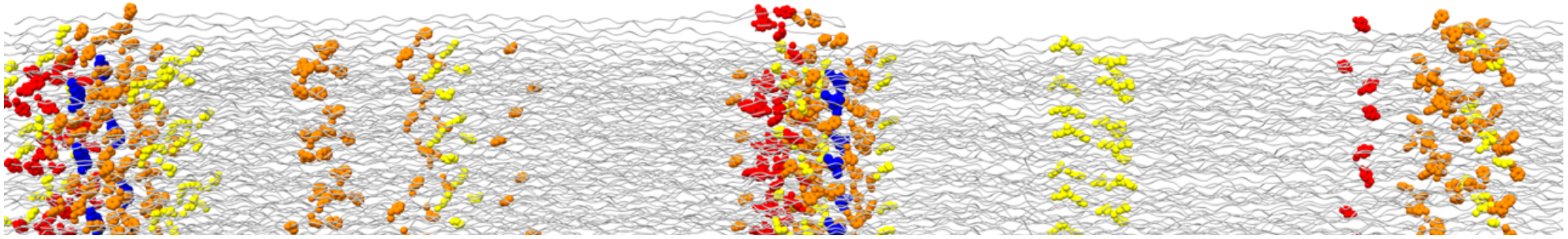
Heidelberg Institute for Theoretical Studies

HITS

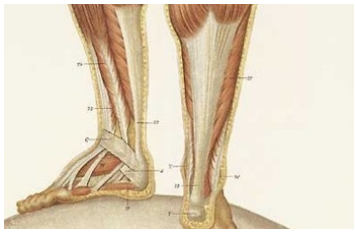
IWR Interdisciplinary Center for Scientific Computing

Simulations of biomaterials under force
Part I: Collagen

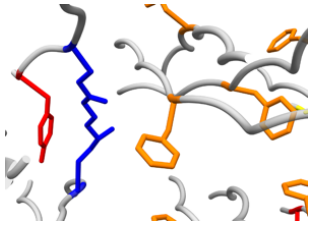
Frauke Gräter, Bogota, 09/2019

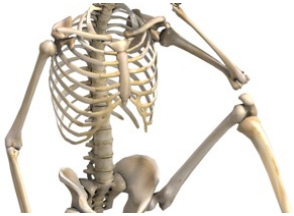


MOLECULAR (bio)mechanics – why?

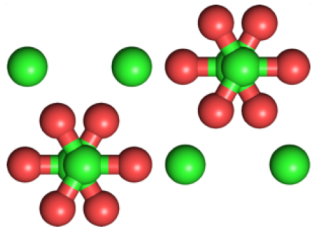


collagen

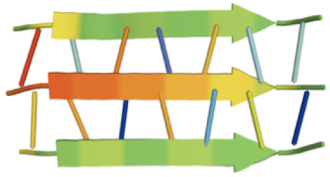




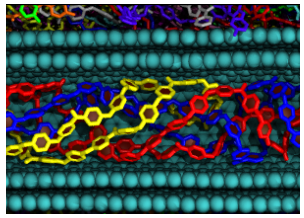
mineralized tissue



silk



polymer



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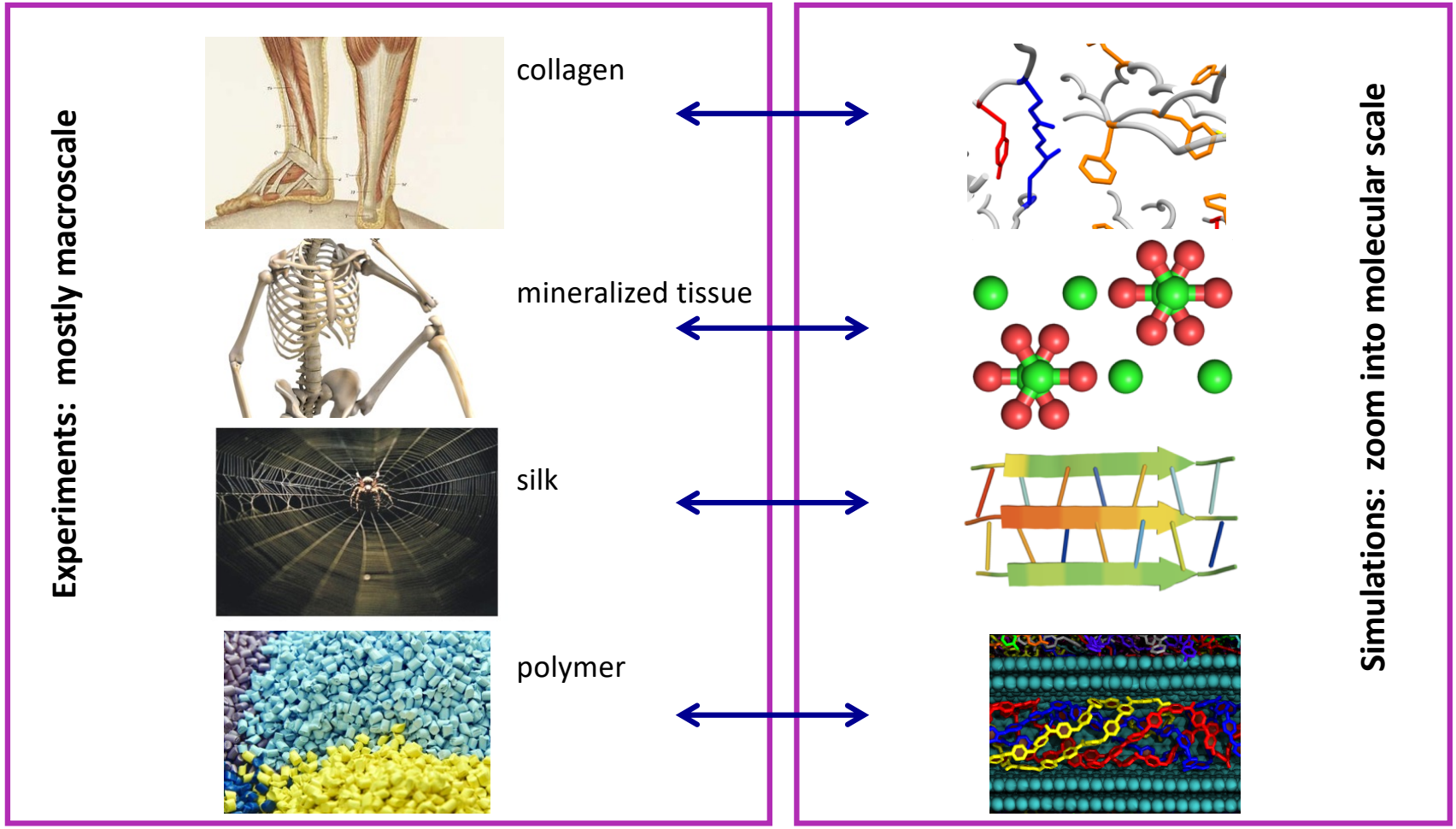

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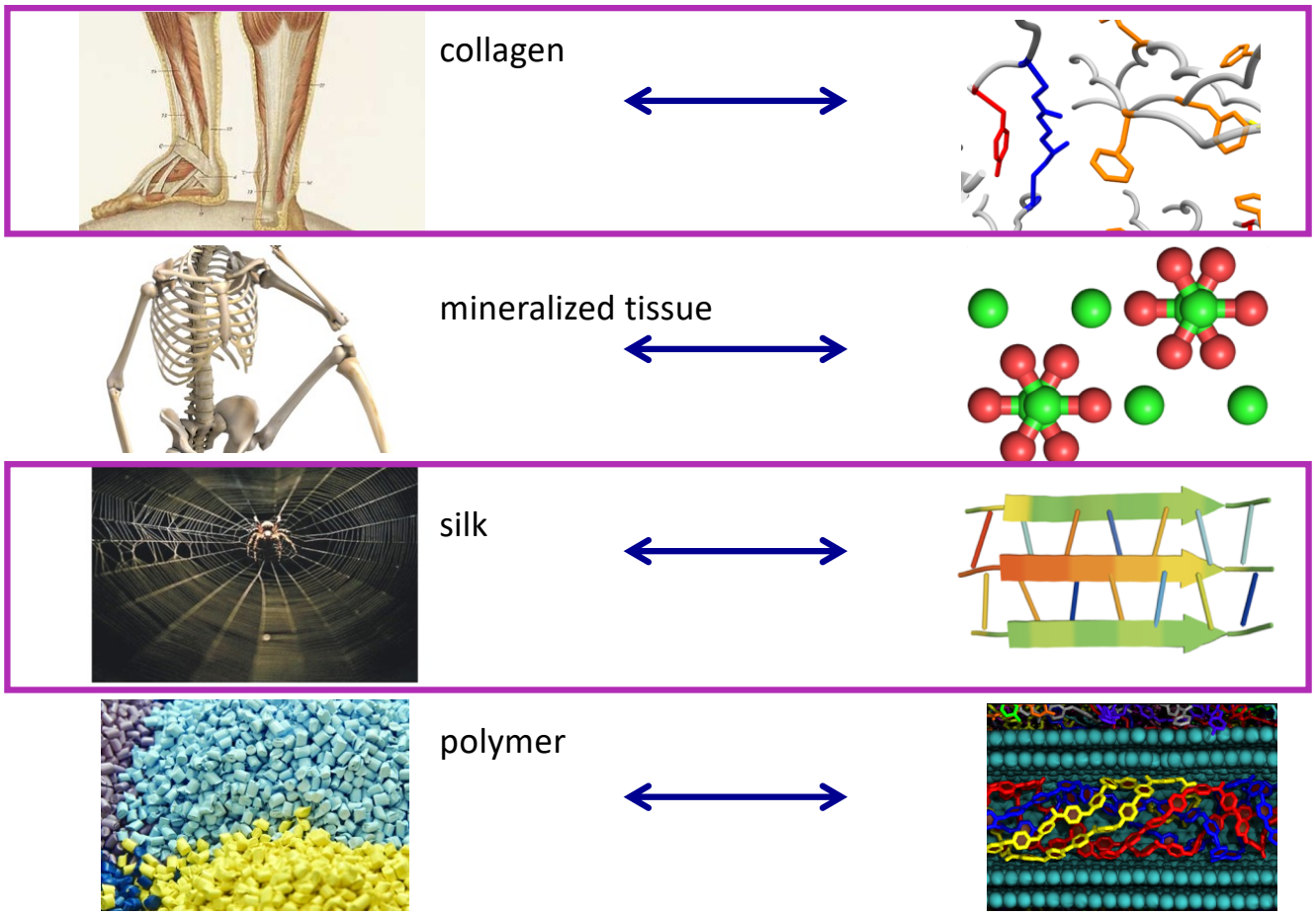
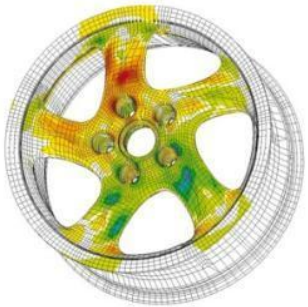


Strain and fracture: force distribution

conventional design tools:
force distribution

in constructions, cars ...



macroscopic structures:
meters

Strain and fracture: force distribution

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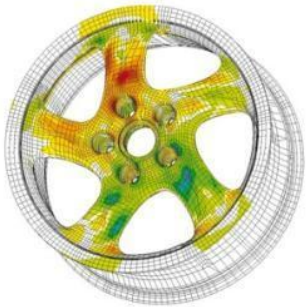
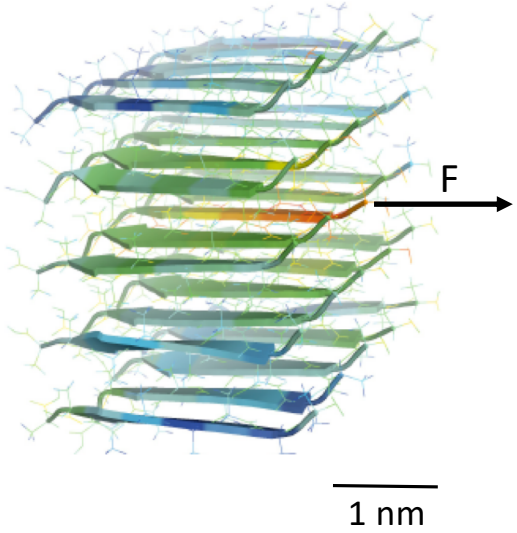


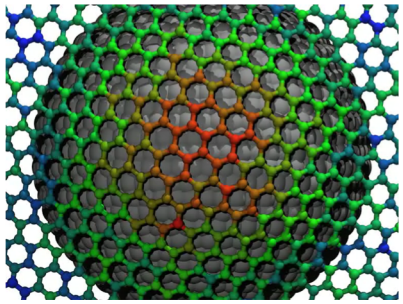
macroscopic structures:
meters

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

e.g.

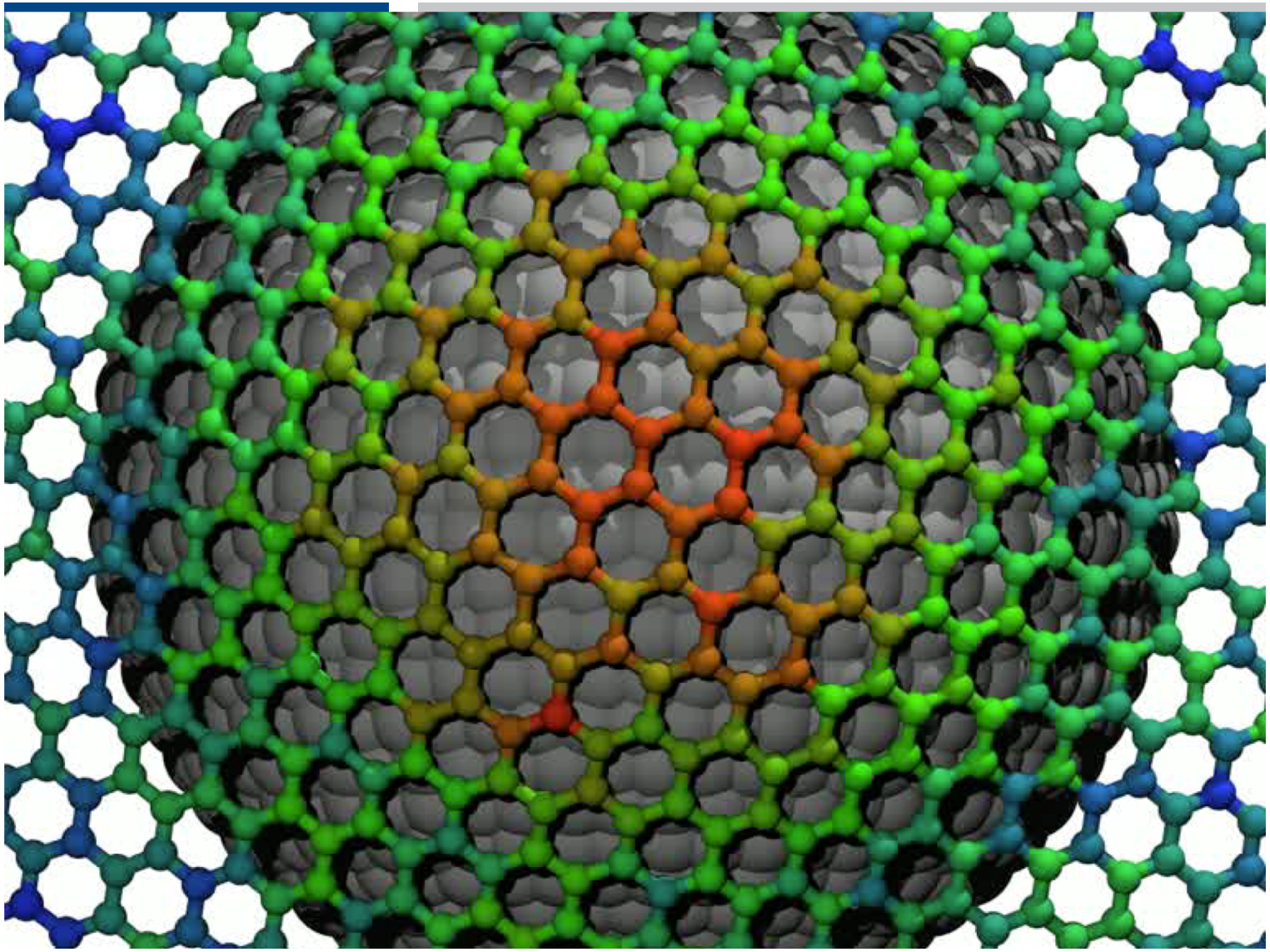


in graphene

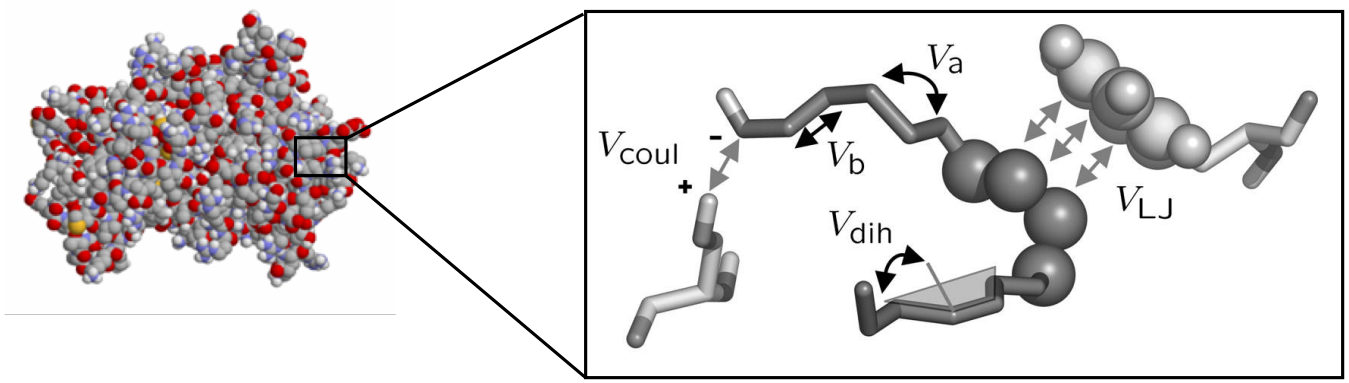


microscopic structures:
~ 10^{-9} meters

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



Forces from Molecular Dynamics simulations



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

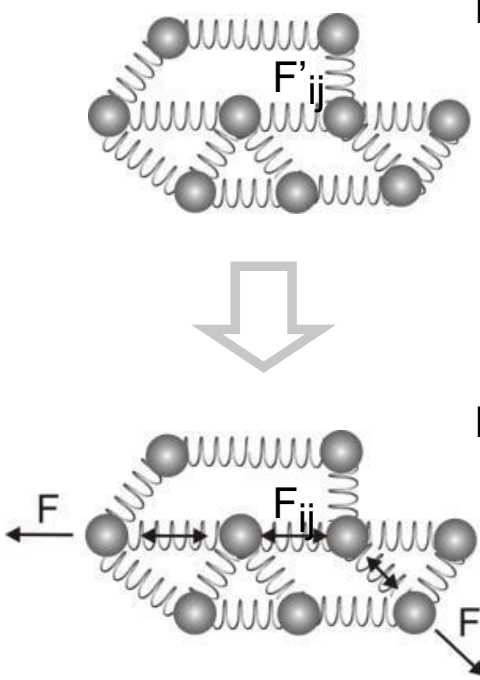
non-bonded interactions

&

2.

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

Forces from Molecular Dynamics simulations

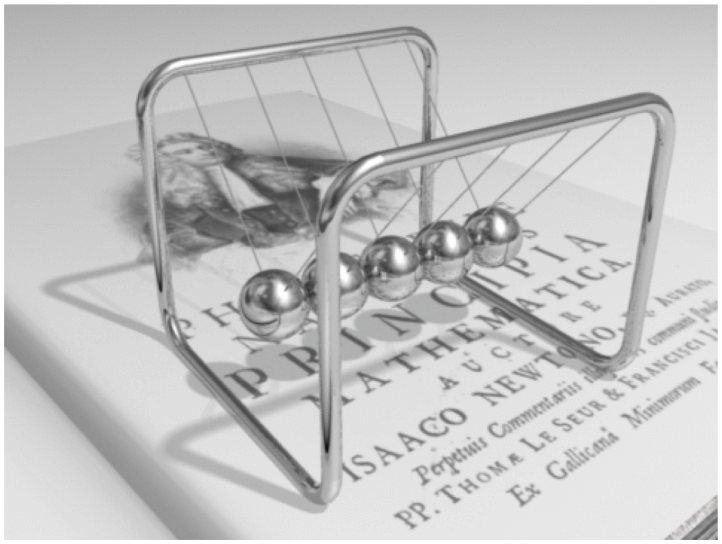


F'_{ij} force between atom i and j in relaxed state

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

change in pairwise forces

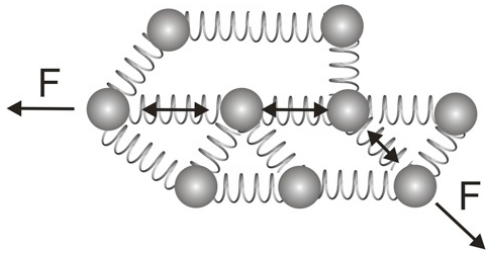
$$\Delta F_{ij} = F_{ij} - F'_{ij}$$



compare: Newton's cradle
(from wikipedia)

Forces from Molecular Dynamics simulations

Force Distribution Analysis
(Gromacs patch, on github)



change in pairwise forces

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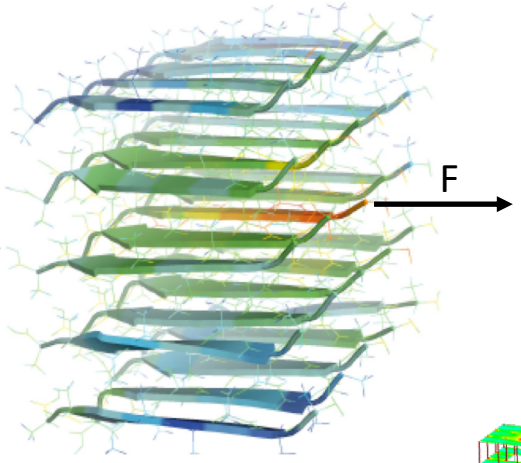
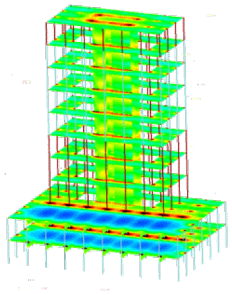


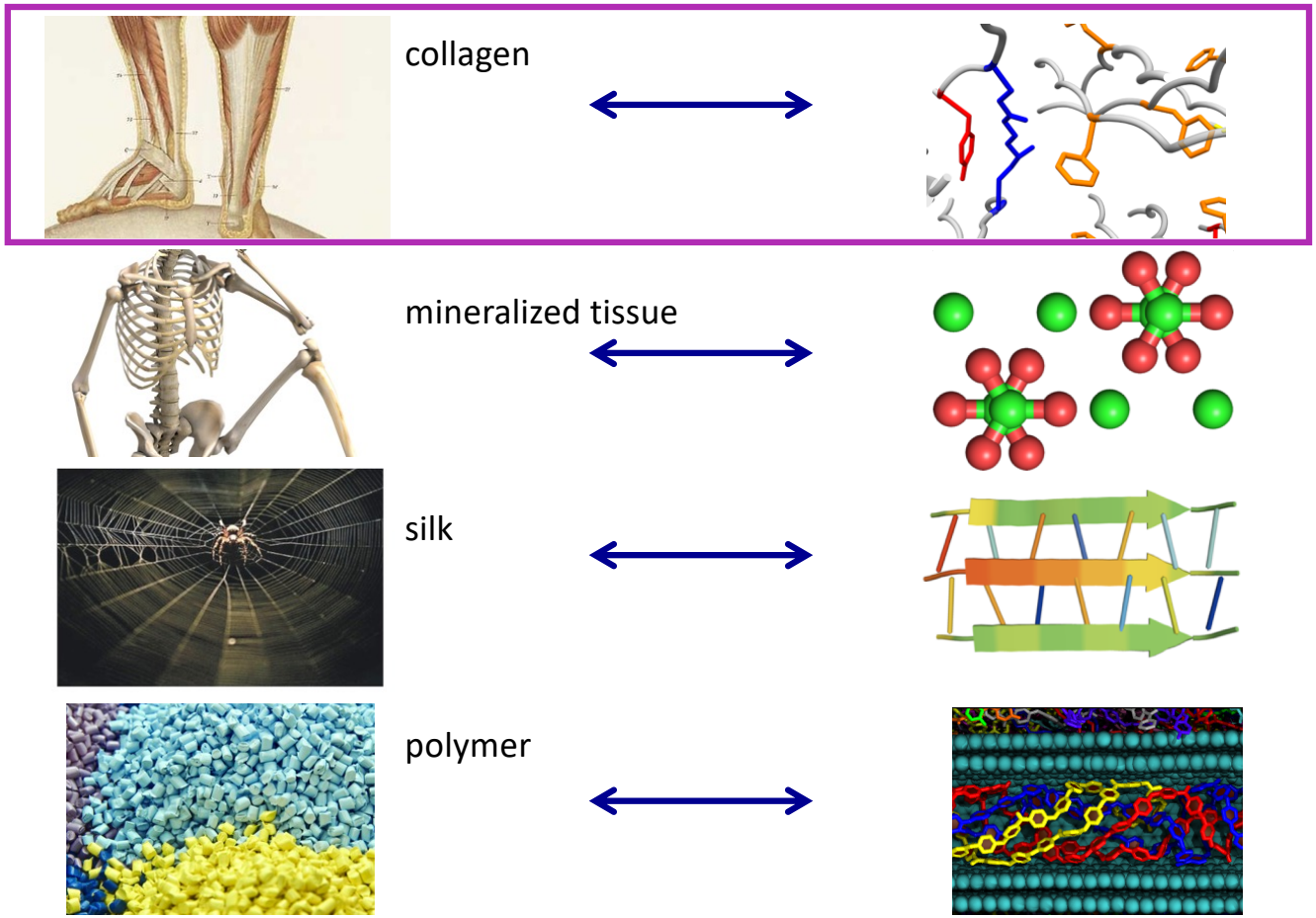
- with many applications to proteins
- here: internal strain in a structural component of silk fibers

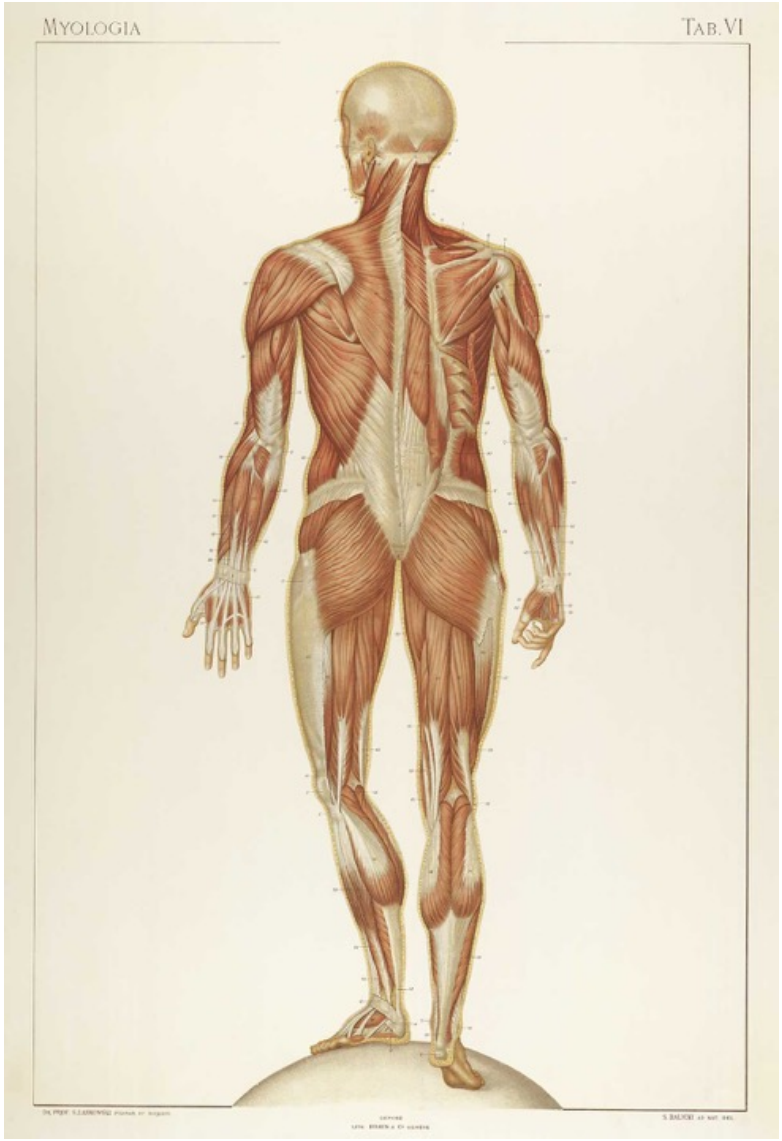
Compare:
force distribution
in large structures



compare: Admal/Tadmor 2010 (LAMMPS), Vanegas/Arroyo 2014 (Gromacs)

MOLECULAR (bio)mechanics – why?

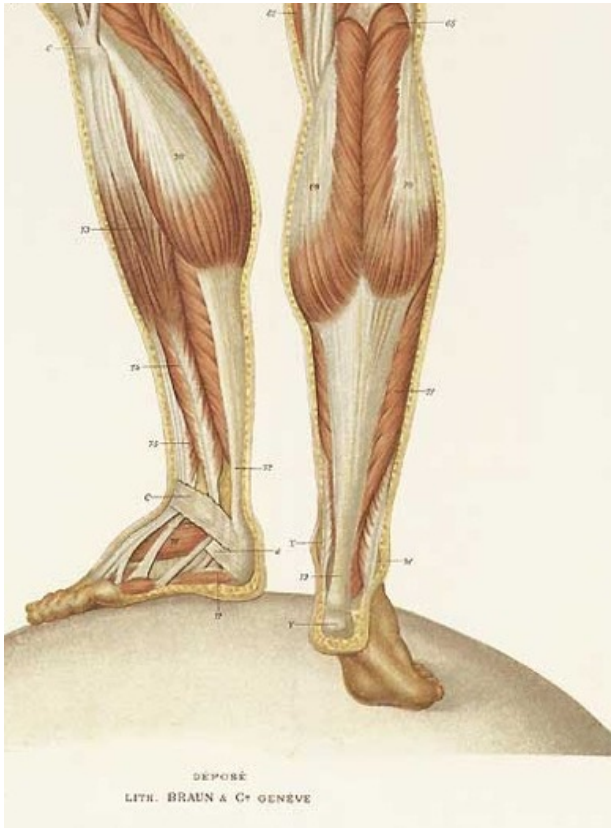




Collagen:
most abundant protein and major load-bearing structure of the body

Anatomic plate from Laskowski's "Anatomie normale du corps humain" (1894), illustrations by Sigismond Balicki

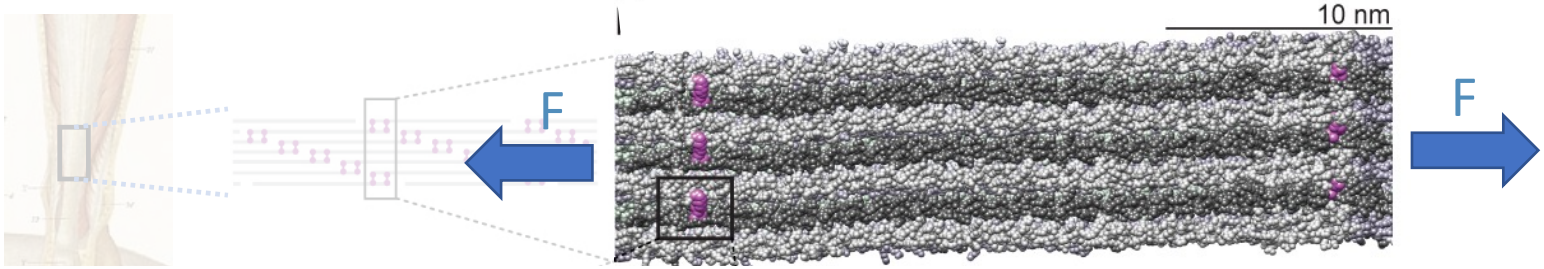
How does collagen behave under force?



highly elastic and resistant against mechanical load

human achilles tendon: bears 90 MPa (several times the body weight)

Collagen: let’s pull a nano-meter sized part of a fibril

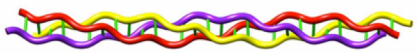


Wanted:
atomistic model
of collagen

Collagen: integrative modelling of all-atom fibril

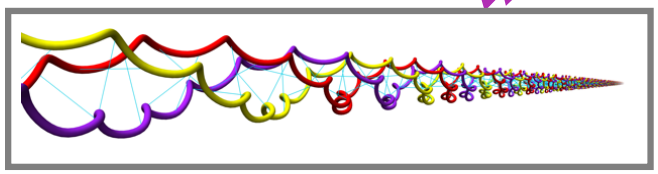
Agnieszka
Obarska-Kosinska

X-ray structures,
high resolution, 1.2-1.8 Å



Kramer et al. J Mol Biol. 1998 etc.

THEBuScr
triple-helical
builder
JK Rainey, MC Goh



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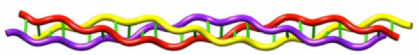

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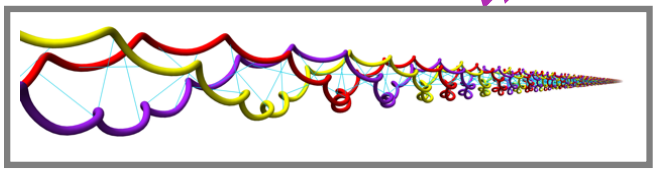
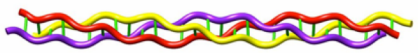


X-ray fiber diffraction structure, low resolution: 5.2 Å axial/11 Å equatorial

Orgel et al, PNAS 2006

Collagen: integrative modelling of all-atom fibril

X-ray structures,
high resolution, 1.2-1.8 Å



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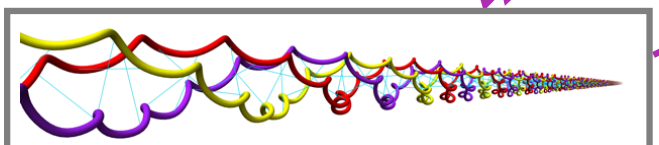

low resolution template

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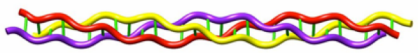

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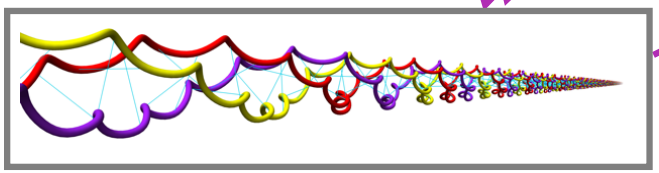

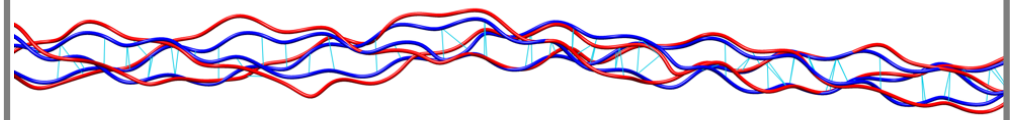

low resolution template
refined model using distance-restraints from high-res data

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Collagen: integrative modelling of all-atom fibril

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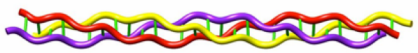

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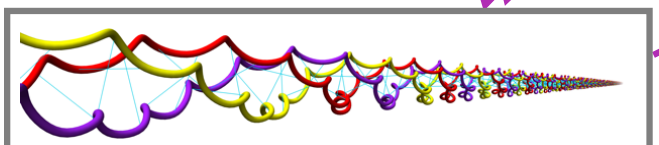

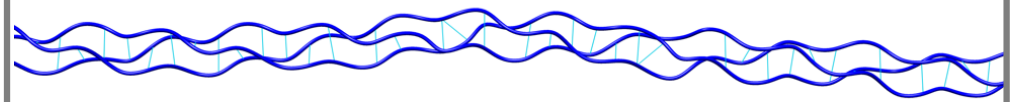

refined model integrating low and high resolution data

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Collagen: integrative modelling of all-atom fibril

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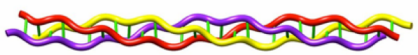
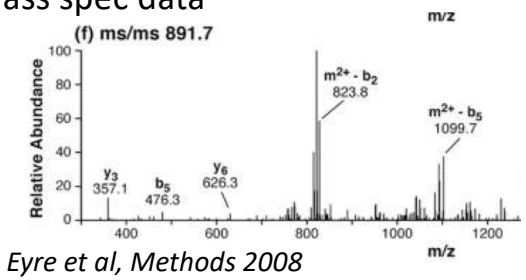
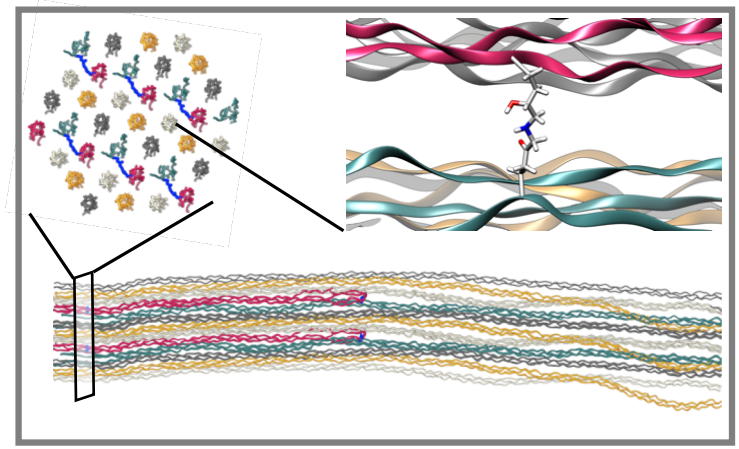


Kramer et al. J Mol Biol. 1998 etc.

Mass spec data



eg Eyre et al, Methods 2008



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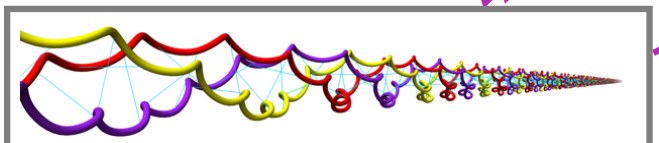

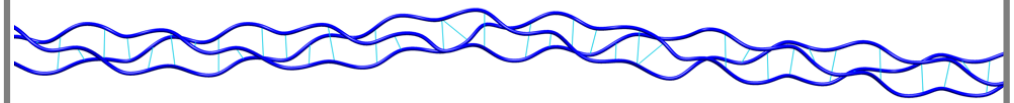

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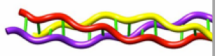
Orgel et al, PNAS 2006

Collagen: integrative modelling of all-atom fibril

Mass spec data

X-ray structures
high resolutio



Kramer et al. J M

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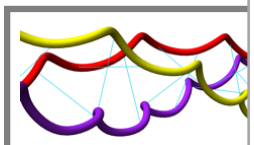
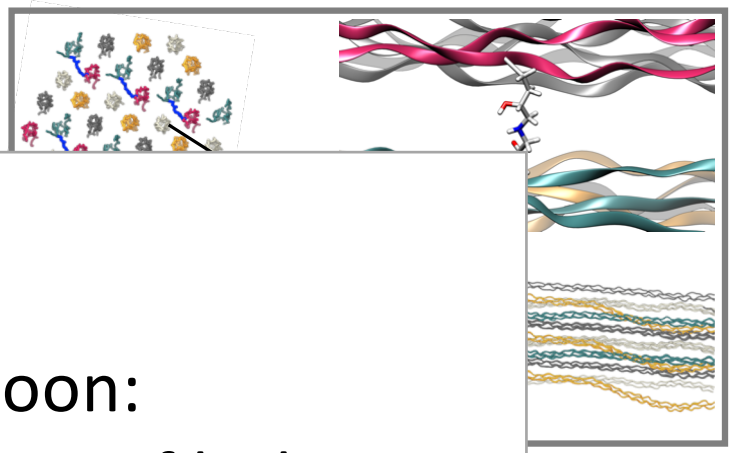
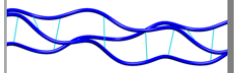






ion data

X-ray fiber di

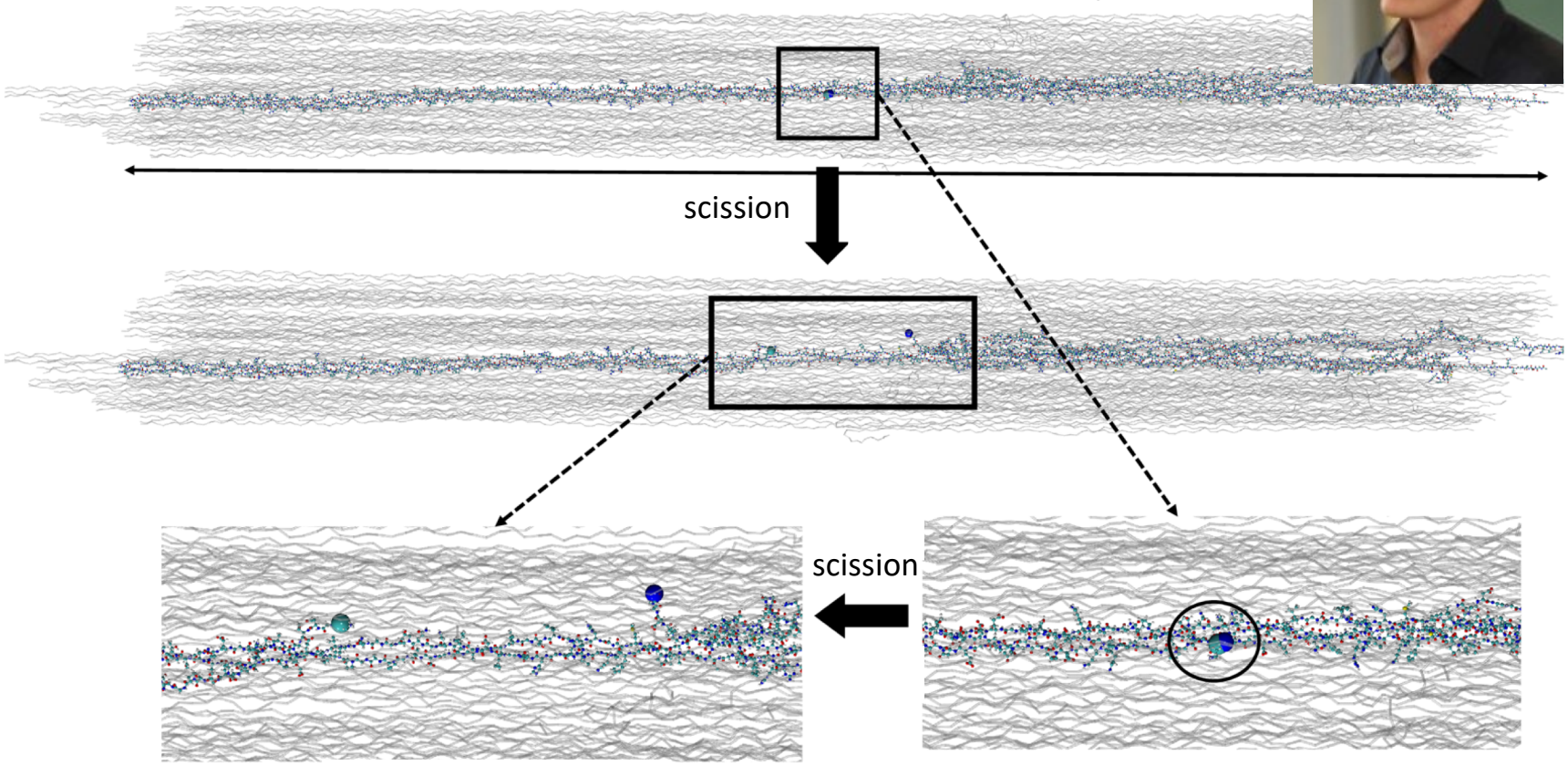
Orgel et al, PNAS 2006

Up and running (hopefully) soon:
web service to generate collagen fibril models at wish

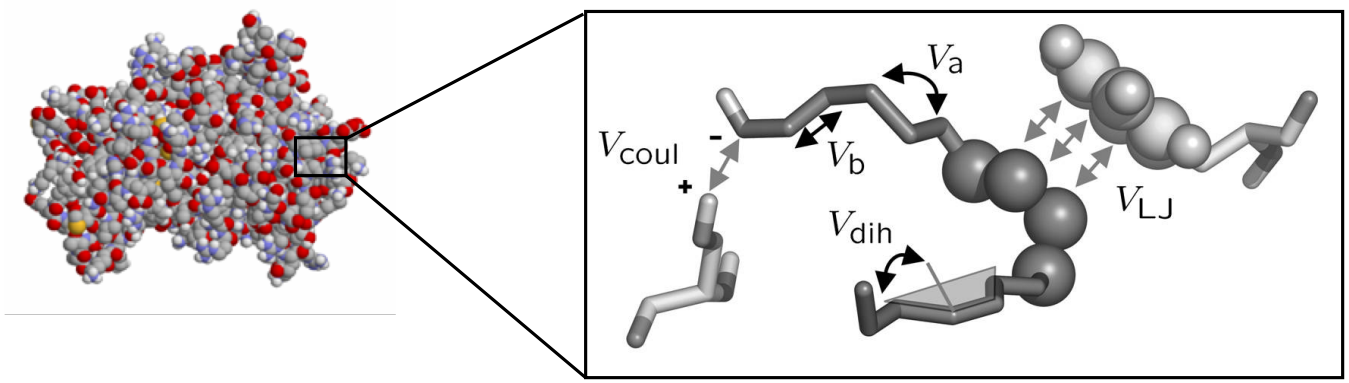
Obarska-Kosinska et al, in preparation

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

Benedikt Rennekamp



Molecular Dynamics simulations: bonds can not rupture!



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\end{aligned}
$$

bonded interactions ⟷

non-bonded interactions ⟷

2.

&

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

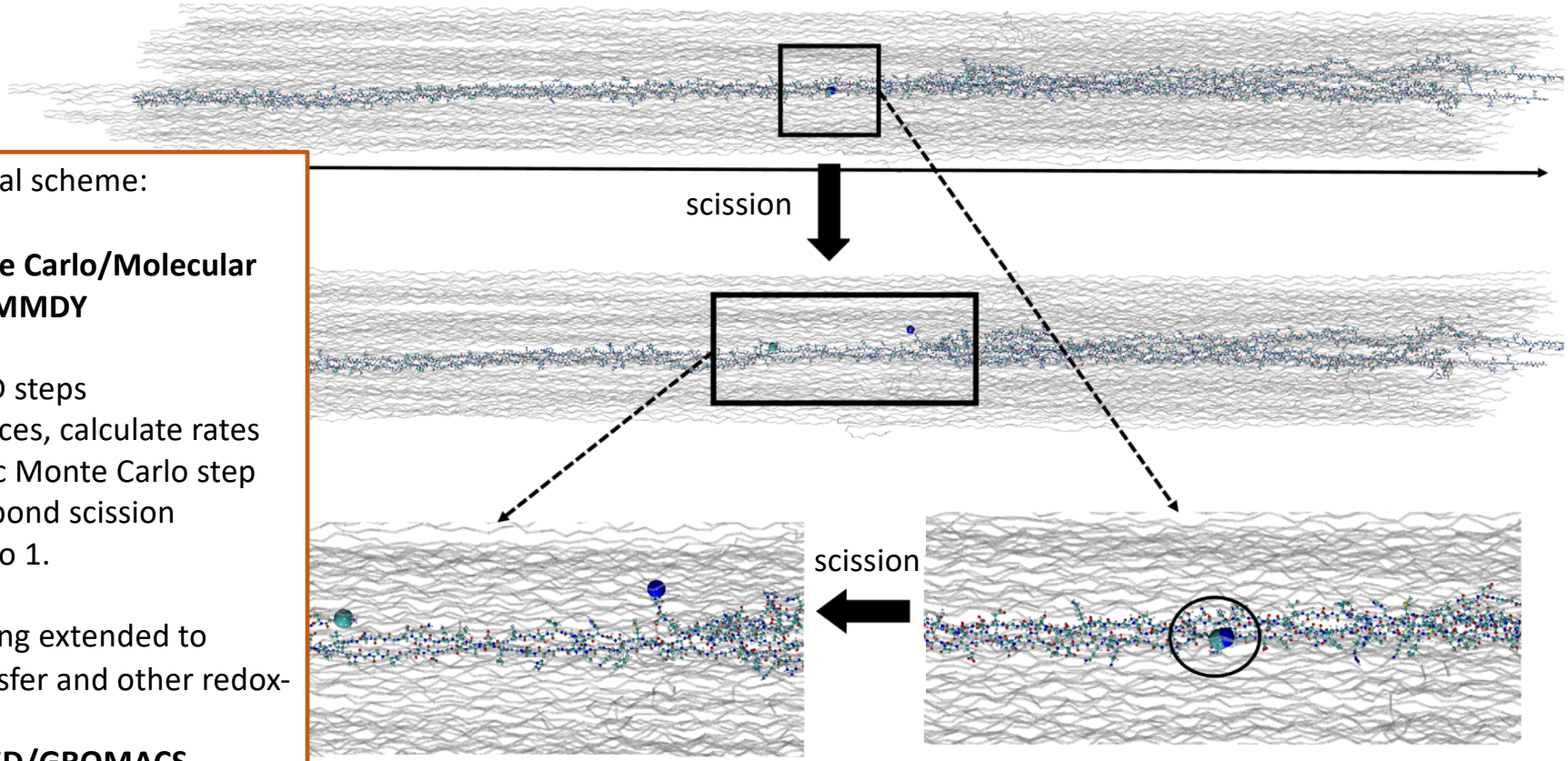
“Reactive” Molecular Dynamics: spontaneous chemical events on-the-fly

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.

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



Rennekamp, Gräter, in review

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,….

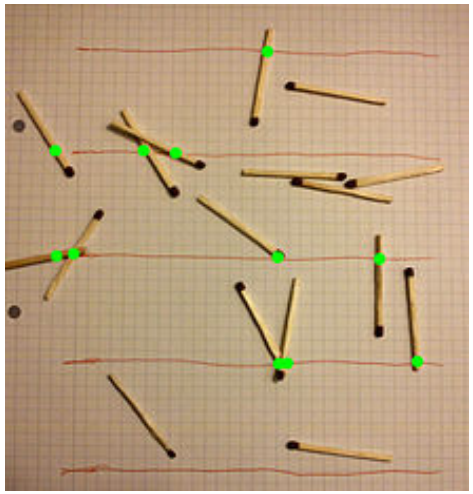
Monte Carlo methods: some history

some history: the name was suggested by Metropolis, at Los Alamos National Laboratories for a method put forward by Fermi/Ulam for calculations of neutron diffusion

Monte Carlo methods: some history

Strength of random sampling:

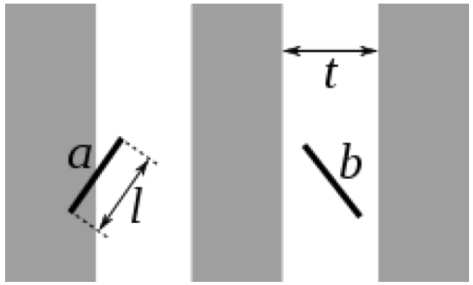
Calculation of π by Laplace
(based on the Buffon Experiment)



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?

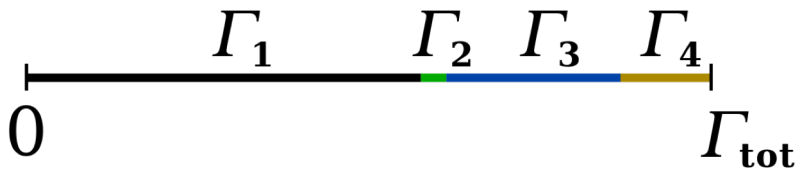
n needles,
h of them crossing the strips
l length of needles
t width of strips

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



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.

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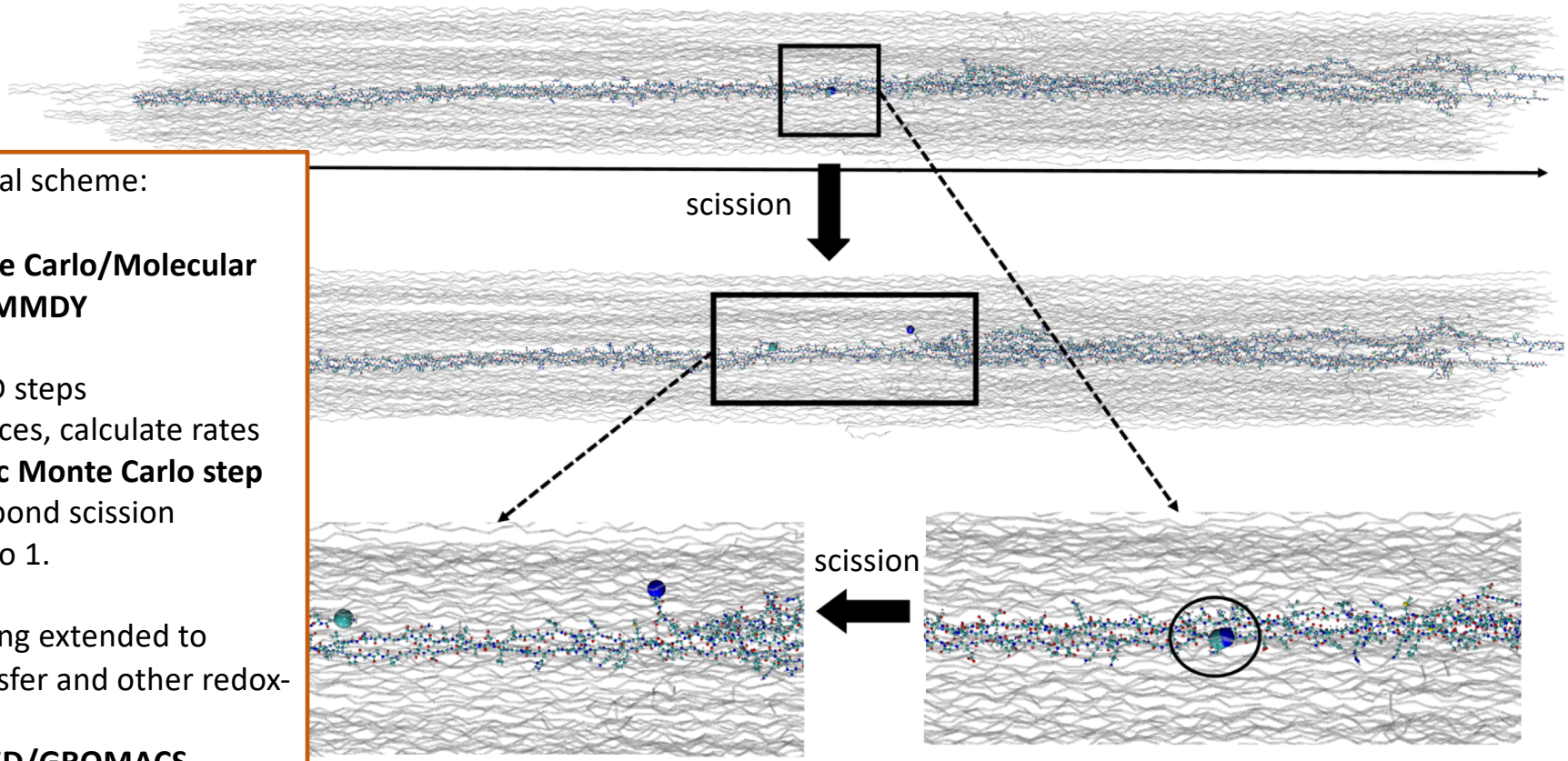
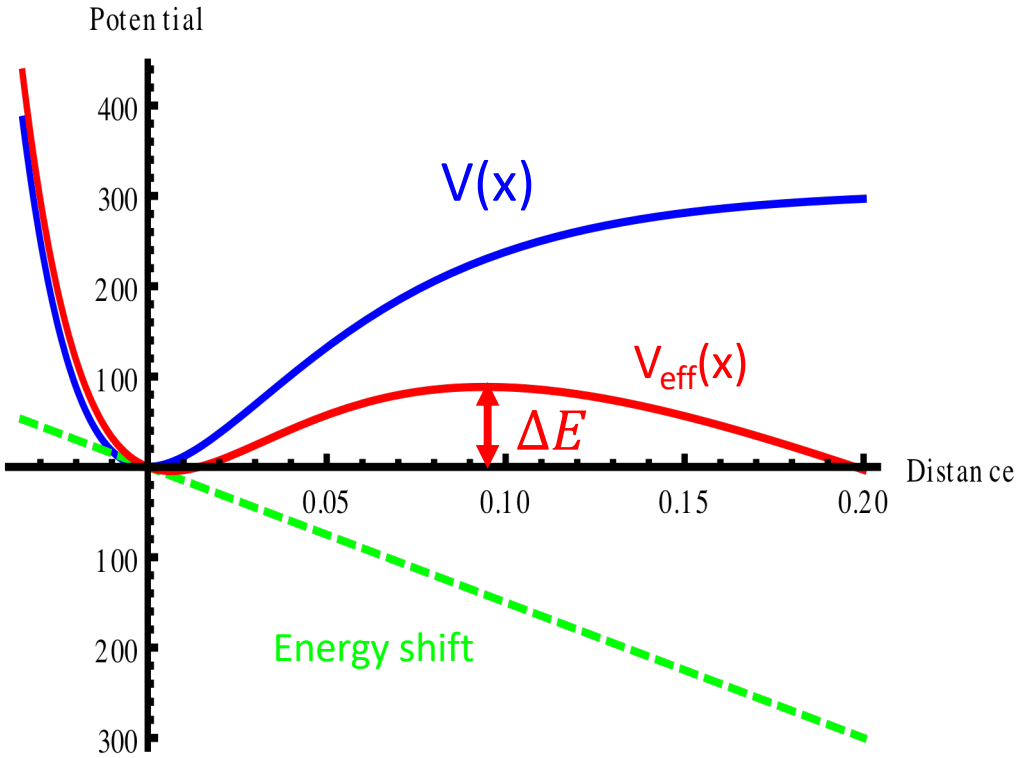
Using **PLUMED/GROMACS**



Rennekamp, Gräter, in review

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.

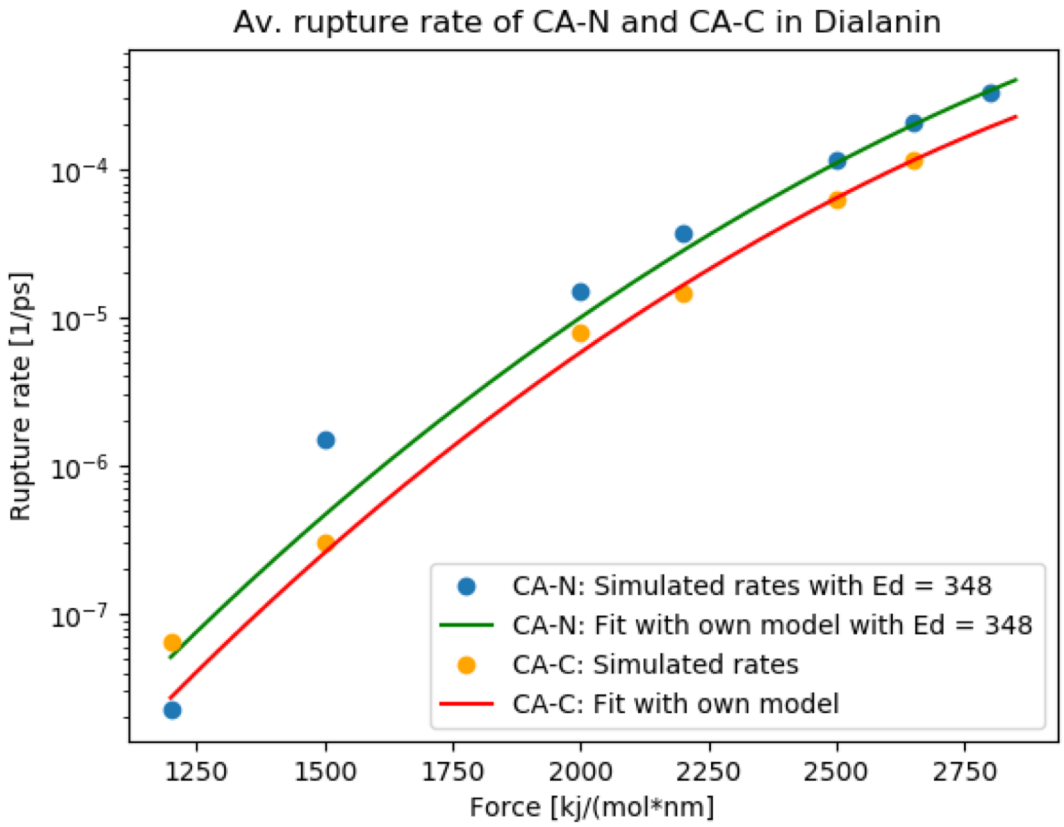
$$V(x) = D[1 - \exp(\beta(x - x_0))]^2$$

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

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

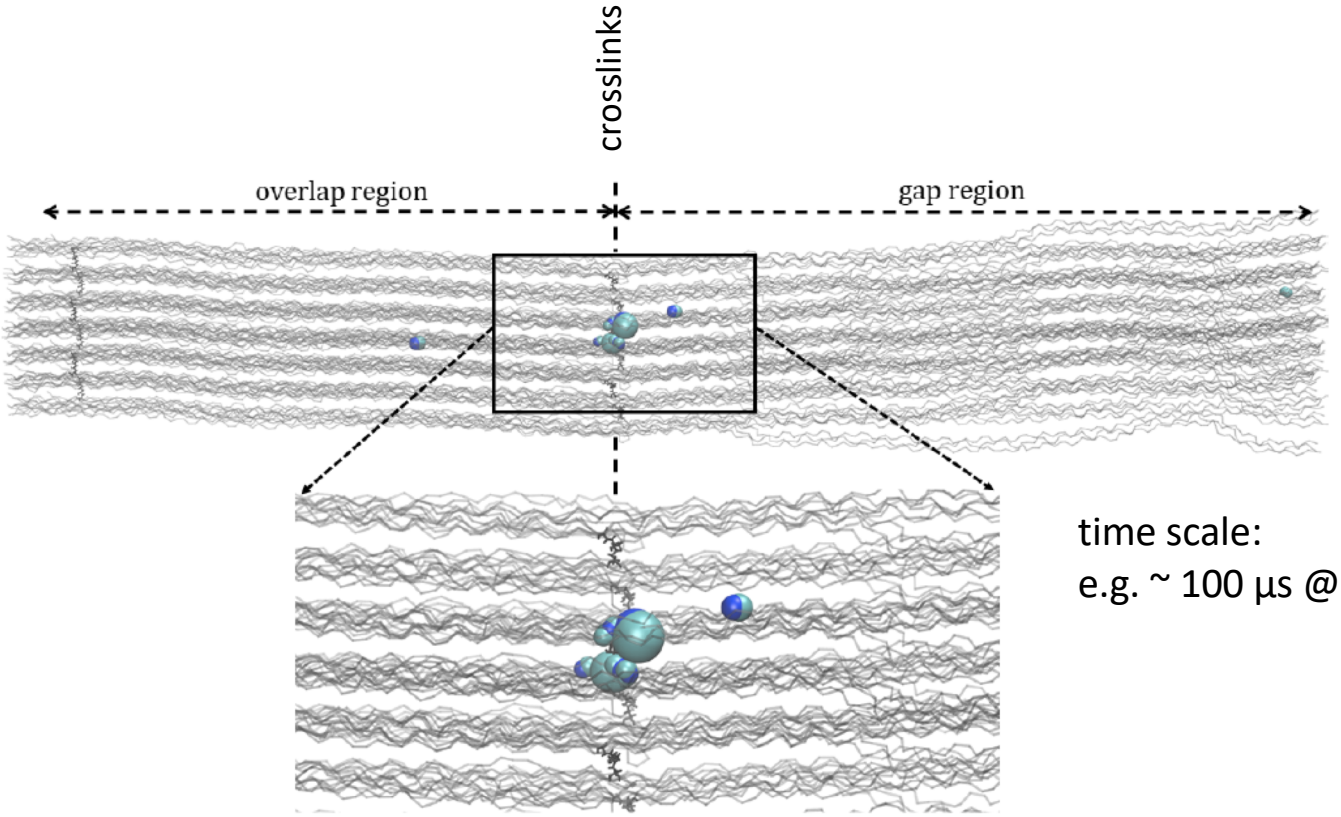
$$\Rightarrow k_{rupture} = A \cdot \exp(-\Delta E / k_B T)$$

Weakest bonds and their rates



E_{dis} (CA-N) = 348 = E_{dis} (CA-C)

It works: Rupture preferentially occurs around crosslinks



time scale:
e.g. ~ 100 µs @ F=1.5 nN

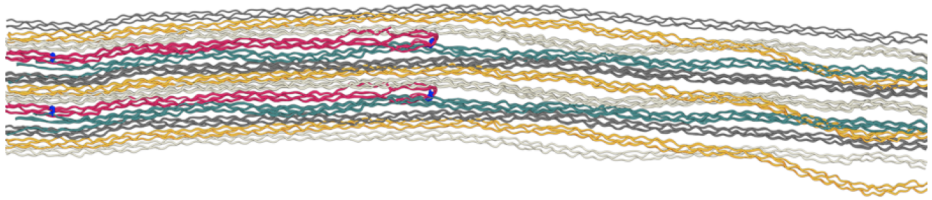
Molecular Biomechanics

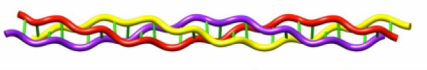
Ana Herrera-Rodriguez
Nicholas Maragakis
Florian Franz
Fabian Kutzki
Christopher Zapp
Agniezska Obarska-Kosinski
Fan Jin
Benedikt Rennekamp
Isabel Martin
Anna Schroeder

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

Collagen: integrative modelling of atomistic system

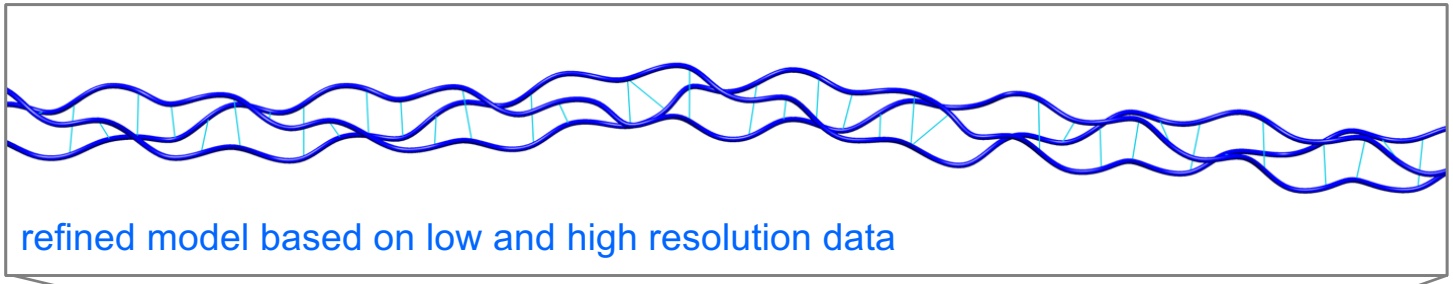
X-ray structures,
high resolution, 1.2-1.8 Å
1Z1R, 1A3J, 1CAG, 1QSU





Kramer et al. J Mol Biol. 1998
Okuyama, Biopolymers. 2009
etc.

THEBuScr
triple-helical
builder
JK Rainey, MC Goh



X-ray fiber diffraction structure 3HR2
low resolution: 5.2 Å axial/11 Å equatorial
Orgel et al, PNAS 2006