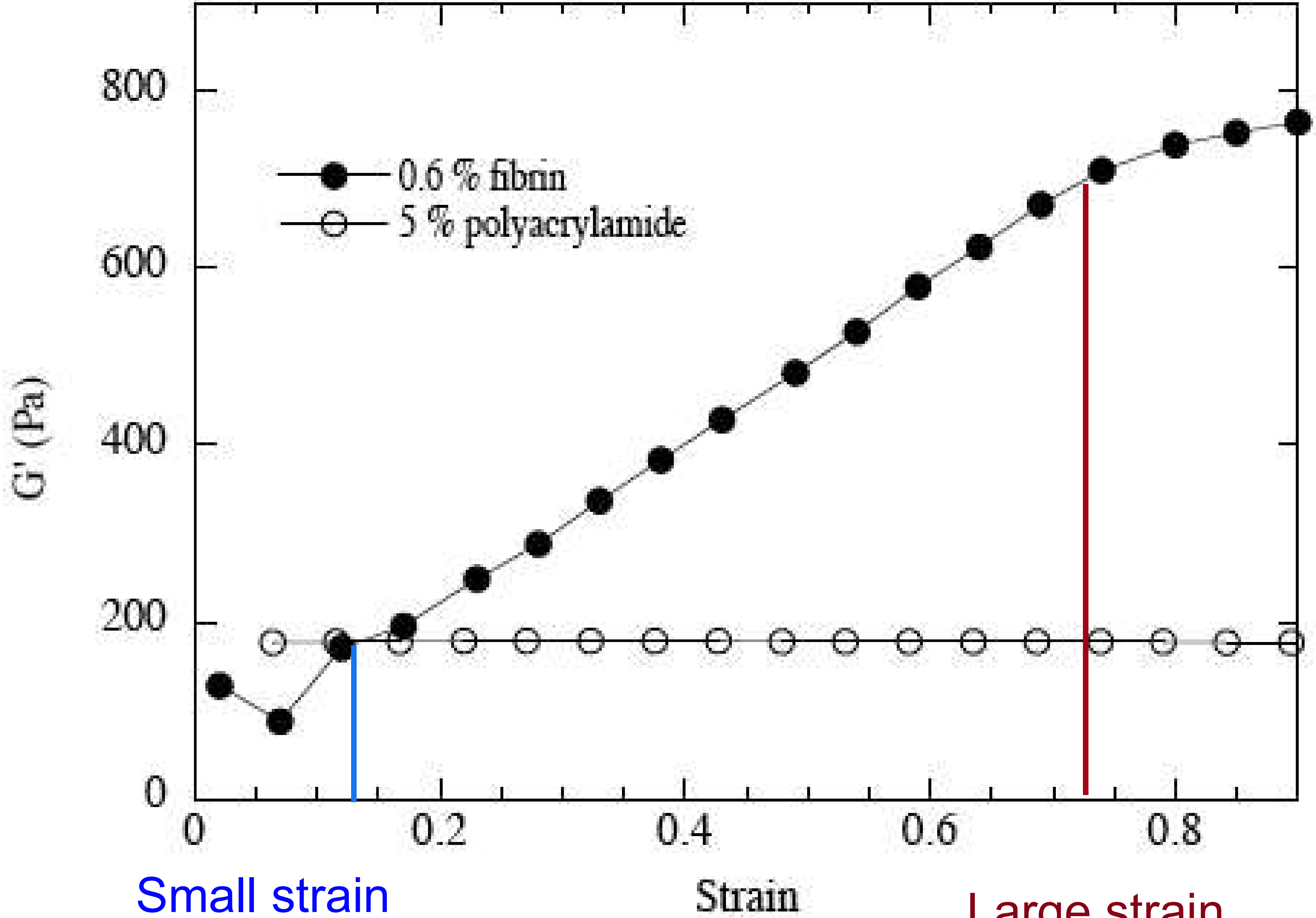
- 100,000 Pa

/ much do they strain their substrate?

v large an area do they probe?

v long do they integrate signal?

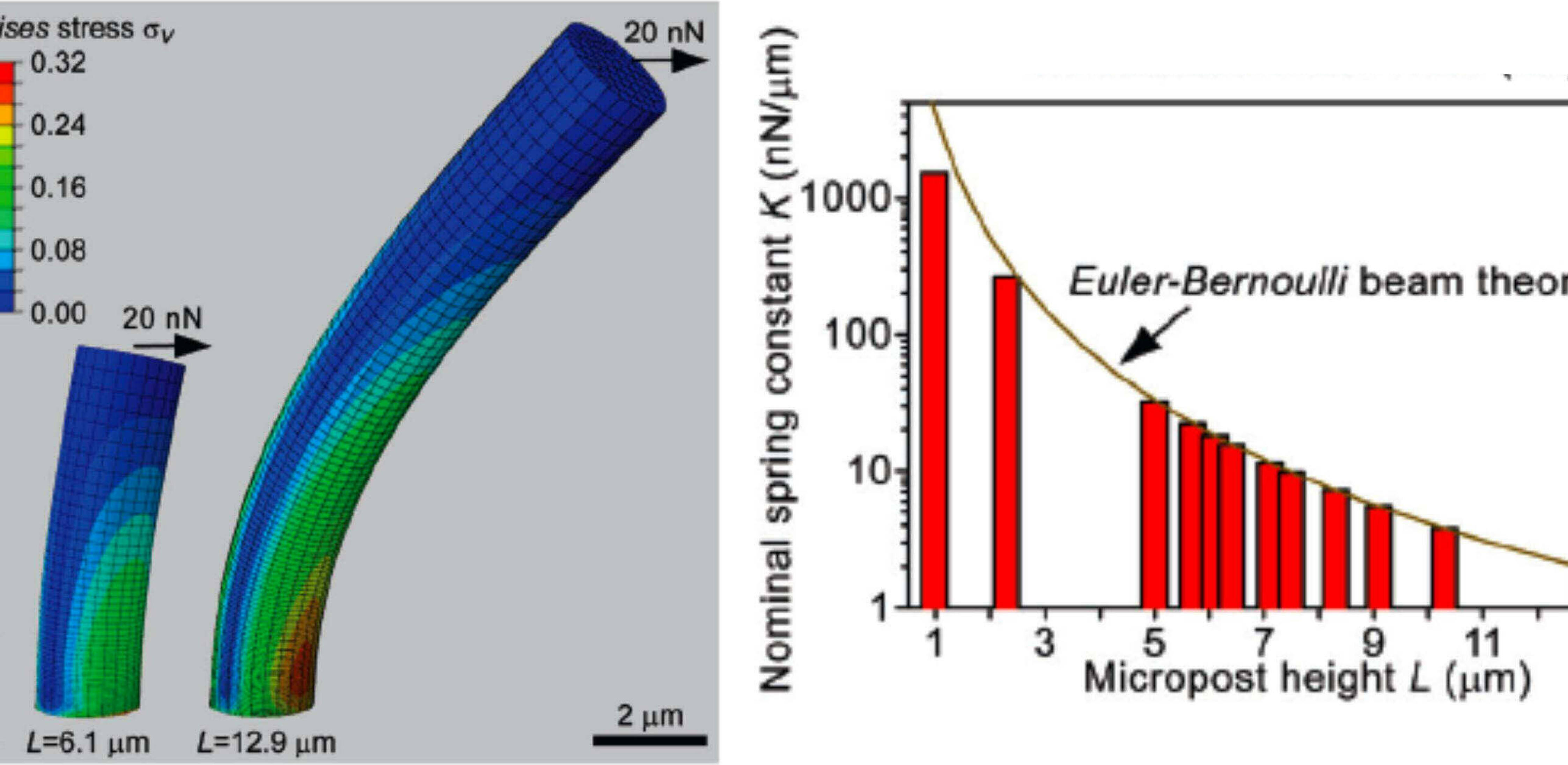
How much the cell deforms its substrate



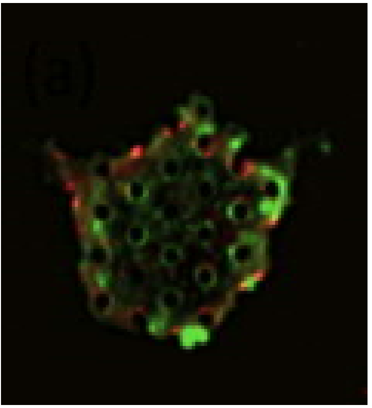
Small strain
Same stiffness

Large strain
Fibrin is stiffer

v large a contact area is needed for mechanosensing

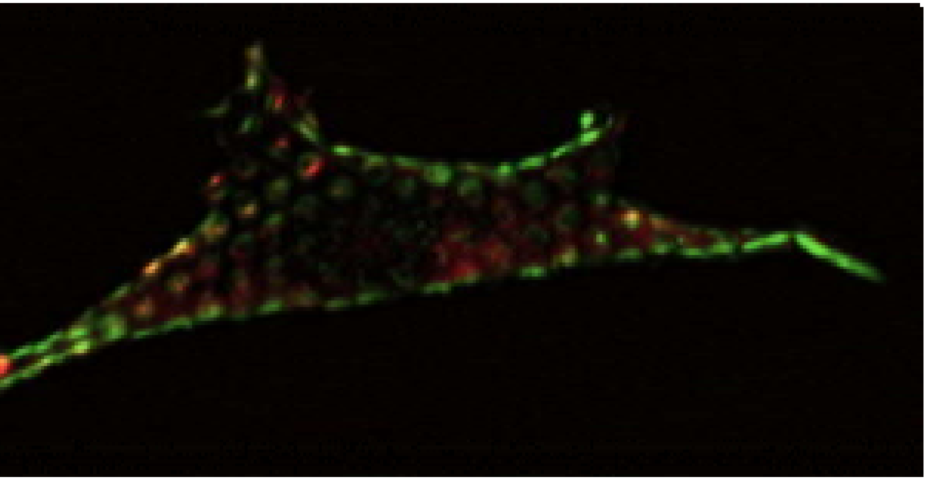


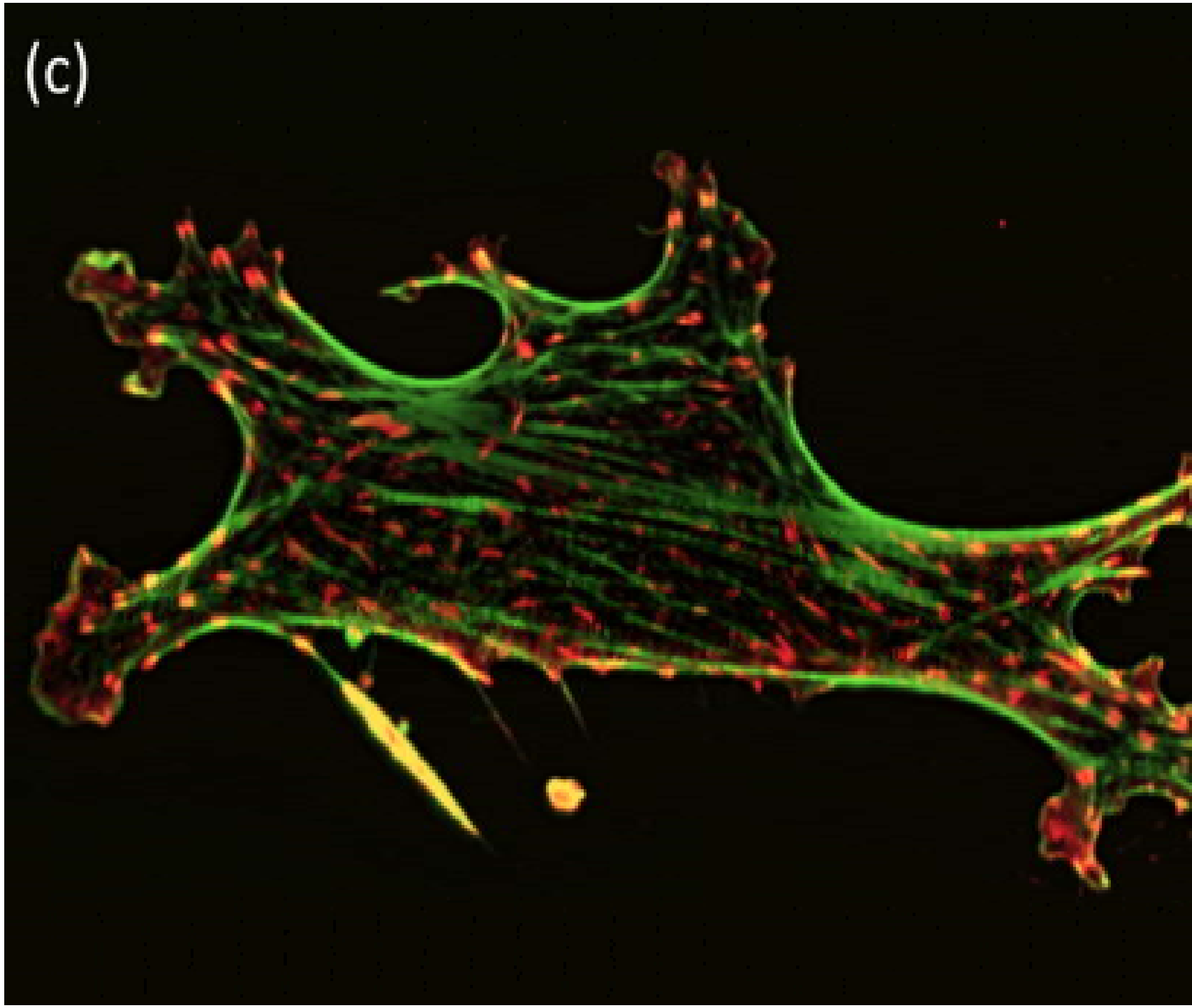
DMS posts of identical composition (>100 kPa) and diameter .8μm), but different length.



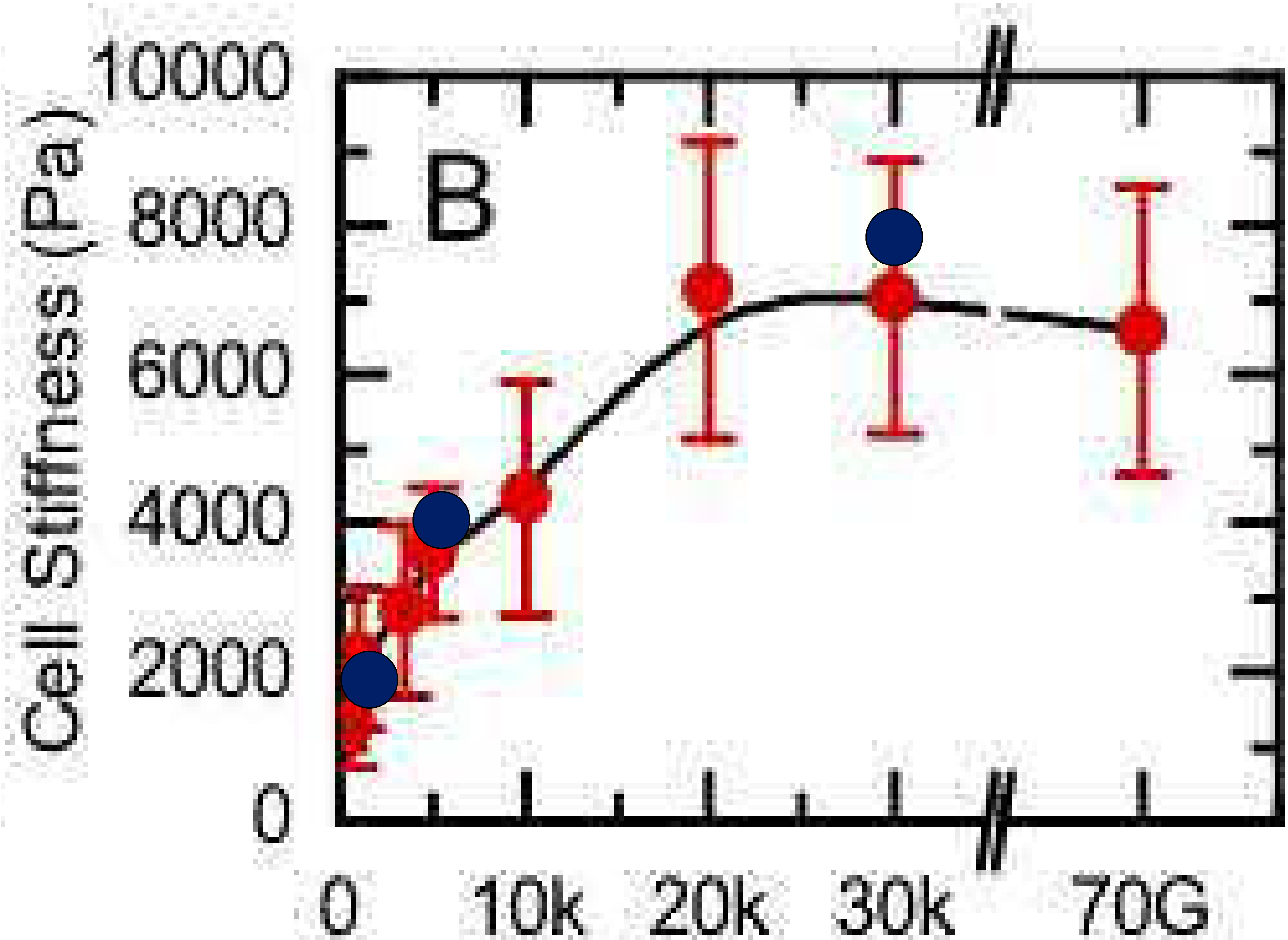
hMSC
on Fn

paxillin
F-actin



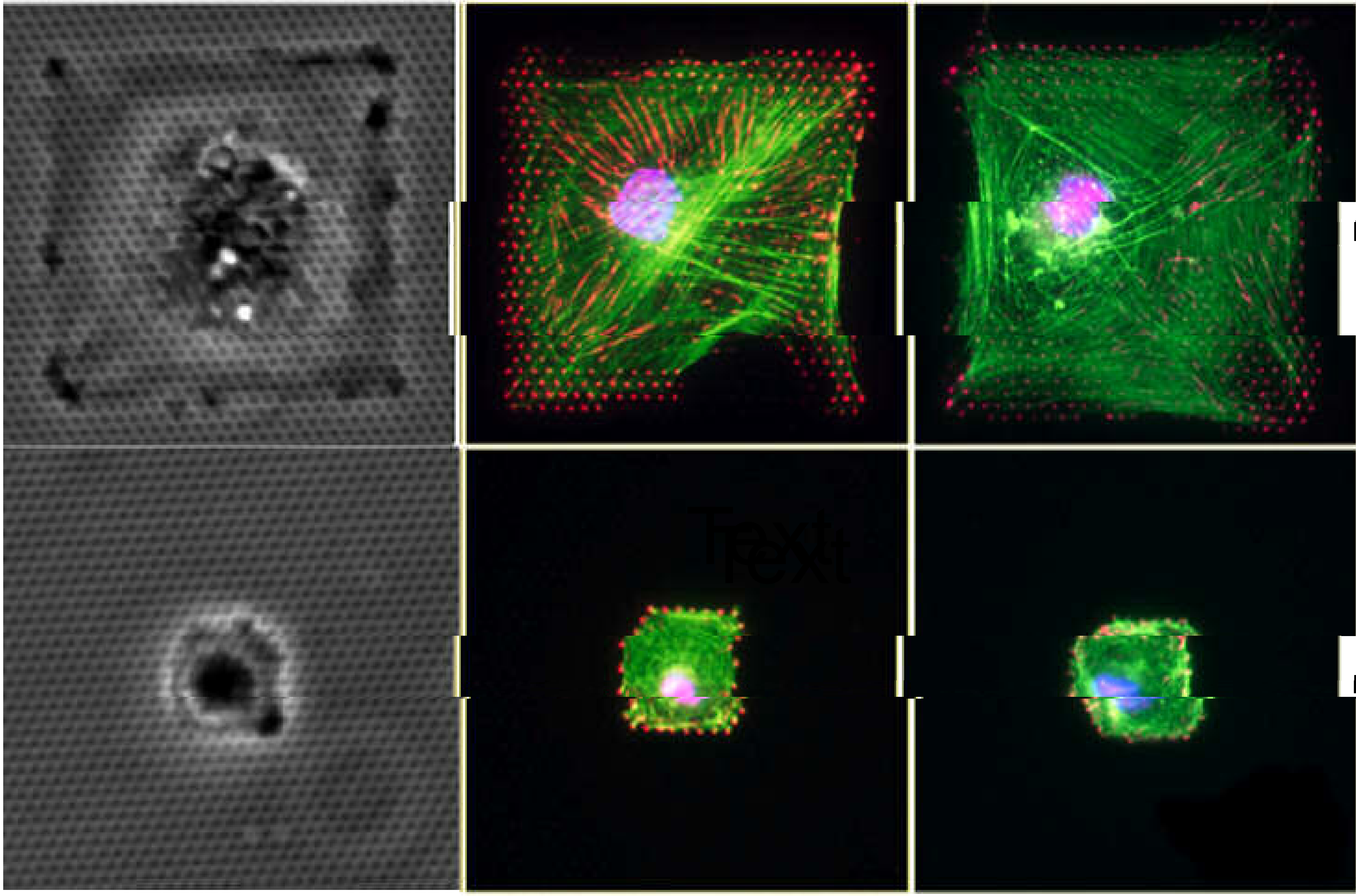


µm PDMS posts (>100 kPa) of different length spaced 6 µm apa
ng posts look soft, short posts look stiff



B
Cell Stiffness (Pa)
10000
8000
6000
4000
2000
0
0
10k
20k
30k
70G

determinant of cell stiffness



F-acti
vincul

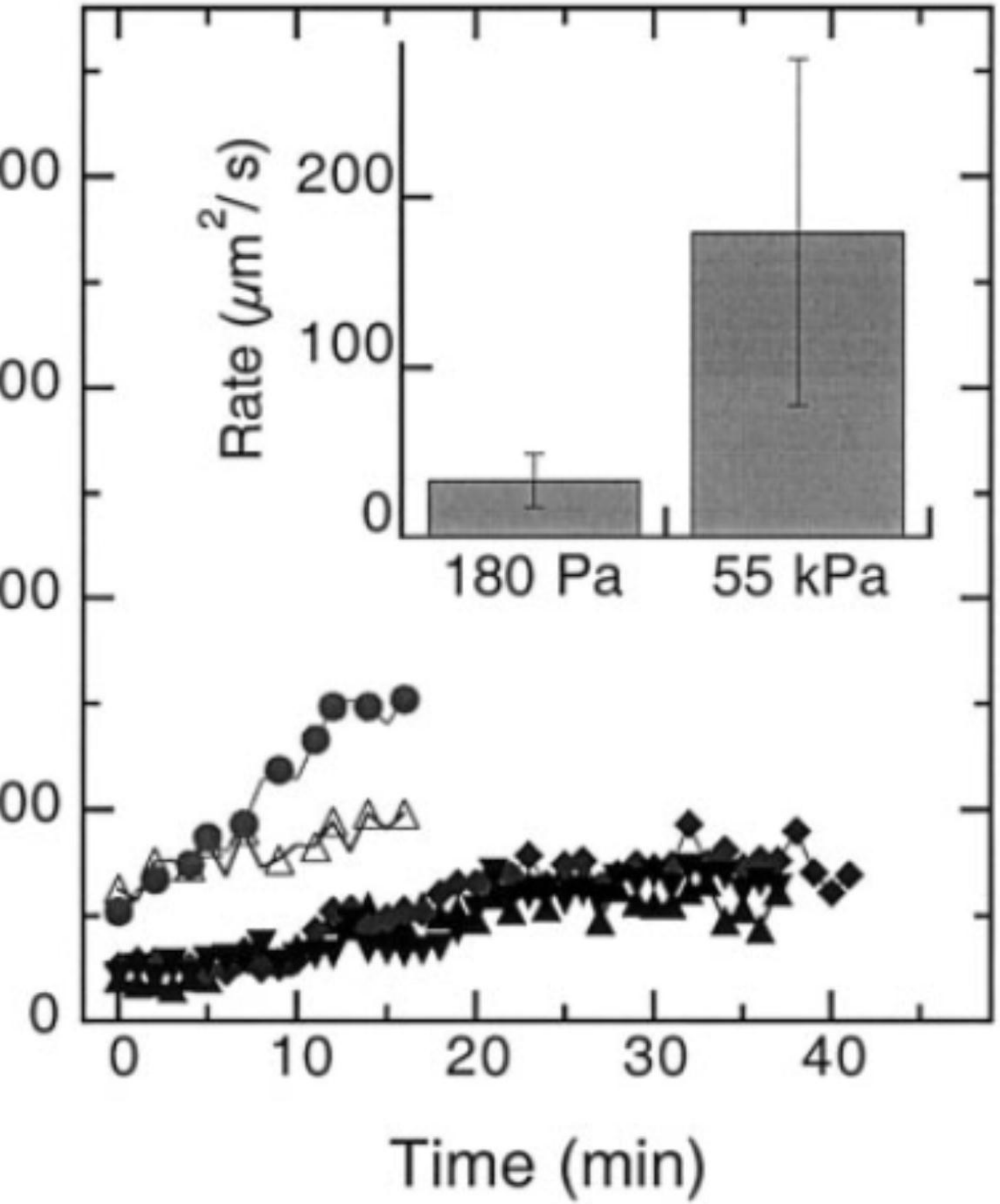
Phase Contrast Stiff Posts Soft Posts

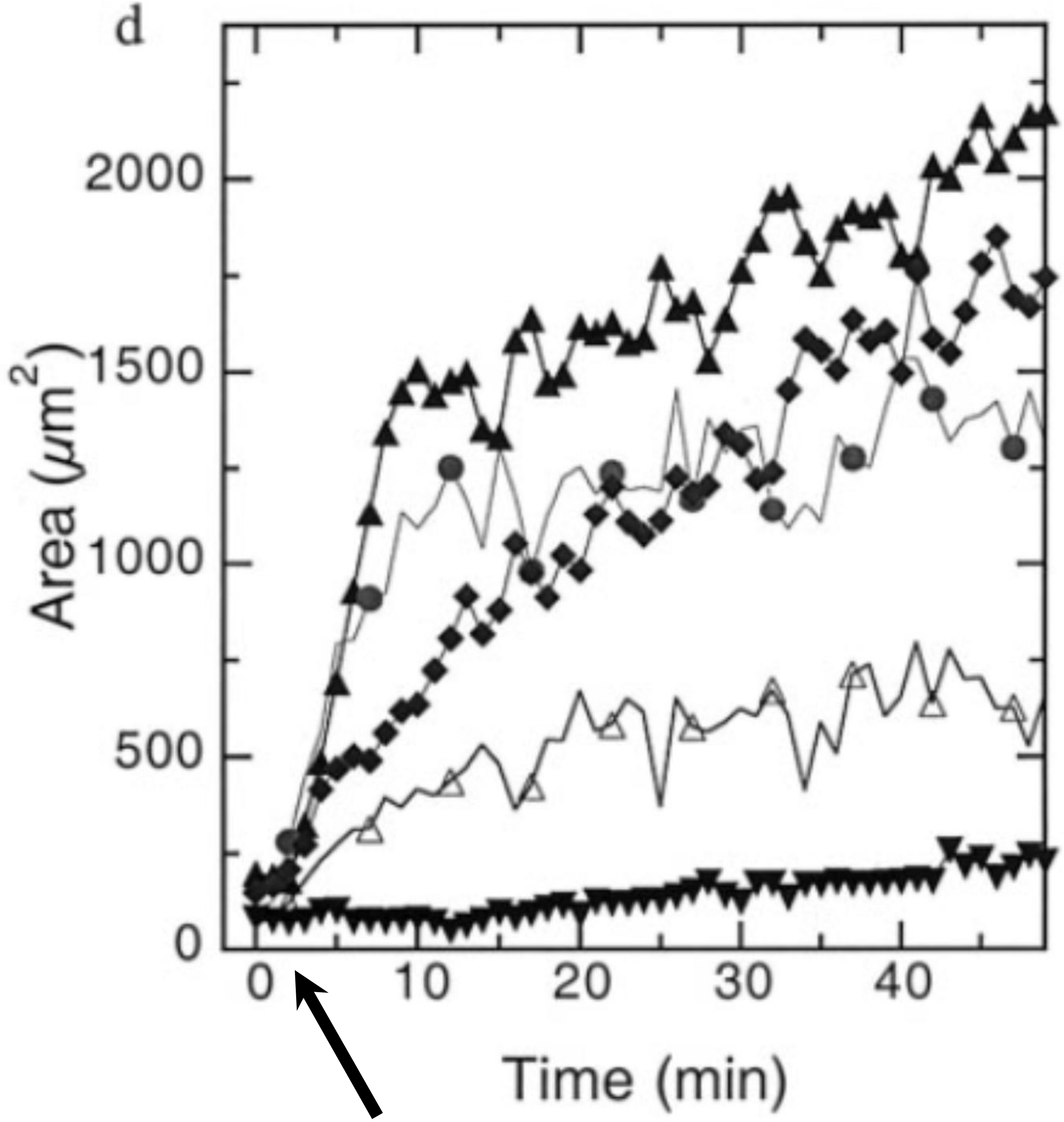
n bone marrow stem cells (hMSC) constrained on square shapes on PMDS microposts.

What is the time needed for mechanosensing?

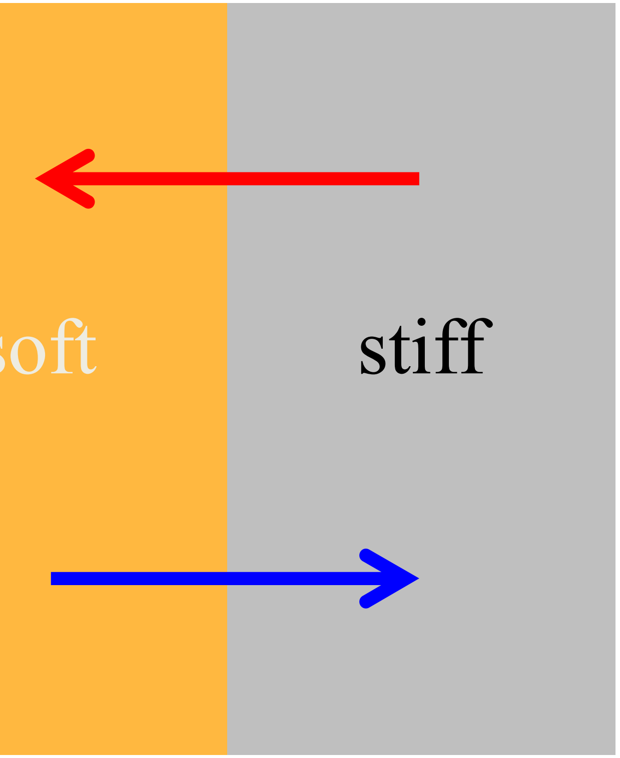
Experimentally what is measured is a cell s response, w
is an upper limit

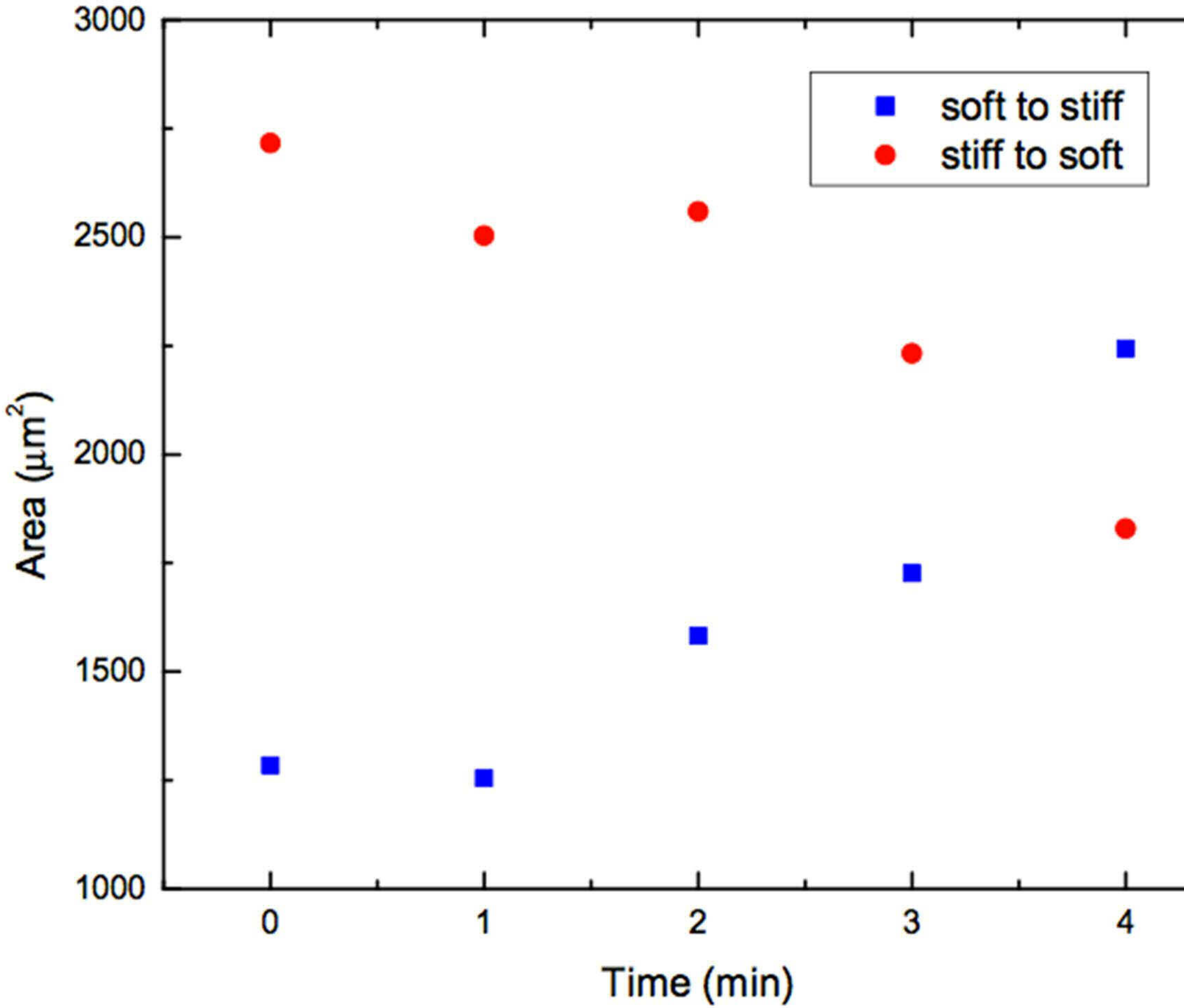
e adhesion ligand density but different stiffness





Two minutes is enough to


soft
stiff


3000
2500
2000
1500
1000
Area (μm²)
0
1
2
3
4
Time (min)
soft to stiff
stiff to soft

ft tissues have well-defined and controlled elastic moduli

ls in vitro do not: their stiffness depends on environment

e strain-stiffening properties of biopolymer gels contribute
issue stiffness and provides effective means to reversibly
fen a cell or tissue.

bstrate stiffness affects each cell type differently, and
nipulating matrix stiffness can influence cell fate.

fness sensing appears to operate on a length scale >1
 and a time >1 s.