Viscoelastic properties of soft tissues: comparison and contrast with polymer networks

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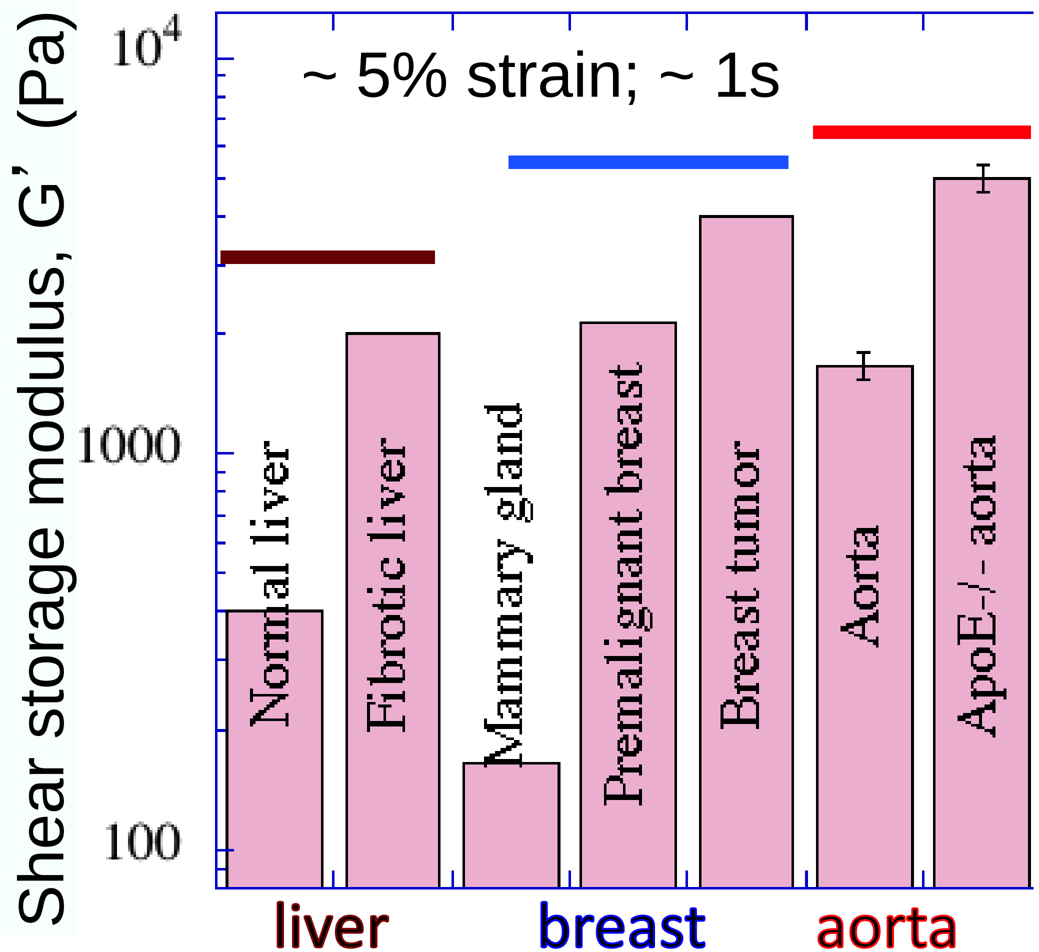
Normal tissues have well-defined stiffness
characterized by an elastic modulus*



Changes in organ stiffness often accompany disease and development – often related to increased collagen XLs

** time and strain-dependent*

Levental et al Soft Matter, 2007
Kothapalli et al. Cell Rep 2013

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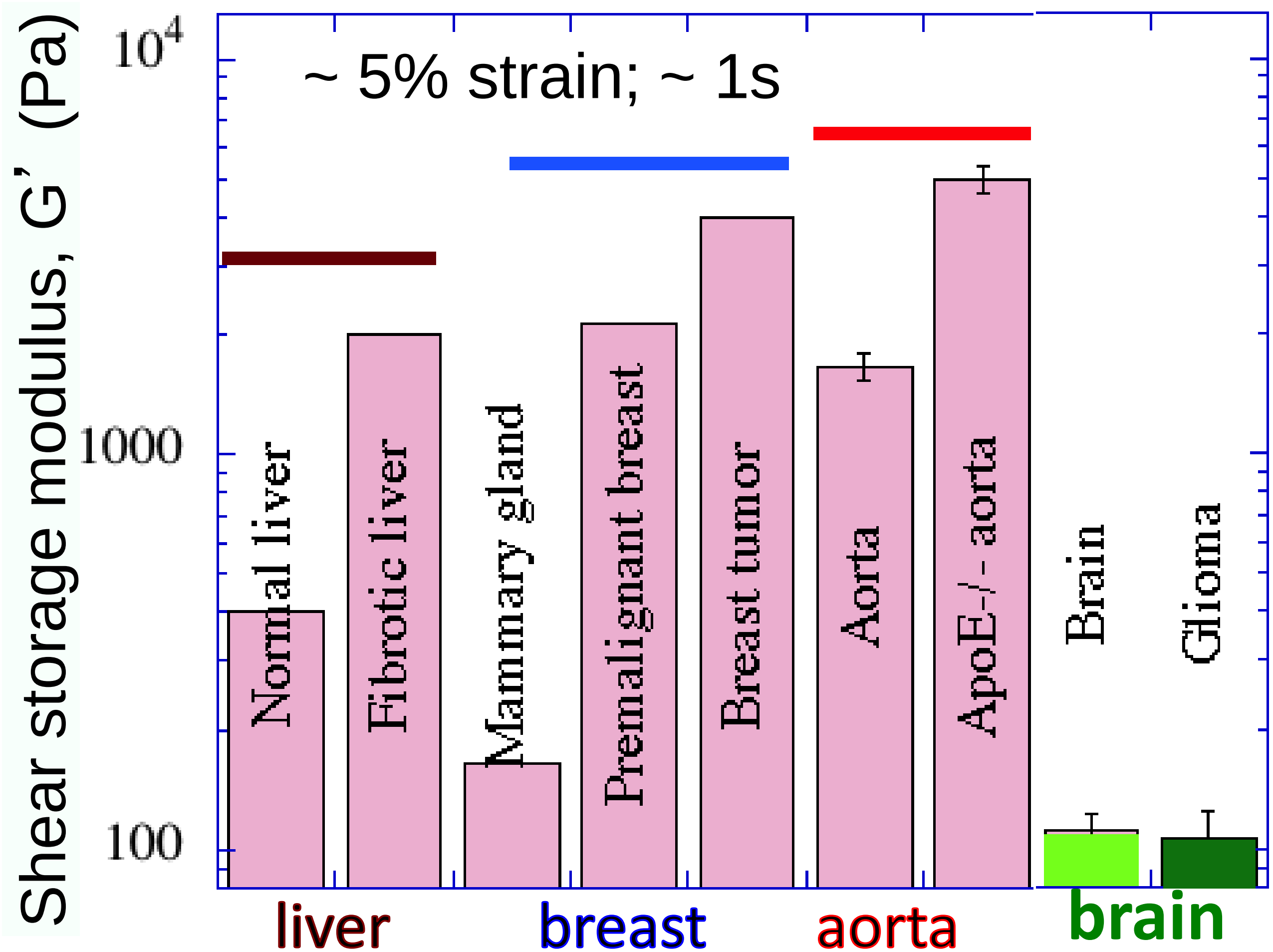


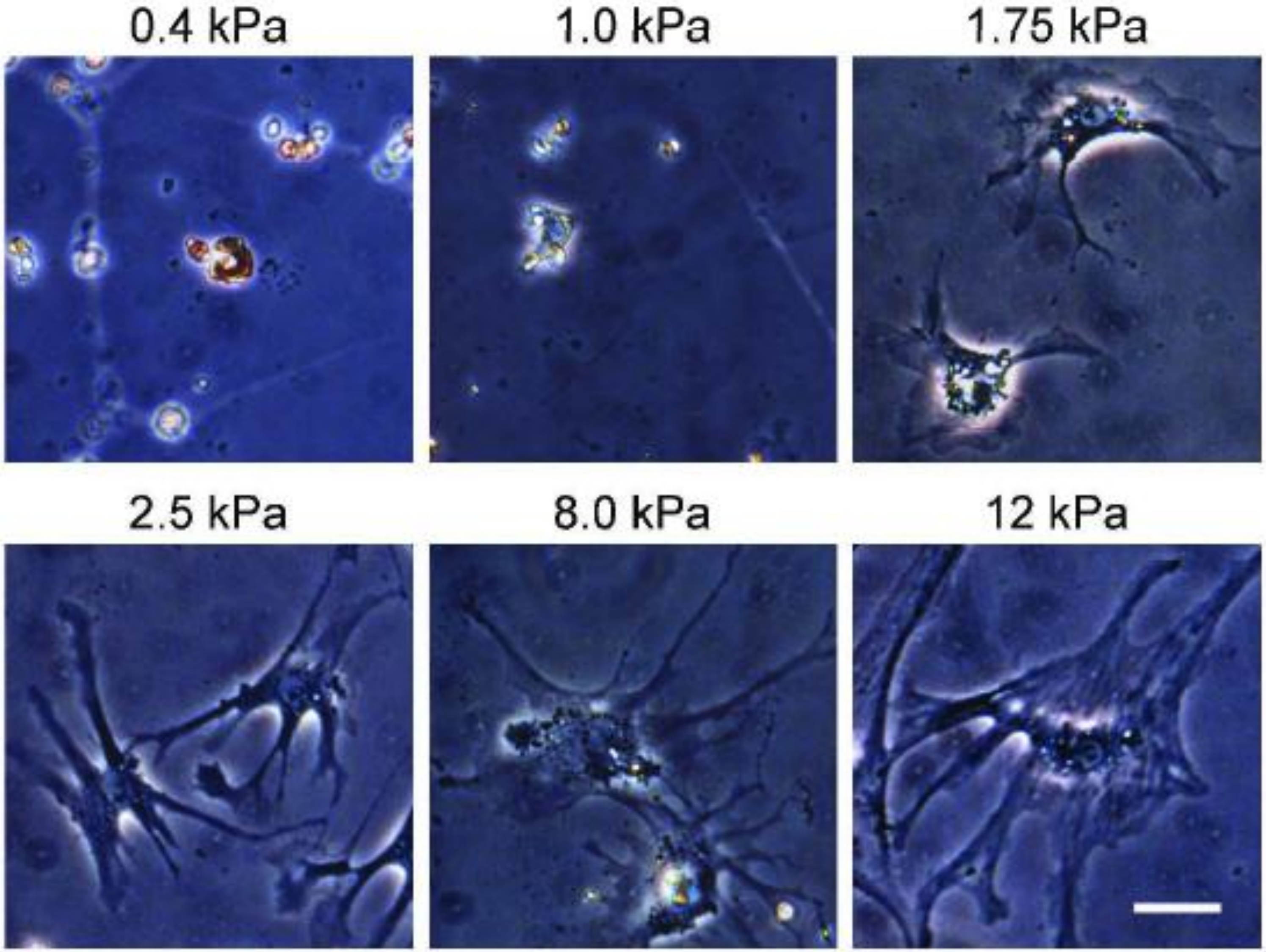
** time and strain-dependent*

Levental et al Soft Matter, 2007
Kothapalli et al. Cell Rep 2013

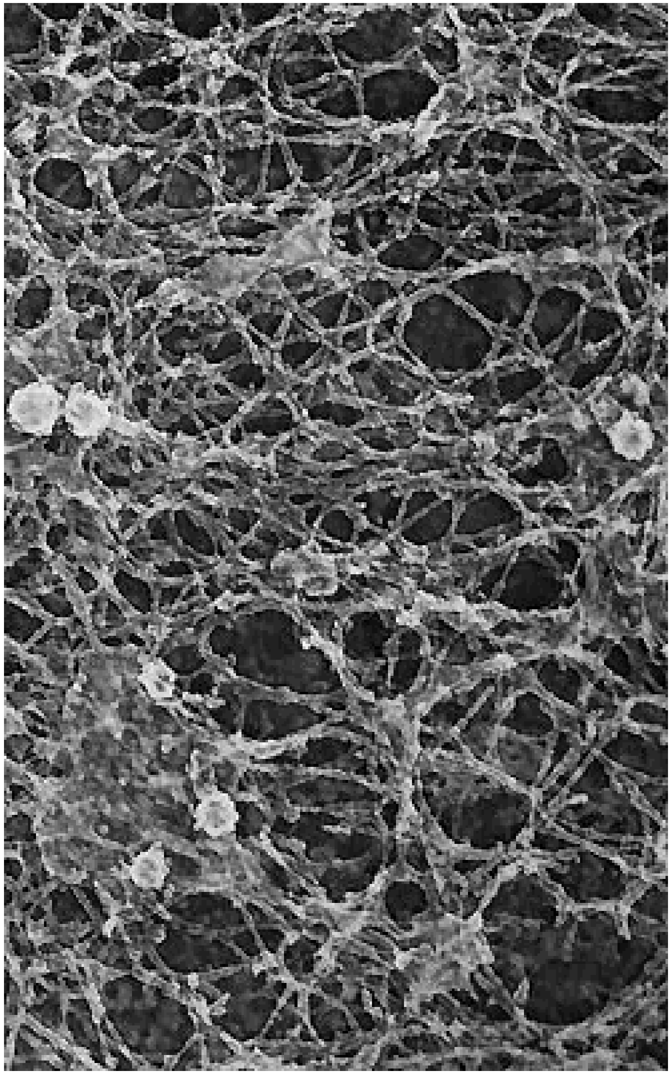
Hepatic stellate cells spontaneously activate on pathologically stiff substrates

Rebecca Wells

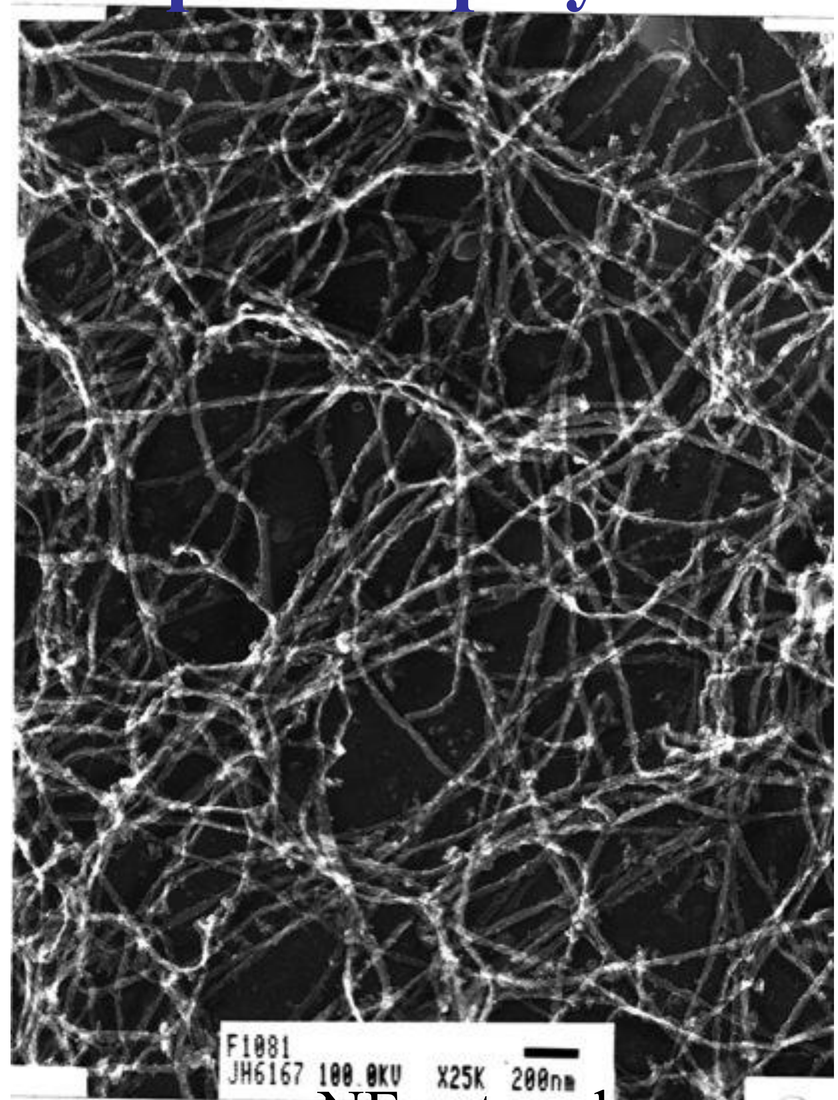
Olsen et al, Am. J. Physiol. 2011



The interior of eukaryotic cells is filled with networks of filamentous protein polymers

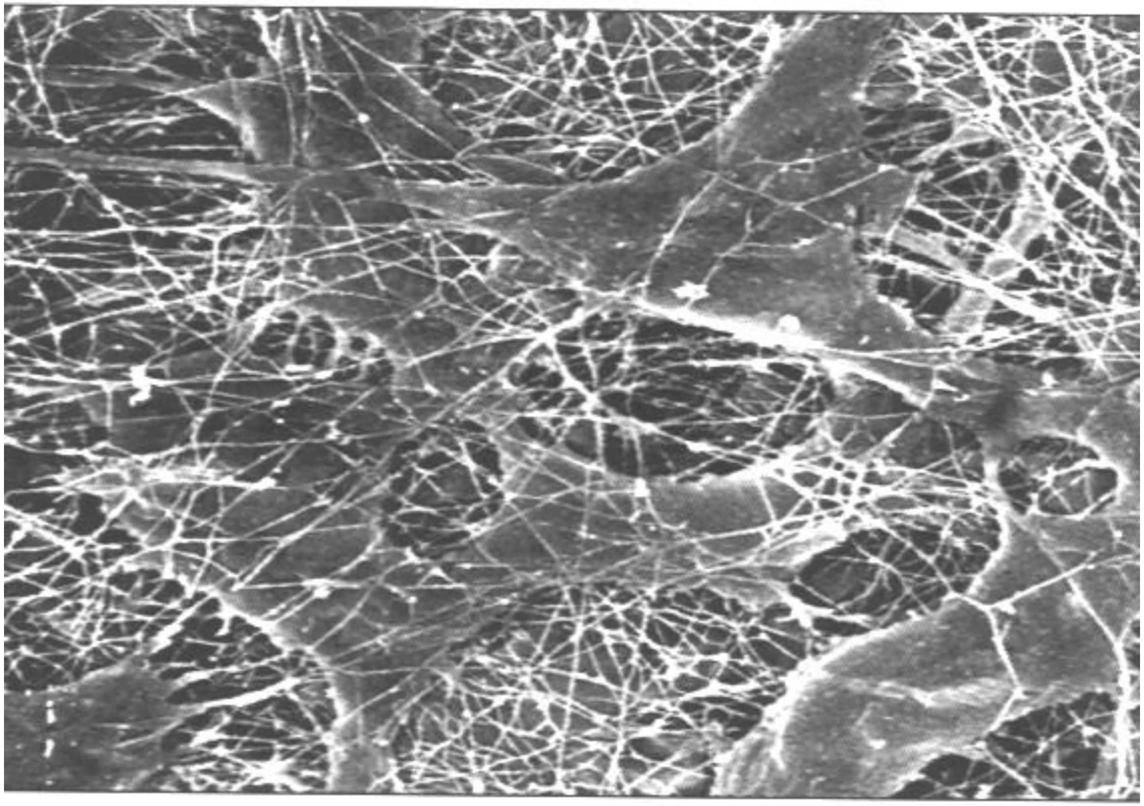


Cortical actin gel
JH Hartwig



NF network
J-F Leterrier

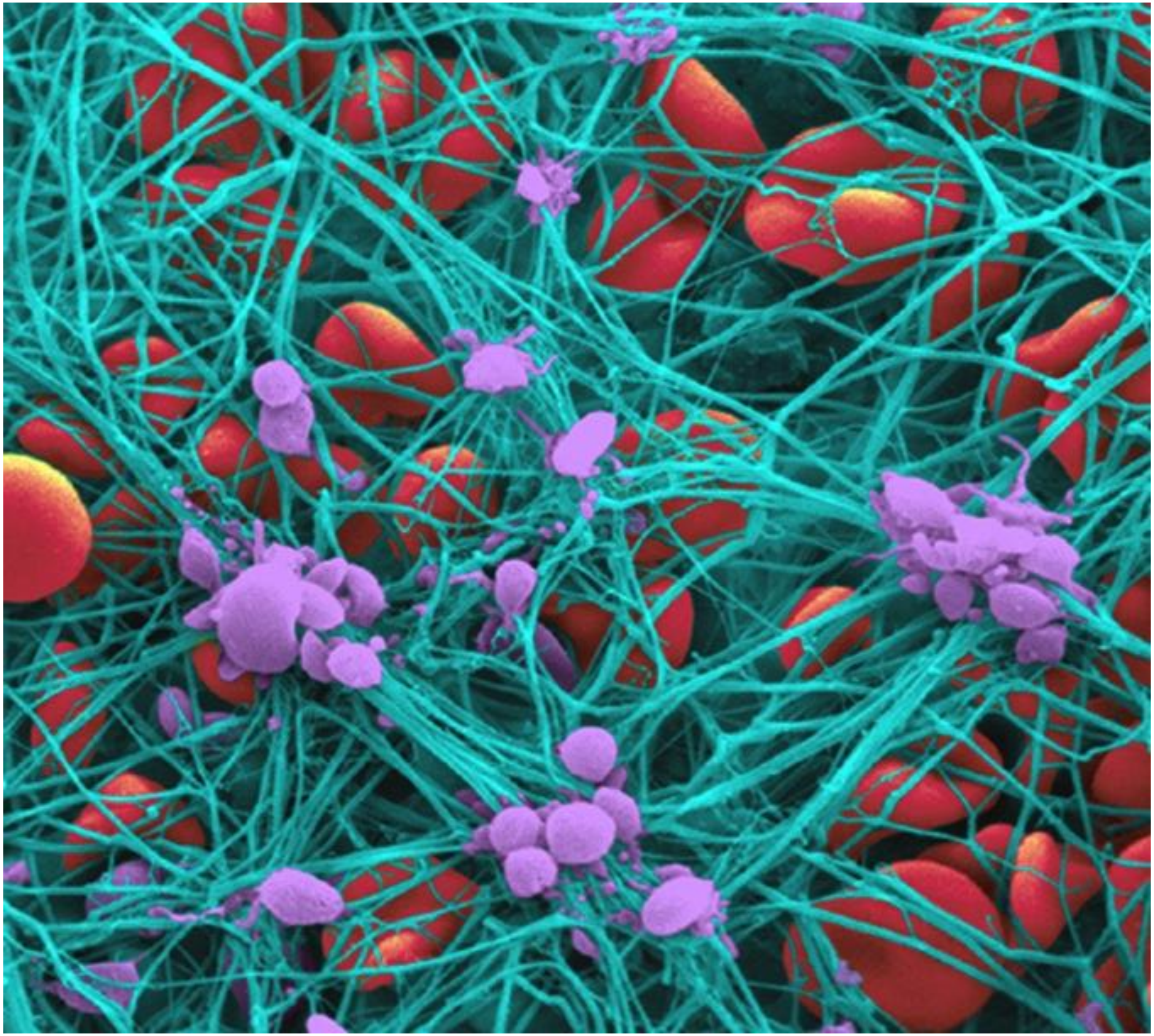
Open meshworks of semiflexible filaments are very common in biology, not limited to the cytoskeleton



(From T. Nishida et al.Invest. Ophthalmol. Vis. Mol Biol Cell 3er Ed-973,1994)

The extracellular matrix surrounding cells (fibroblasts) is composed of semiflexible polymer filaments (collagen)

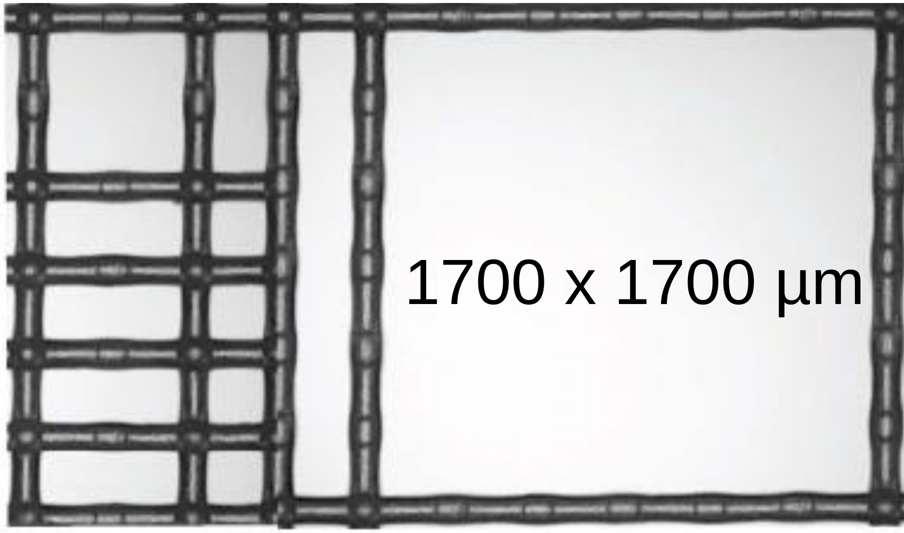
Blood cells (**erythrocytes**, **platelets**) embedded in a **fibrin** clot



3 μm

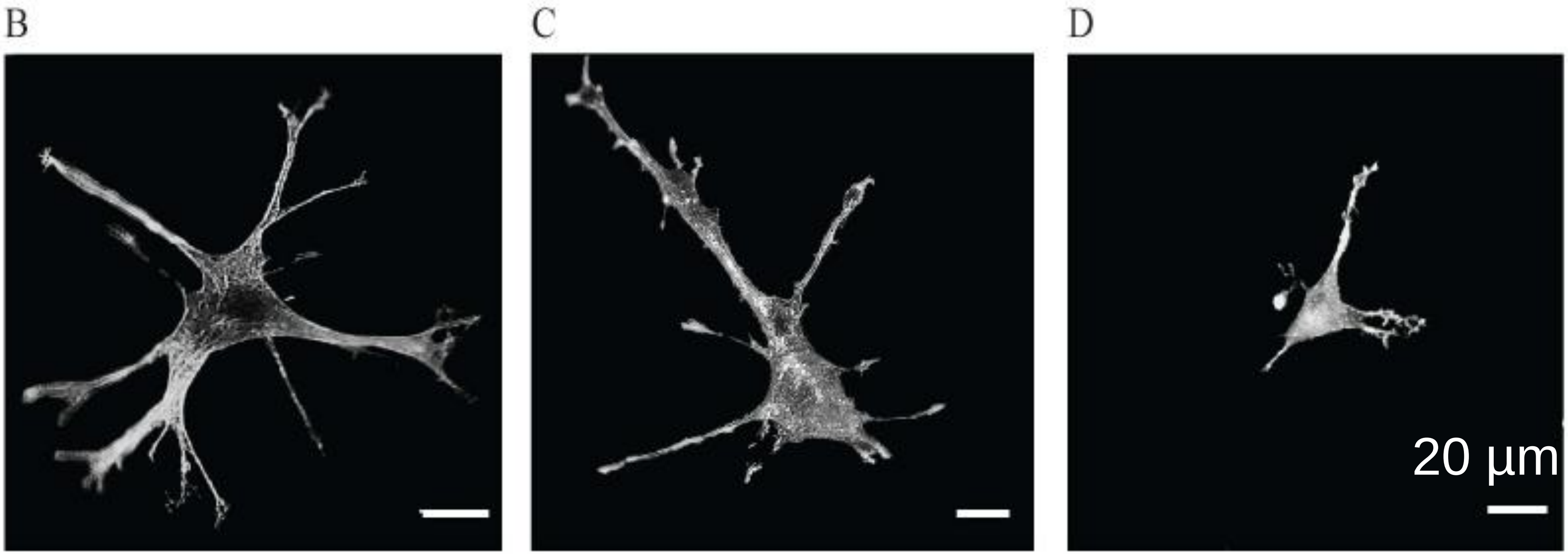
Scanning EM of 10x diluted human blood clot - John Weisel

Rigid boundary sensing by fibroblasts on collagen



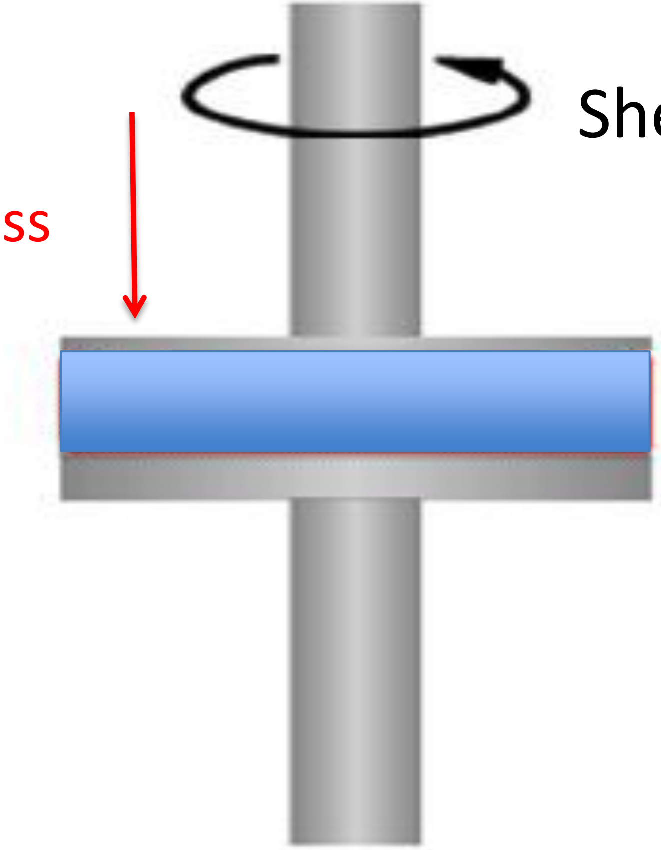
Cells on collagen gels within rigid boundaries

Mohammadi H, PAJ, McCulloch CA
2014, Biomaterials 35: 1138-1149

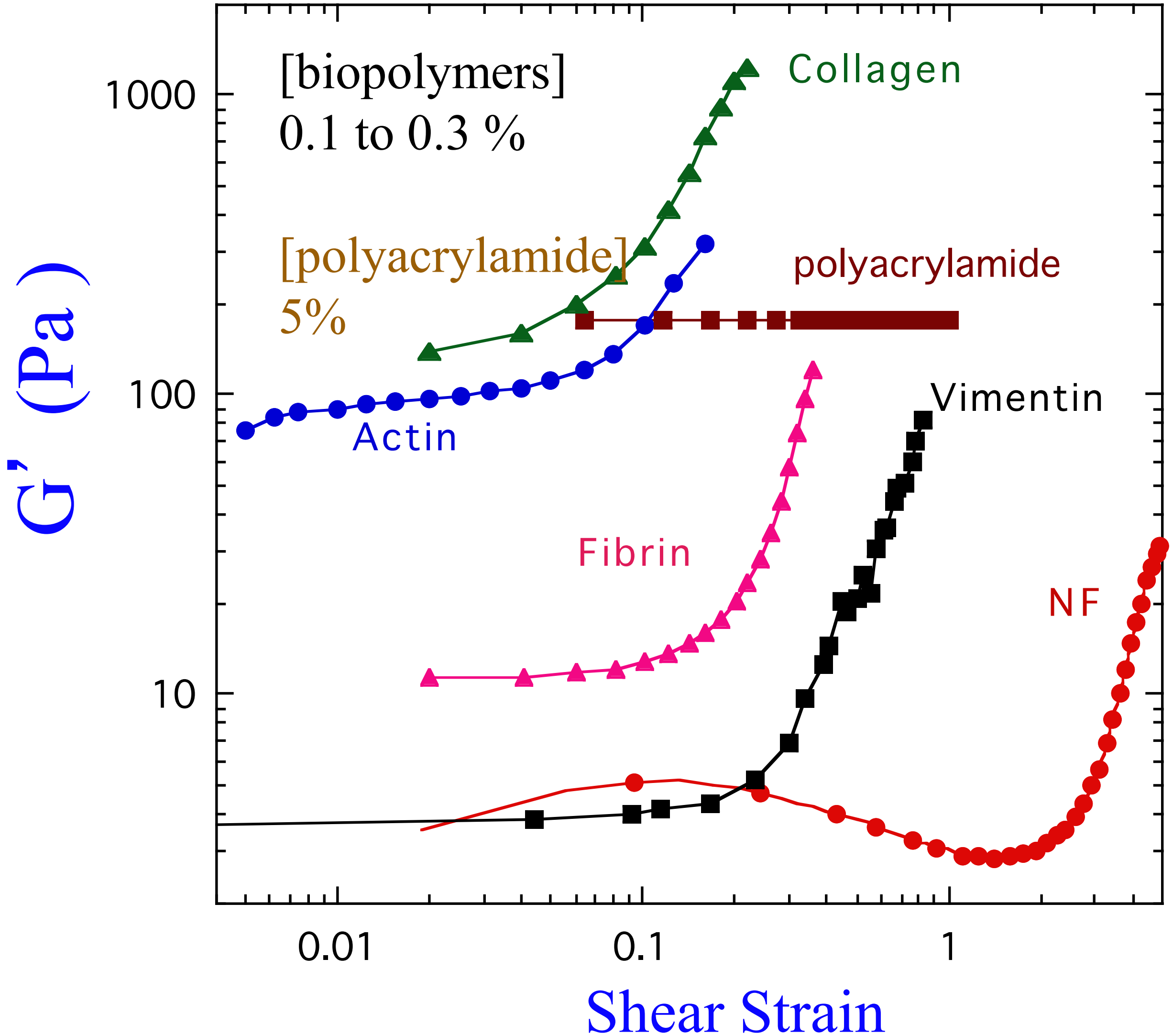


200 x 200 µm | 500 x 500 µm | 1700 x 1700 µm

Rheologic characterization of polymer gels and tissues
Combining uniaxial stress with shear deformation



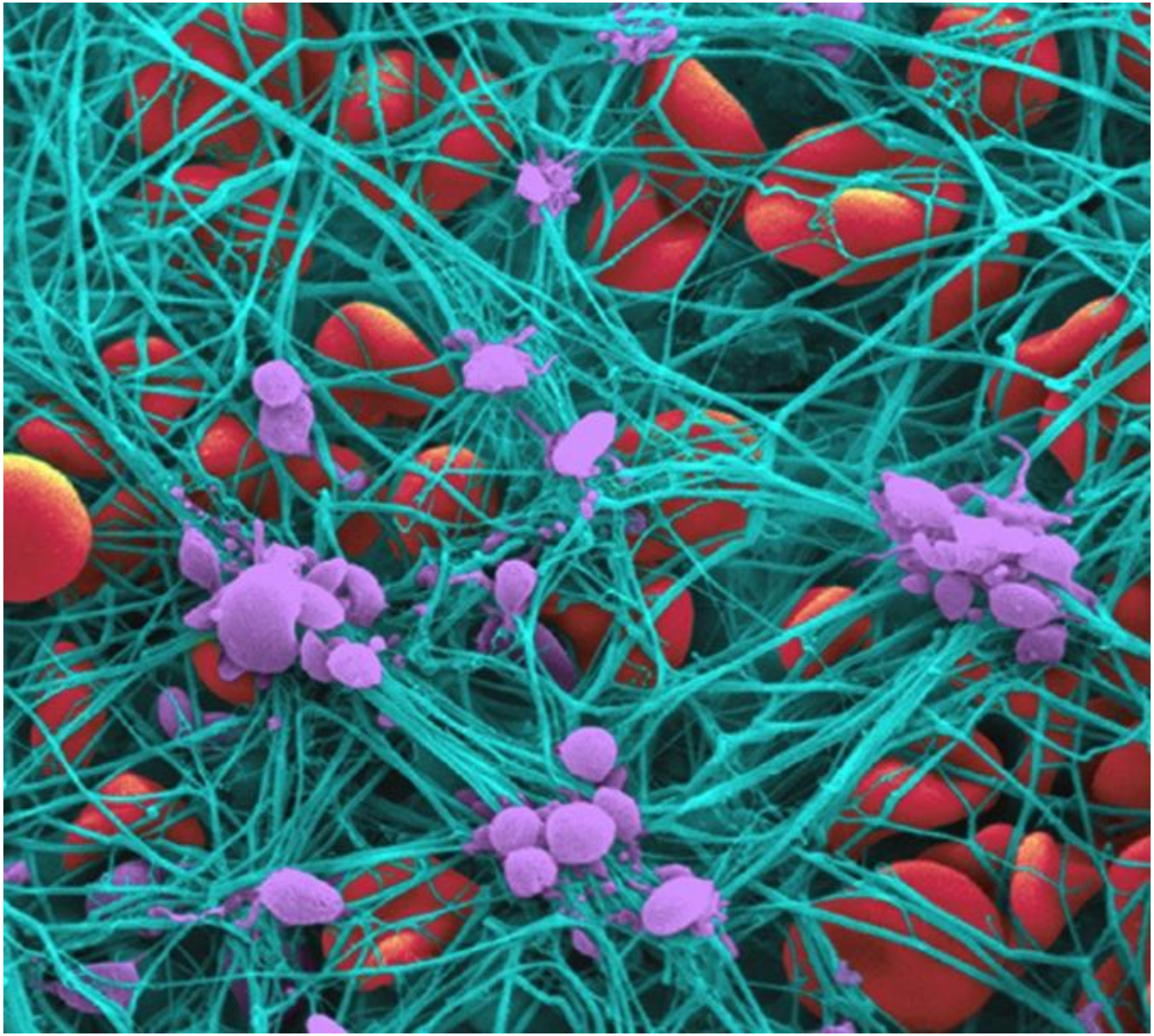
Both cytoskeletal and ECM networks are strain stiffening



Storm, 2005

Non-linear elasticity allows cytoskeletal and ECM networks to stiffen by internal stress, without increasing polymer mass or XLs.

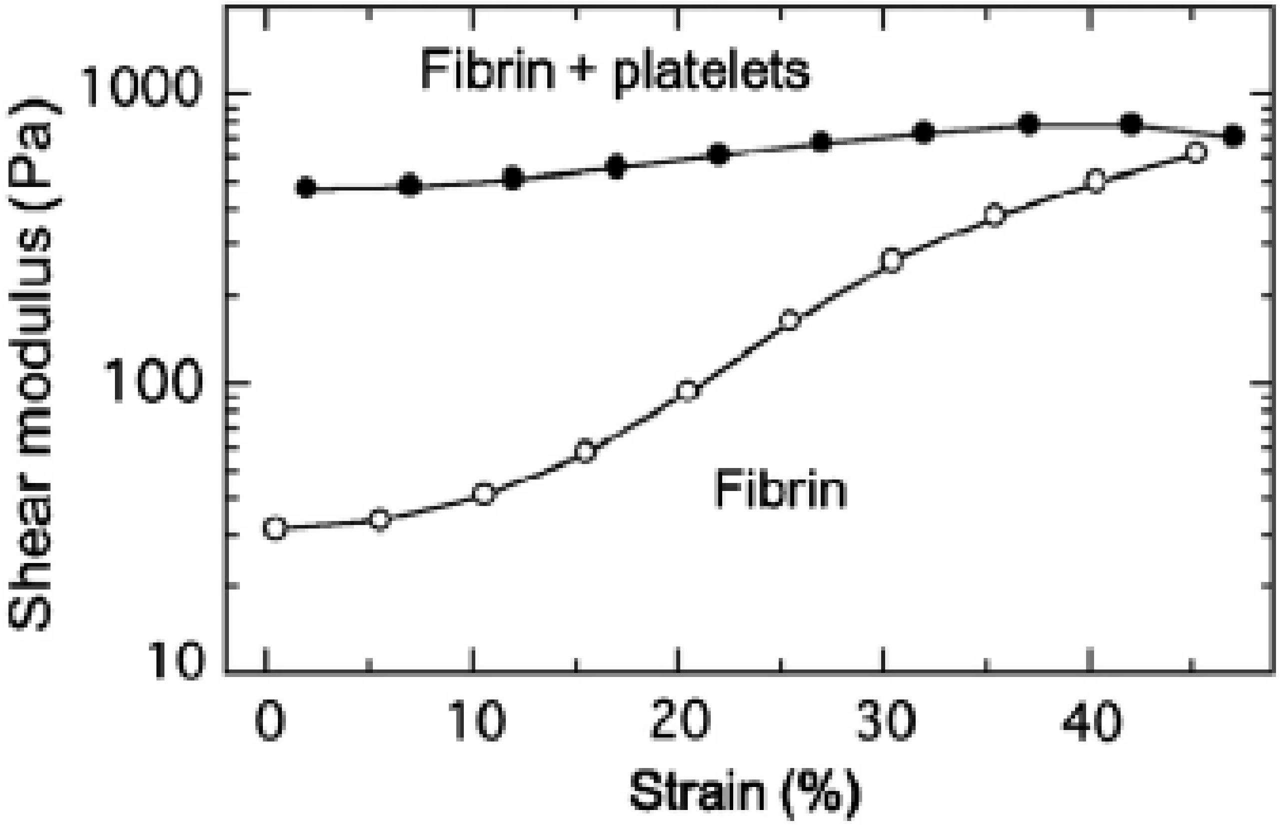
Effect on contractile **platelets** on rheology of a **fibrin** network



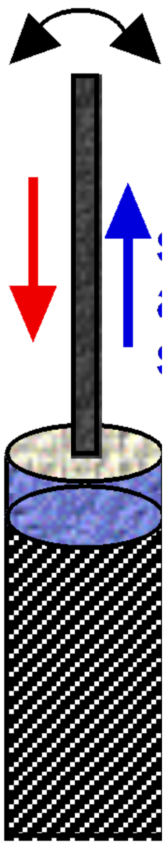
3 μm

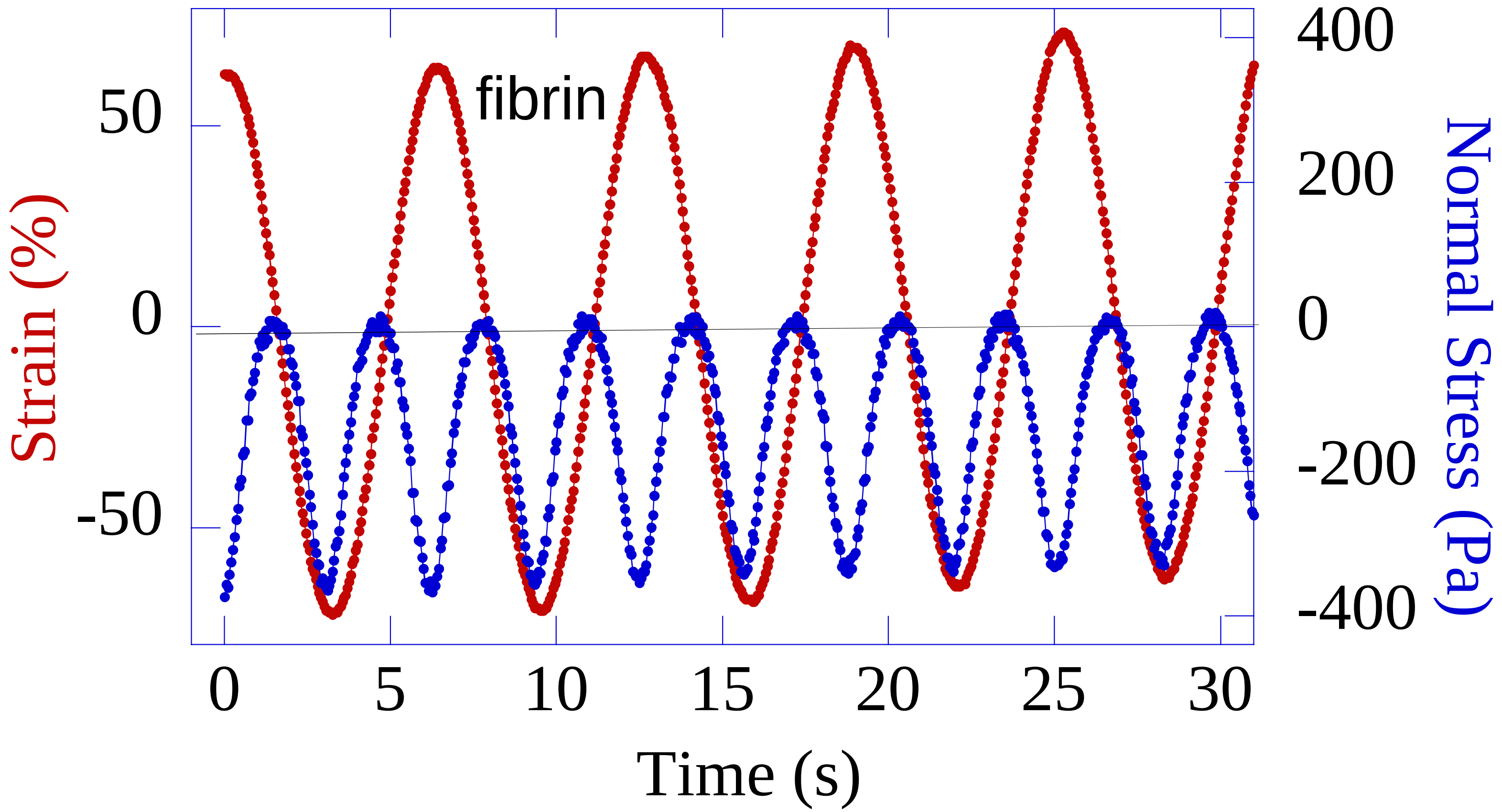
Scanning EM of human blood clot - John Weisel

Internal stress generated by platelets increases low strain shear modulus and eliminates strain stiffening



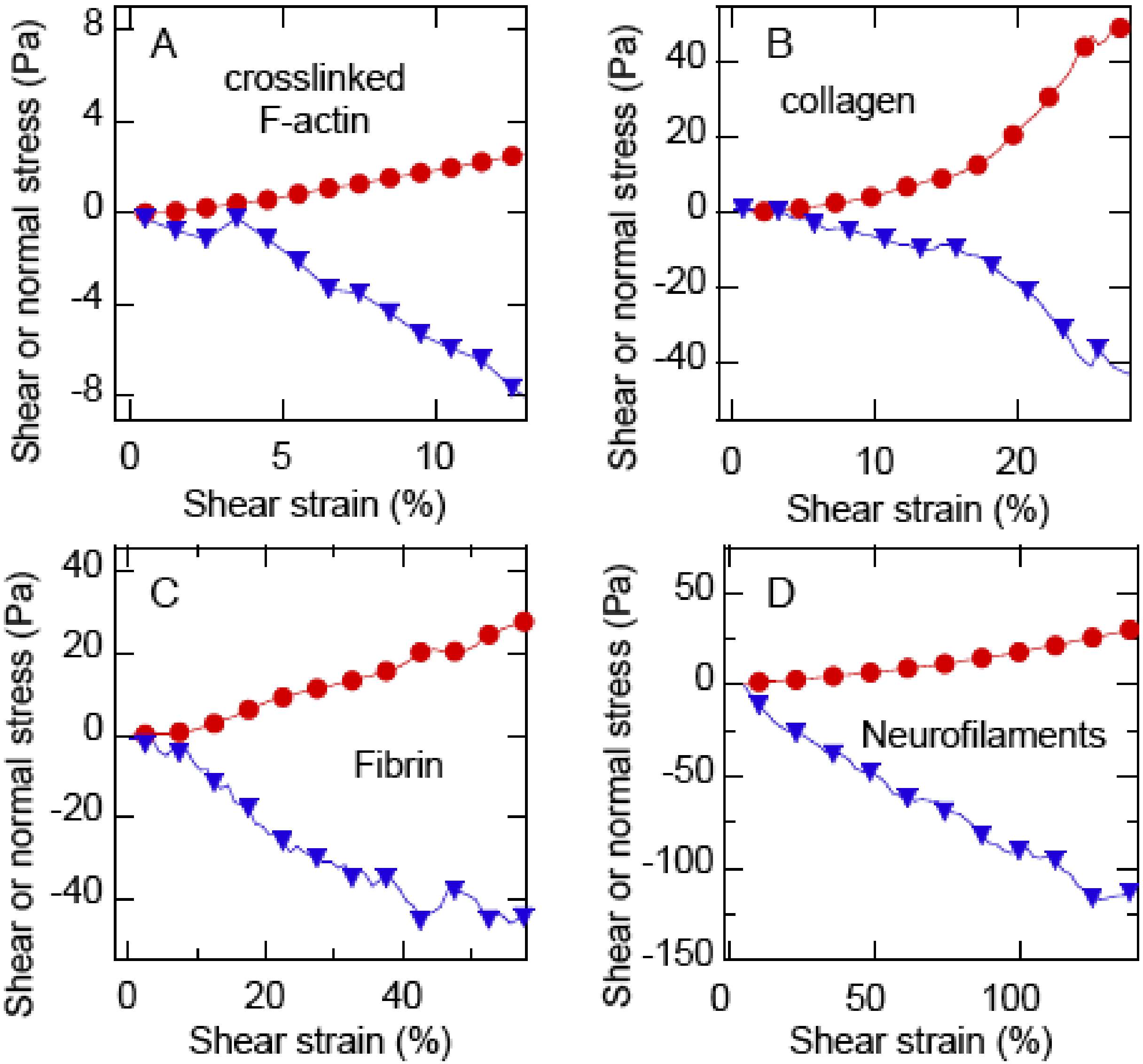
During oscillatory deformation, semiflexible polymer networks exert negative normal stress at twice the strain frequency

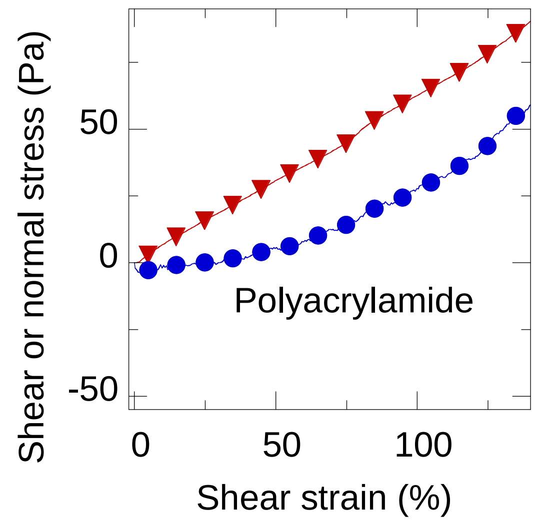




Nat. Mat. 2006

Biopolymer gels show non-linear **shear stress** and negative **normal stress**





Synthetic gel of flexible polyacrylamide has small positive normal stress

Conclusion 1

Both the cytoskeleton and extracellular matrix are formed by semiflexible or rigid polymer networks.

These polymer networks:

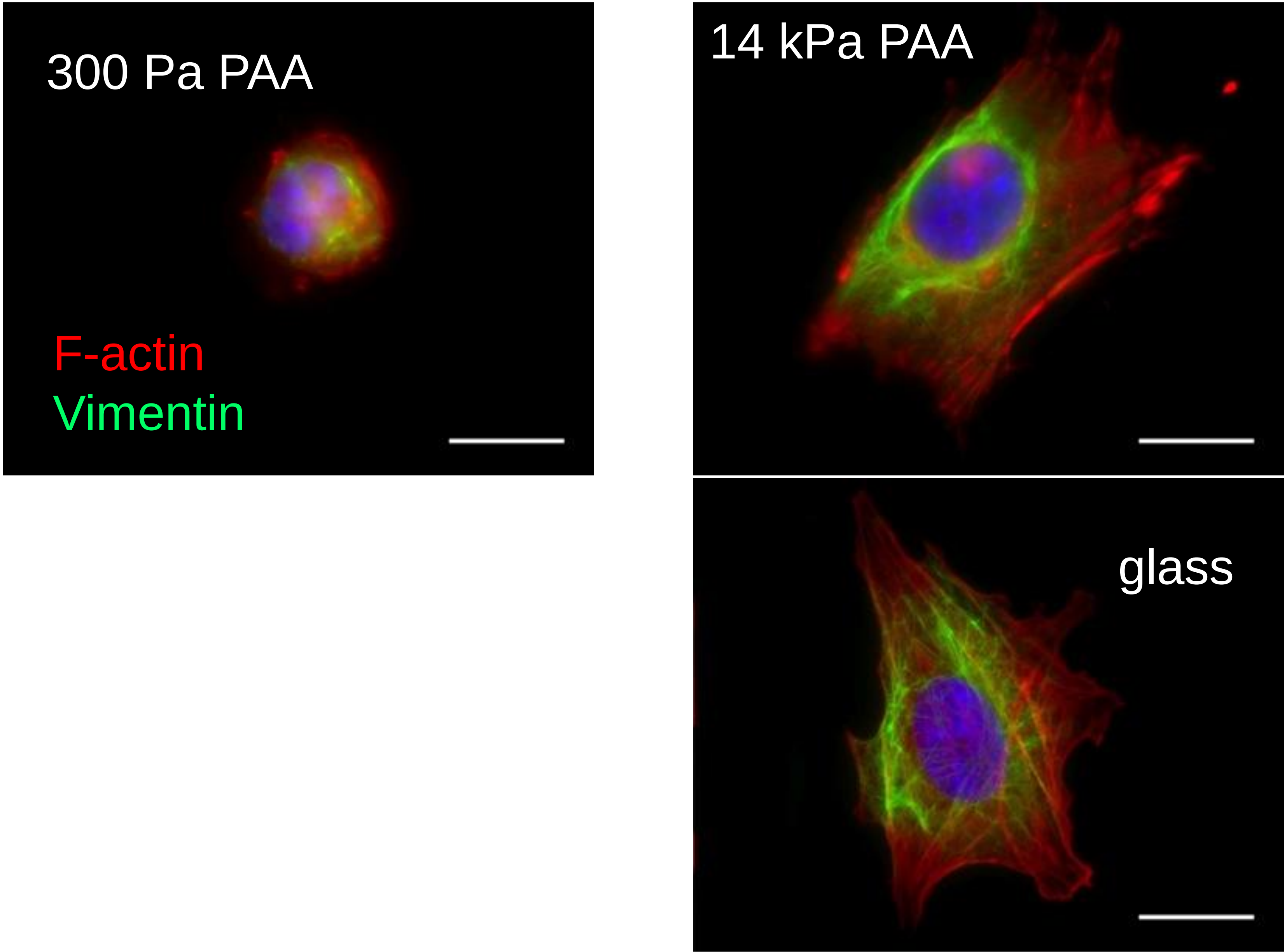
- Stiffen with increasing shear strain
- Develop negative normal stress when deformed in shear

Internal contraction of ECM gels by cell increases their stiffness by mechanisms related to their nonlinear strain-stiffening rheology

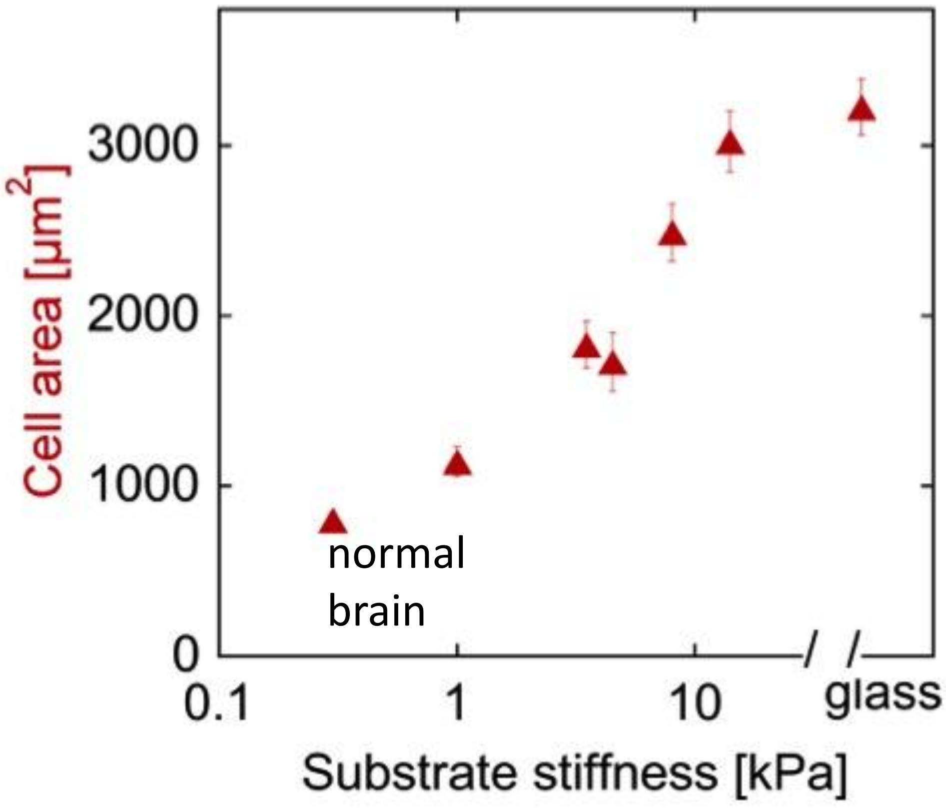
Back to cell mechanics

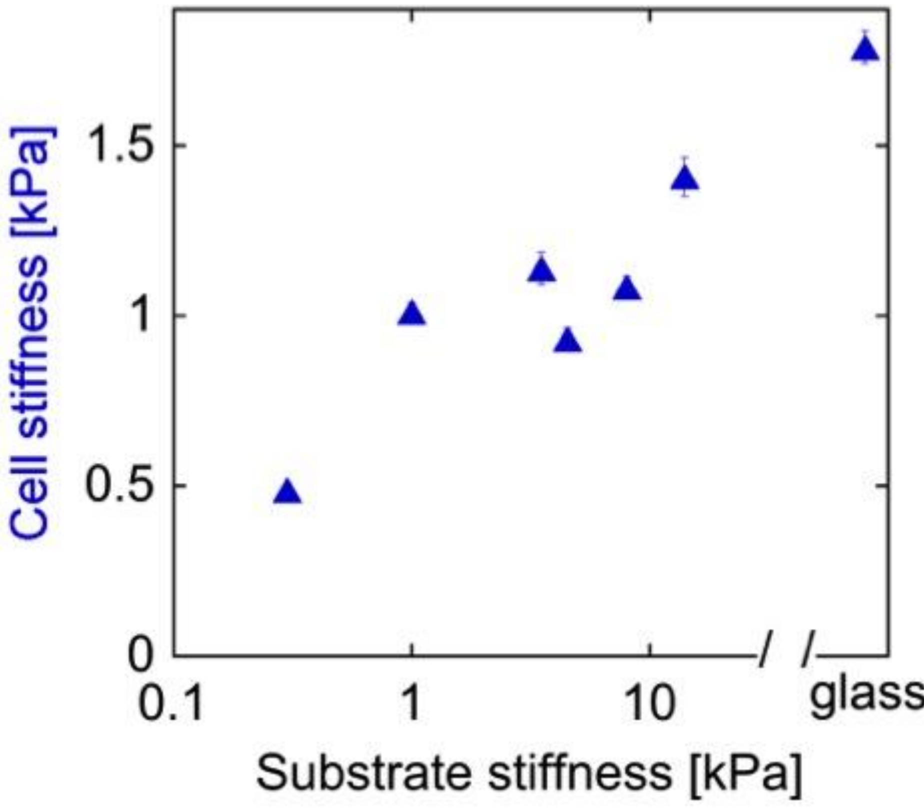
Stiffness sensing by glioma cells
Mechanical properties of brain and glioma tumors

LBC3 glioma cells on collagen 1- coated gels



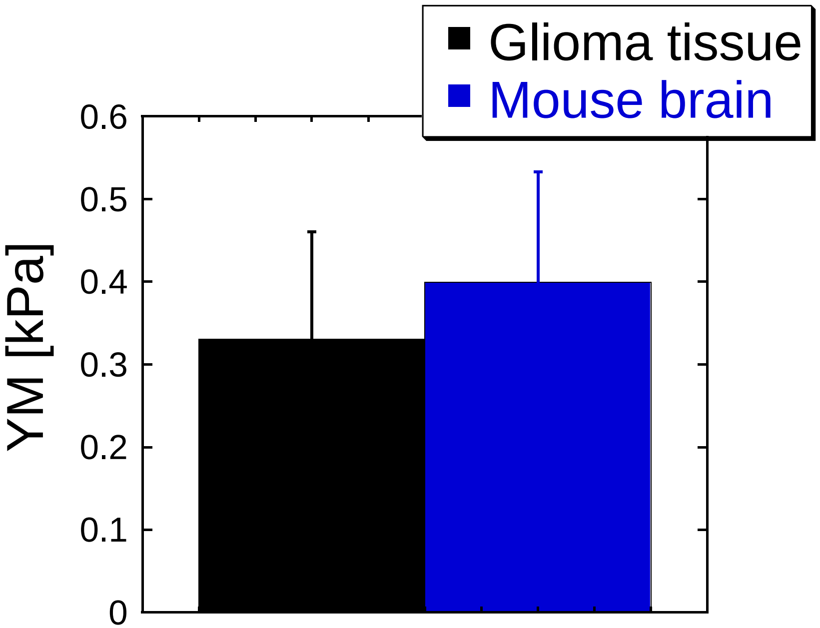
Glioma cells in culture are responsive to substrate stiffness





Glioma cells respond to stiffness differences in the soft range relevant to CNS tissue

so: Are gliomas stiffer than normal brain?

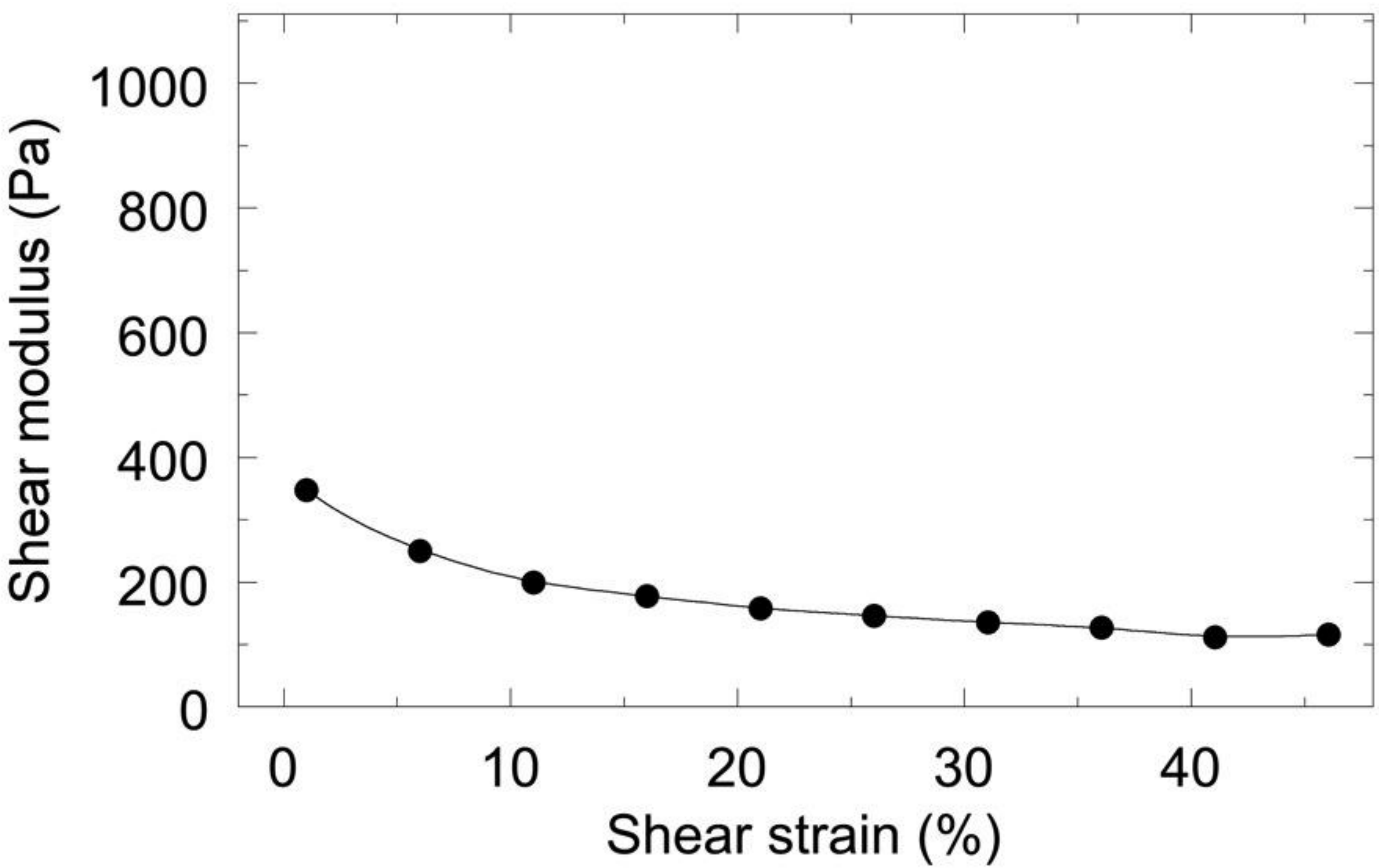


Ave of 10 different glioma samples

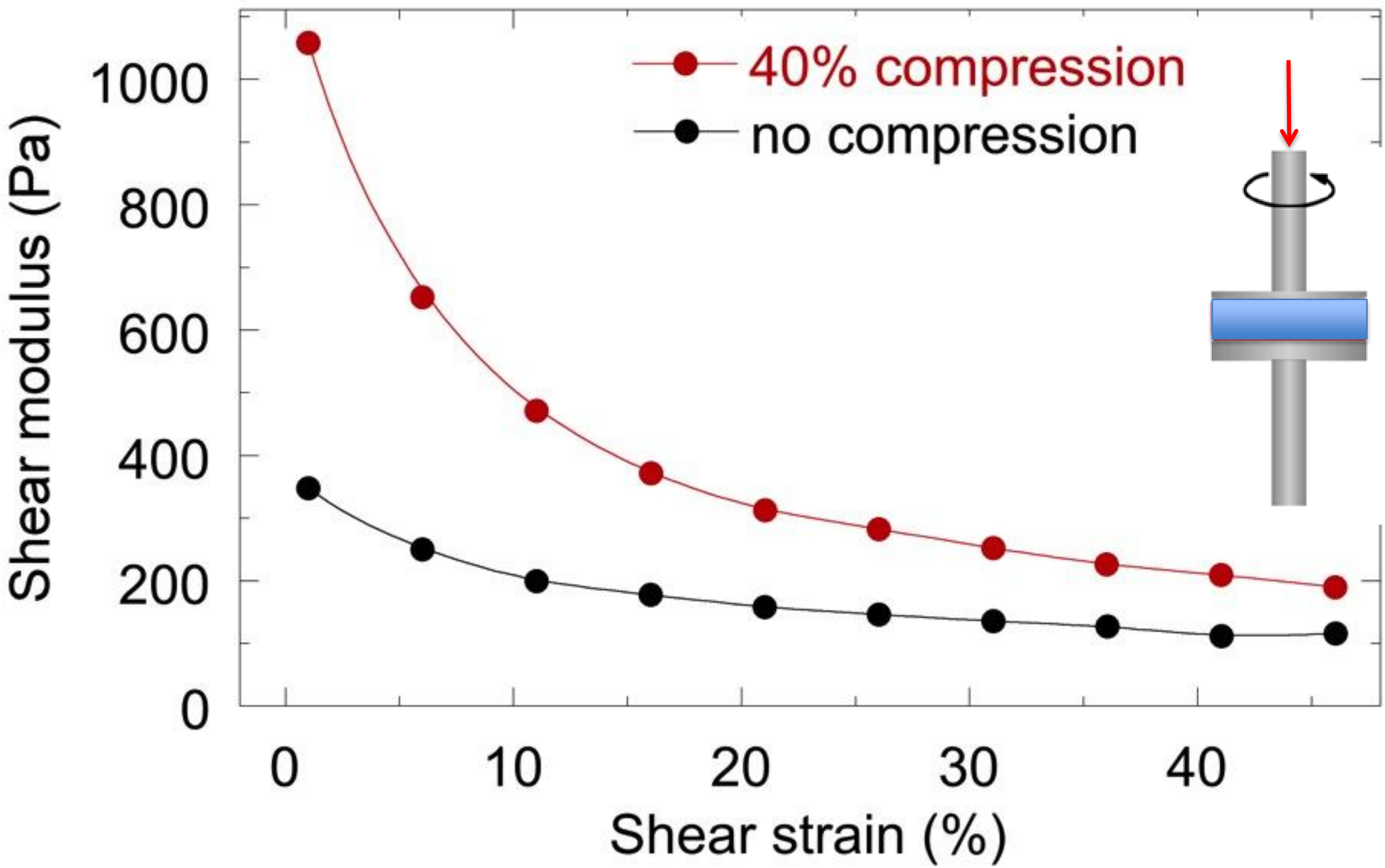
No, at least not the low strain Young modulus of excised tissue. however.....

Maybe brain strain-stiffens like semiflexible polymer gels

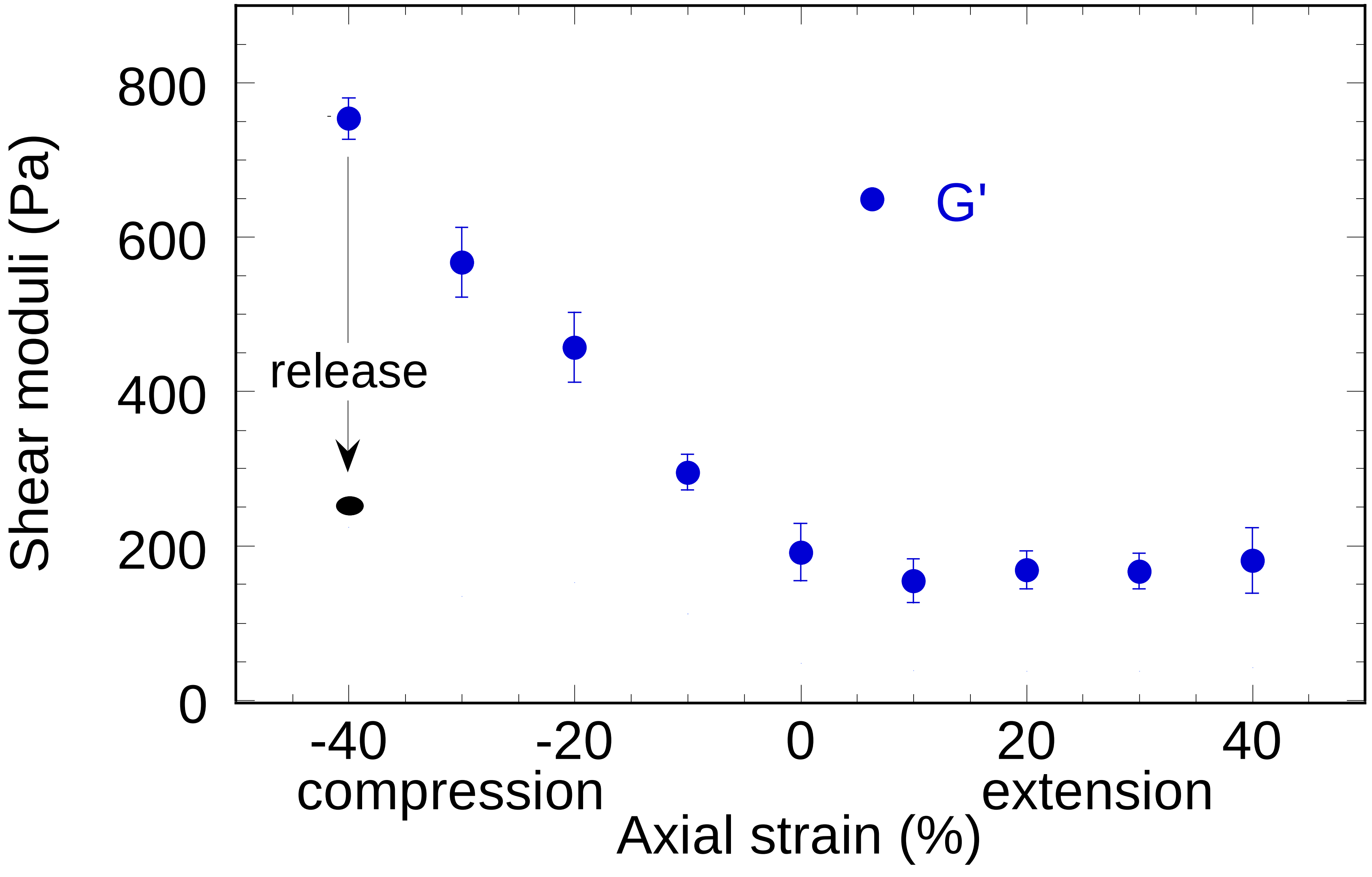
Brain does not exhibit strain-stiffening

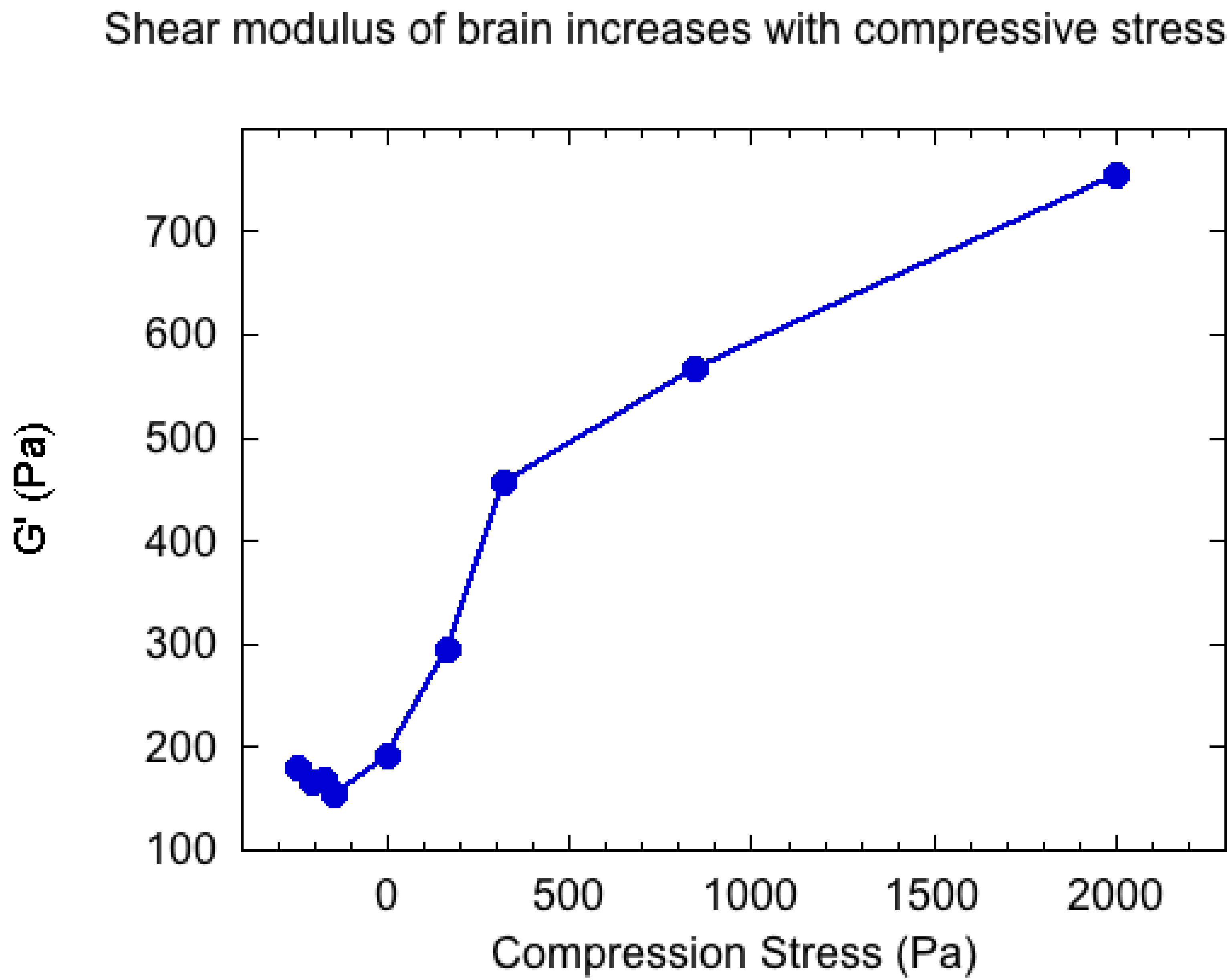


Brain stiffens in compression but not in shear

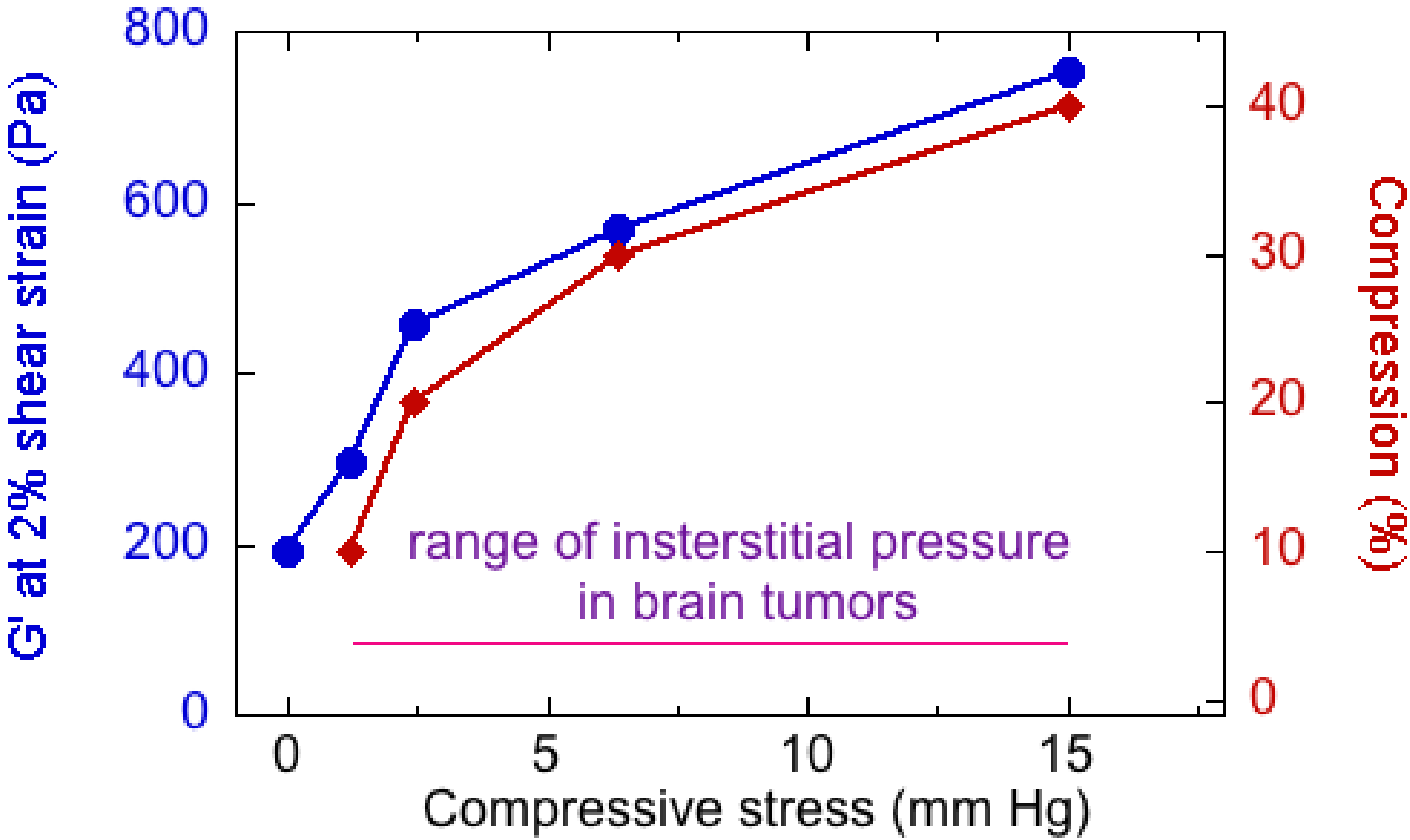


Brain stiffens in compression but not in extension

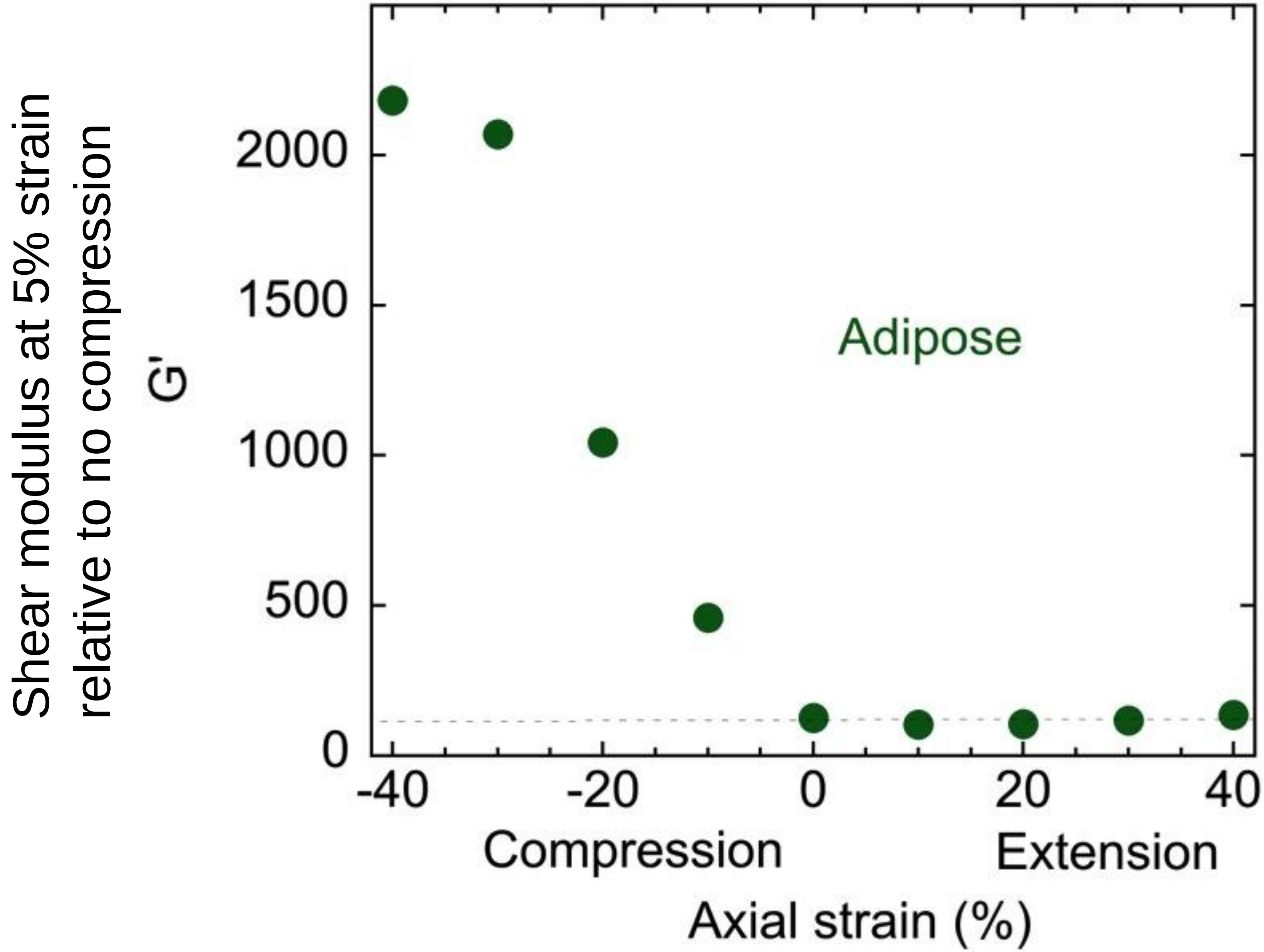



Shear modulus of brain increases with compressive stress
G' (Pa)
700
600
500
400
300
200
100
0
500
1000
1500
2000
Compression Stress (Pa)

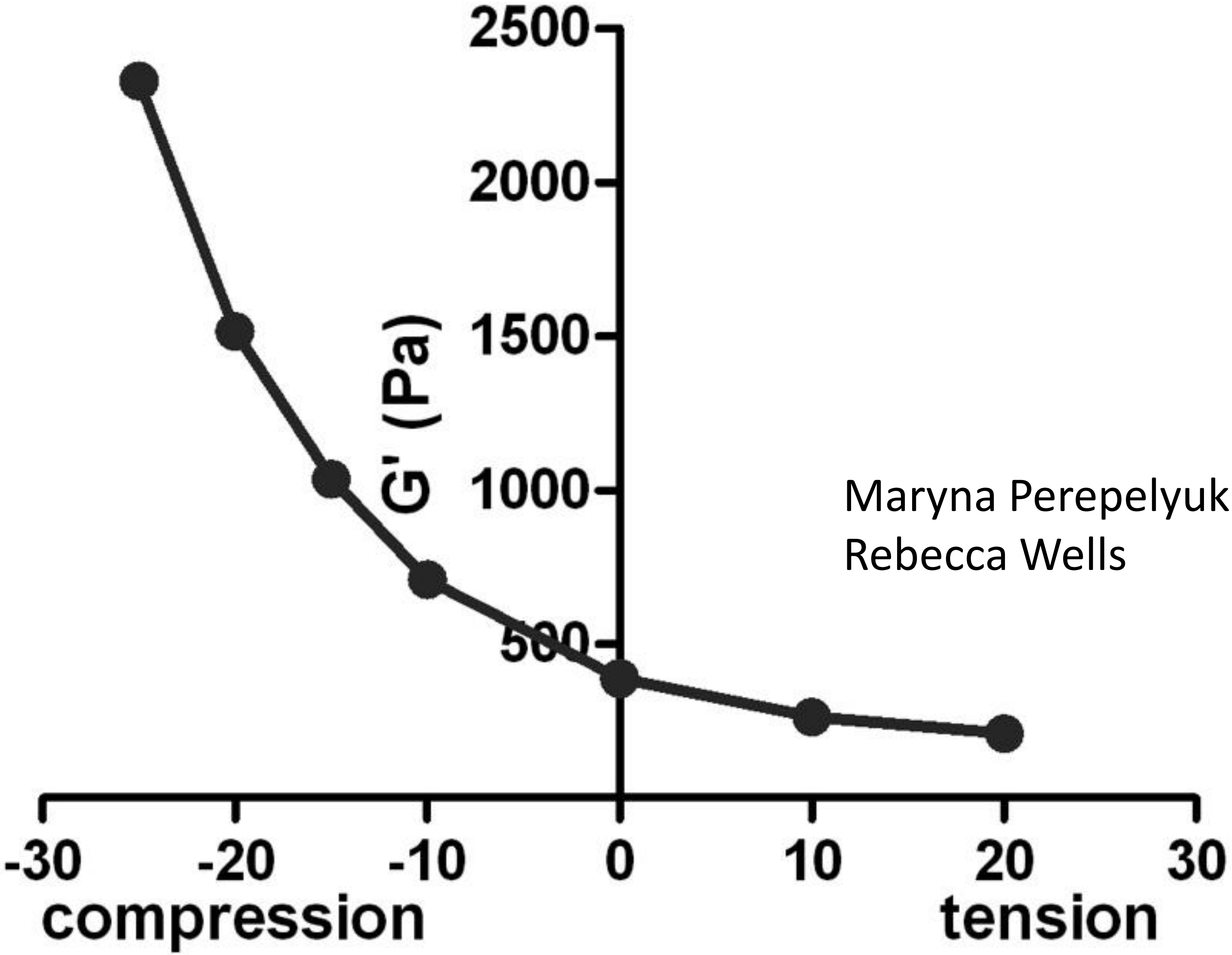
Increased pressures in glioma are sufficient to increase tumor stiffness



Adipose tissues also stiffen under compression

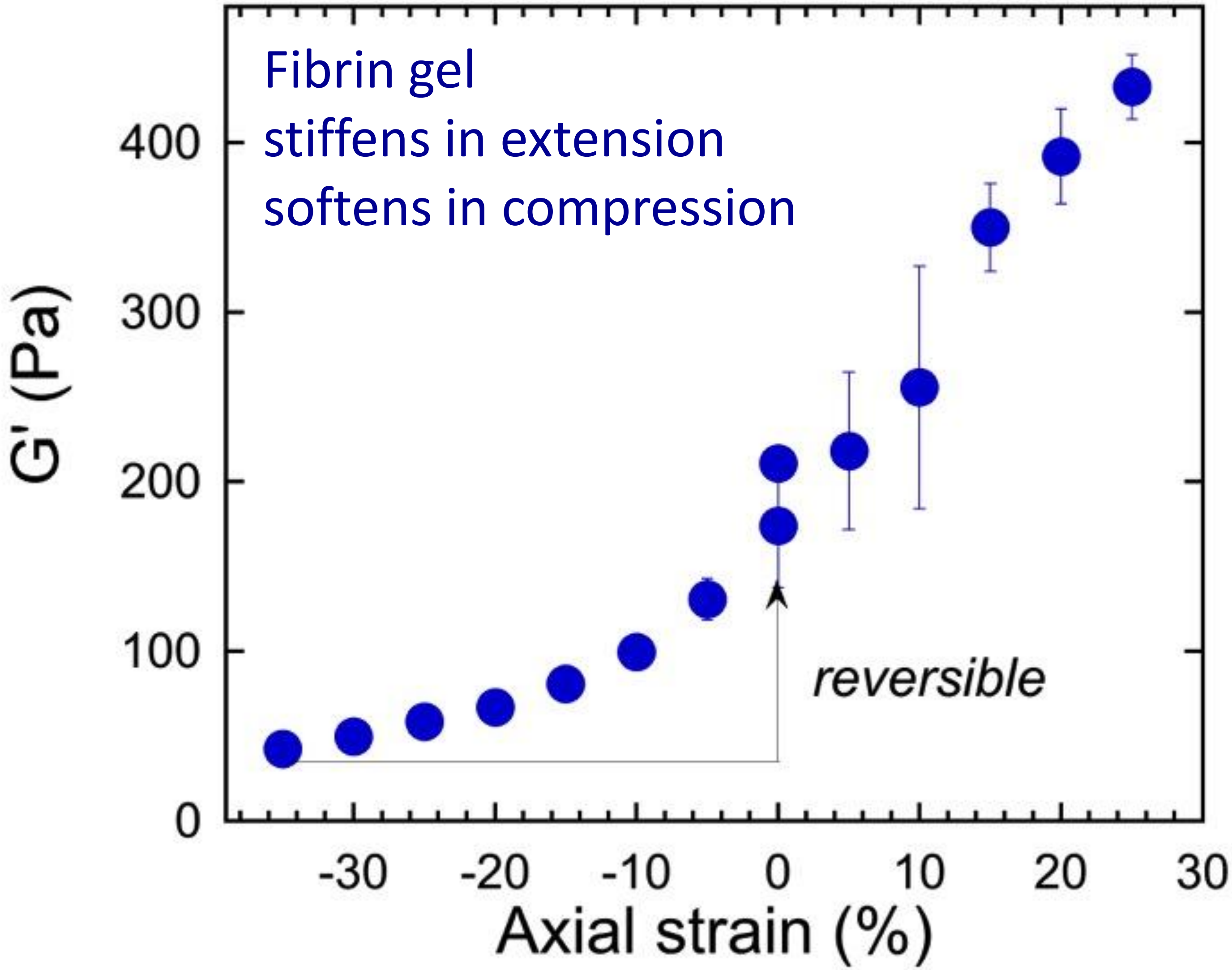


Liver also stiffens in compression



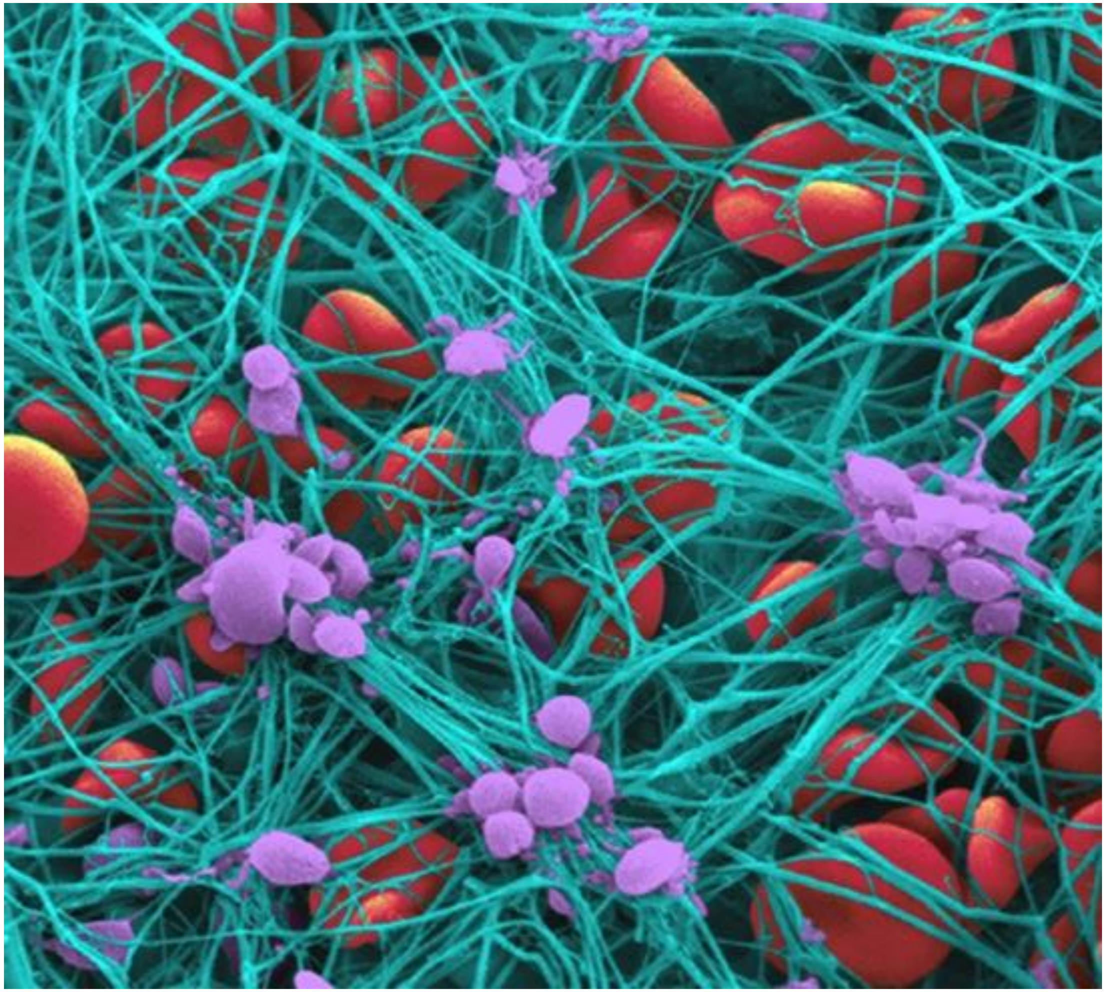
Maryna Perepelyuk
Rebecca Wells

Is compression stiffening a feature of crosslinked semiflexible polymer networks? NO



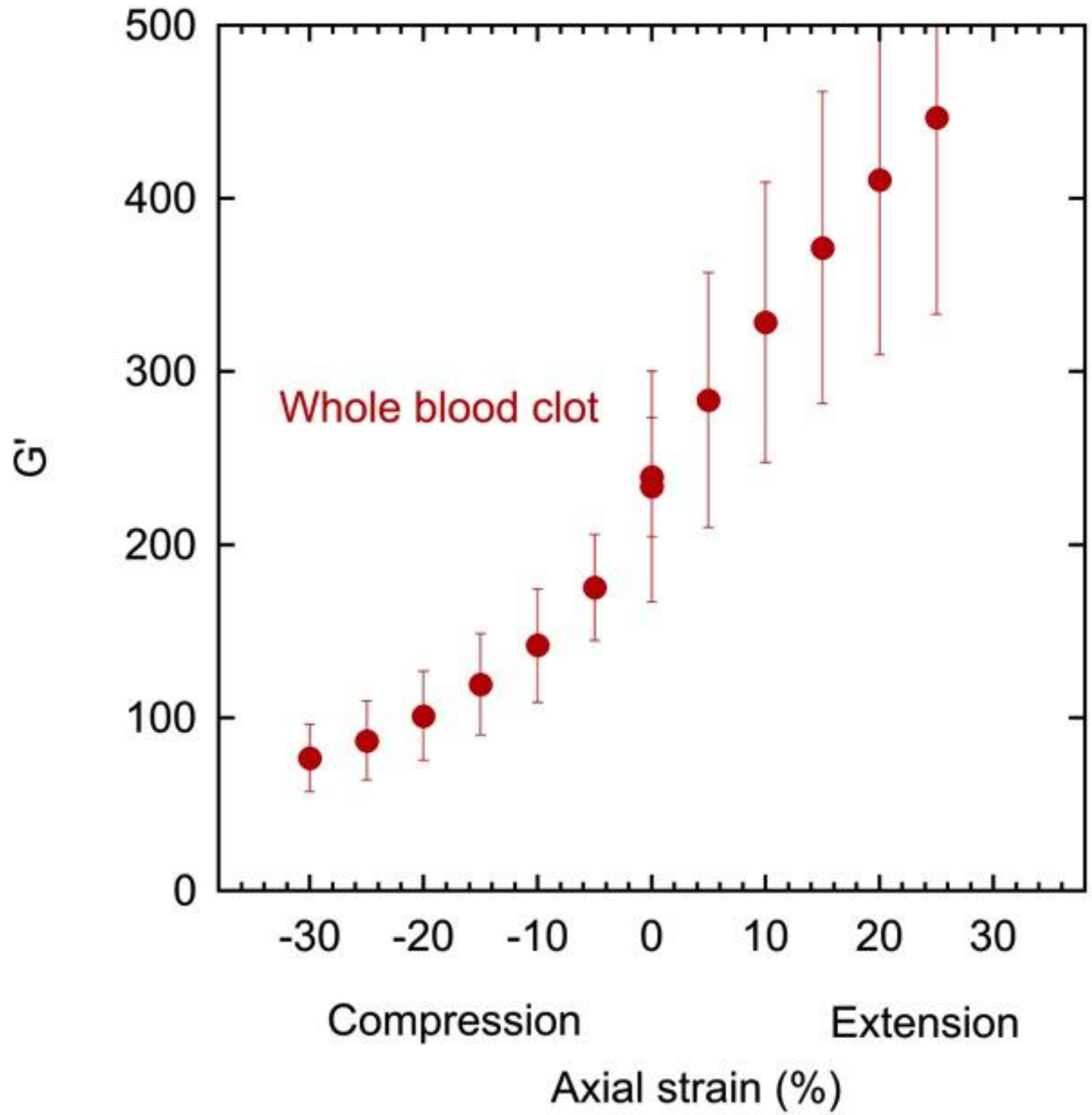
Why are tissues not like semi-flexible polymer networks:

Because they have cells in the network? Like inclusions

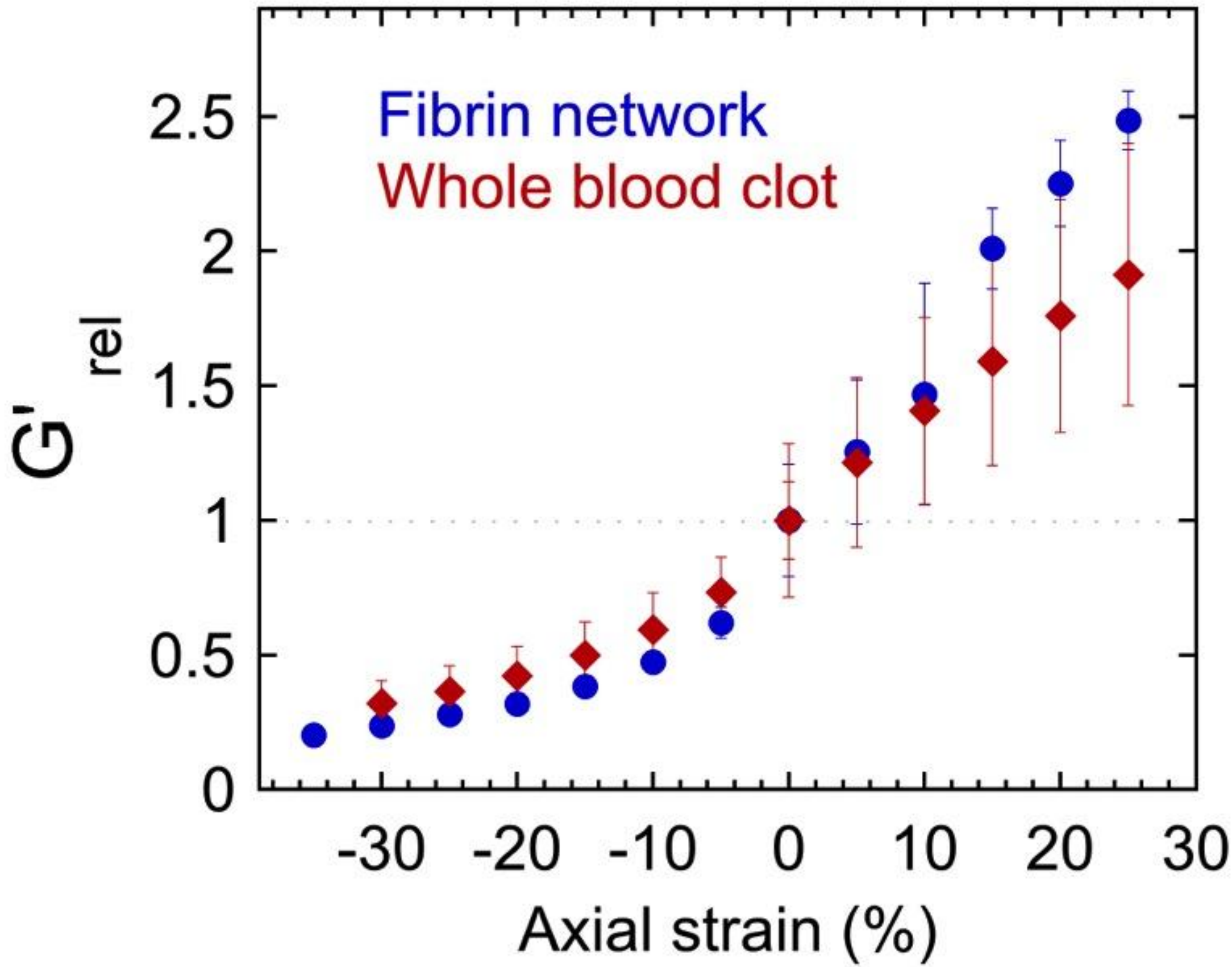


~3x diluted
blood clot

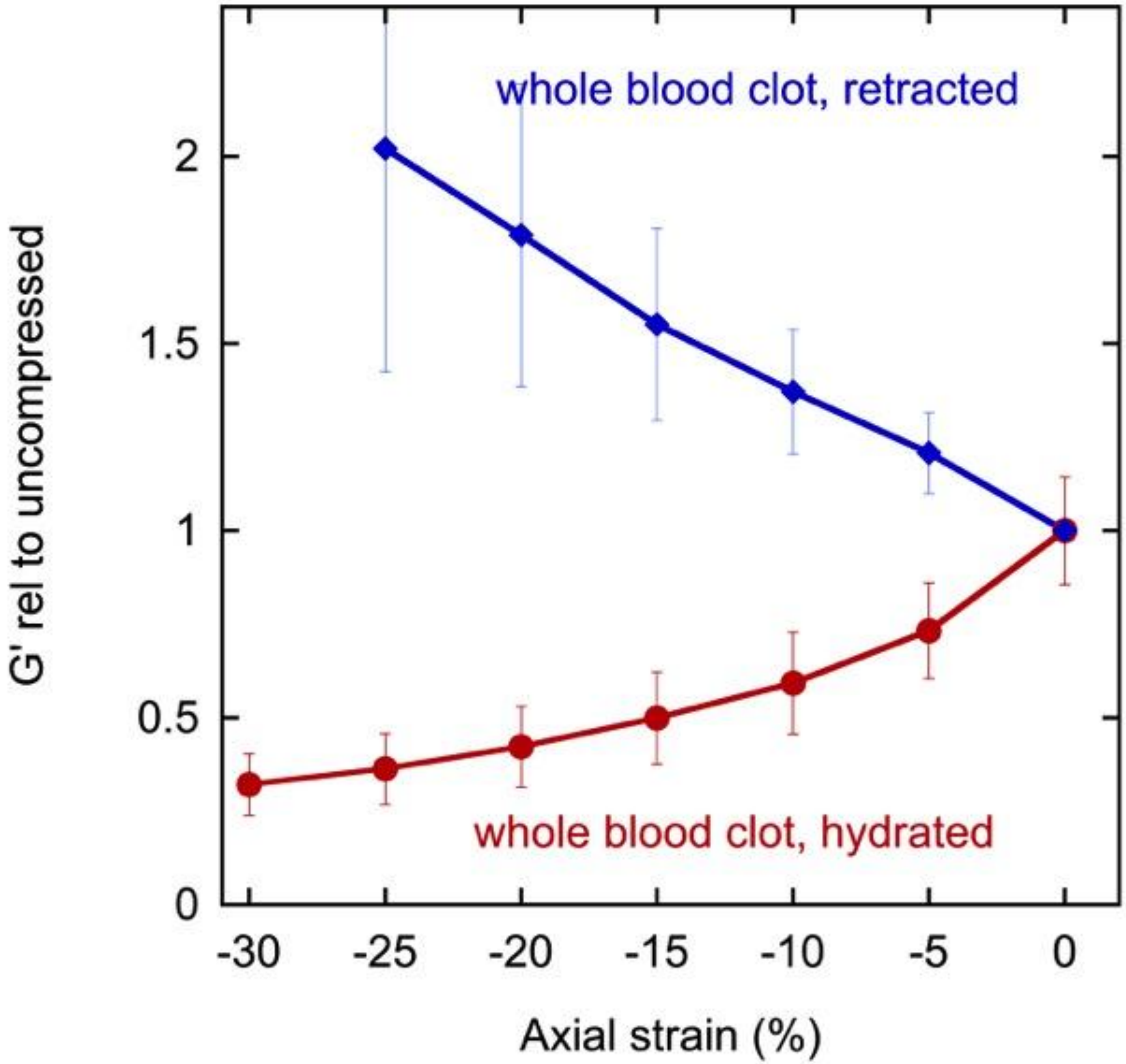
Whole blood clots stiffen in extension but not in compression



Rheology of blood clots is dominated by its fibrin network



When internal tensions drive excess liquid from blood clot, it switches from compression-softening to compression-stiffening



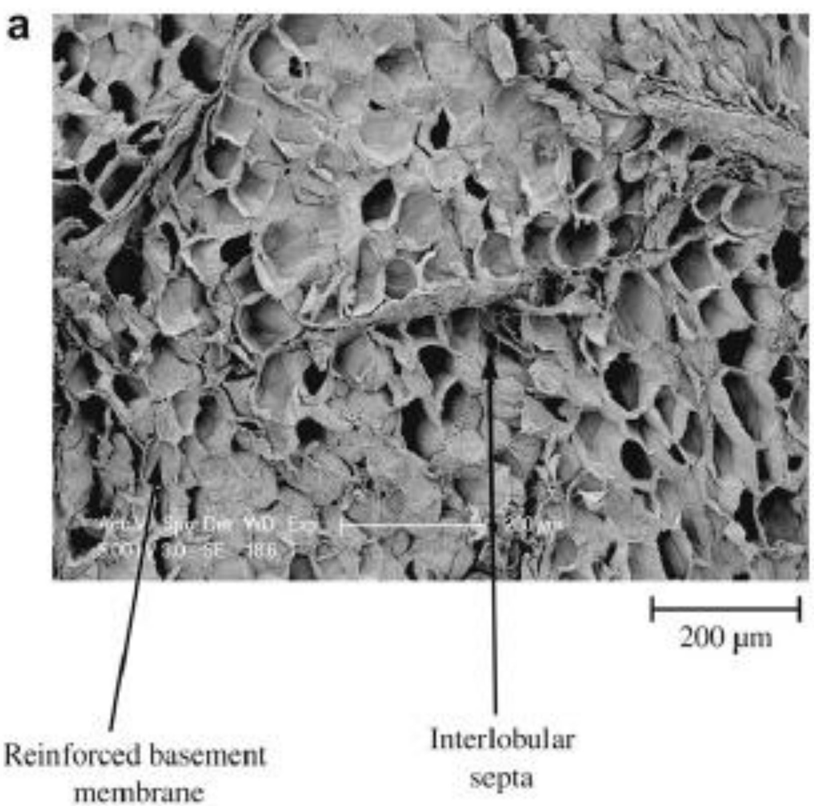
What kind of material stiffens under compression but softens under extension?

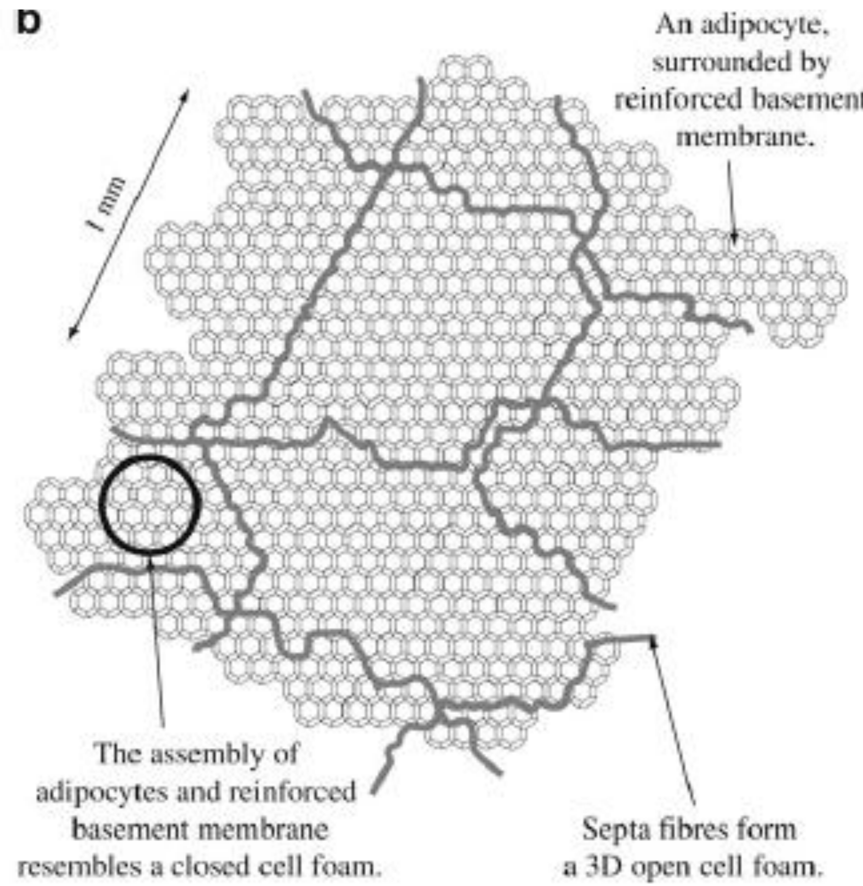
The compressive response of porcine adipose tissue from low to high strain rate

Kerstyn Comley, Norman Fleck*

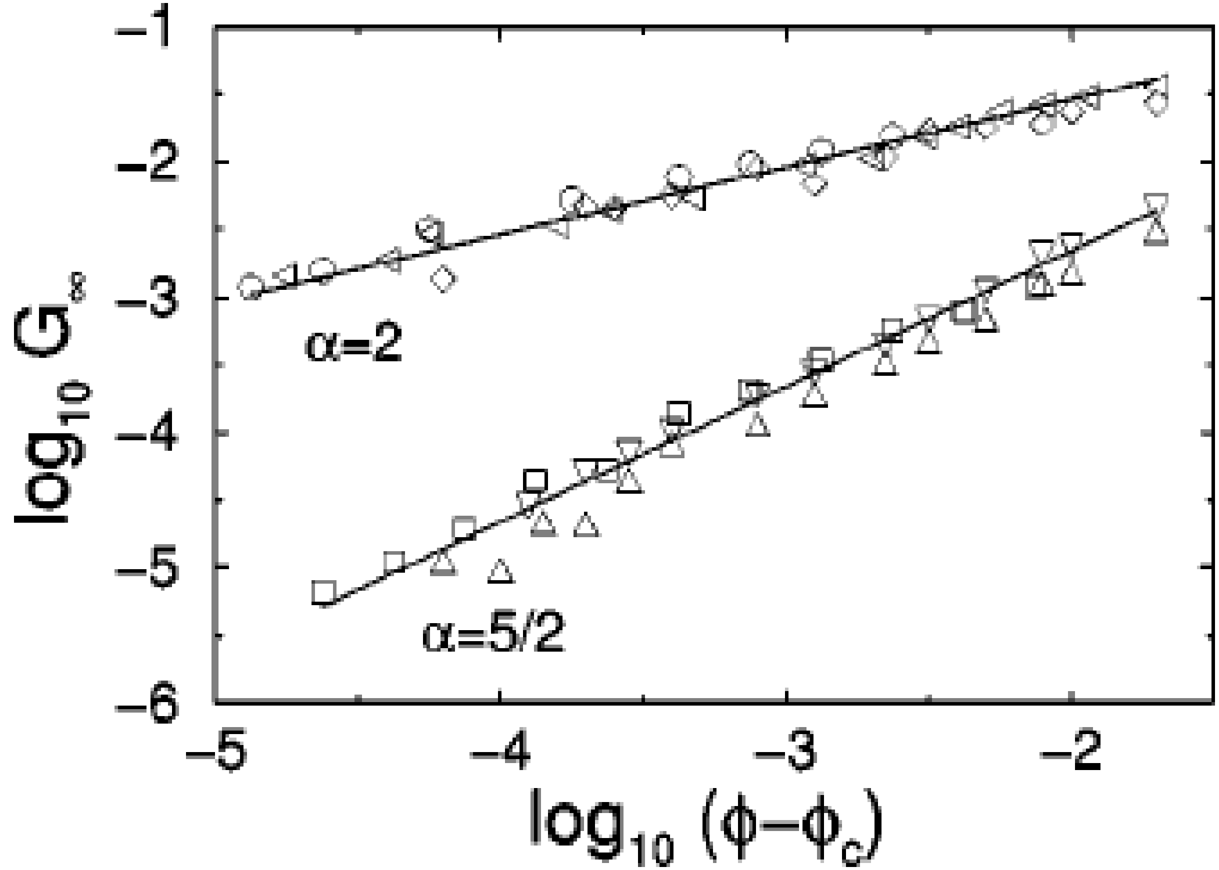
Cambridge University Engineering Department, Trumpington Street, Cambridge CB1 2PZ, UK

International Journal of Impact Engineering 46 (2012) 1e10





Do soft tissues act like colloidal systems close to jamming?



O'hern CS, Silbert LE, Liu AJ, Nagel SR (2003) Jamming at zero temperature and zero applied stress: The epitome of disorder. Physical Review E 68.

Conclusions

Semiflexible polymer networks exhibit shear-stiffening and negative normal stress

- enables cell contraction-generated stiffening
- Stiffen in extension, soften in compression

Soft tissues stiffen under compression, but soften in extension or shear

– no similarity with polymer networks
– possible relation to tumor pressure