Mechanics, Education and Research Universities: Perspectives for the 21st Century, Cambridge, Massachusetts, May 12, 2016

In celebration of the accomplishments and vision of Prof. C. Fong Shih on the occasion of his 70th birthday!

Applications of mechanics in biology: some perspectives at present and future

Huajian Gao (Brown University)

"If anyone ever asks me to look to the future, I always say I can't even understand the present."

- John W. Hutchinson

Traditional perception of mechanics vs biology

➢ Mechanics is quantitative

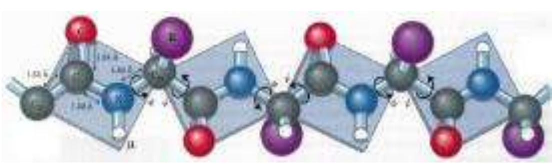
$$\boldsymbol{\varepsilon} = \frac{1}{2}\left(\mathrm{grad}^T\,\mathbf{u} + \mathrm{grad}\,\mathbf{u} - \mathrm{grad}^T\,\mathbf{u}\,\mathrm{grad}\,\mathbf{u}\right)$$

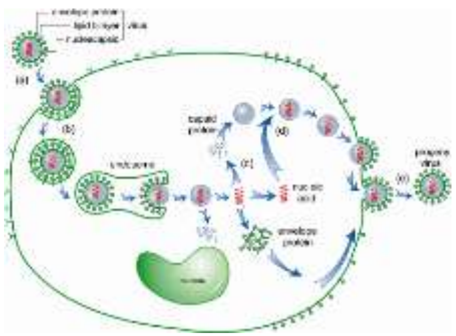
$$\mathbf{P} = J\boldsymbol{\sigma}\mathbf{F}^{-T}, \quad \mathbf{S} = \mathbf{F}^{-1}\mathbf{P} = J\mathbf{F}^{-1}\boldsymbol{\sigma}\mathbf{F}^{-T}, \quad \mathrm{div}\,\boldsymbol{\sigma} + \mathbf{b} = \rho\dot{\mathbf{v}}$$

$$\boldsymbol{\sigma} = \lambda(\nabla\cdot\mathbf{u})\mathbf{I} + \mu\left(\nabla\mathbf{u} + (\nabla\mathbf{u})^T\right)$$

$$\frac{\partial}{\partial t}(\rho\mathbf{u}) + \nabla\cdot(\rho\mathbf{u}\otimes\mathbf{u} + p\mathbf{I}) = \nabla\cdot\boldsymbol{\tau} + \rho\mathbf{g}$$

➢ Biology is often qualitative/descriptive





(Alberts et al., Molecular Biology of the Cell)

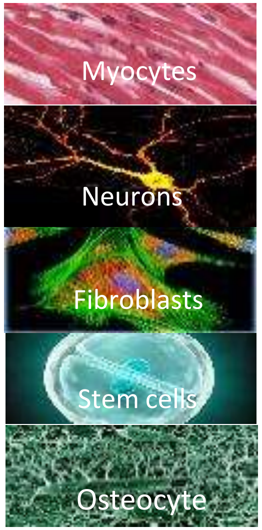


Image from the web

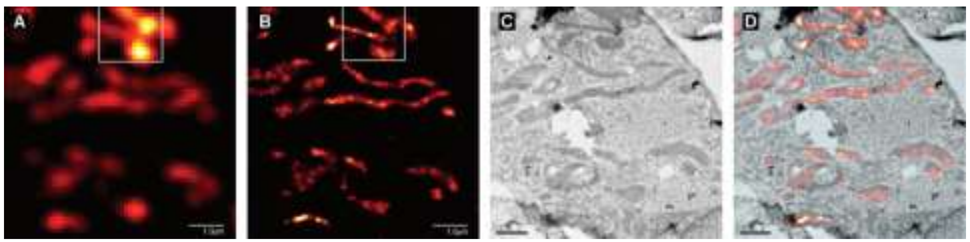
But, this is rapidly changing…

Breakthrough advances in bioimaging techniques

2014 Nobel Prize in Chemistry was awarded to Eric Betzig, W.E. Moerner and Stefan Hell for "the development of super-resolved fluorescence microscopy," which brings "optical microscopy into the nanodimension."

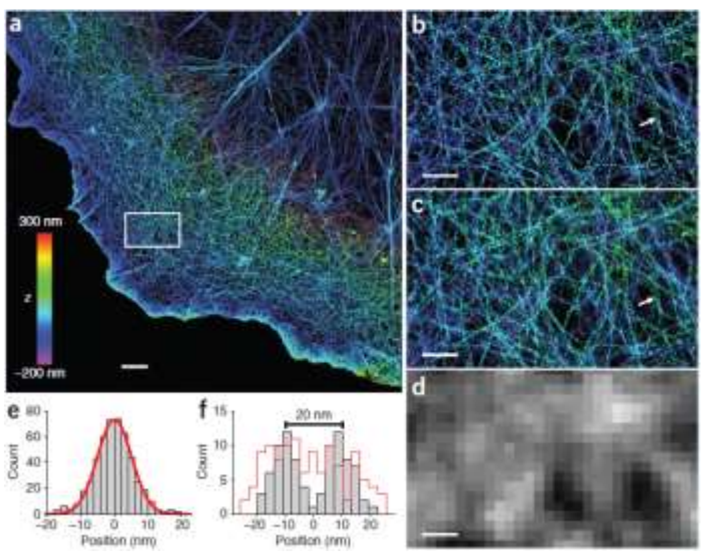
Photo activated localization microscopy (PALM)

TIRF PALM TEM PALM/TEM



(E. Betzig et al., Science, 2006)

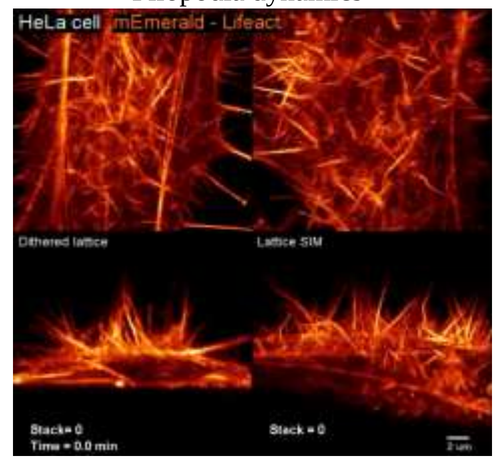
Stochastic optical reconstruction microscopy (STORM)



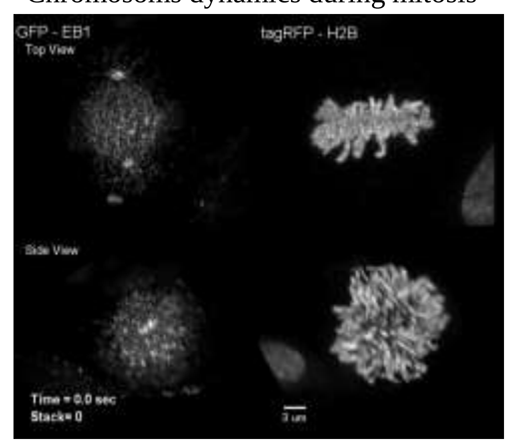
(X. Zhuang et al., Nature Methods, 2012)

Lattice light-sheet microscopy

Filopodia dynamics



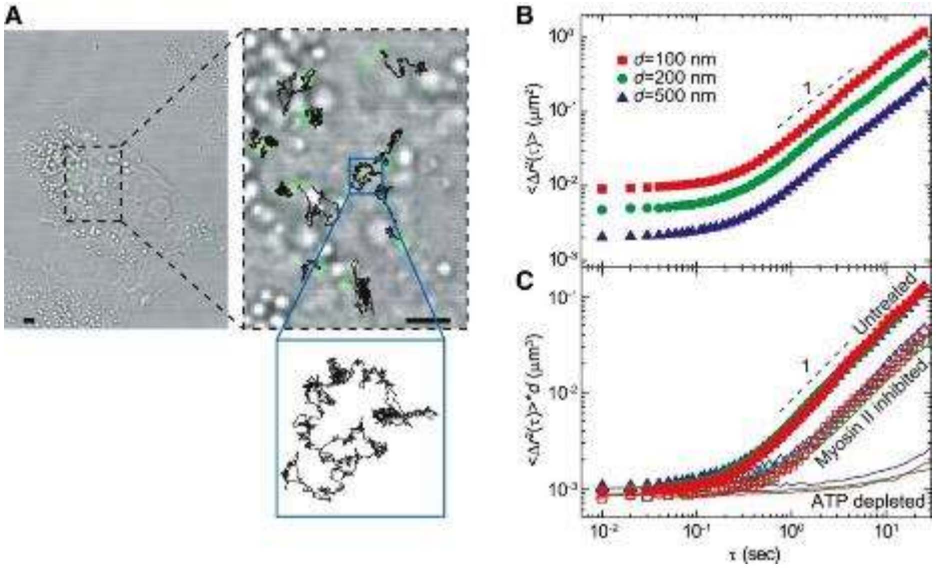
Chromosoms dynamics during mitosis



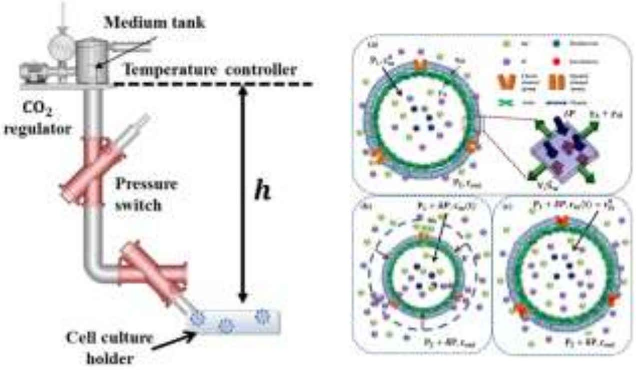
(E. Betzig et al., Science, 2014)

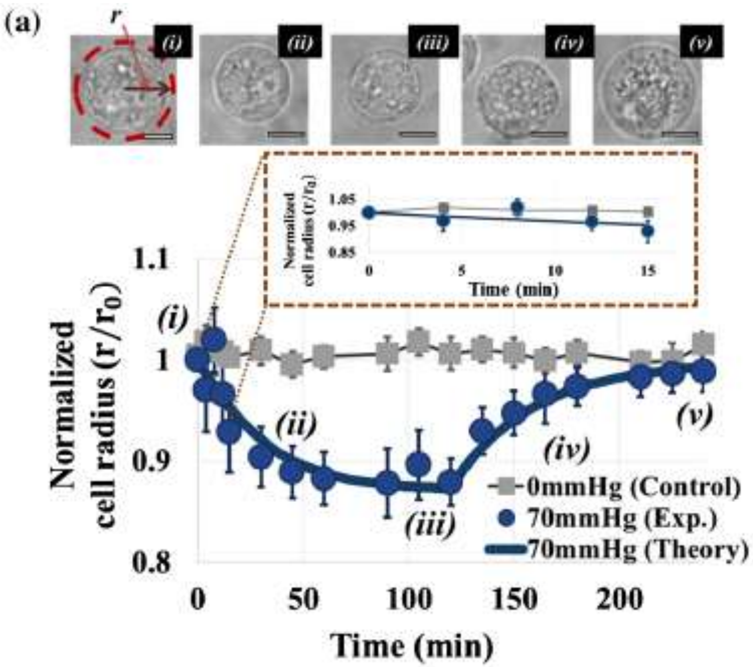
New experimental capabilities enable "quantitative probing" of biological systems and revealing new phenomena!

Movements of Microinjected Tracer Particles in Living Cells

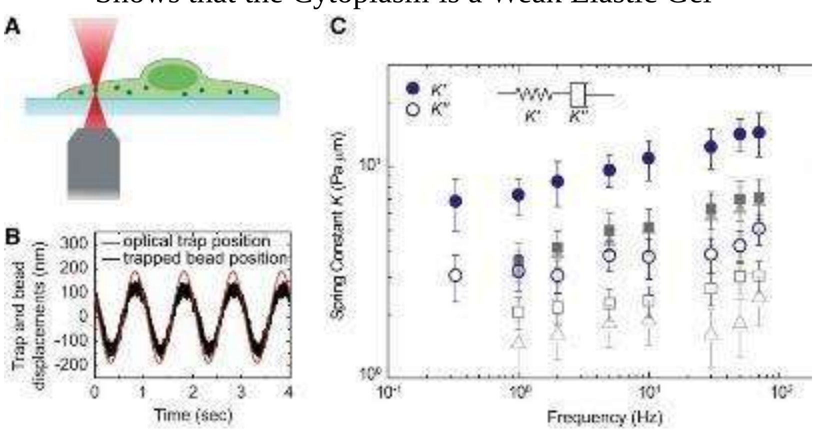


Volumetric response of cells to pressure changes





Optical-Tweezer Active Microrheology Measurement Shows that the Cytoplasm is a Weak Elastic Gel



(D. A. Weitz, et al., Cell, 2014)

(Hui et al., PRL, 113, 118101. 2014)

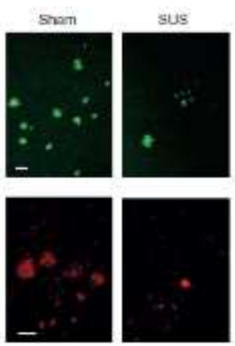
And even mechanistic approach to treating disease…

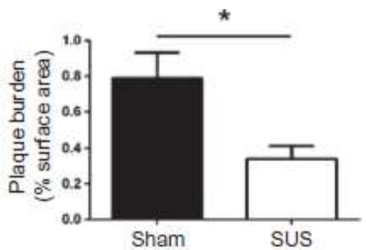
ALZHEIMER'S DISEASE

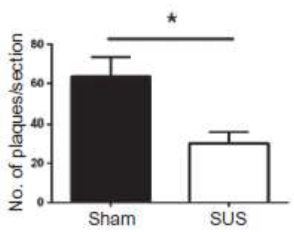
Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer's disease mouse model

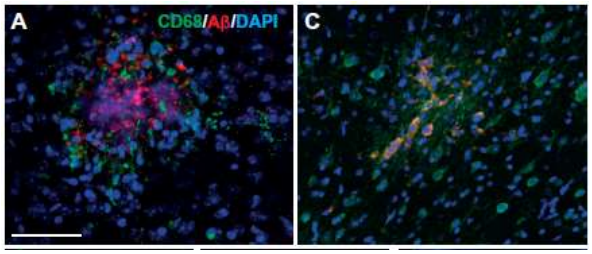
Gerhard Leinenga and Jürgen Götz* (*Science Translational Medicine*, Vol. 7, 278ra33, 2015)

Amyloid-β (Aβ) peptide has been implicated in the pathogenesis of Alzheimer's disease (AD). We present a nonpharmacological approach for removing Aβ and restoring memory function in a mouse model of AD in which Aβ is deposited in the brain. We used repeated scanning ultrasound (SUS) treatments of the mouse brain to remove Aβ, without the need for any additional therapeutic agent such as anti-Aβ antibody. Spinning disk confocal microscopy and high-resolution three-dimensional reconstruction revealed extensive internalization of Aβ into the lysosomes of activated microglia in mouse brains subjected to SUS, with no concomitant increase observed in the number of microglia. Plaque burden was reduced in SUS-treated AD mice compared to sham-treated animals, and cleared plaques were observed in 75% of SUS-treated mice. Treated AD mice also displayed improved performance on three memory tasks: the Y-maze, the novel object recognition test, and the active place avoidance task. Our findings suggest that repeated SUS is useful for removing Aβ in the mouse brain without causing overt damage, and should be explored further as a noninvasive method with therapeutic potential in AD.



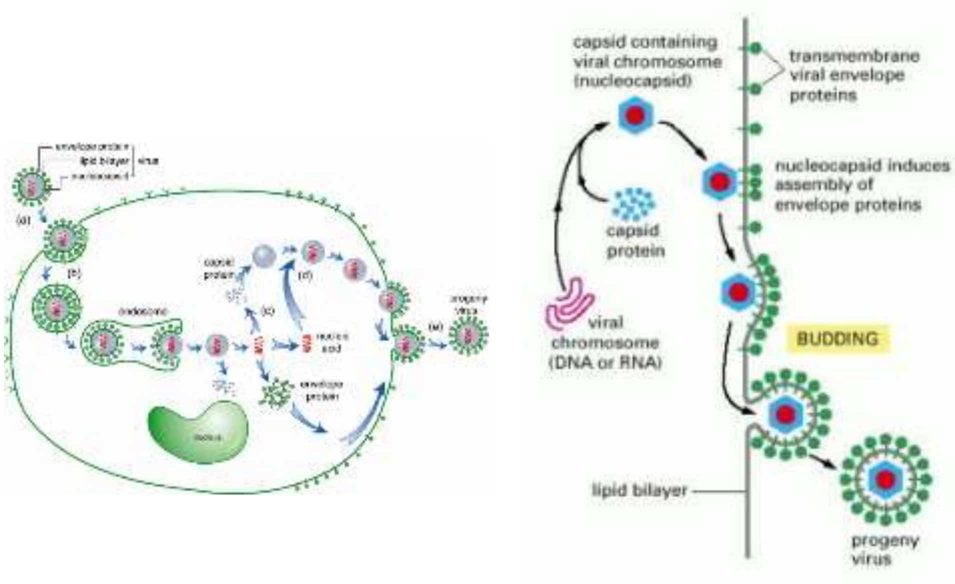




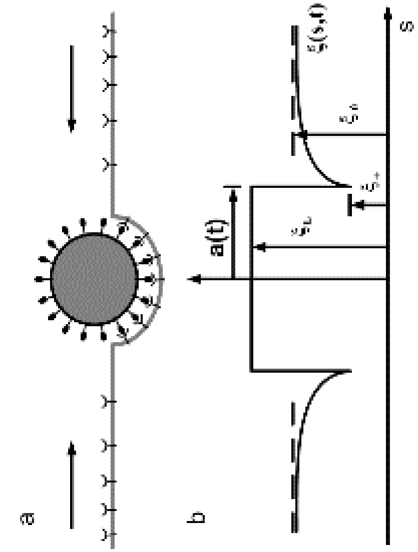


Ultrasound was shown to (1) reduce Aβ and amyloid plaque load in plaque-forming APP23 transgenic mice; (2) induce microglial activation; (3) activate uptake of Aβ into microglial lysosomes and clearance of plaques; (4) restore memory functions in Alzerimer mice

Mechanics of receptor-mediated cell uptake of viruses and NPs



(Alberts et al., Molecular Biology of the Cell)



(Gao et al., PNAS, **102**, 9469-9474, 2005)

Life cycle of virus:

- Binding with receptors on host cell
- Entry into host cytoplasm
- Biosynthesis of viral components
- Assembly of viral components
- Budding out of host cell

Applications:

- NP-based nanomedicine
- Gene and drug delivery systems
- Inter- and intracellular transport
- Health effects of NPs in polluted air
- NP-based bio-imaging (quantum dots)

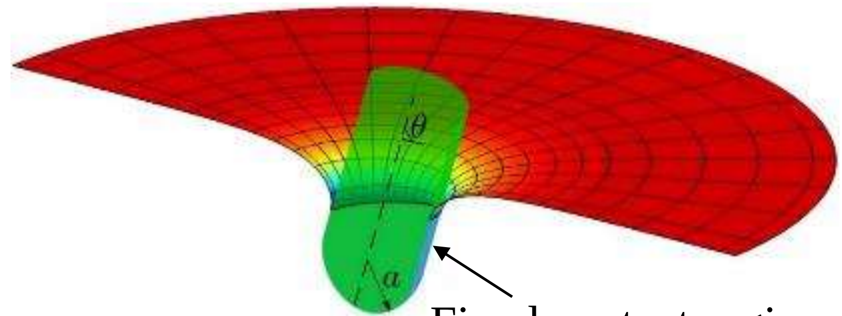
Cell uptake of nanoparticles is similar to that of viruses. While the process is qualitatively known for decades, the need for a quantitative theory arose with the development of nanotechnology and nanomedicine

Cell entry of 1D nanomaterials: theory

(Yi, Shi and Gao, *Nano Letters*, Vol. 14, 1049−1055, 2014)

$$E_{tot}(\theta) = \int 2\kappa H^2 dA + \sigma \Delta A$$

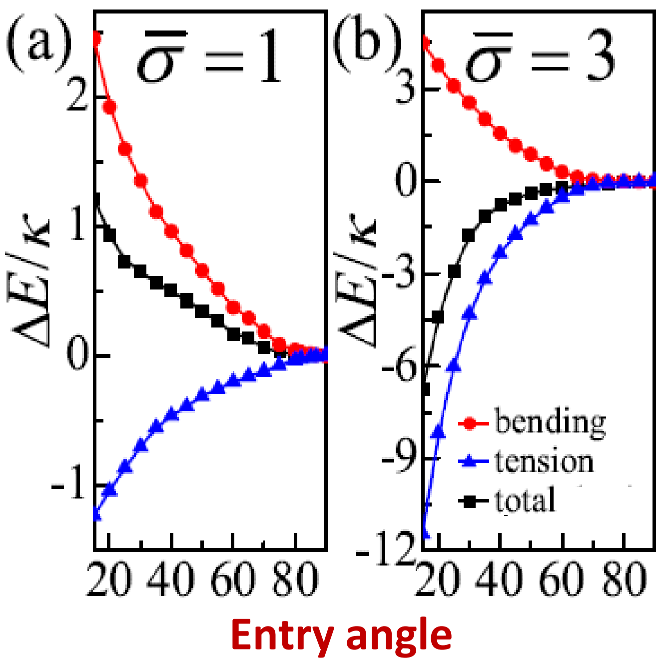
membrane bending — membrane tension

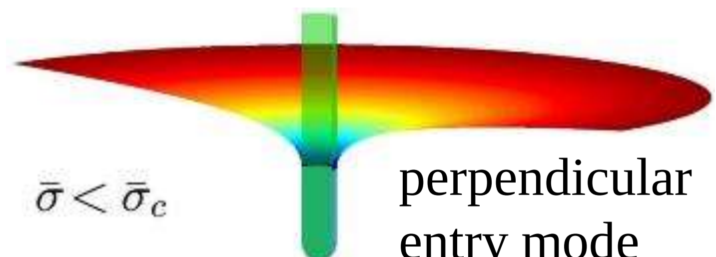


Fixed contact region A_c

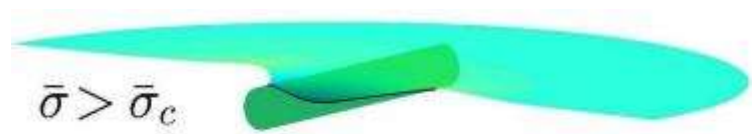
Dimensionless parameters: $\bar{\sigma} \equiv 2\sigma a^2 / \kappa$

$\bar{\sigma}_c \equiv 2\pi / 5$ (~1.26)





perpendicular entry mode



parallel adhering mode

Fundamental modes of cell entry

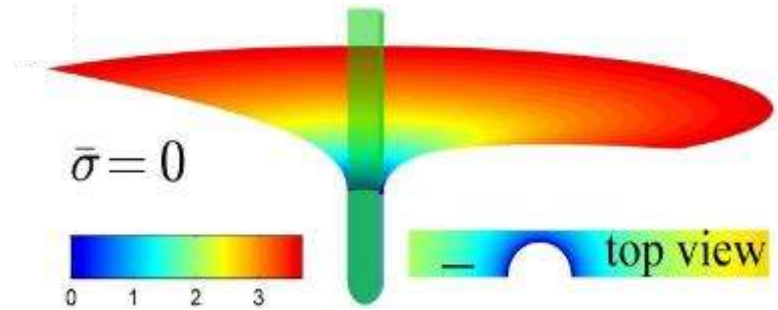
Perpendicular mode: $\bar{\sigma} < \bar{\sigma}_c$

Bending energy dominates

$$E_{bend} = \int 2\kappa H^2 dA$$

$$\left(E_{bend}\right)_{\min} = 0 \quad \Rightarrow \quad H = 0$$

Catenoid



$$x^2 + y^2 = a^2 \cosh^2(z/a)$$

$$\kappa_{1,2} = \pm a^{-1} \mathrm{sech}^2(z/a)$$

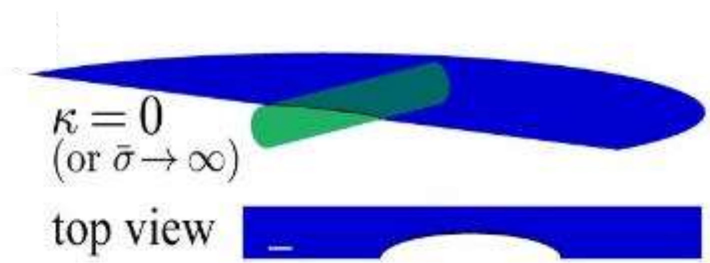
Horizontal mode: $\bar{\sigma} > \bar{\sigma}_c$

Tension energy dominates

$$E_{tension} = \sigma \Delta A$$

$$\Delta A = A_c - \pi a^2 / \sin\theta$$

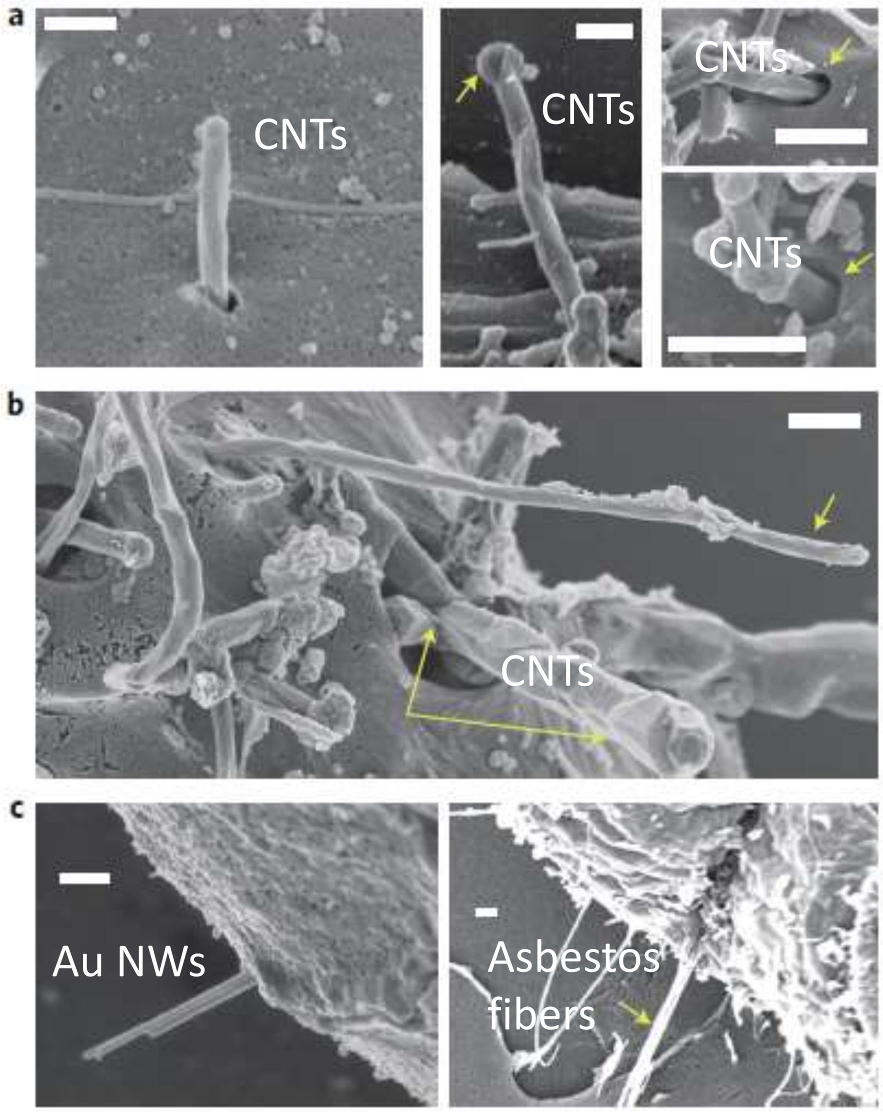
$$\left(E_{tension}\right)_{\min} \Rightarrow \theta \to 0$$



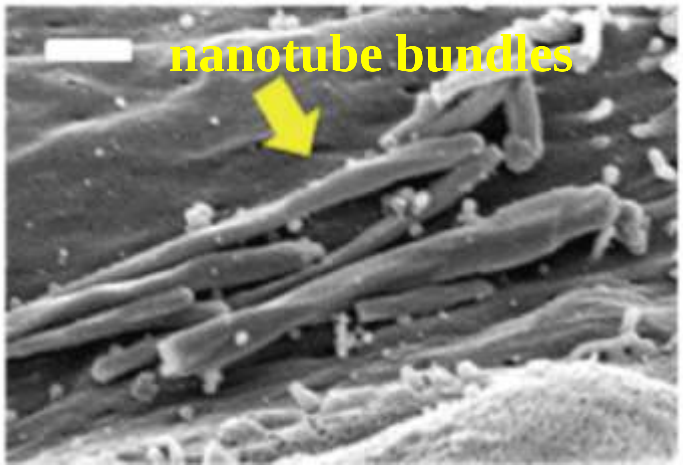
(Yi et al., *Nano Letters*, **14**, 1049−1055, 2014)

Cell entry of 1D nanomaterials: experiment

$$a < a_c = \sqrt{5\sigma/\pi\kappa}$$



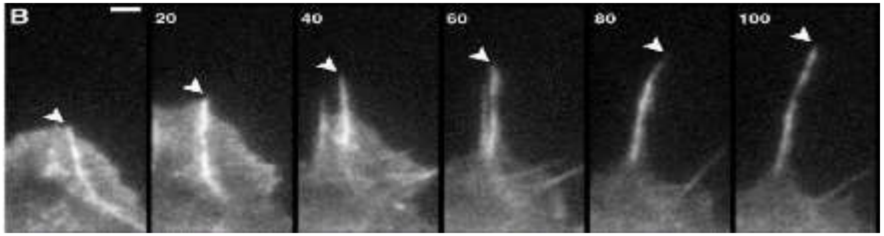
$$a_{eff} > a_c$$



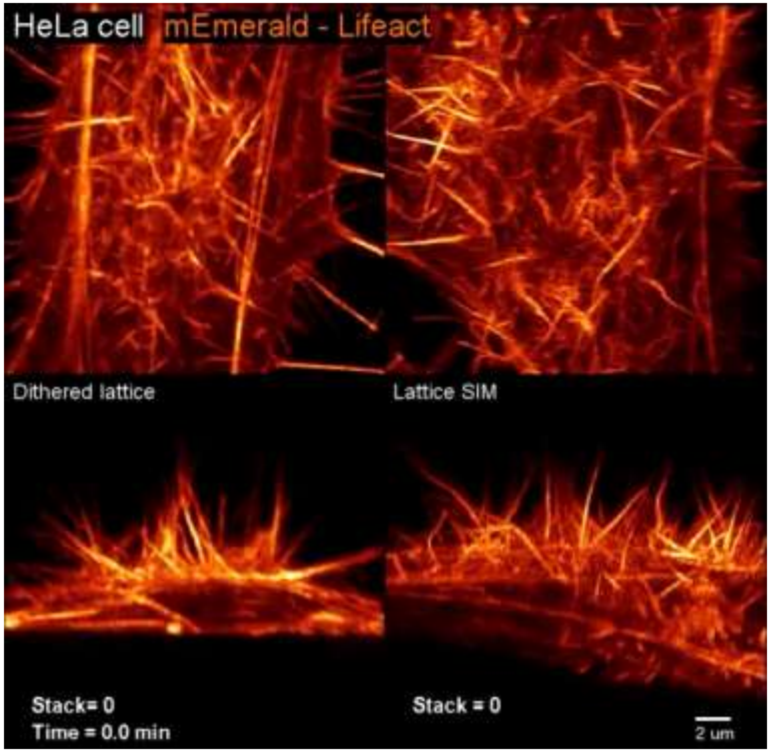
- **1D nanomaterials (e.g. CNTs, NWs, Asbestos nanofibers) enter cells via the tip first, perpendicular entry mode.**
- **Fiber bundles adopt the horizontal mode of interaction.**

(Shi, von dem Bussche, Hurt, Kane, Gao, Nature Nanotech, 2011)

Filopodia dynamics in living cells: mechanical instability



T.M. Svitkina *et al*., J. Cell Biol. 160, 409 (2003)



(Eric Betzig lab, Howard Hughes Med Inst, Science, 2014)

Our theory indicates that 1D protruding nanostructures on cells become unstable at the critical condition:

$$\bar{\sigma} = 2\sigma a^2 / \kappa = 2\pi / 5$$

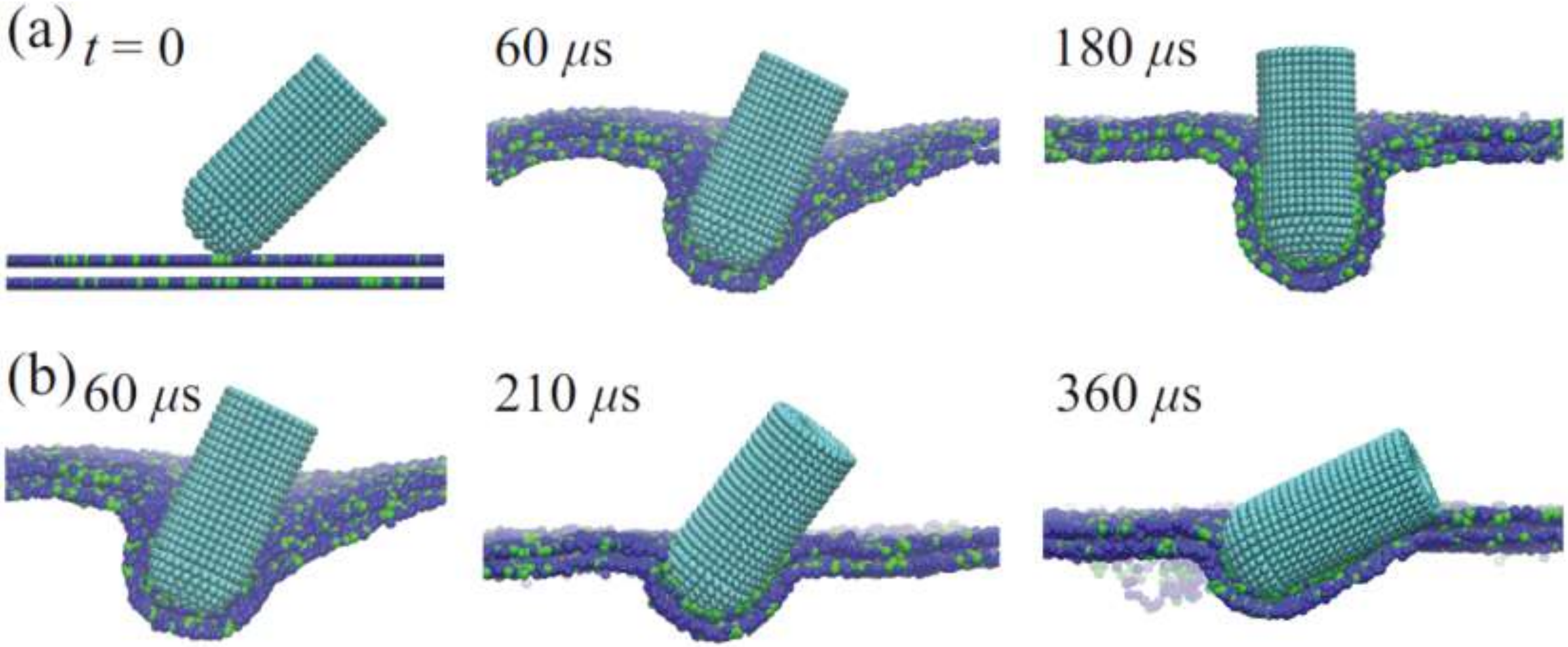
or

$$a_c = \sqrt{\frac{5\sigma}{\pi\kappa}} = 40 - 150 \ \ nm$$

Filopodia form and grow by merging of microtubules. Our theory show they are governed by an intrinsic instability controlled by a competition between membrane bending and tension energies

MD simulations of cell entry mode transition

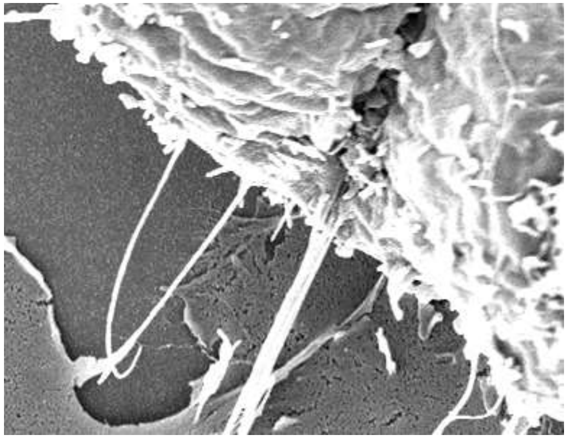
N-varied DPD method



$(a)\ \bar{\sigma} = 0.3436 < \bar{\sigma}_c$ $\qquad$ $(b)\ \bar{\sigma} = 7.4 > \bar{\sigma}_c$

(Yi, Shi and Gao, *Nano Letters*, Vol. 14, 1049−1055, 2014)

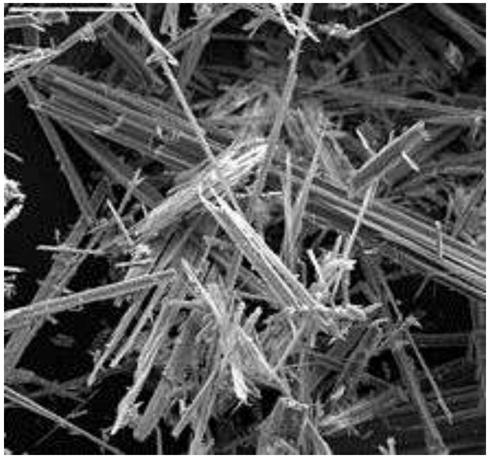
Mechanistic origin of frustrated endo- and phagocytosis



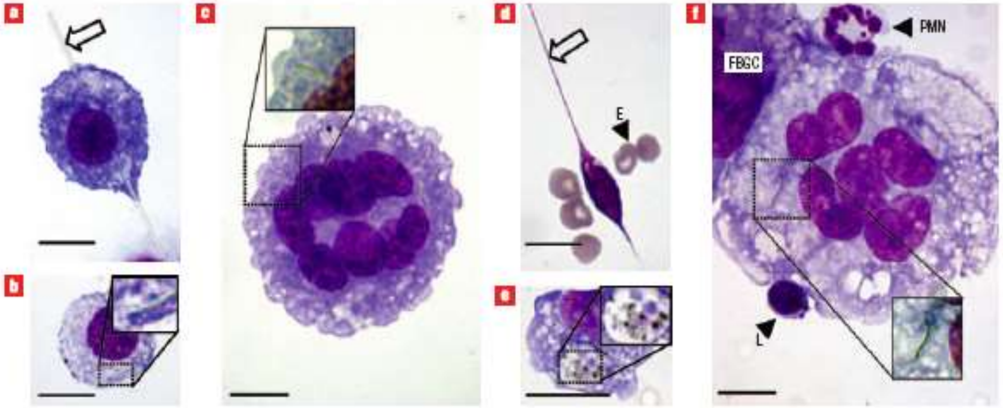
(Shi et al., Nature Nanotech, 2011)

$$a < \sqrt{5\sigma/\pi\kappa}$$

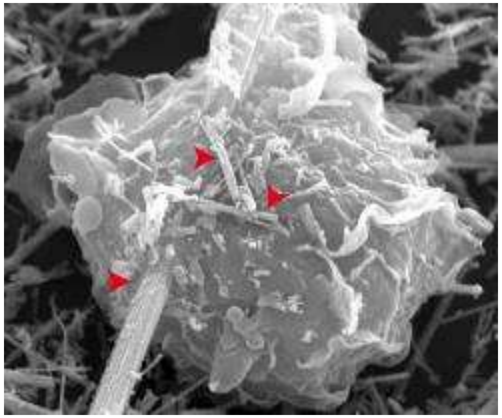
$$\approx 40-150 \;\; nm$$



Asbestos nanofibers

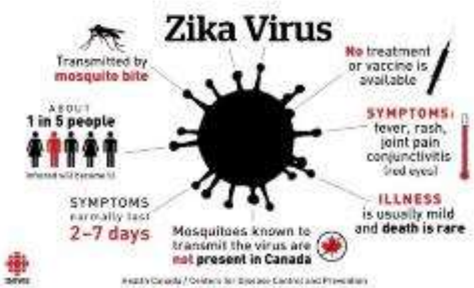


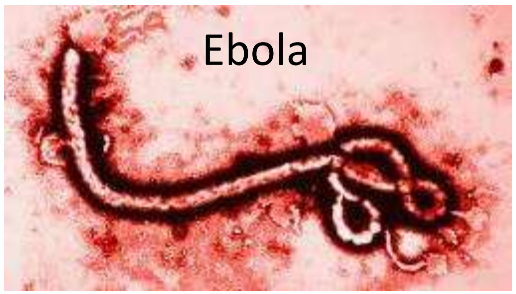
Poland et al., 2008, Nature Nanotech, 423-428.

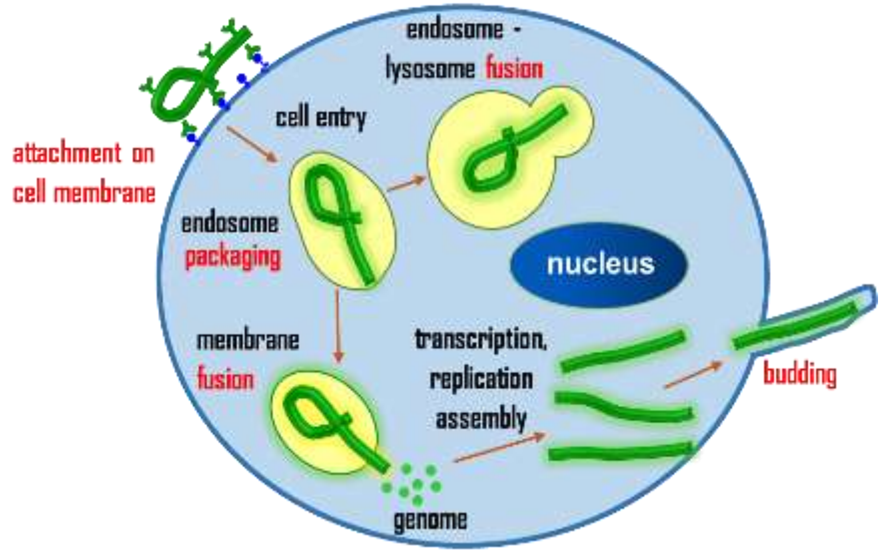


Asbestos fibers induce lung cancer

Broad society concerns…

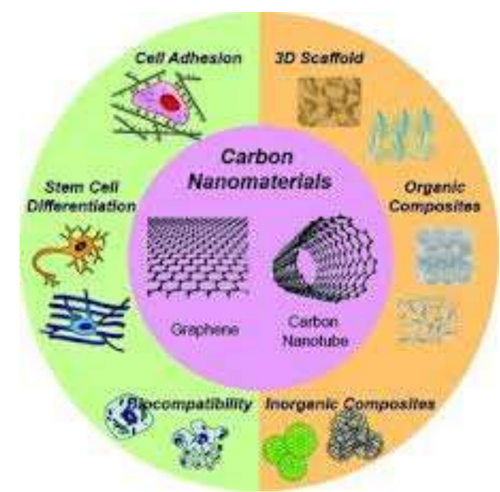






Images from the web

Environmental impact of nanomaterials



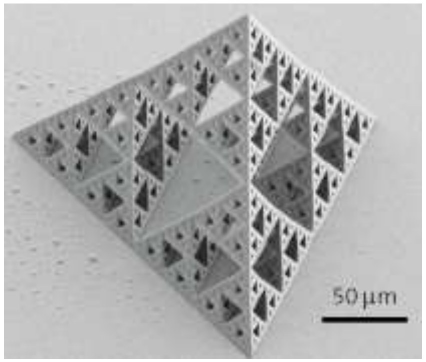
- As of 2013, carbon nanotube production exceeded **several thousand tons per year**, with applications in energy storage, automotive parts, boat hulls, sporting goods, water filters, thin-film electronics, coatings, actuators and electromagnetic shields [1].
- Global production of graphene was around **15 tons** in 2009 [2] but now stands at around **150 tons** in 2014 [3].

[1] De Volder et al., Science, 339: 535–539. 2013. doi:10.1126/science.1222453.
[2] Segal, Nature Nanotechnology, 4, 612-614, 2009, doi:10.1038/nnano.2009.279
[3] http://www.telegraph.co.uk/finance/businessclub/10936423/Graphene-maker-aims-to-build-British-billion-pound-venture.html

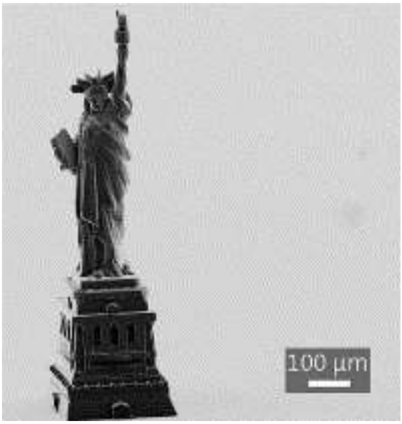
Biology could also influence engineering:

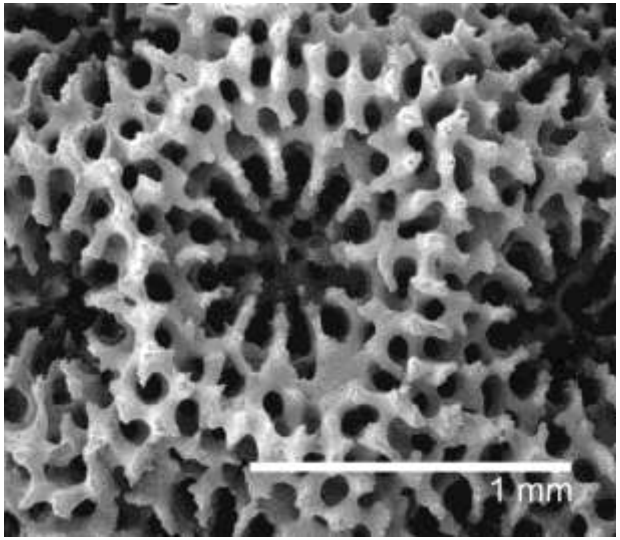
Bio-inspired materials design through additive manufacturing

Biomimetic and biological materials through 3D printing



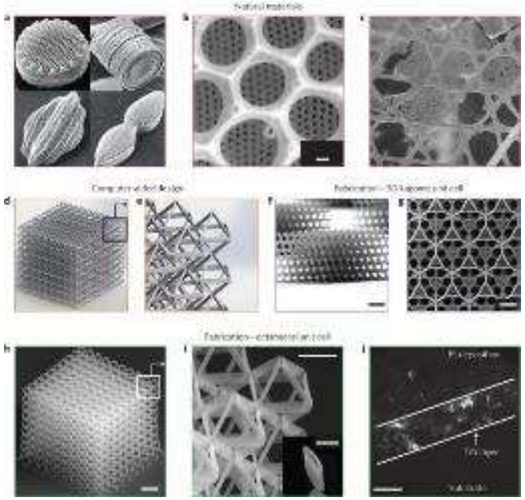
Eiffel Tower



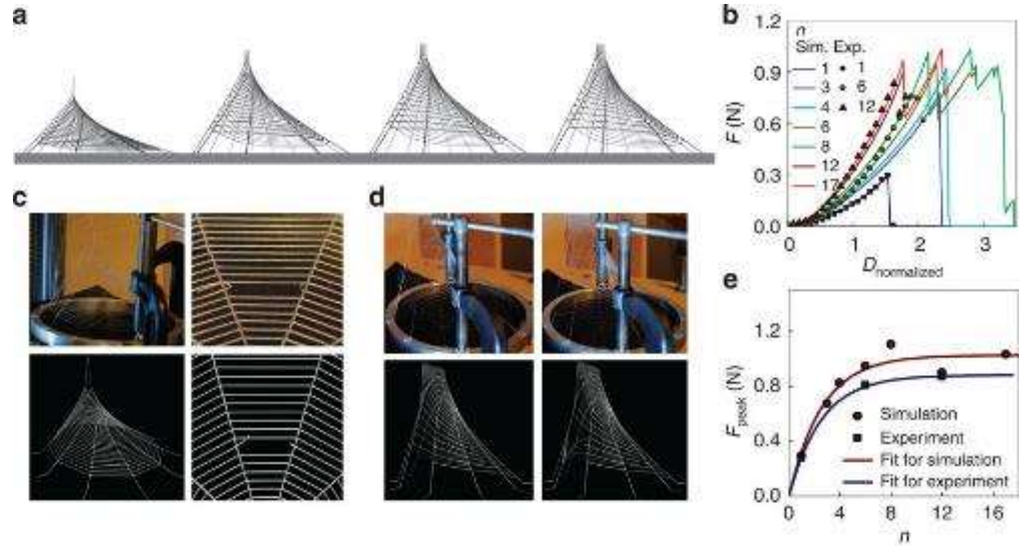


(Images from the web)

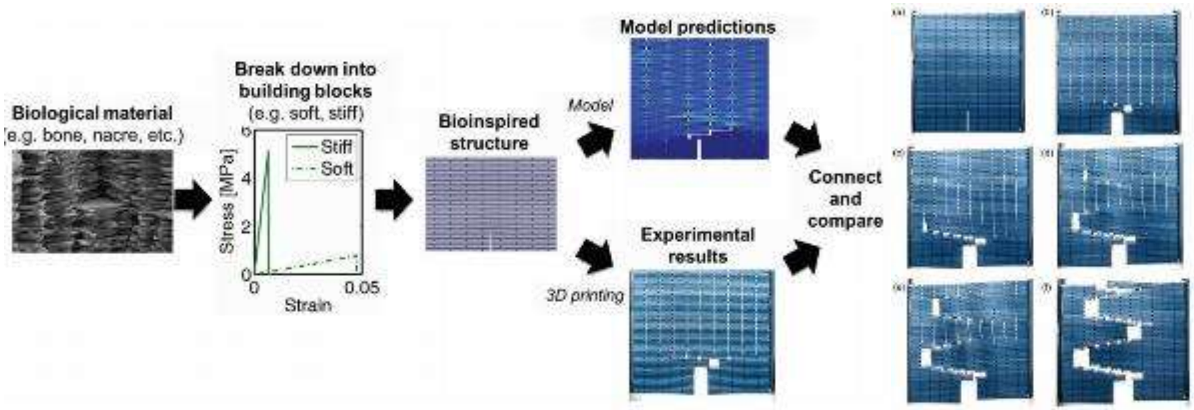
Biomimetic materials through 3D printing

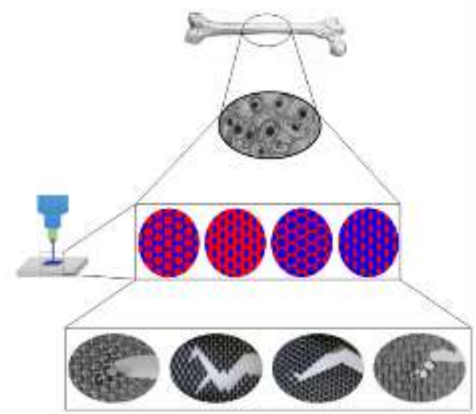


(Julia Greer, et al. *Nature Materials*, 2013)



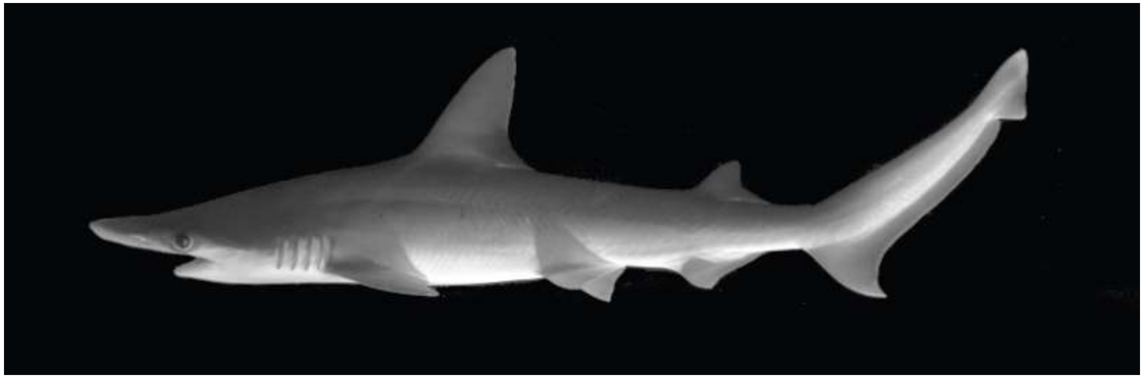
Jennifer Lewis, et al. *Nature Comm*, 2015).

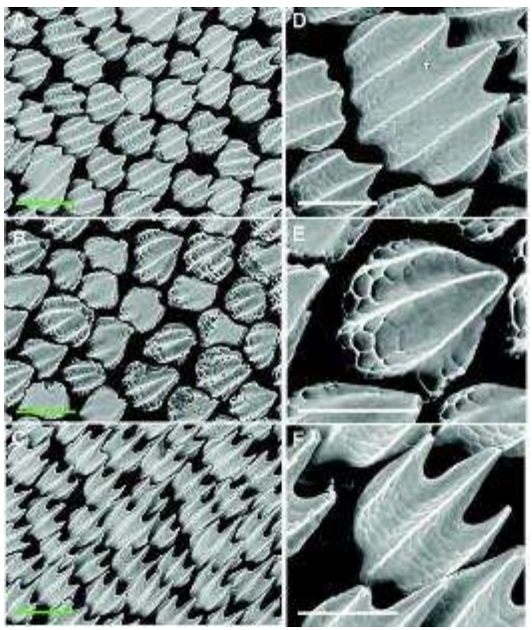


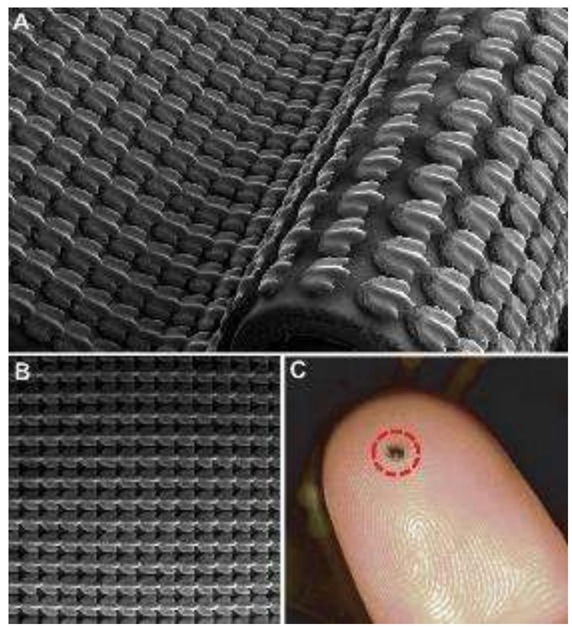


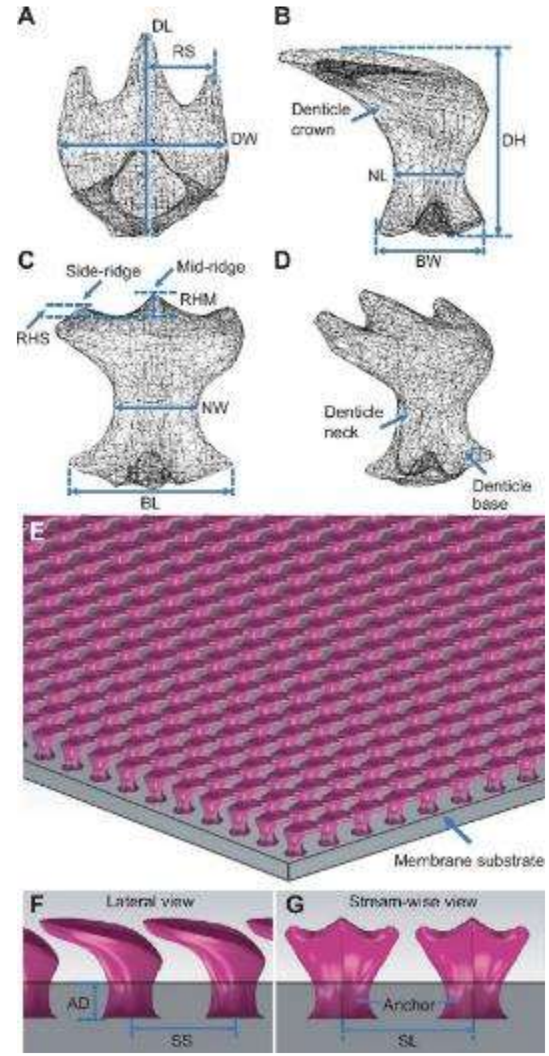
Markus Buehler, et al, *Advanced Functional Materials* (2013, 2016)

Shark mimic skin for drag reduction







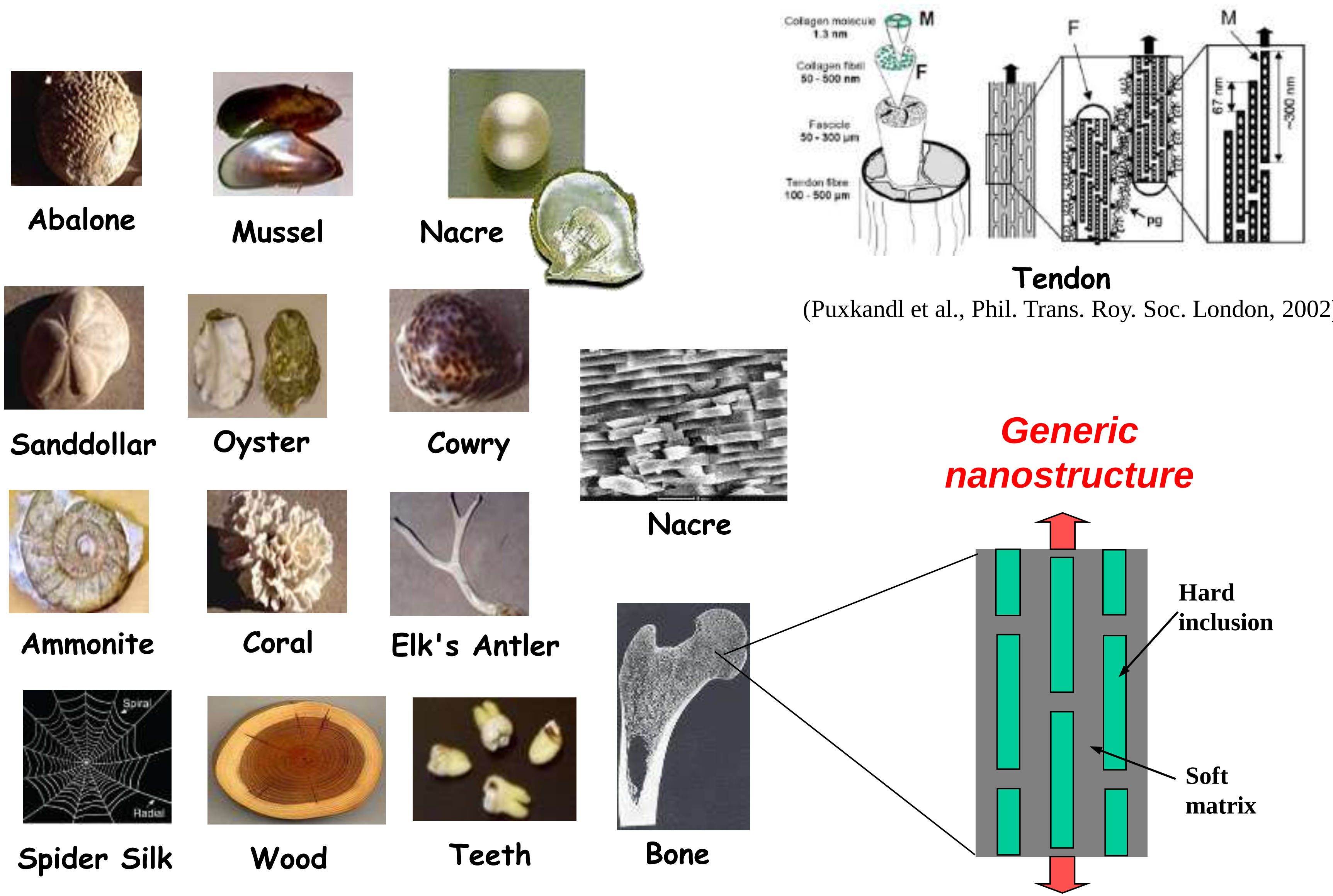


Wen, Li, James C. Weaver, and George V. Lauder. "Biomimetic shark skin: design, fabrication and hydrodynamic function." *Journal of Experimental Biology* 217, no. 10 (2014): 1656-1666.

What are Nature's principles of constructing tough materials?

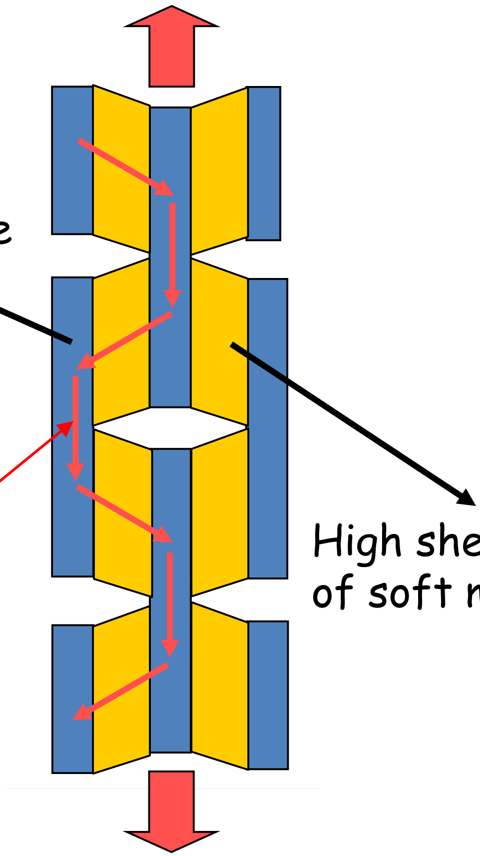
1. Soft material strategy
2. Hard material strategy

Convergent evolution in load-bearing biological materials



Soft material strategy: staggered tension-shear structure

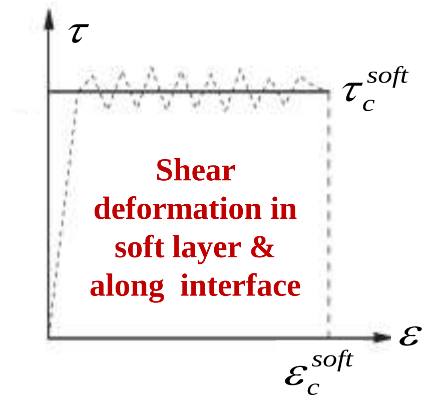
(Gao et al., PNAS, **100,** 5597–5600, 2003; Zhang et al., Proc. Roy. Soc. B, 278, 519-525, 2010)



Elastic modulus

$$\frac{1}{E} = \frac{4(1-\Phi)}{G_{soft}\Phi^2\rho^2} + \frac{1}{\Phi E_{hard}}$$

Plastic dissipation



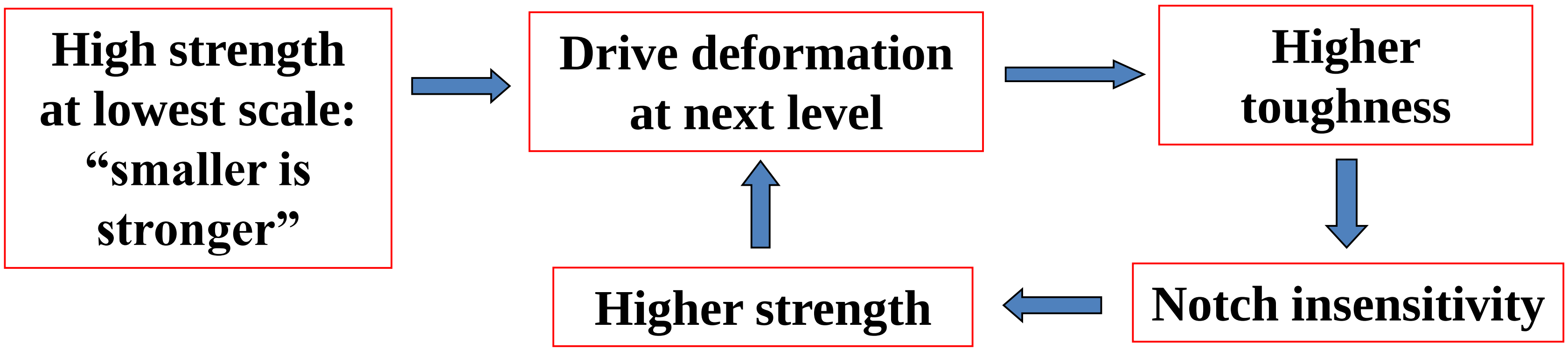
$$\sigma_c^{hard} \geq 2\sqrt{\frac{2(1-\Phi)E_{hard}}{\Phi}\left(\tau_c^{soft}\varepsilon_c^{soft}\right)}$$

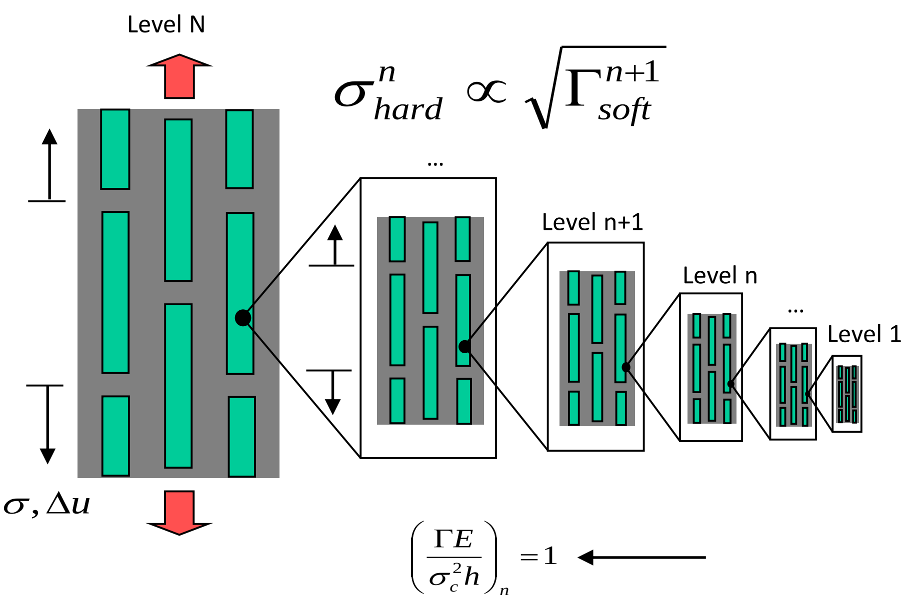
Dissipated Energy/volume

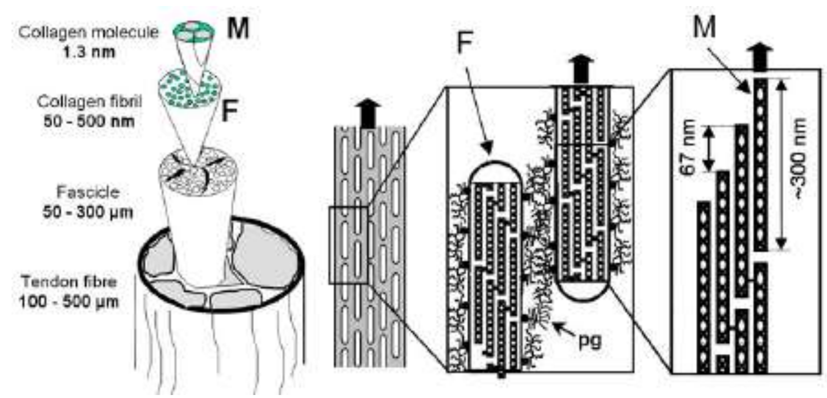
- **Strength and toughness of material go hand-in-hand (no trade-off!)**
- **Hard particles sustain large tensile load, while soft material dissipates energy through shear (i.e. a soft material toughening strategy)**

Mechanical principle of structure hierarchy

(Gao, IJF, 2006; Zhang et al., Proc. Roy. Soc. B, 2010)



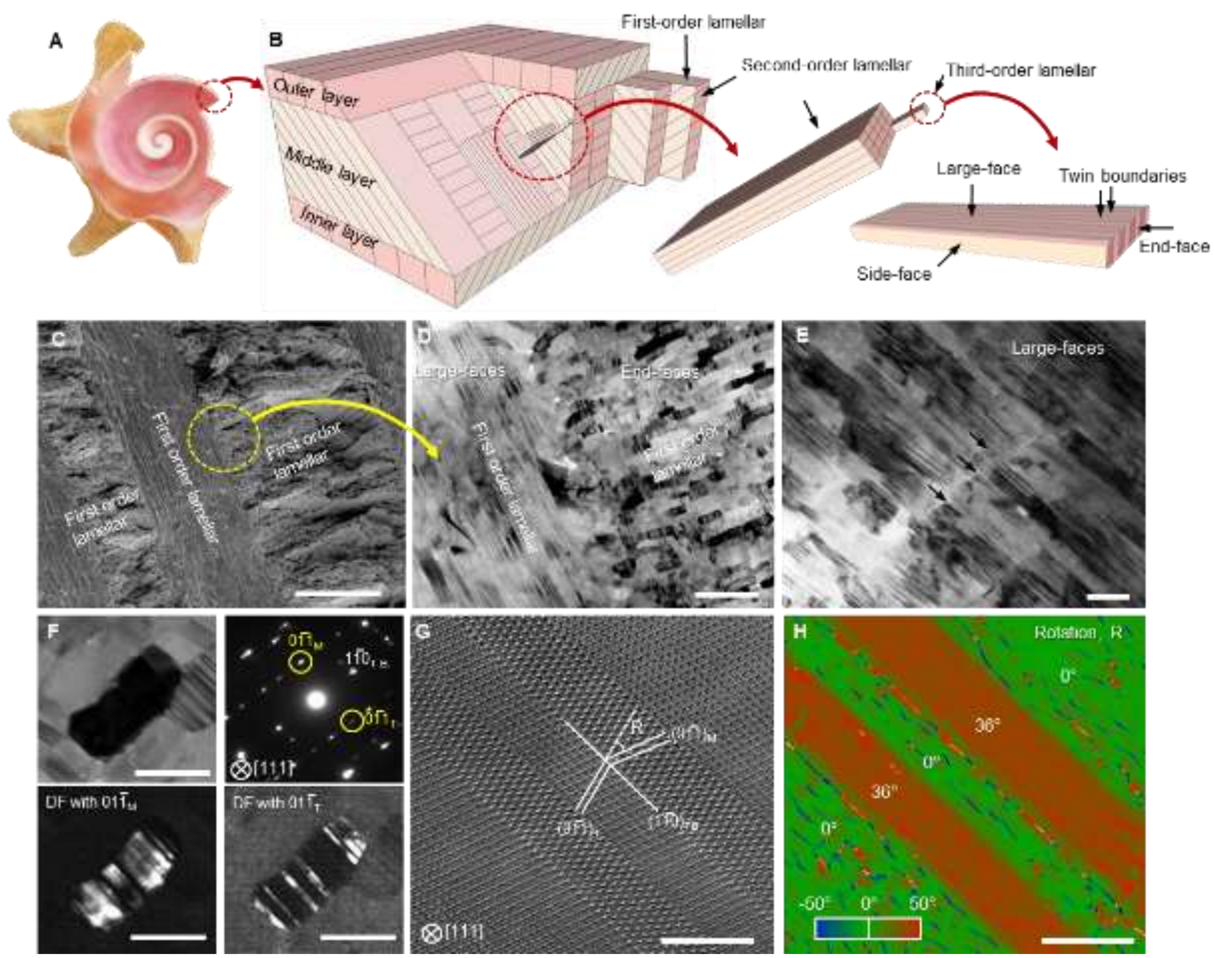


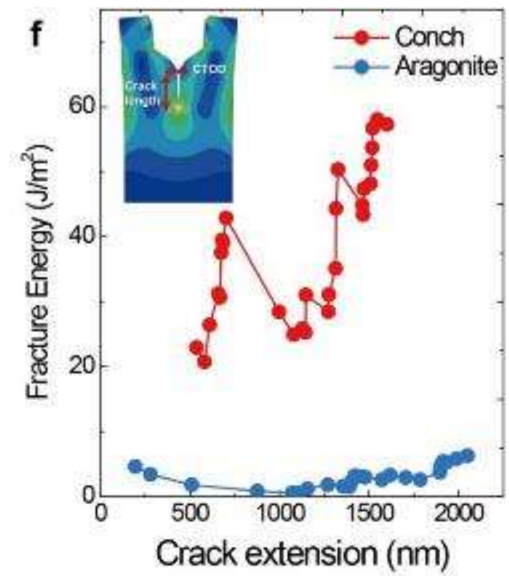


(Puxkandl et al., Phil. Trans. Roy. Soc. London, 2002)

- **Strength-toughness trade-off addressed by hierarchy**
- **Bottom level structure plays the key role**

Hard material strategy: nanotwinning

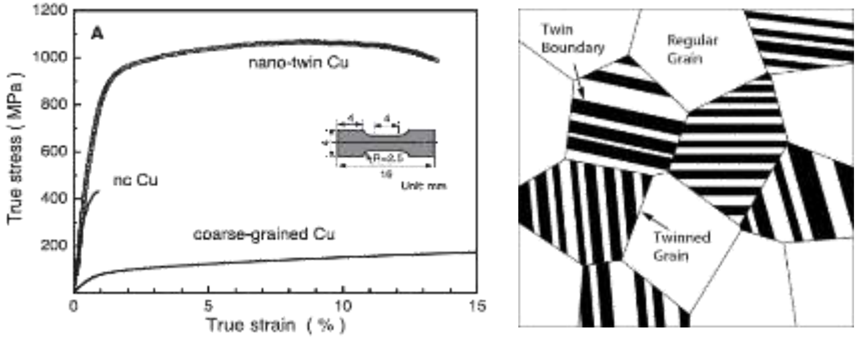




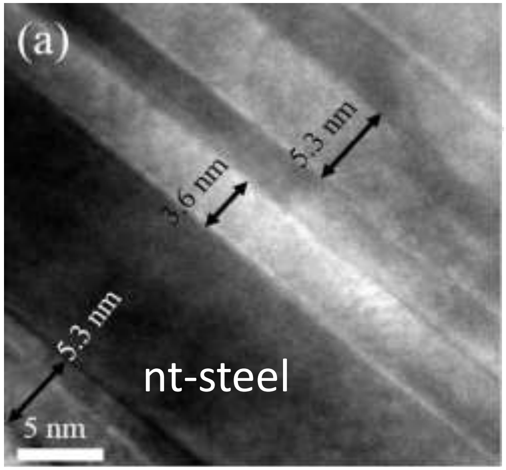
Nanotwinning enhances the fracture energy of aragonite by an order of magnitude

(Shin et al., *Nature Comm.*, **7**, 10772, 2016)

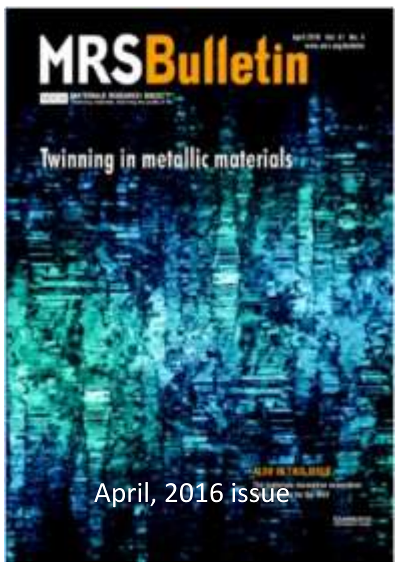
Nanotwinned metals

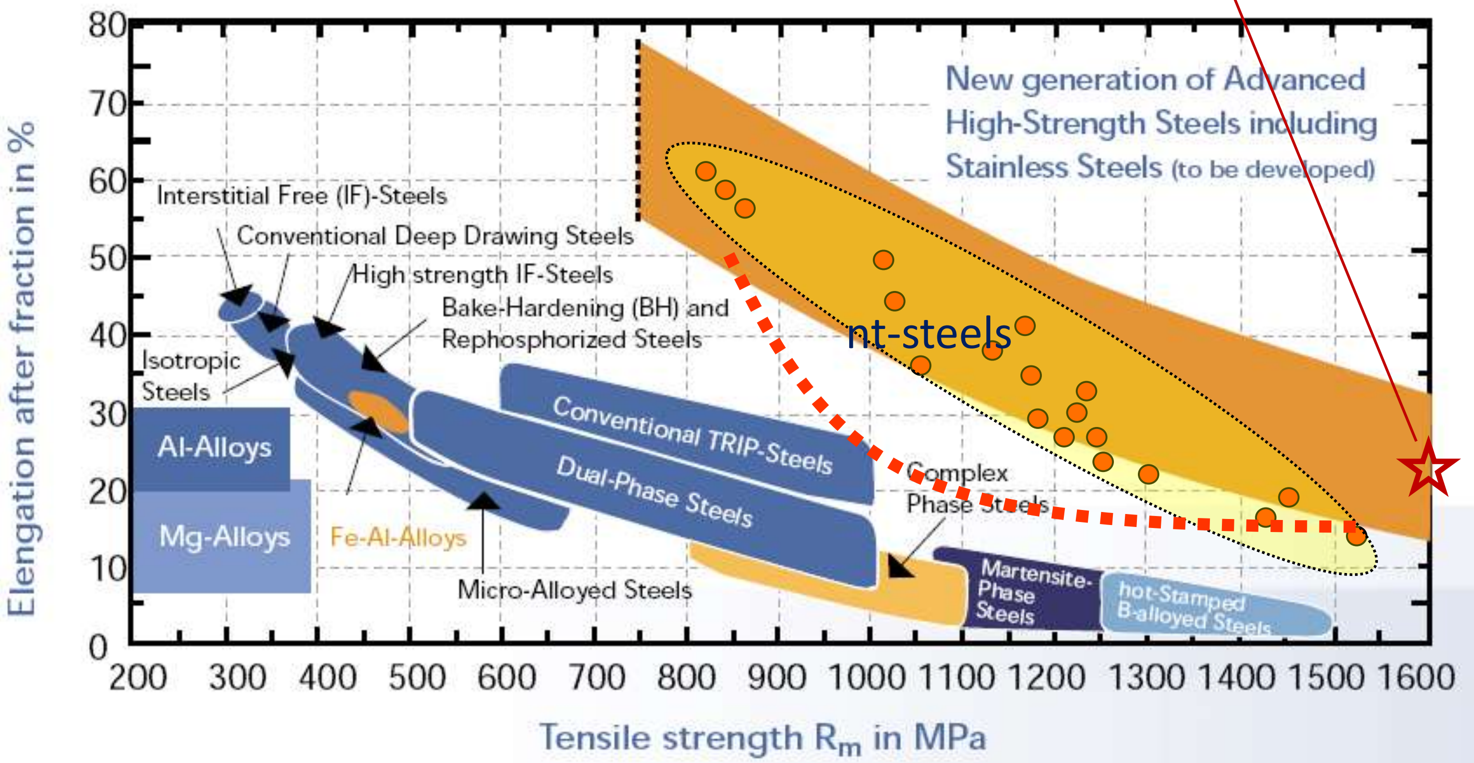


(Lu et al., *Science*, 2004, 2009)



(Zhou et al., Acta Mater., 111, 96e107, 2016)





Some perspectives for the future

"The best way to predict the future is to create it."
- Abraham Lincoln

- **Traditionally mechanics is thought to be quantitative while biology often qualitative. Today these fields are brought closer than ever by unprecedented bioimaging techniques, quantitative experimental tools and even mechanistic approaches to disease treatment. It can be anticipated that there will be rich opportunities at the interface between mechanics and biology in the coming decades.**
- **Advances in bioimaging techniques during the last decade are making it possible to develop and validate mechanics theories/models to understand fundamental biological phenomena at the cellular and subcellular scales (such as cell uptake of viruses and nanomaterials).**
- **Additive manufacturing (e.g., 3D printing) may be ushering in a golden age for biomimetic/bioinspired materials. This will call for fundamental understanding of the mechanical principles in biological materials (e.g., toughness of bone/shells, drag reduction of shark skins, etc).**

Thank you!