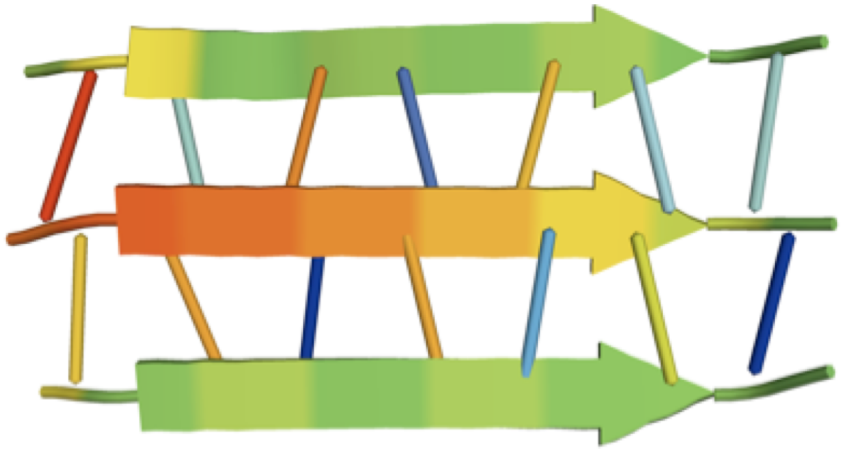
Heidelberg Institute for Theoretical Studies

HITS

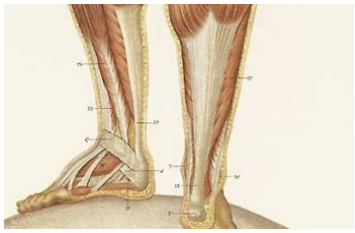
IWR Interdisciplinary Center for Scientific Computing

Simulations of biomaterials under force
[part I: Collagen]
part II: Silk

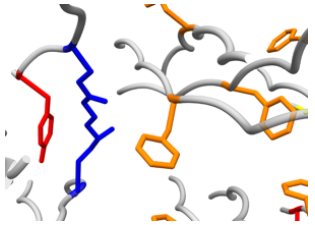
Frauke Gräter, Bogota, 09/2019

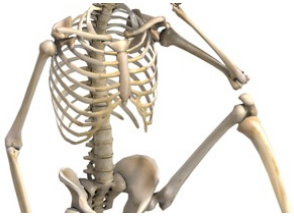


MOLECULAR (bio)mechanics – why?

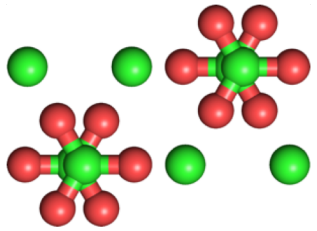


collagen

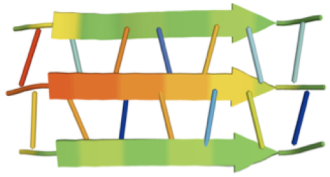




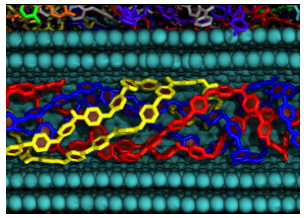
mineralized tissue



silk



polymer



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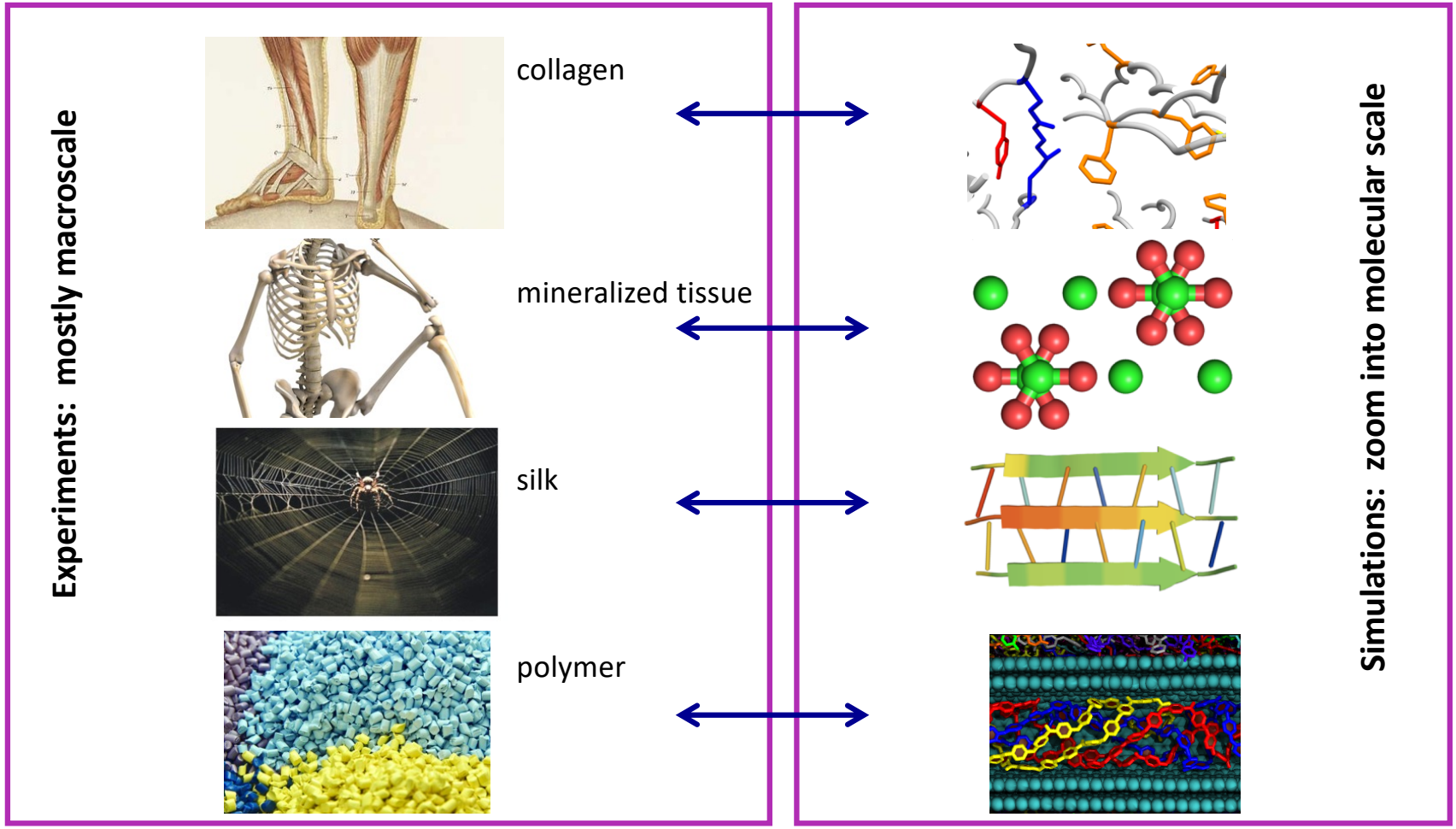

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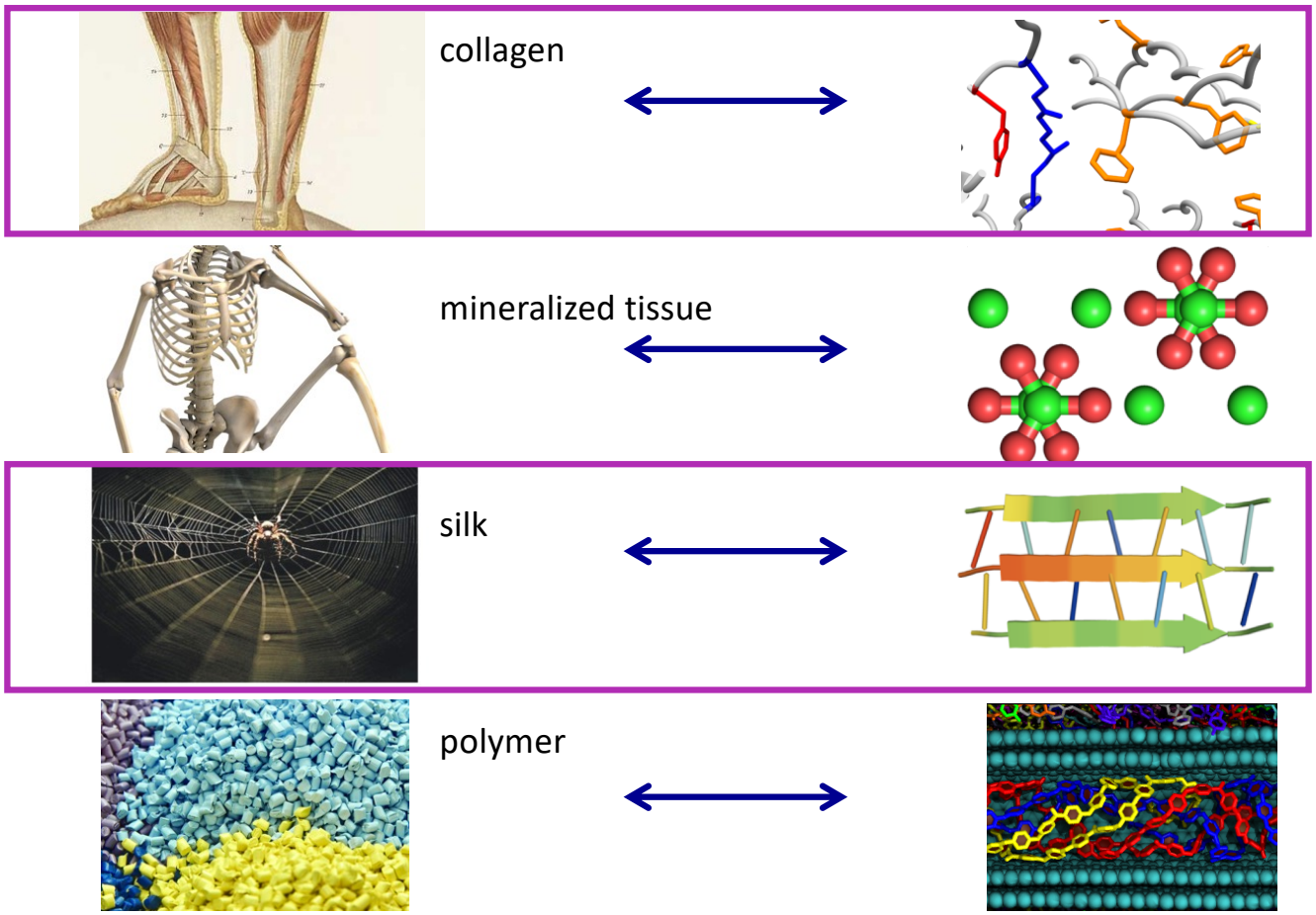
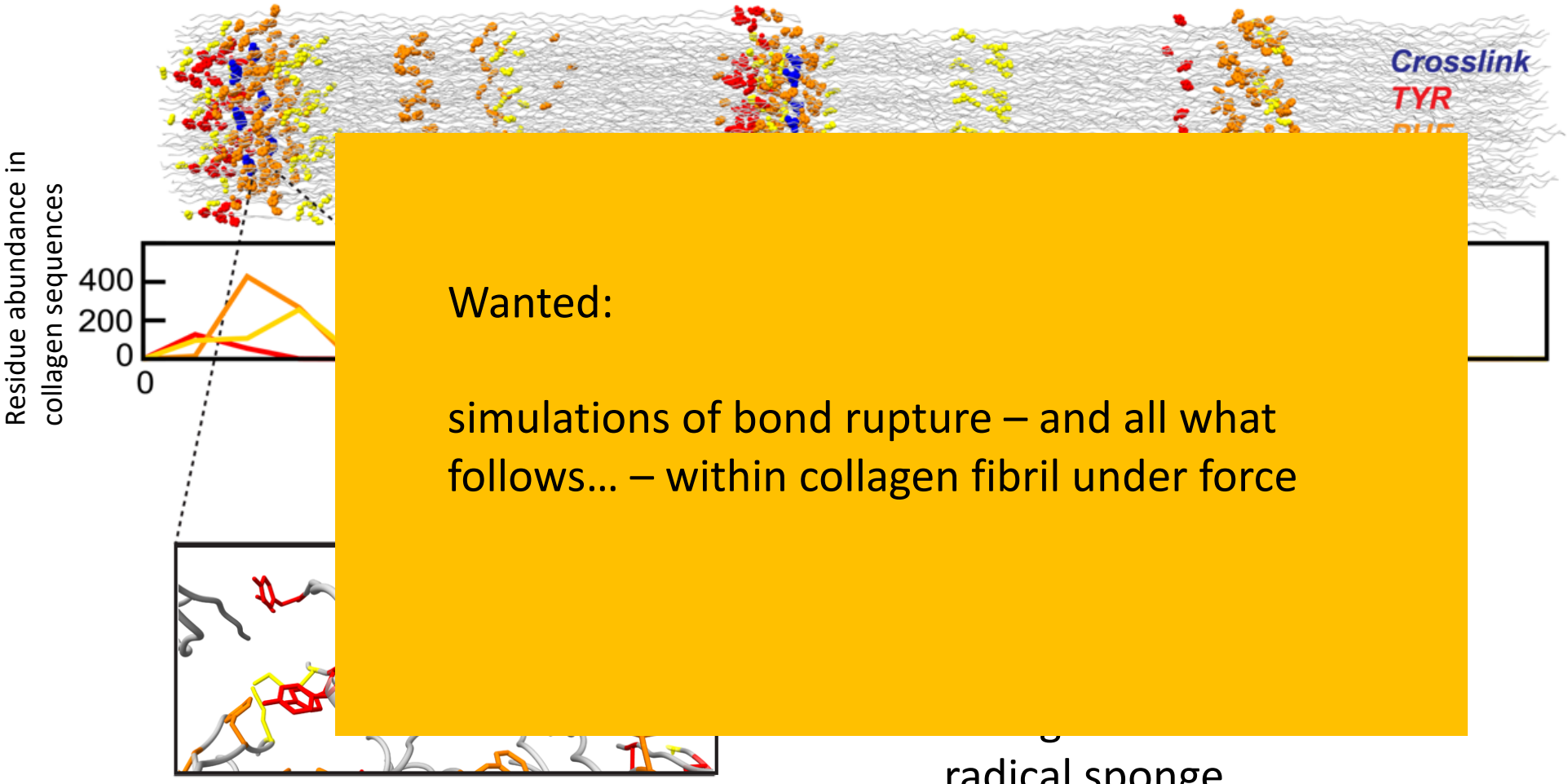




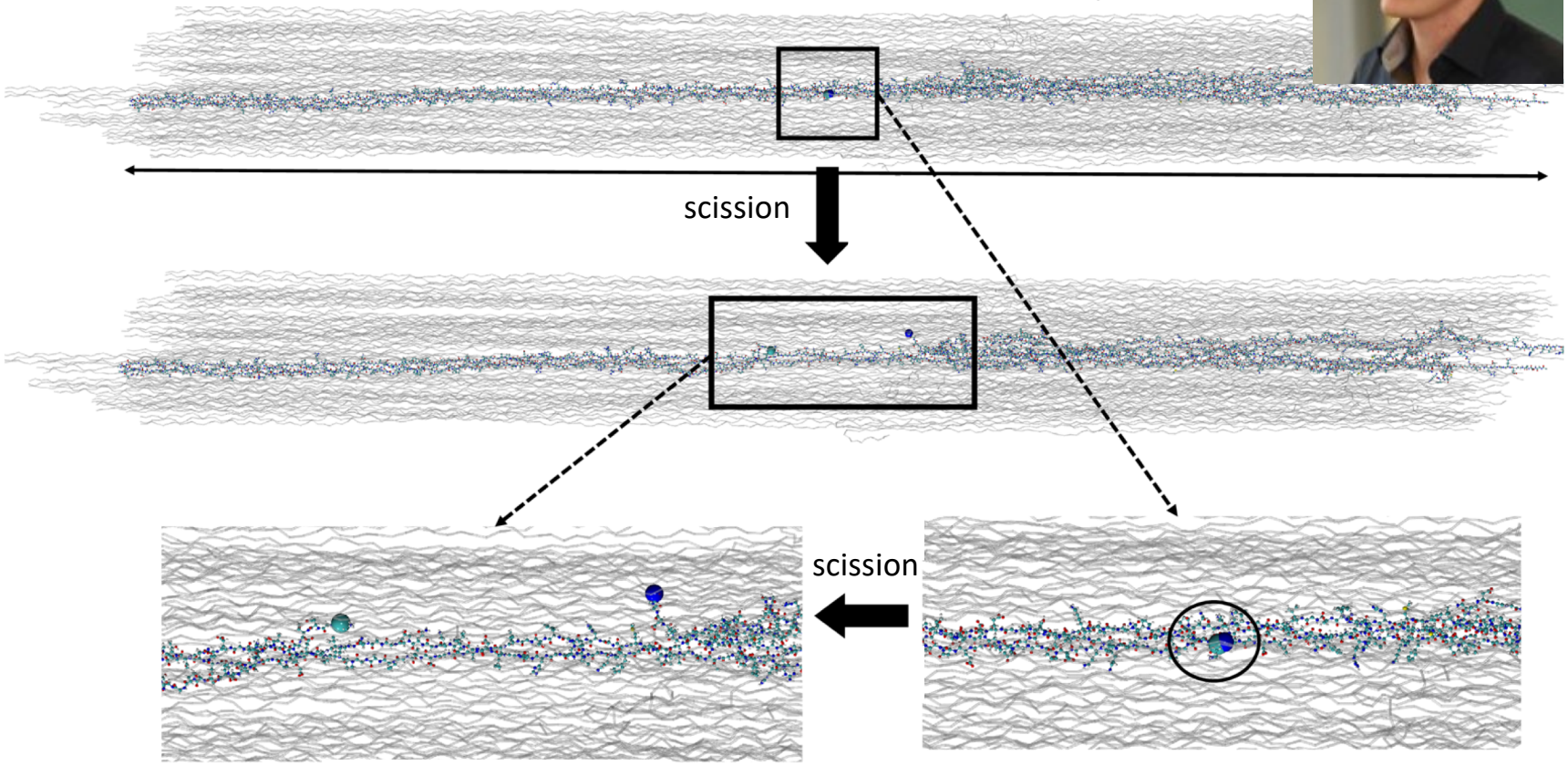
Wanted:

simulations of bond rupture – and all what follows… – within collagen fibril under force

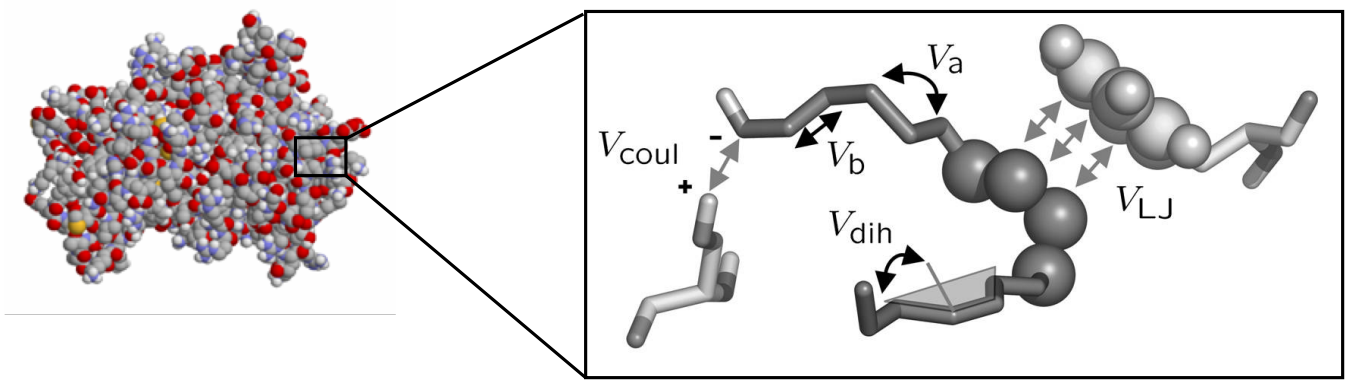
radical sponge

Reactive Molecular Dynamics: spontaneous chemical events on-the-fly

Benedikt Rennekamp



Molecular Dynamics simulations: bonds can not rupture!



1.

$$
\begin{aligned}
E = & \sum_{bonds} \frac{k_i}{2}(l_i - l_{i,0})^2 \\
& + \sum_{angles} \frac{k_i}{2}(\Theta_i - \Theta_{i,0})^2 \\
& + \sum_{torsions} \frac{V_n}{2}(1 + cos(n\omega - \gamma)) \\
& + \sum_{i=1}^{N} \sum_{j=i+1}^{N} (4\epsilon_{ij}((\frac{\sigma_{ij}}{r_{ij}})^{12} - (\frac{\sigma_{ij}}{r_{ij}})^{6}) + (\frac{q_i q_j}{4\pi\epsilon_0 r_{ij}}))
\end{aligned}
$$

bonded interactions

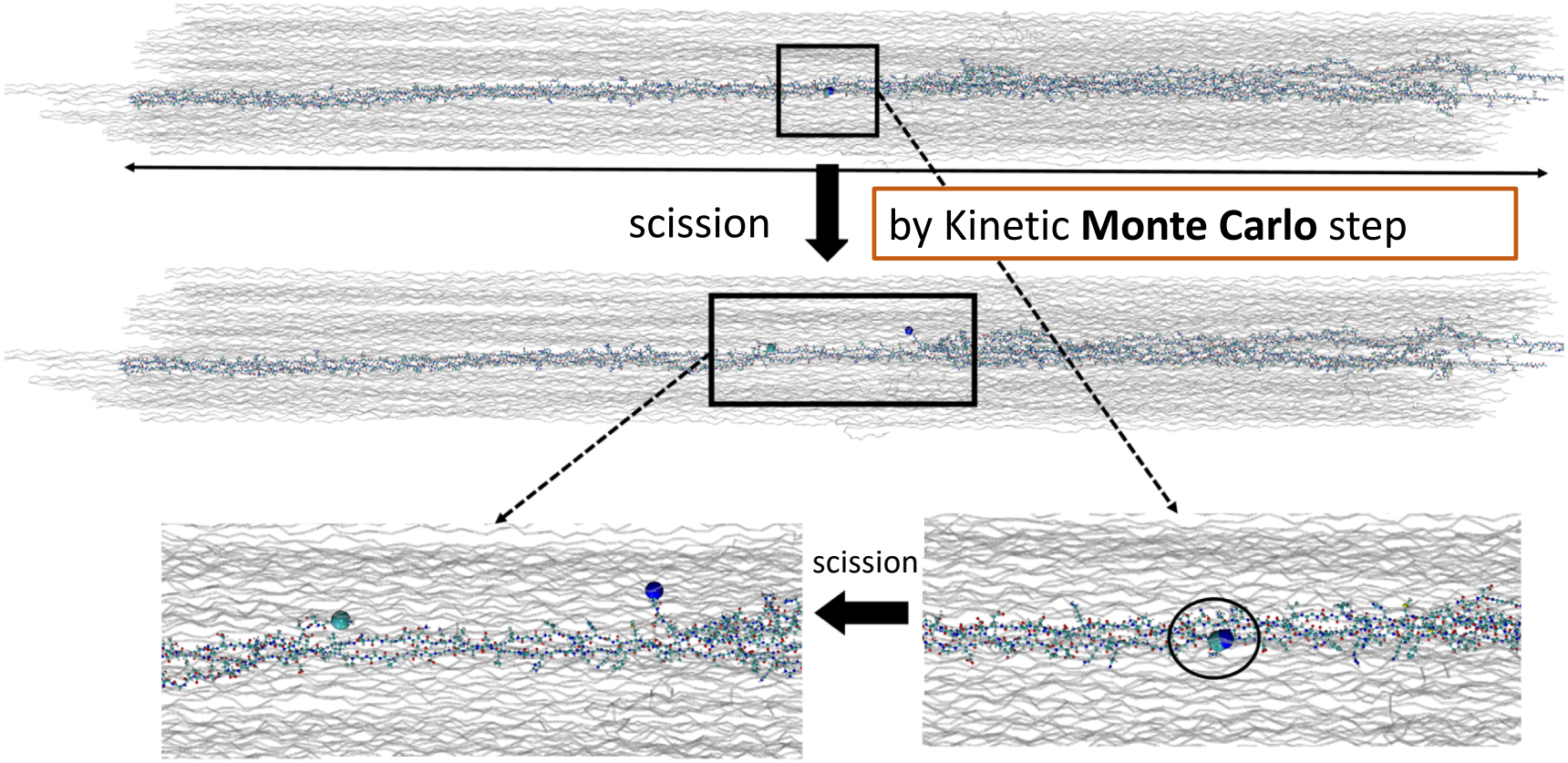
non-bonded interactions

2.

&

$$F_i = \frac{\delta E}{\delta r_i} = m_i \frac{d^2 r_i}{dt^2}$$

“Reactive” Molecular Dynamics: spontaneous chemical events on-the-fly



Monte Carlo methods

stochastic simulation methods, **sample randomly** to get obtain an approximate numerical result for a complex (high-dimensional?) problem

flavors:

- Monte Carlo integration
- Metropolis Monte Carlo
- Quantum Monte Carlo
- kinetic Monte Carlo

applications:

e.g. optimization, simulations of solids/molecules/polymers, weather, astro, finance, law,….

Monte Carlo methods: some history

- name was suggested by Metropolis, at Los Alamos National Laboratories for a method put forward by Fermi/Ulam
- used for calculations of neutron diffusion

Monte Carlo methods: some history

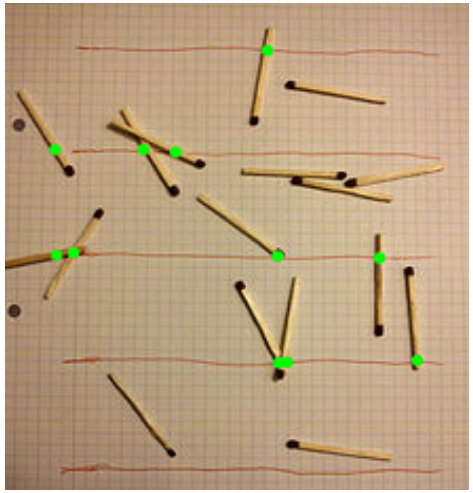
Earliest example:

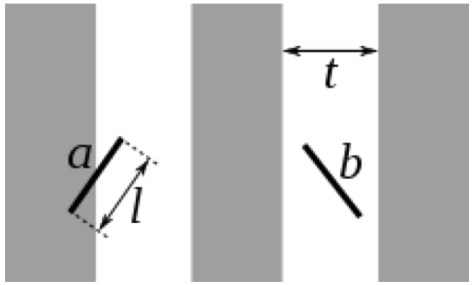
Calculation of π by Laplace
(based on the Buffon Experiment)

Suppose we have a floor made of parallel strips of wood, each the same width, and we drop a needle onto the floor. What is the probability that the needle will lie across a line between two strips?

n needles,
h of them crossing the strips
l length of needles
t width of strips

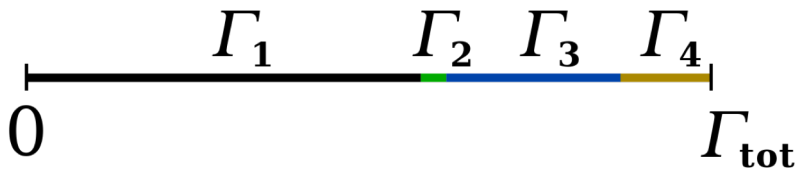
$$\pi \approx \frac{2l \cdot n}{th}$$





wikipedia

Kinetic Monte Carlo



- Calculate different rates Γ_i
- Draw random number R between 0 and Γ_{tot}
- Carry out corresponding event
- Draw another random number T between 0 and Γ_{tot}
- Update time with $\Delta t = log(1/\mathrm{T})$

Advantages:

- any time scale reachable (lower rates just lead to higher time steps)

Disadvantages:

- jump in time: no continuous trajectory
- requires good guesses for rates

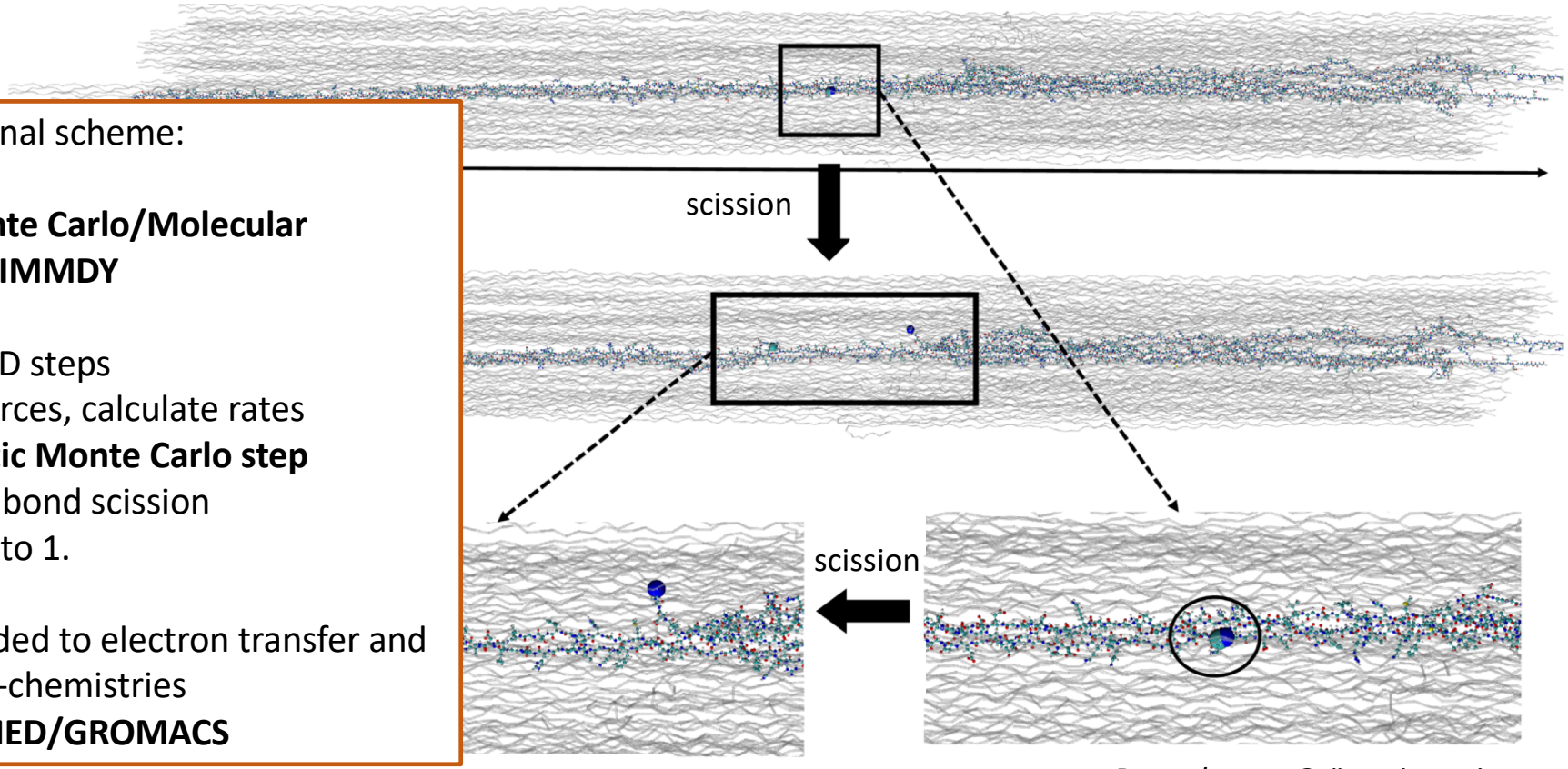
“Reactive” Molecular Dynamics: spontaneous chemical events on-the-fly

Computational scheme:

Kinetic Monte Carlo/Molecular Dynamics KIMMDY

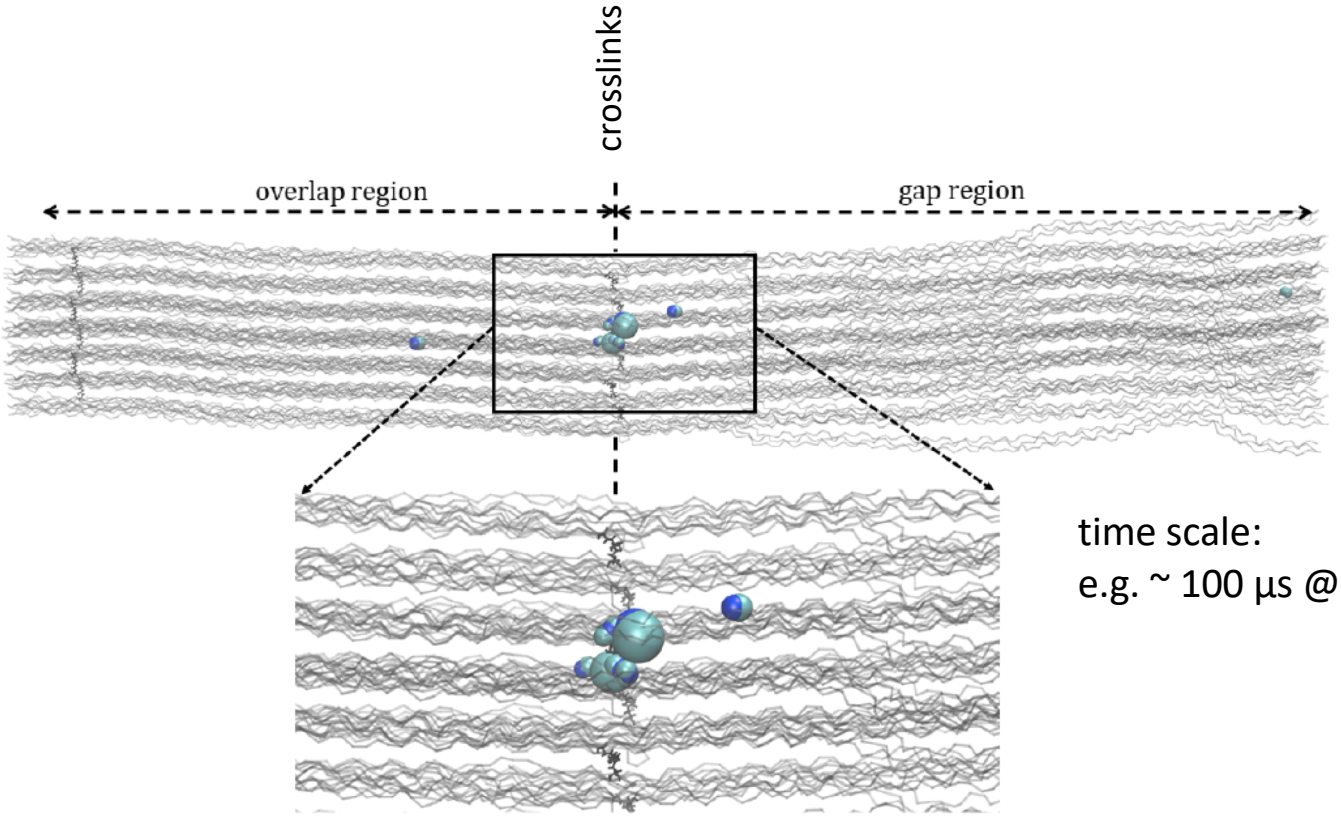
1. Run n MD steps
2. Check forces, calculate rates
3. **Do kinetic Monte Carlo step**
4. Perform bond scission
5. Go back to 1.

to be extended to electron transfer and other redox-chemistries
Using **PLUMED/GROMACS**



Rennekamp, Gräter, in review

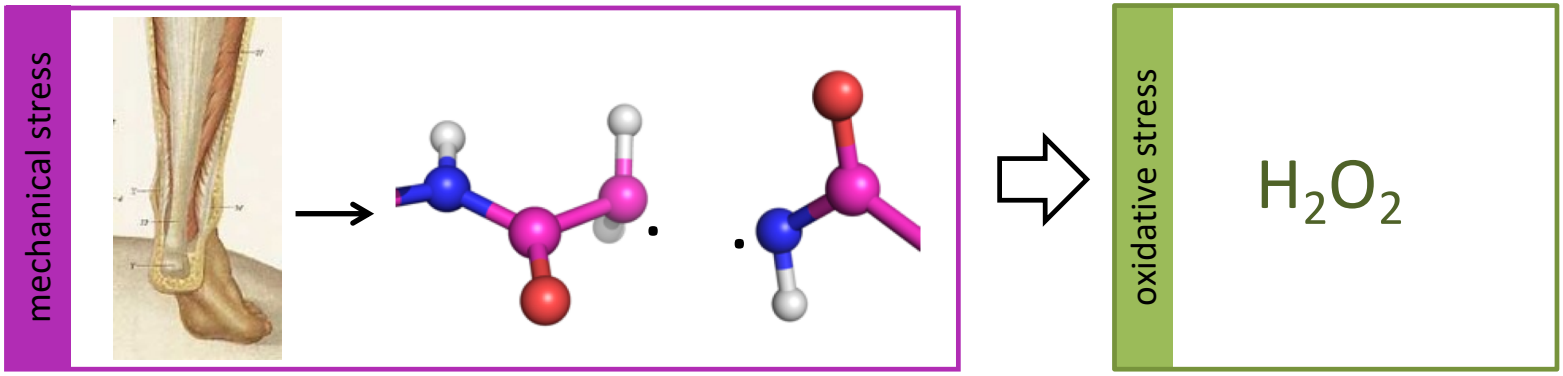
It works: Rupture preferentially occurs around crosslinks



time scale:
e.g. ~ 100 µs @ F=1.5 nN

Conclusions:

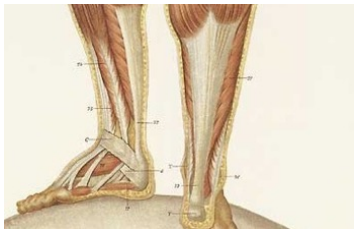
YES: High loads on our collagen results in radicals



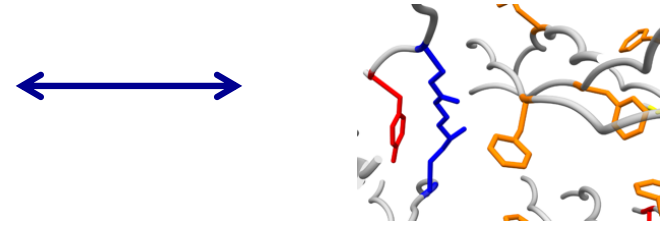
Move yourself! But only until it starts hurting…

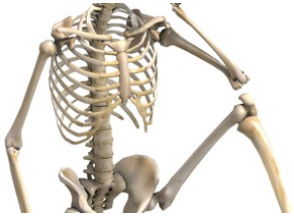
Zapp, Obarska-Kosinska* et al, in review*

MOLECULAR (bio)mechanics – why?

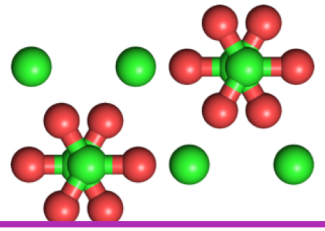


collagen

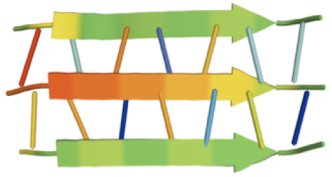




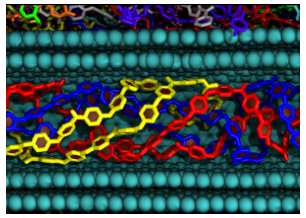
mineralized tissue



silk



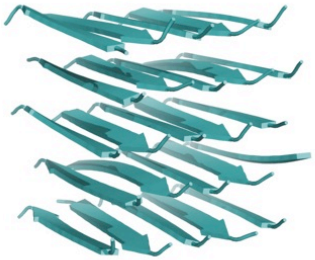
polymer



Molecular simulations & continuum mechanics

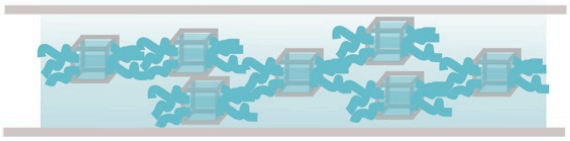
Order and disorder in silk

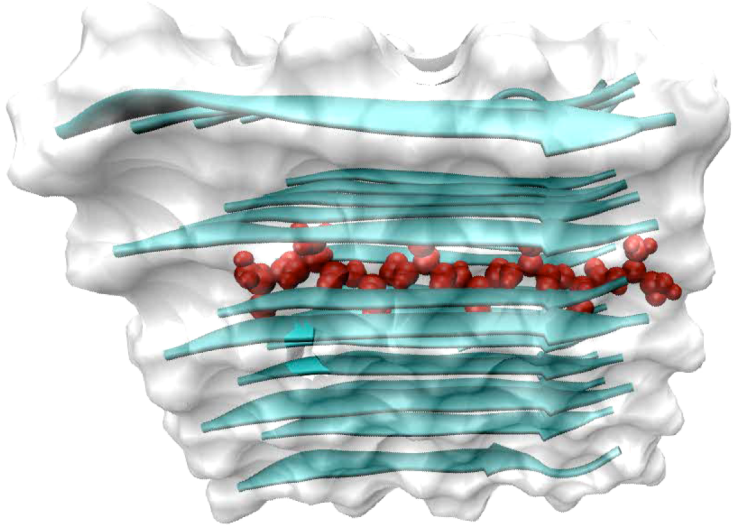
silk molecular structure:



poly(alanine)

disordered
sequence
glycine rich

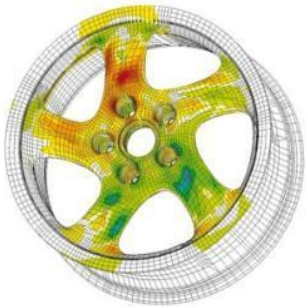




Strain and fracture: force distribution

conventional design tools:
force distribution

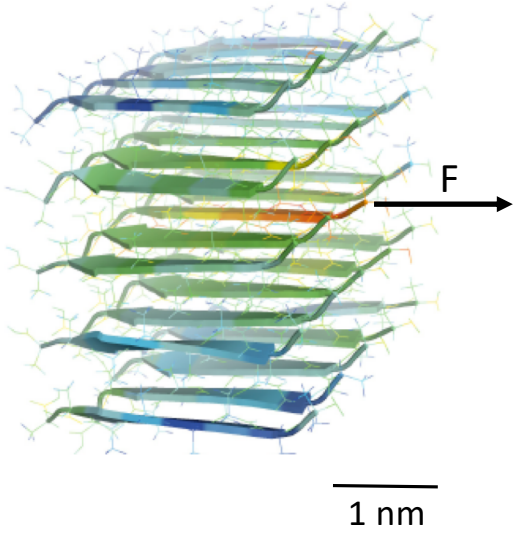
in constructions, cars ...



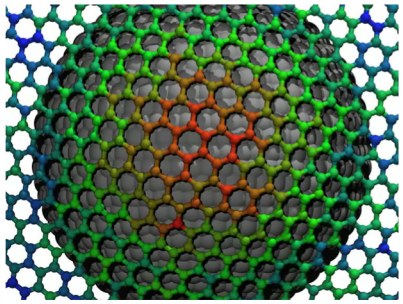
macroscopic structures:
meters

our method:
force distribution in (bio)molecules at atomistic level

e.g.



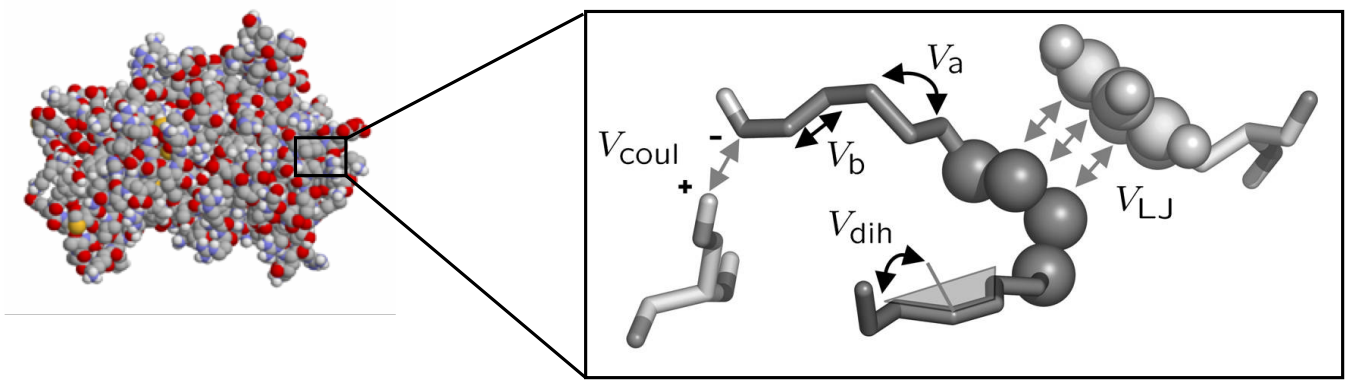
in graphene



microscopic structures:
~ 10^{-9} meters

W. Stacklies, et al, PLoS Comp Biol, 2009
Costescu et al, BMC Biophys, 2012

Forces from Molecular Dynamics simulations



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$$

bonded interactions

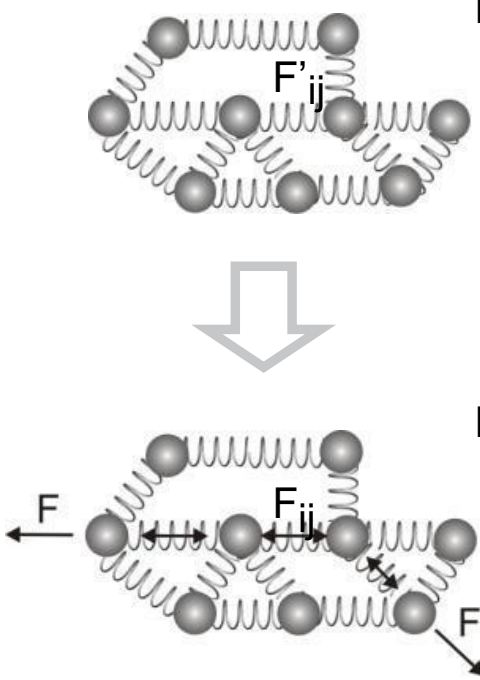
non-bonded interactions

&

2.

$$F_i = \frac{\delta E}{\delta r_i} = m_i \frac{d^2 r_i}{dt^2}$$

Forces from Molecular Dynamics simulations



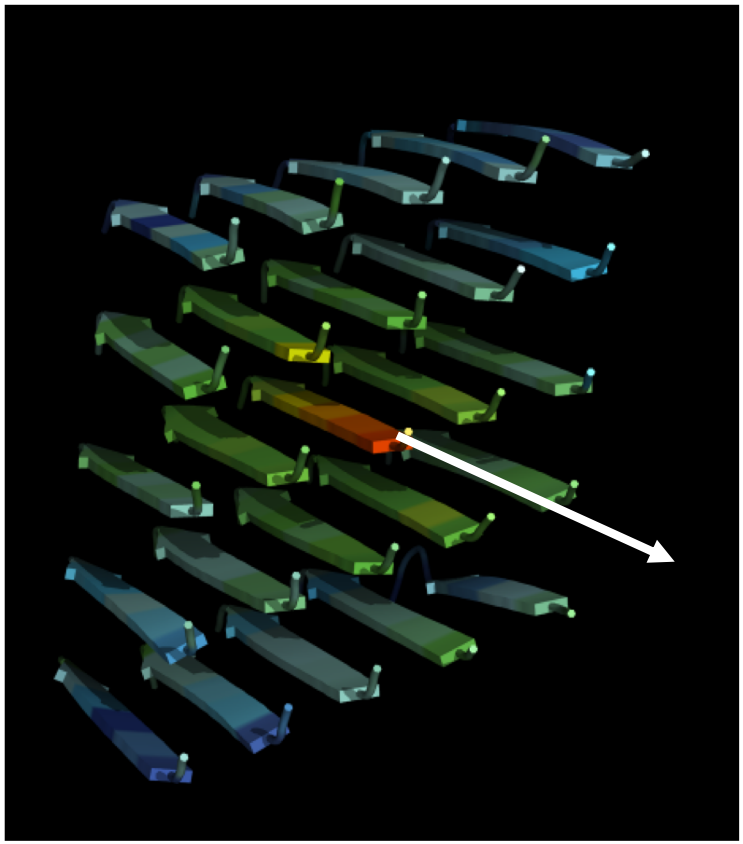
F'_{ij} force between atom i and j in relaxed state

F_{ij} force between atom i and j in stretched state

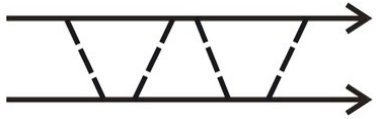
change in pairwise forces

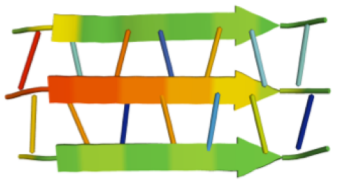
$$\Delta F_{ij} = F_{ij} - F'_{ij}$$

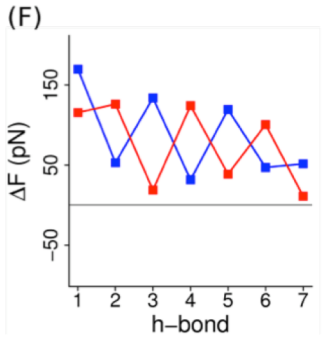
Mechanics of silk fibers



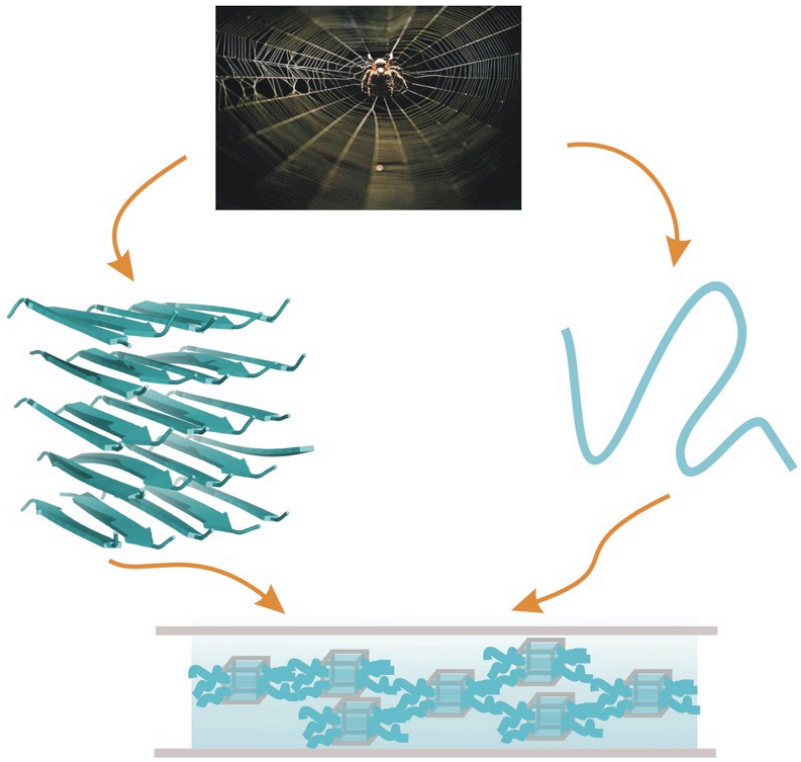
zigzag pattern of
hydrogen bonds
crucial for stabilization





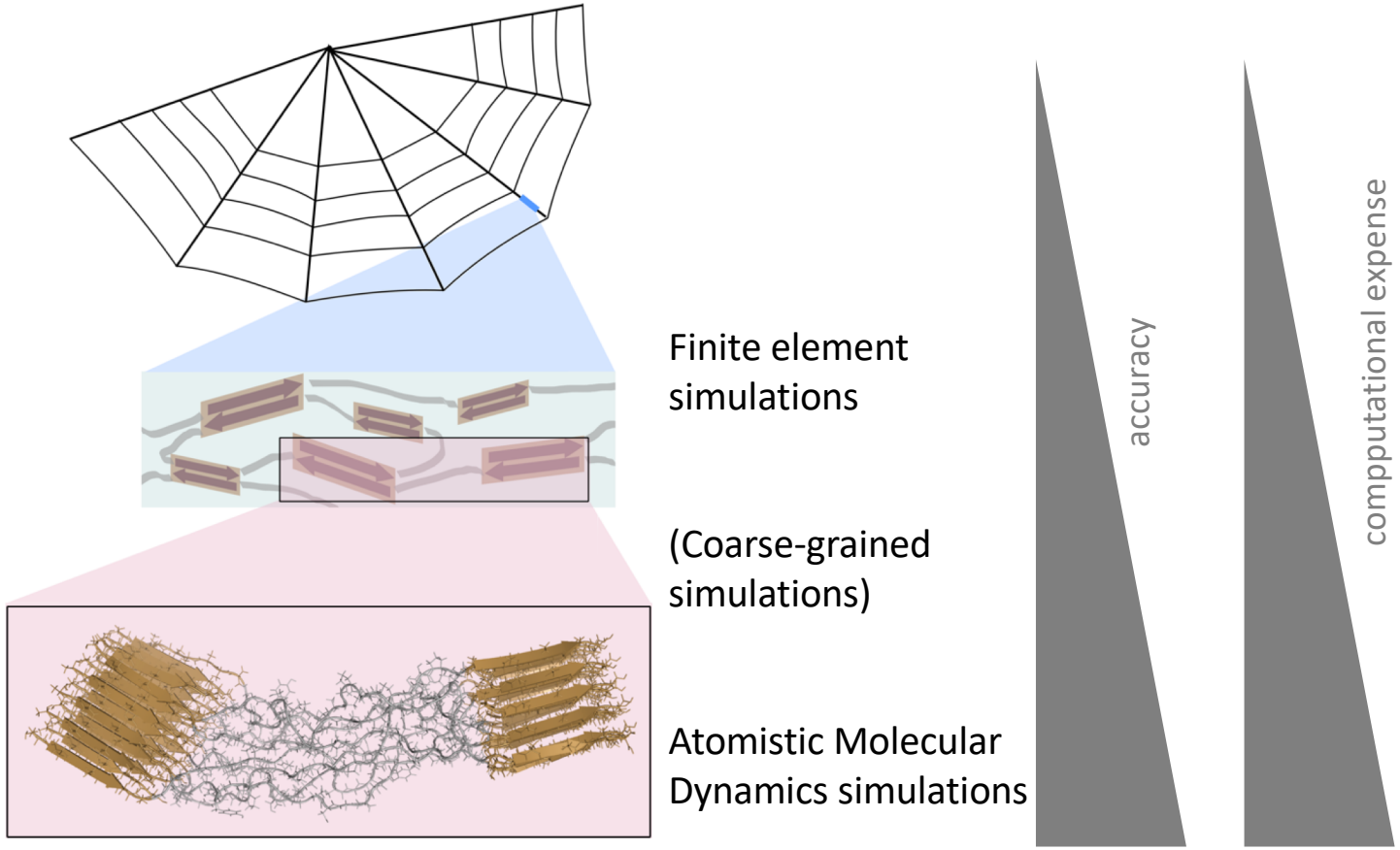


How to predict mechanics on whole fiber scale?



All-atom will not work….

Our method: bottom-up multiscale simulations



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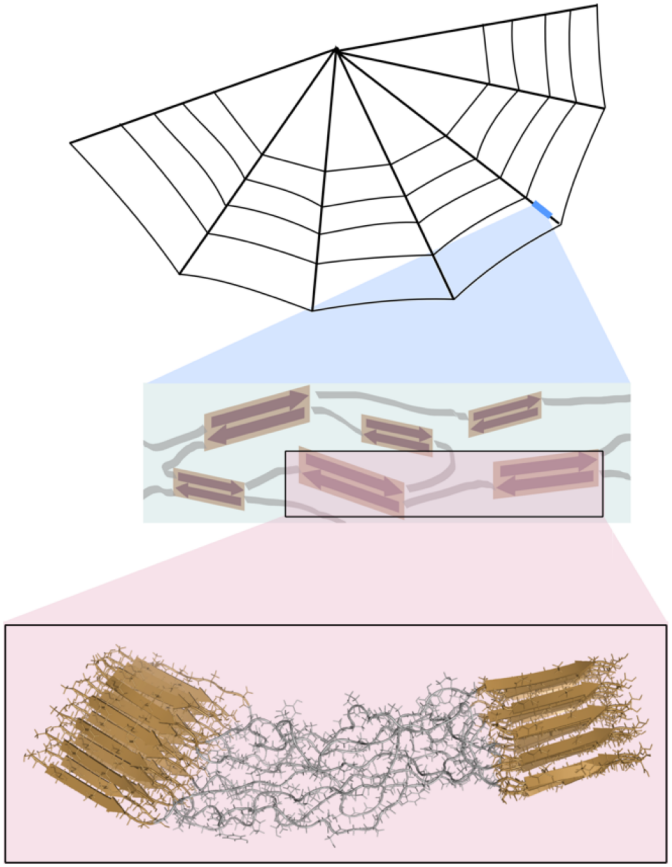
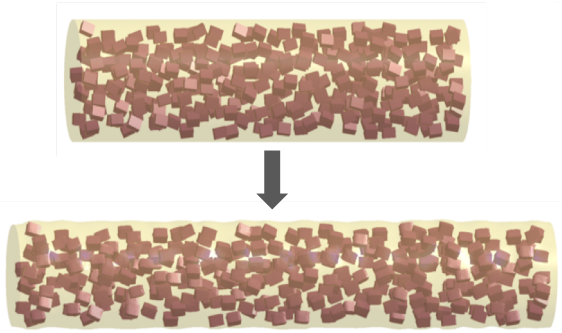


infer properties on
macroscopic scale

derive properties on
molecular scale

Refined bottom-up finite element model of silk fibers

- structural parameters from SAXS, SANS et
- mechanical parameters from a large set of Molecular Dynamics simulations: elastic moduli, shearing moduli, Poisson's ratio
- varied to test robustness
- validation by comparison with macroscopic silk mechanics

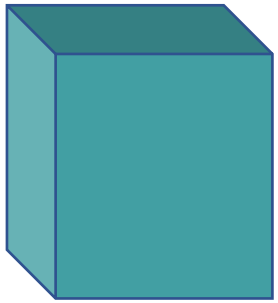


Xiao et al, BJ 2009
Cetinkaya et al, BJ 2011
Cetinkaya et al, PCCP 2011
Patil et al, PLoS One 2014
Patil et al, BJ 2014
Wagner et al, Sci Rep 2017

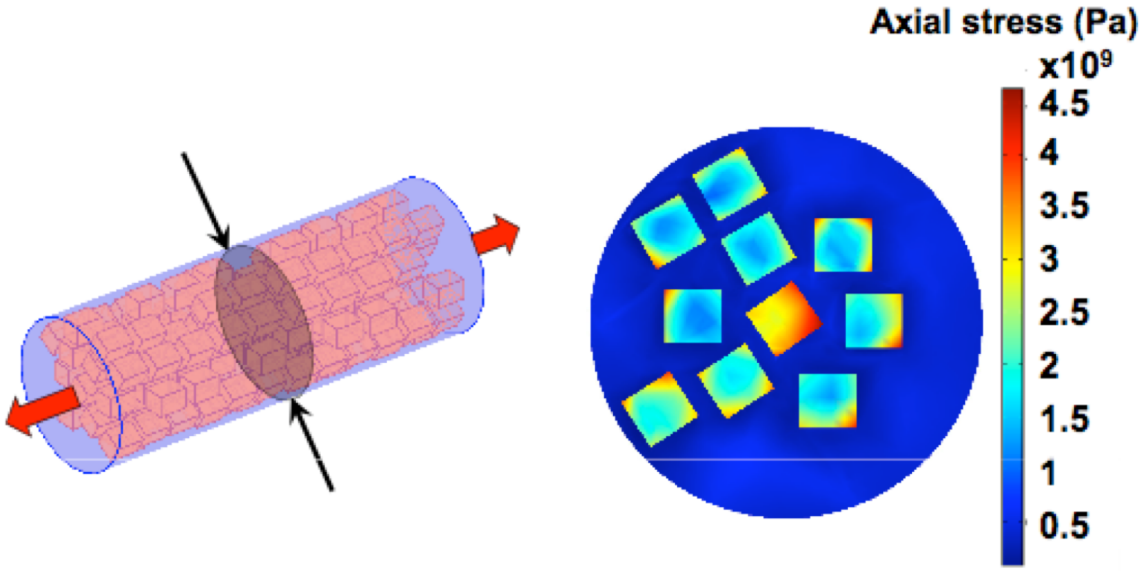
Refined bottom-up finite element model of silk fibers

bear in mind: this complex structure…

….now is nothing but a cube

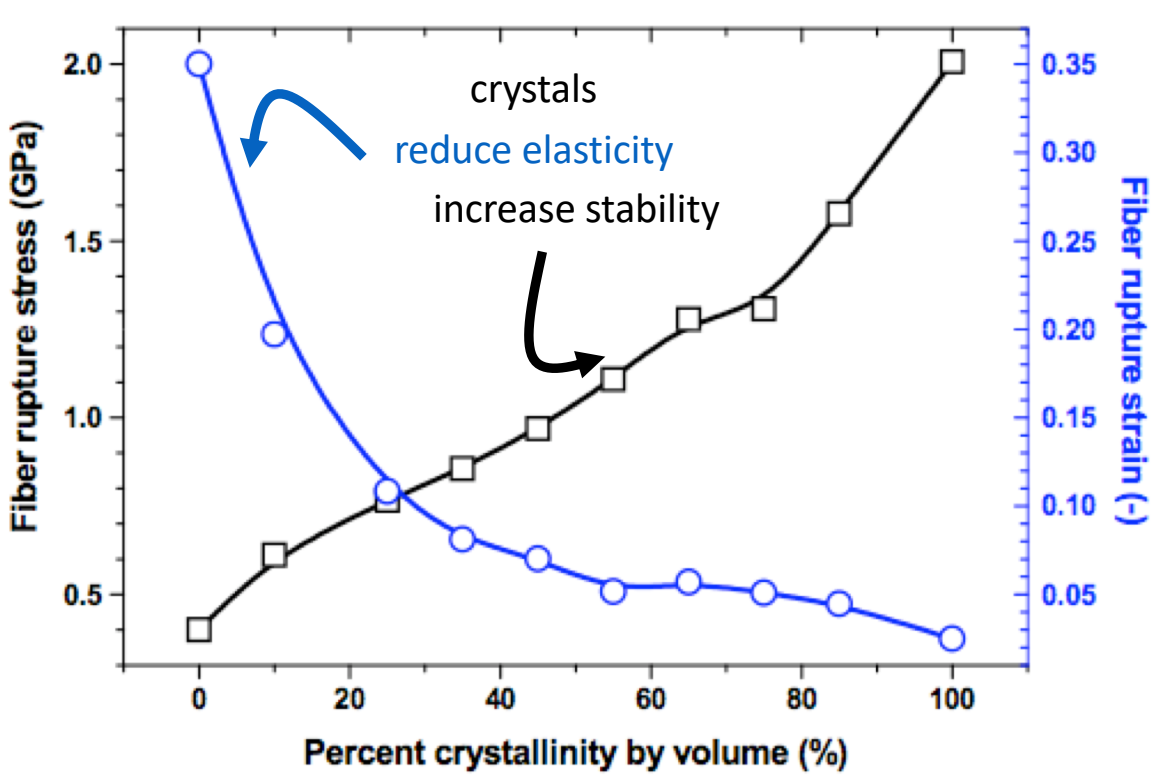


Our first simple finite element model of silk



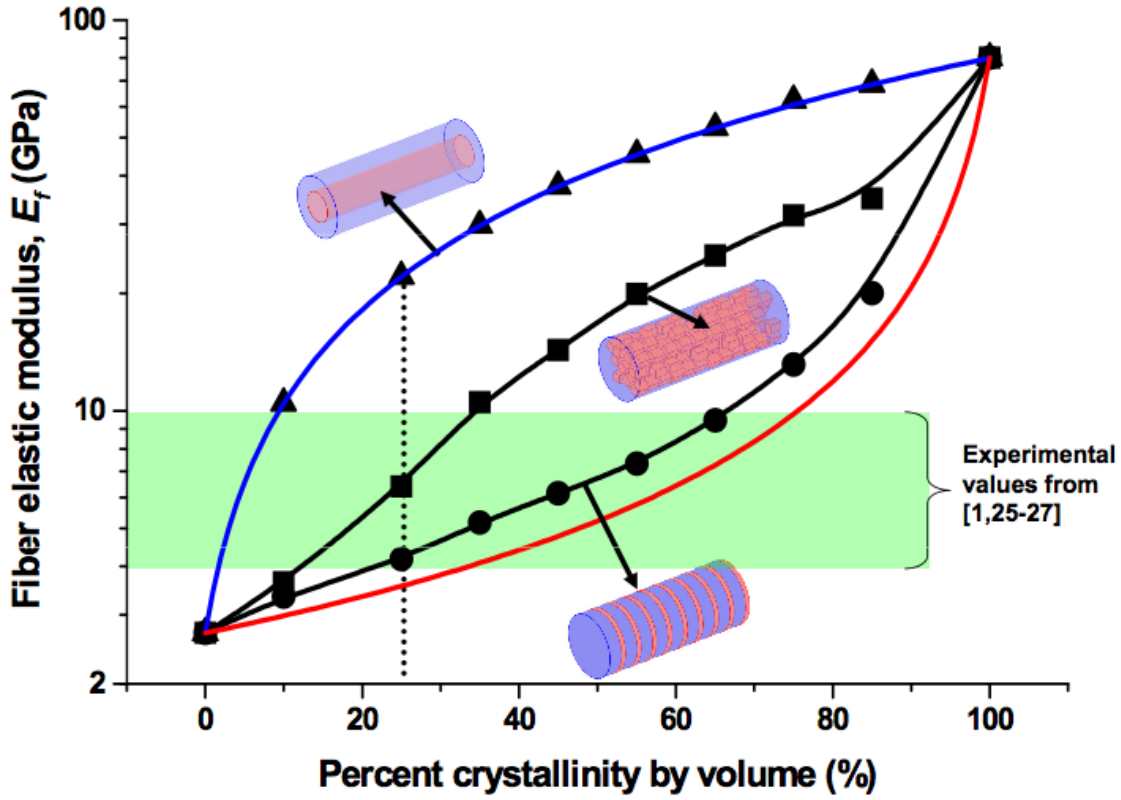
Our first simple finite element model of silk

stress =
force/area



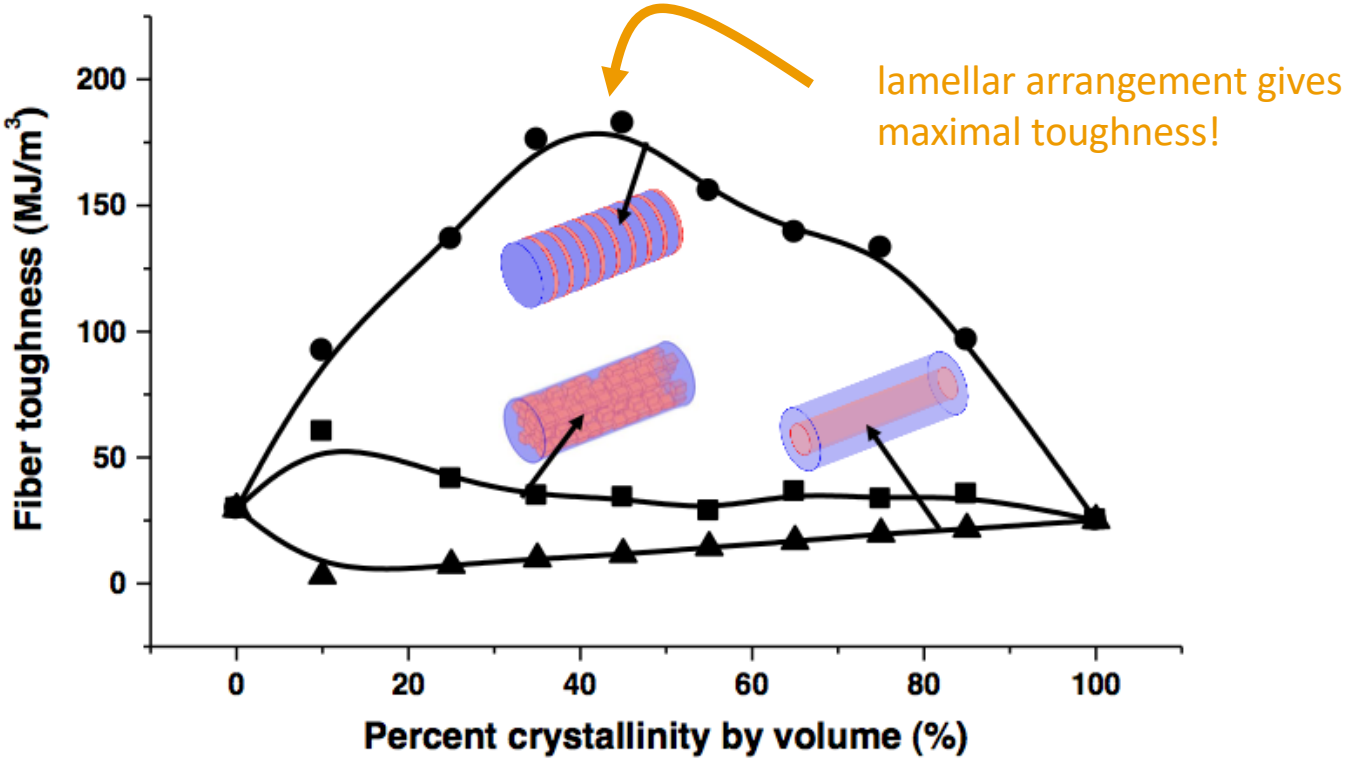
strain =
elongation relative
to initial length

Our first simple finite element model of silk

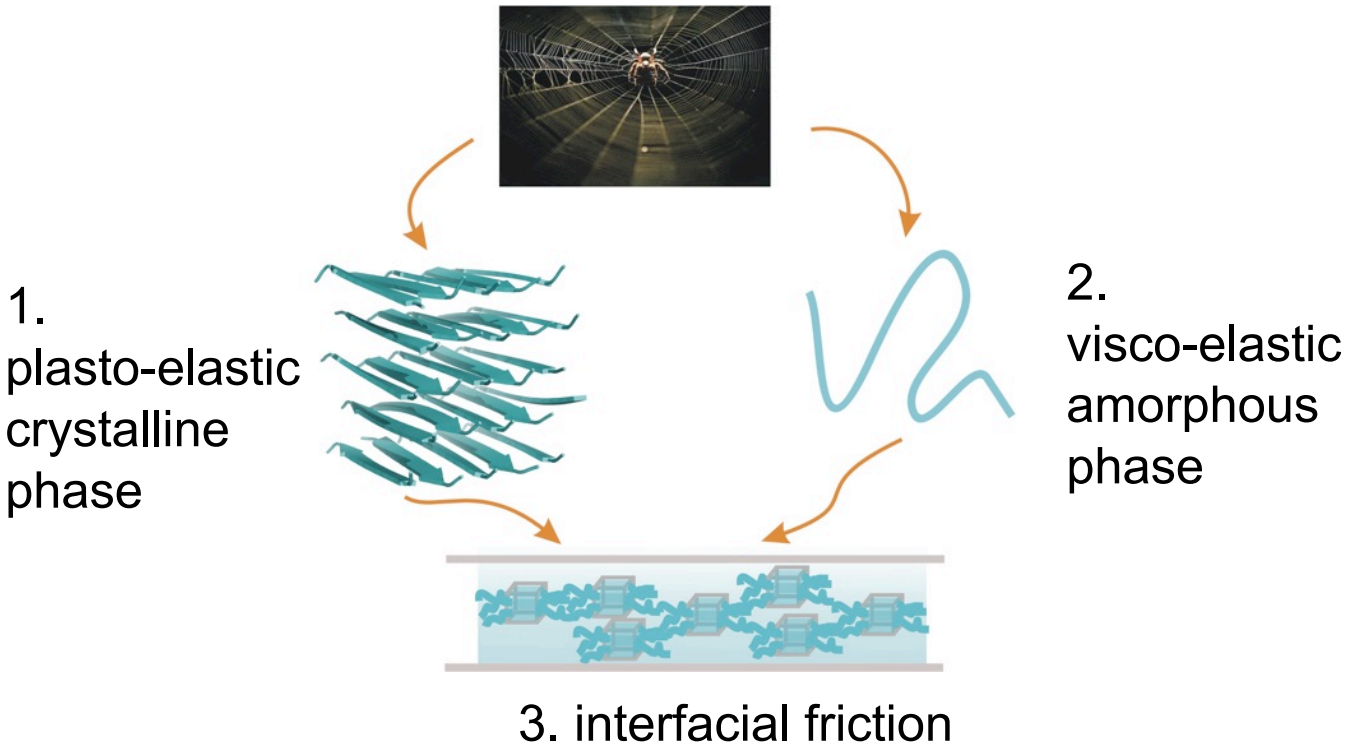


Toughness depends on long-range order

toughness =
energy
absorbed until
rupture
OR
integral under
stress-strain
curve

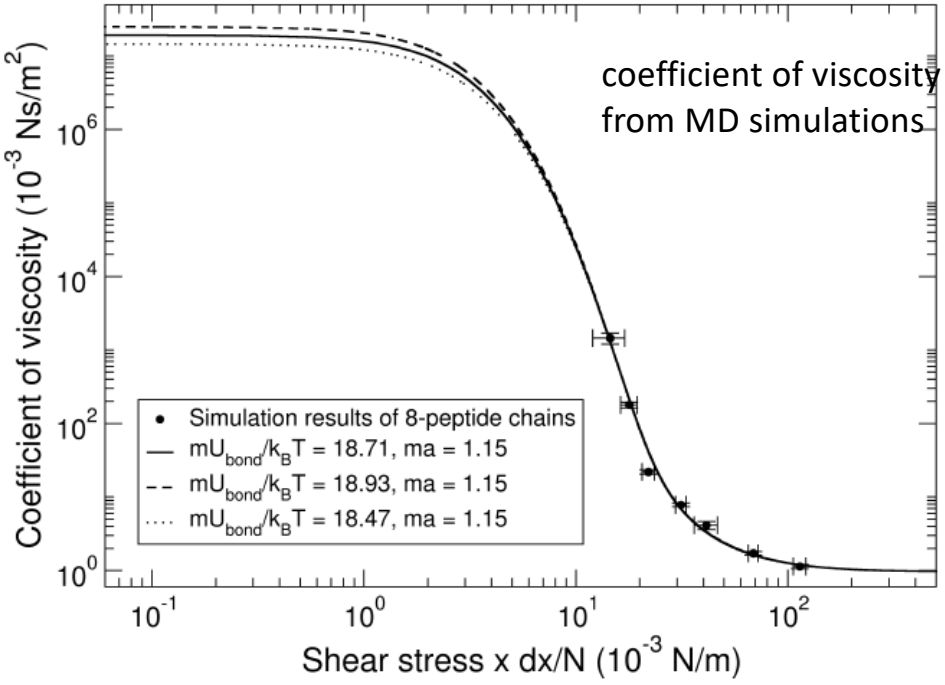


Next step: towards more realistic visco-elastoplastic silk



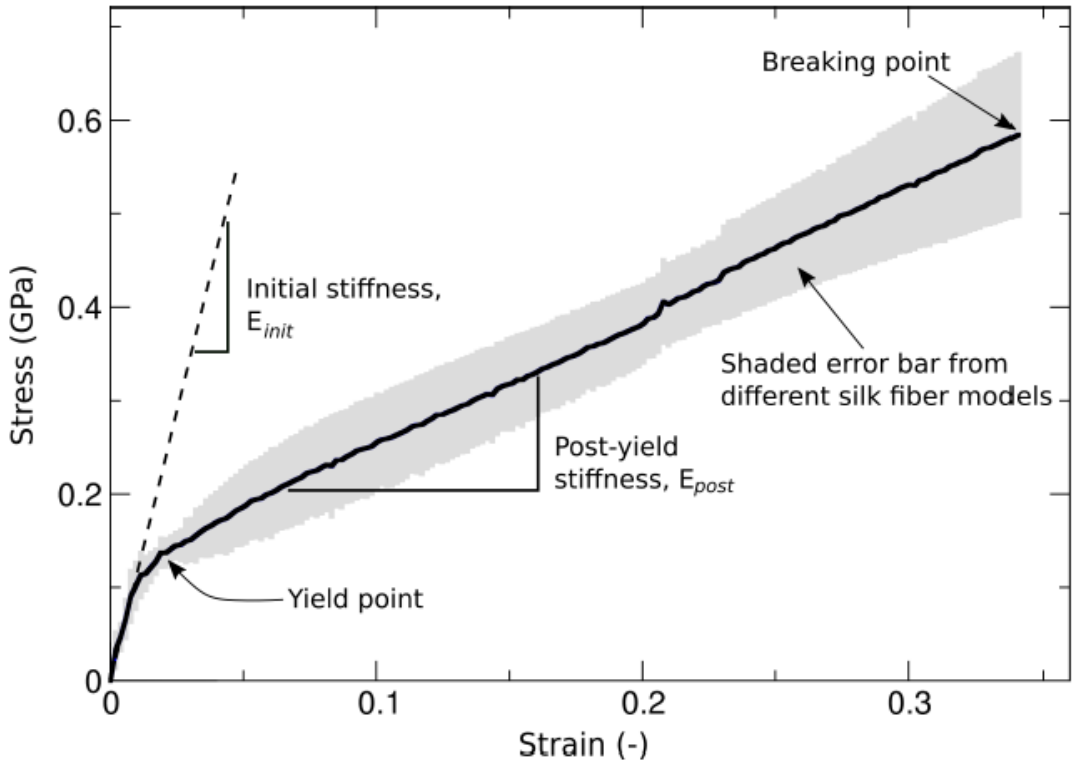
Next step: towards more realistic visco-elastoplastic silk

2. viscous amorphous phase



Patil et al, BJ 2014; Patil et al, PLoS One

Next step: towards more realistic visco-elastoplastic silk

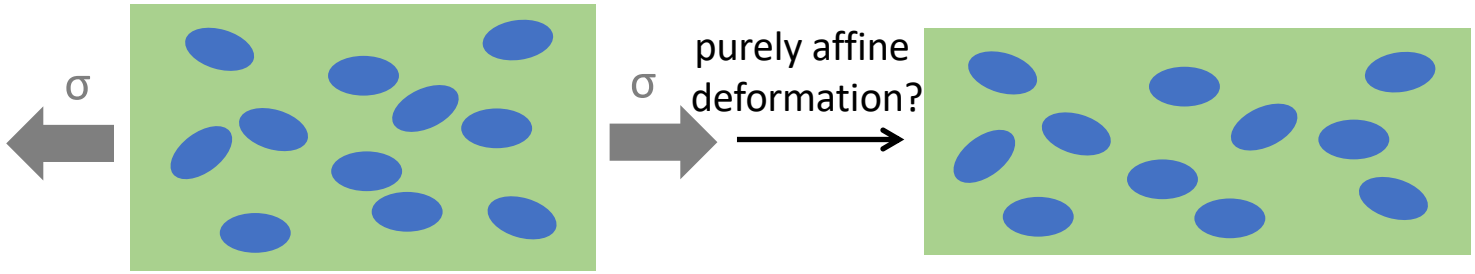


Next step: towards more realistic visco-elastoplastic silk

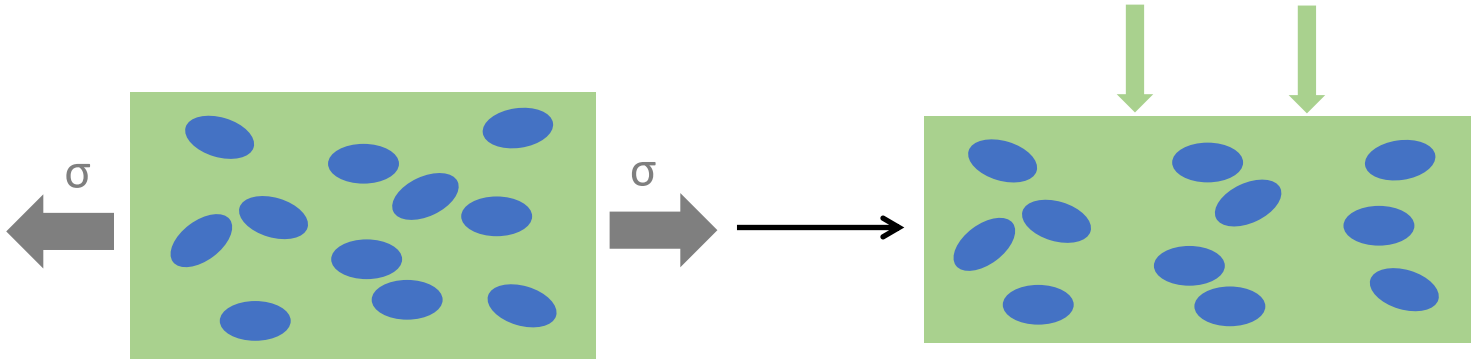
	Our Simulations results	Experiments by Denny(1976) [9]	Experiments by Gosline(1999) [3]
Ultimate Strength(GPa)	0.5-0.671	0.7-1.3	1.08-1.61
Extensibility	0.32-0.36	0.23-0.45	0.27-0.40
Initial stiffness or	6.5-8.1	3.8-9.8	7.0-10.0
Post-yield stiffness(GPa)	1.1-1.7	1.5-5.1	N/R
Toughness(MJ/m^3)	101-135	160	120-180

Hysteresis: ~70% similar to experimental values for these strain rates

Using this new model: self-ordering in spider silk fibers



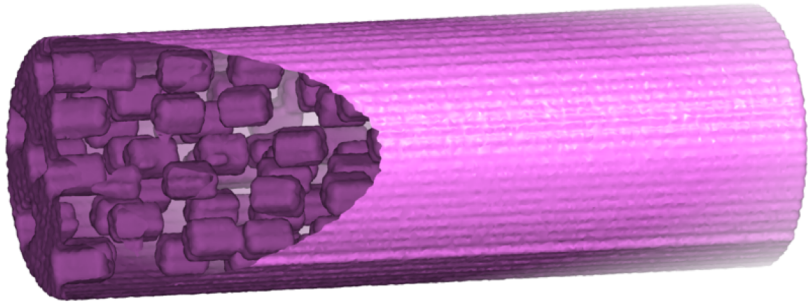
Using this new model: self-ordering in spider silk fibers



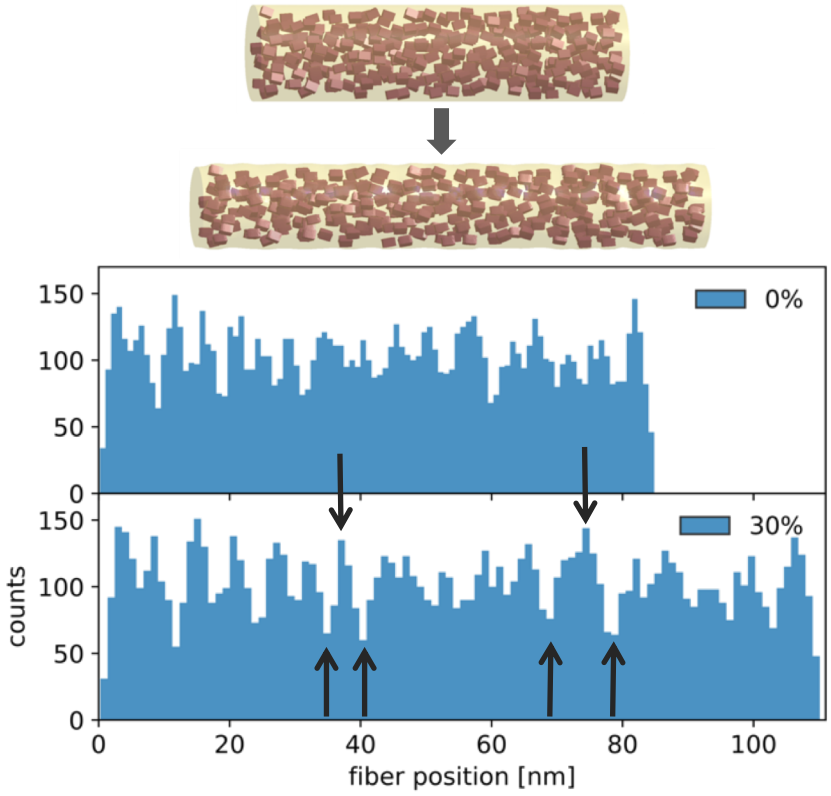
Finite element model

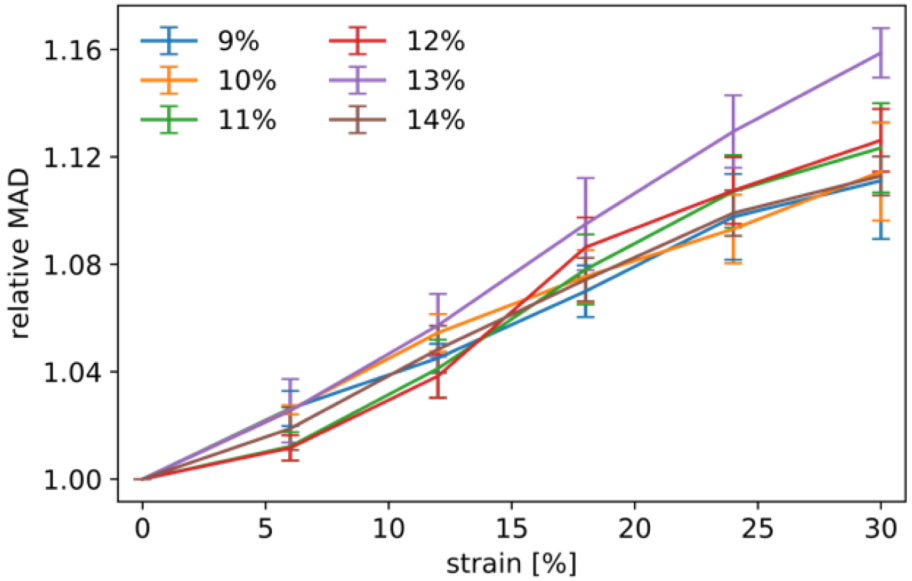
cubes represent beta-sheet crystals, sizes/angles from scattering experiments

surrounded by soft amorphous matrix



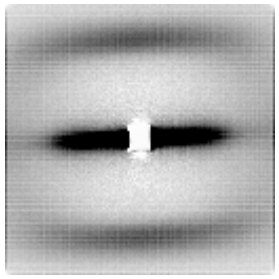
Stretch-induced self-ordering: computational prediction



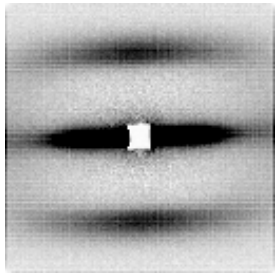


BUT: is this real? Any experiments to test this?

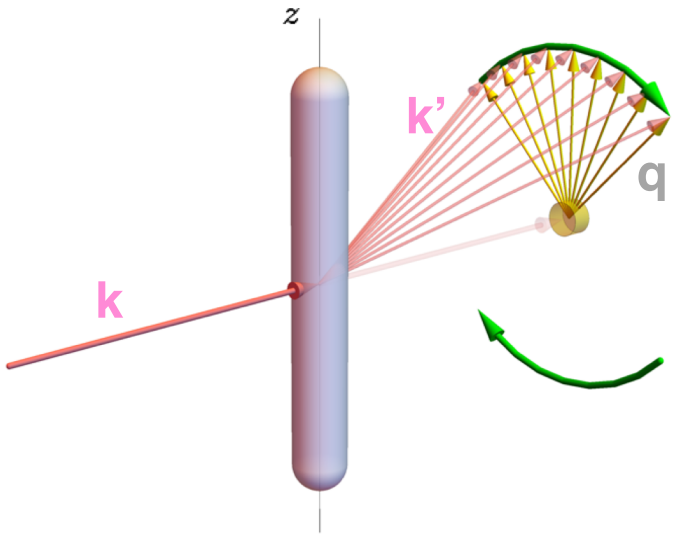
Stretch-induced self-ordering: confirmed by small angle neutron scattering

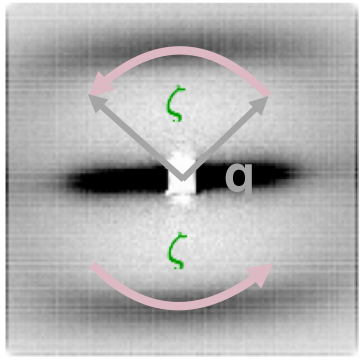


stress



- angular integration in $\zeta \in \left[-\frac{\pi}{4}, \frac{\pi}{4}\right]$

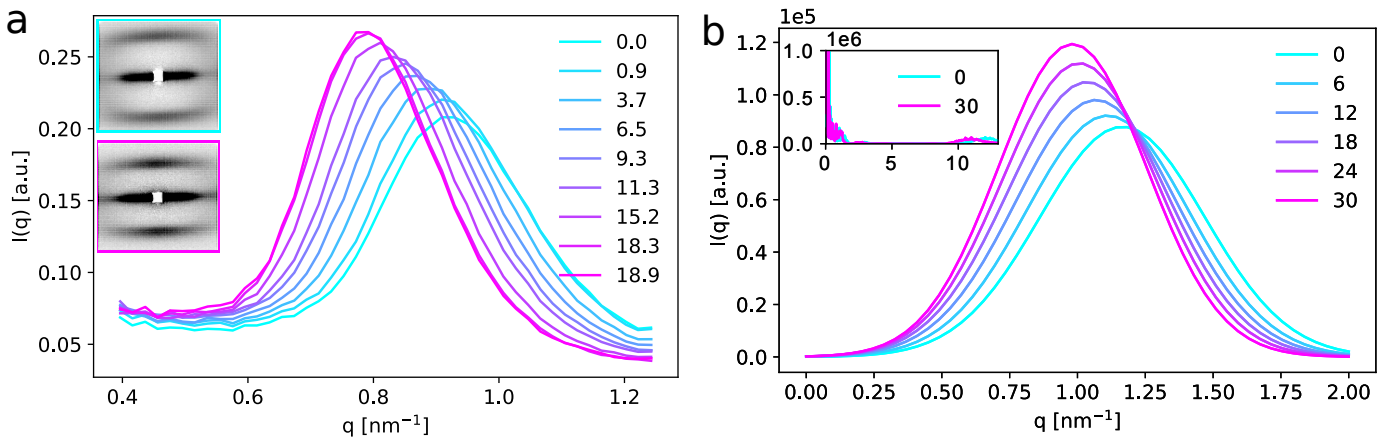




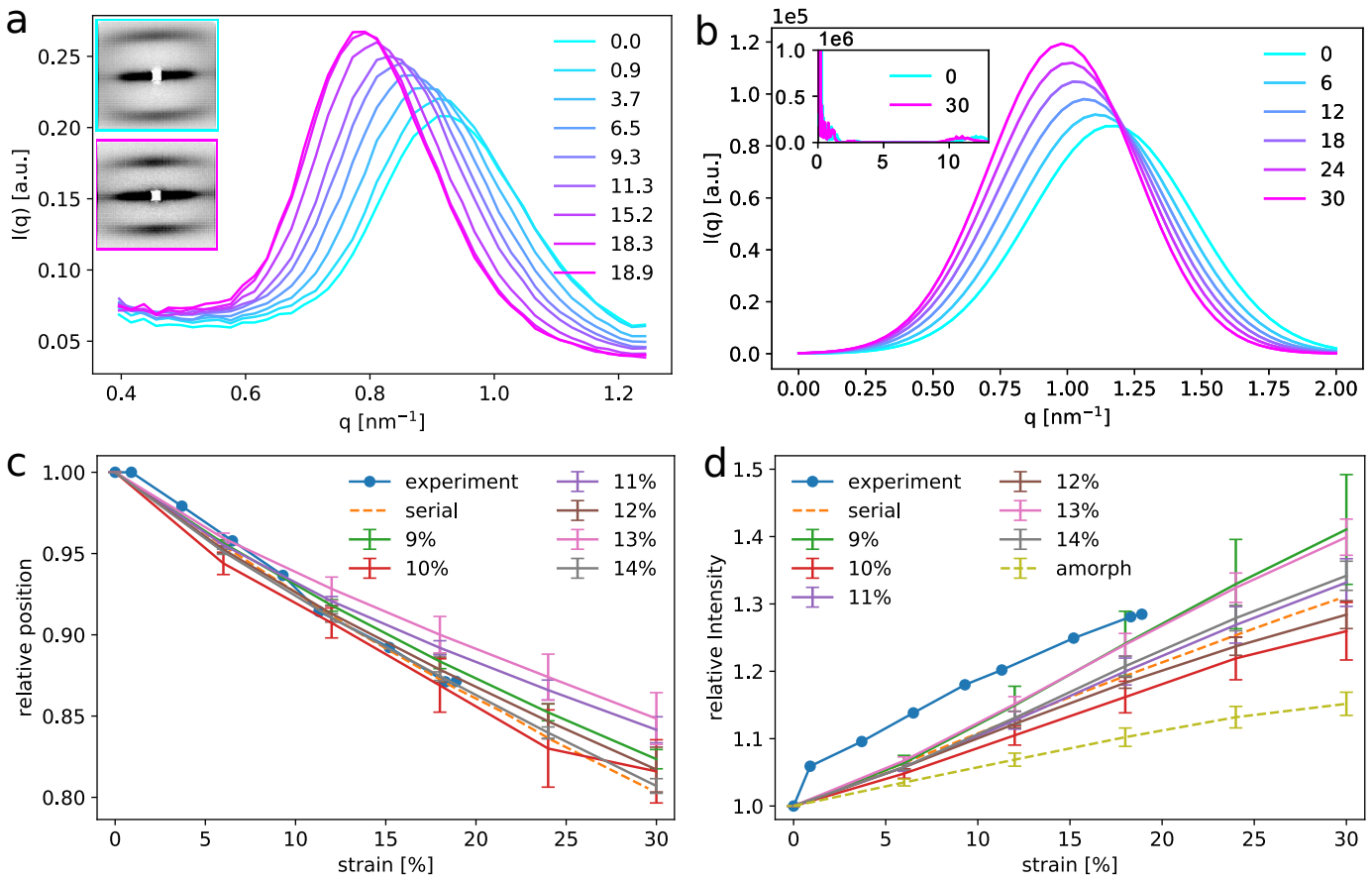
- apply rotation matrix on q and sum over ζ :

$$S(q) = \frac{1}{N}\sum_{\zeta}\sum_{i,j}^{N} e^{-i\langle \mathbf{R}(\zeta)\mathbf{q},\mathbf{r}_{ij}\rangle}$$

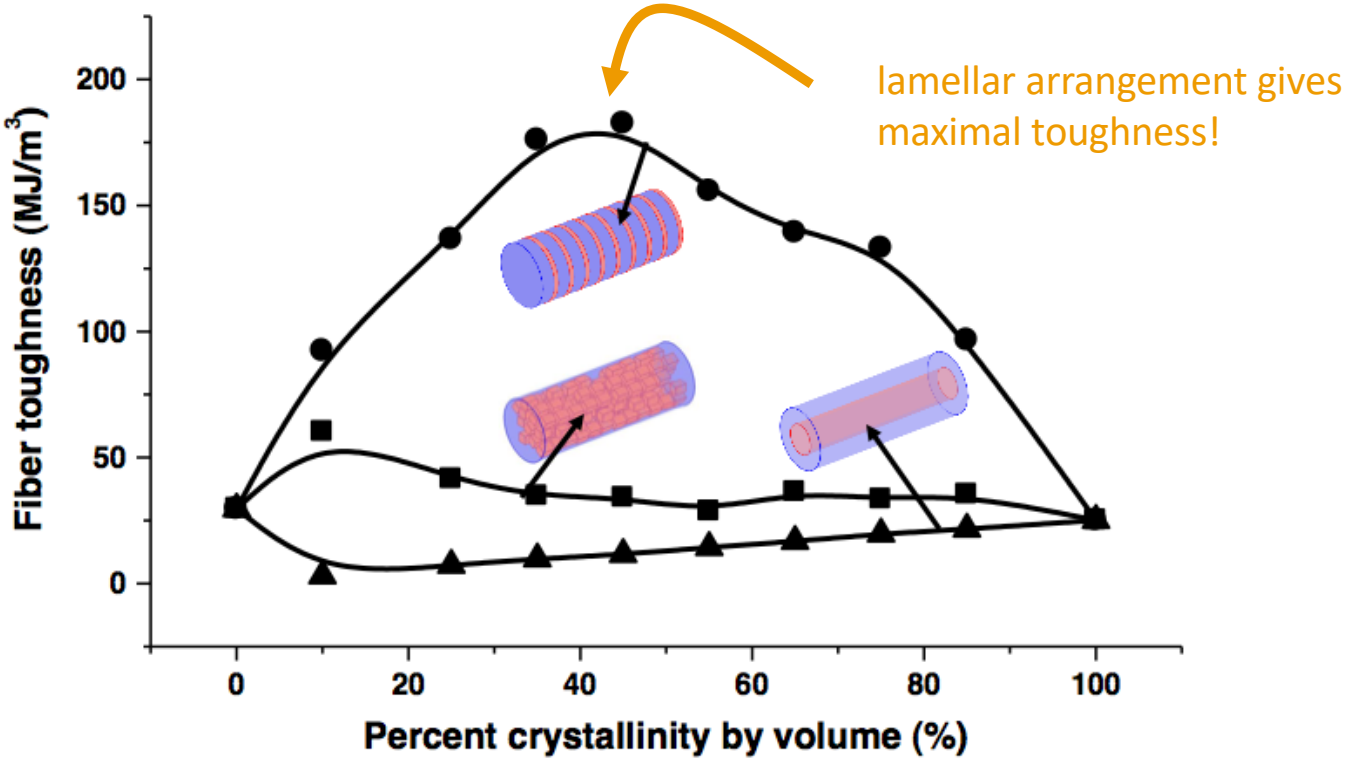
Stretch-induced self-ordering: confirmed by small angle neutron scattering



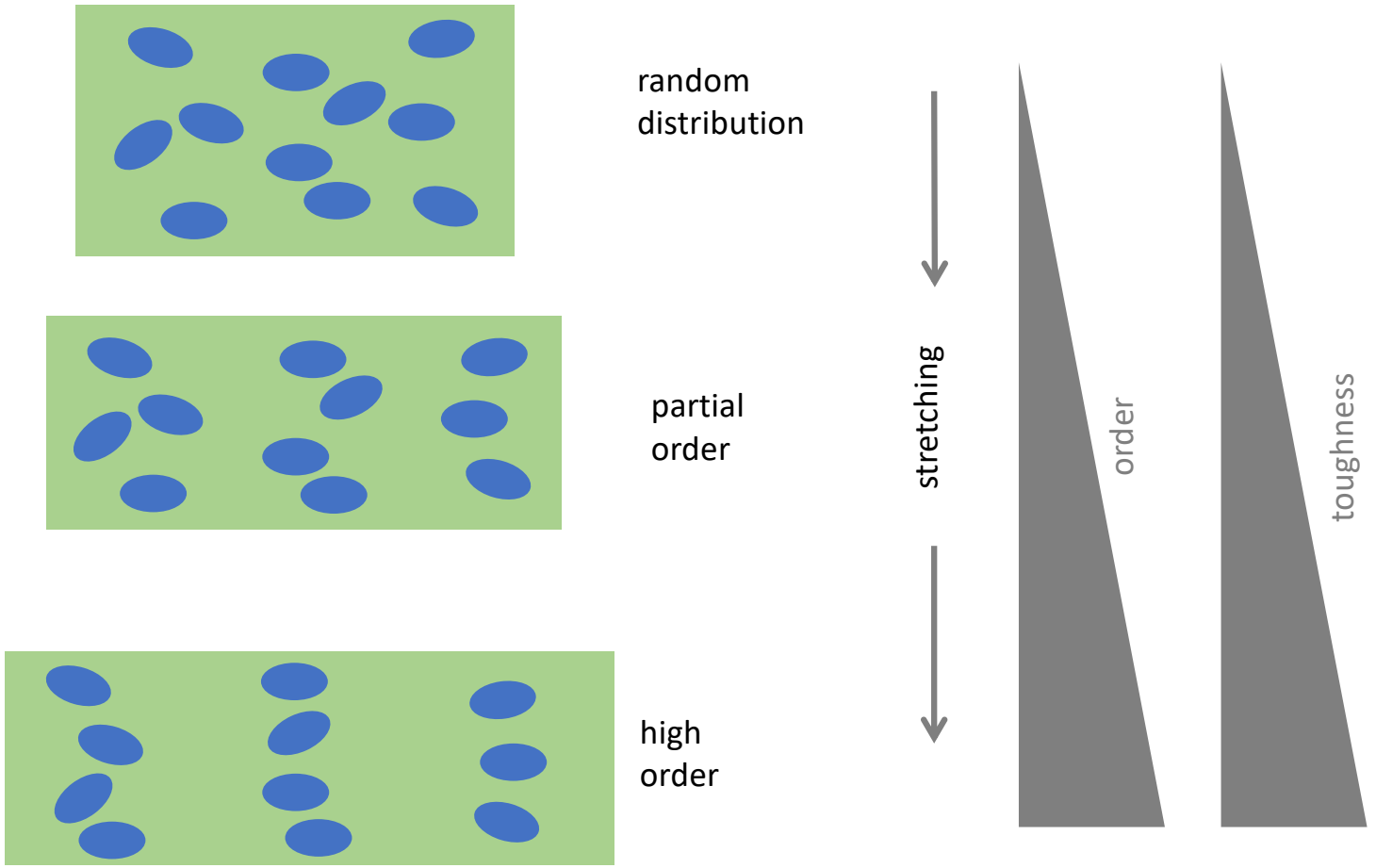
Stretch-induced self-ordering: confirmed by small angle neutron scattering



Toughness depends on long-range order

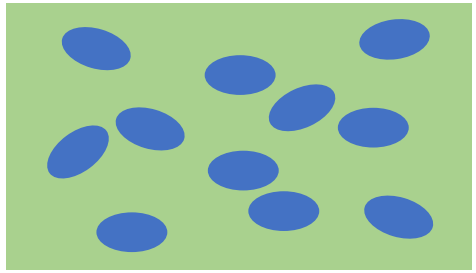


Stretch-induced self-ordering



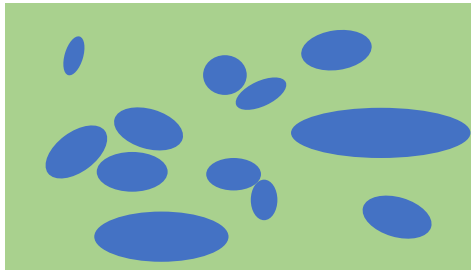
Stretch-induced self-ordering: silk as a block copolymer

silk or block-copolymer



crystallizes into similarly-sized nanoparticles from (Ala)x

semi-crystalline polymer (e.g. polystyrene)

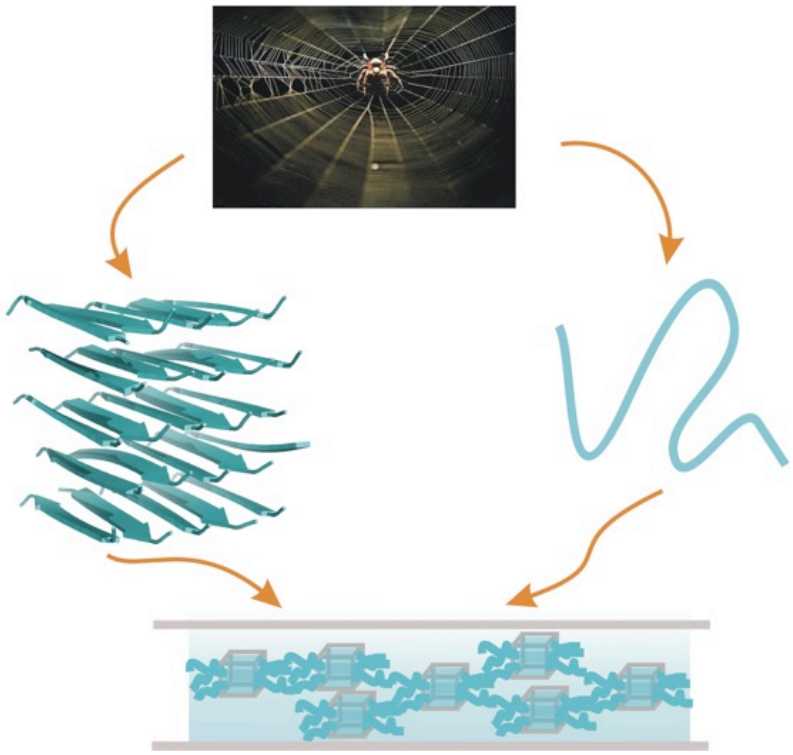


crystallizes here and there and everywhere

Conclusions

MD simulations & Finite element analysis can in combination bridge scales

Quantitative predictions by simulations? Yes!



Molecular Biomechanics

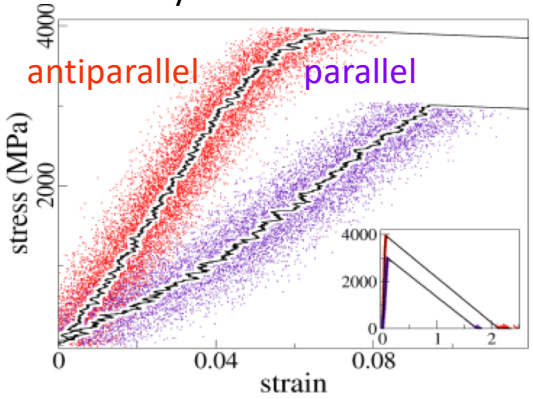
Ana Herrera-Rodriguez
Nicholas Maragakis
Florian Franz
Fabian Kutzki
Christopher Zapp
Agniezska Obarska-Kosinski
Fan Jin
Benedikt Rennekamp
Isabel Martin
Anna Schroeder

$$:
Klaus Tschira foundation
DFG, Volkswagen Foundation,
AvH,
Toyota

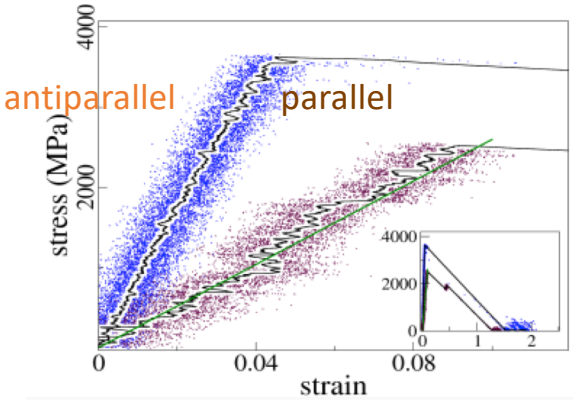
Mechanics of silk fibers

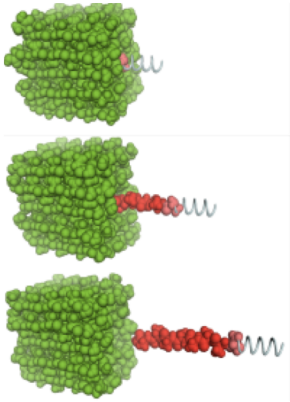
stress-strain curve
from Molecular Dynamics

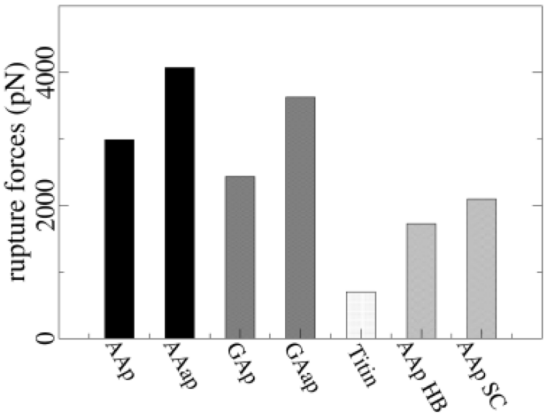
GA



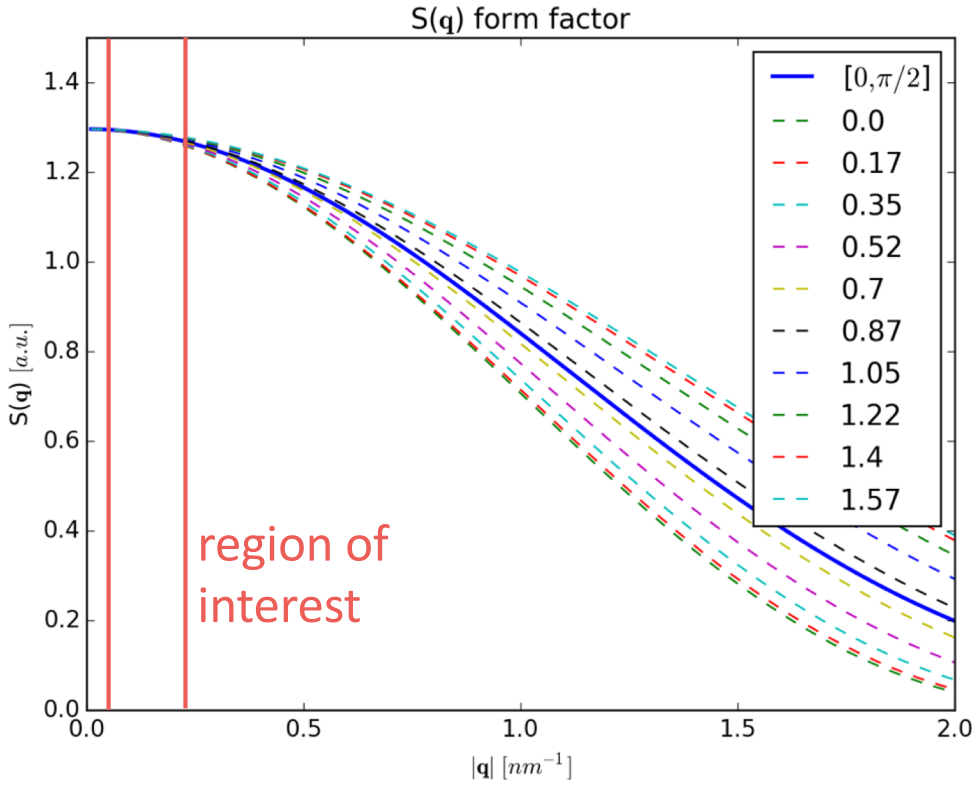
AA

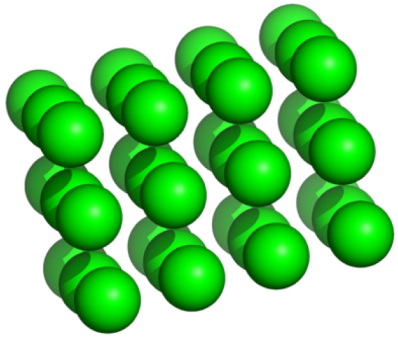




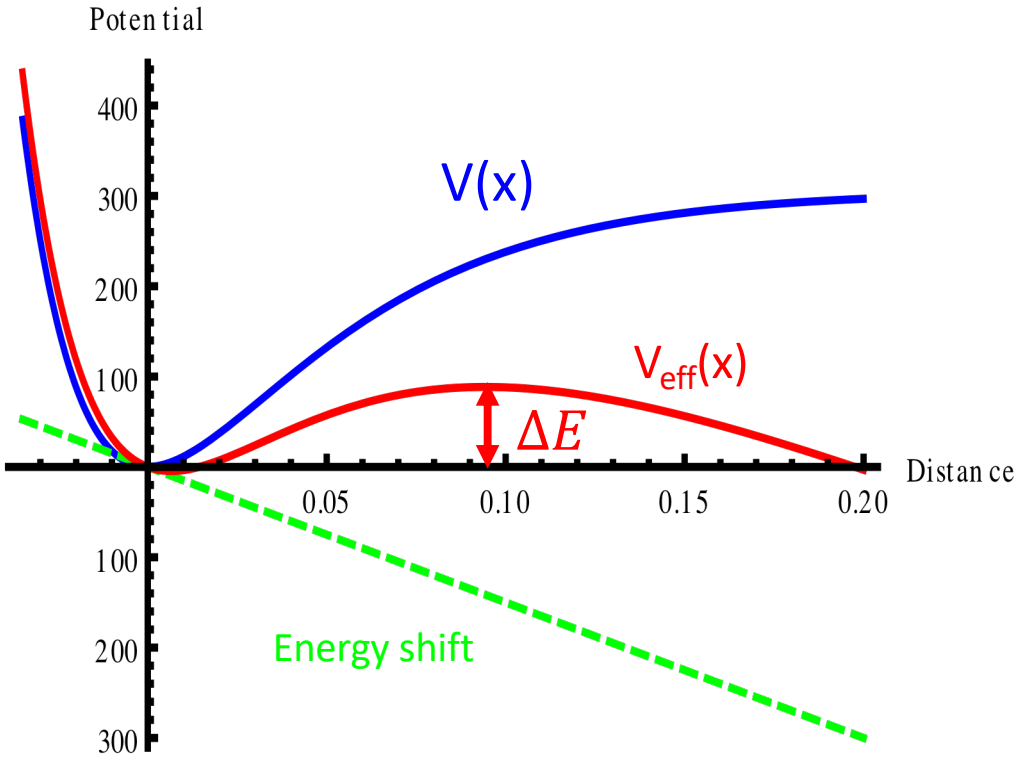


Form factor only





Model: How to calculate rupture rates?



Using Bell-Evans model for the potential and Arrhenius kinetics to calculate rupture rates; taking parameters for the potential from force field.

$$V(x) = D[1 - \exp(\beta(x - x_0))]^2$$

$$V_{eff} = V(x) - x \cdot V'(x_{curr})$$

$$\Delta E = V_{eff}(x_{max}) - V_{eff}(x_{min})$$

$$\Rightarrow k_{rupture} = A \cdot \exp(-\Delta E / k_B T)$$