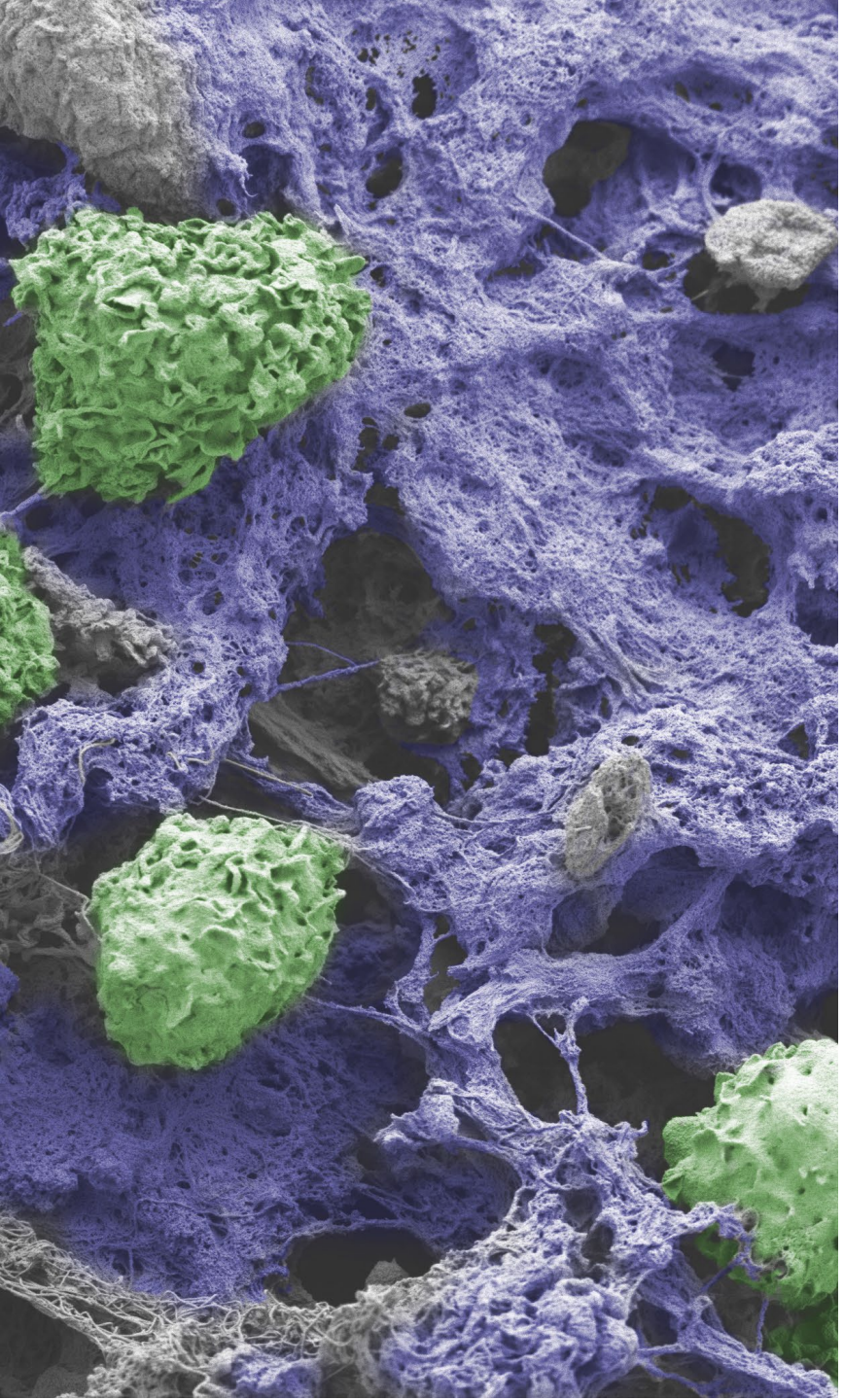
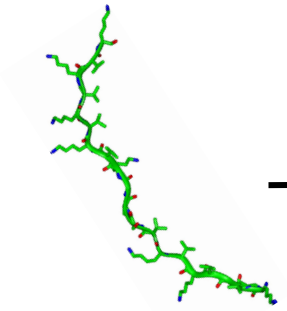


The Impact of Chirality on Self-Assembled Peptide Gels

National Academies of Sciences
Engineering and Medicine
2025

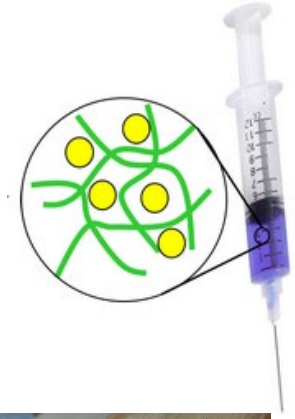
Joel P. Schneider, Ph.D.

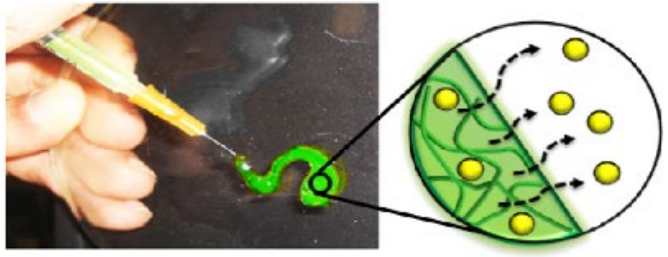
Syringe Injectable Hydrogels for Localized Therapeutic Delivery



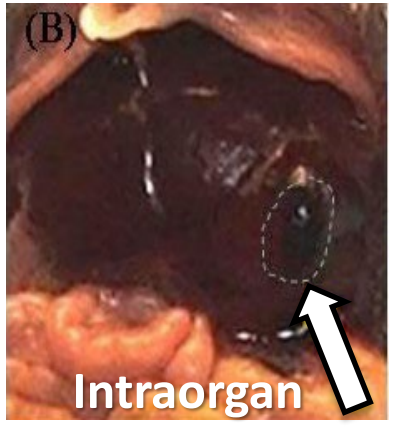
Triggered Self-assembly
& Gelation

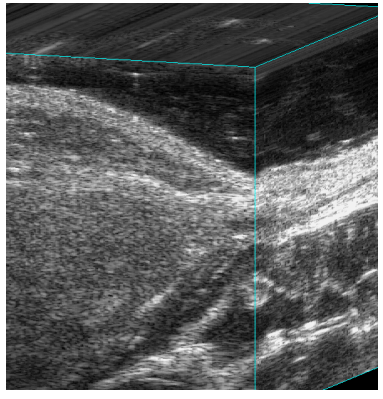
+ Therapeutic



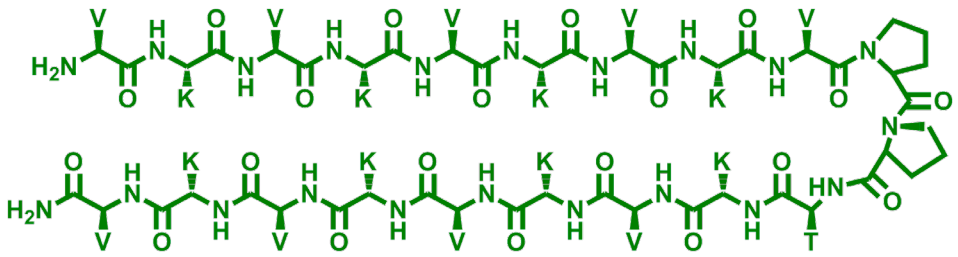


Trigger = pH, Salt, Heat,
Light, Metal ions, Cell culture media,
Enzymatic action

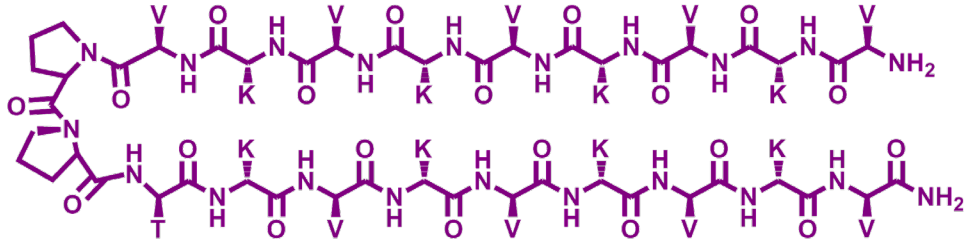




Controlling Biodegradation using Enantiomeric Peptide Mixtures

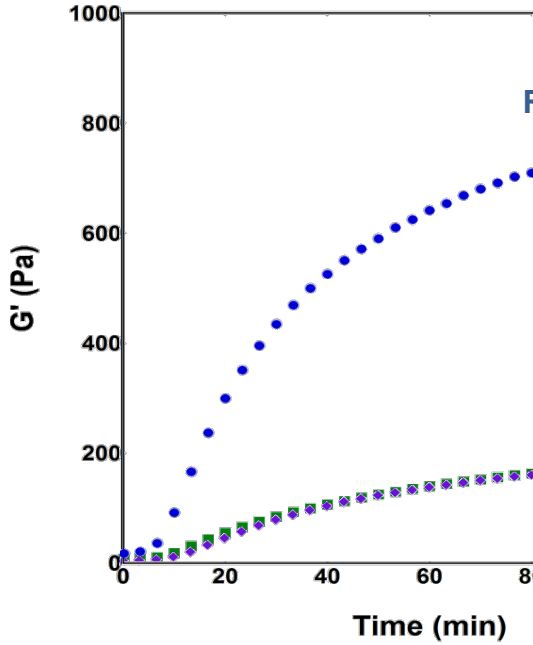


MAX1: VKVKVKVKV^{D}P^{L}PTKVKVKVKV-NH$_2$

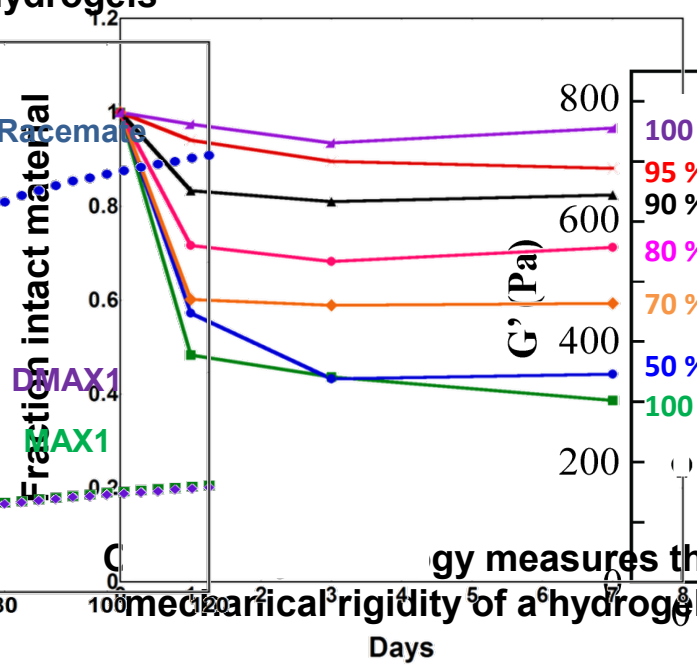


DMAX1: *VKVKVKVKV*^{L}P^{D}*PTKVKVKVKV*-NH$_2$

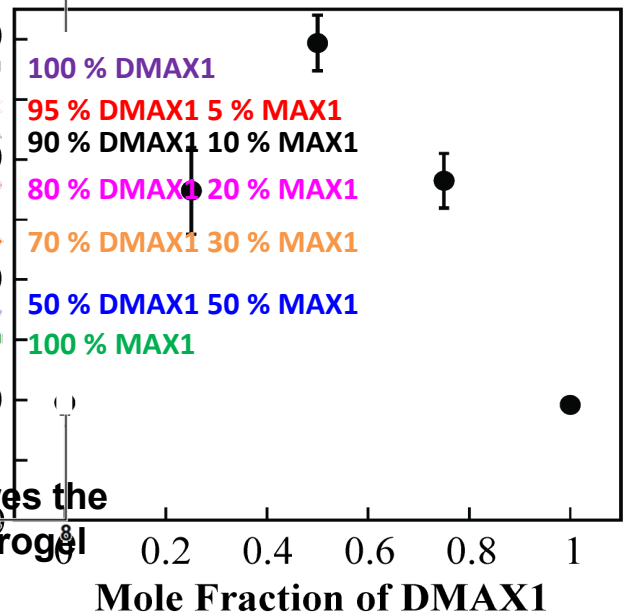
Rheology of 1 wt% Hydrogels



Hydrogel Degradation by Trypsin (125 nM)



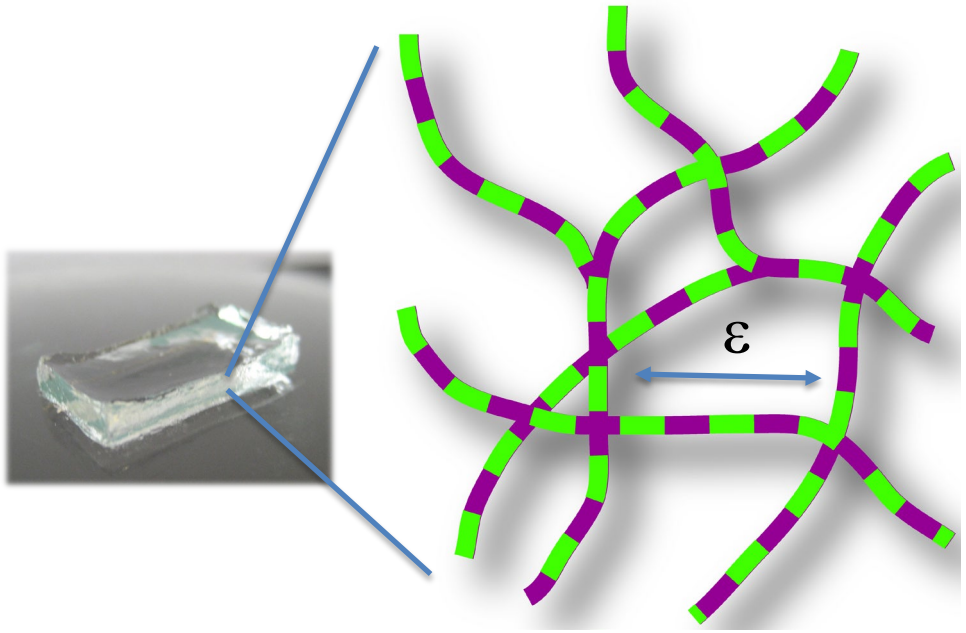
Mole Fraction Titration
(total material = 1 wt%)



gy measures the
mechanical rigidity of a hydrogel

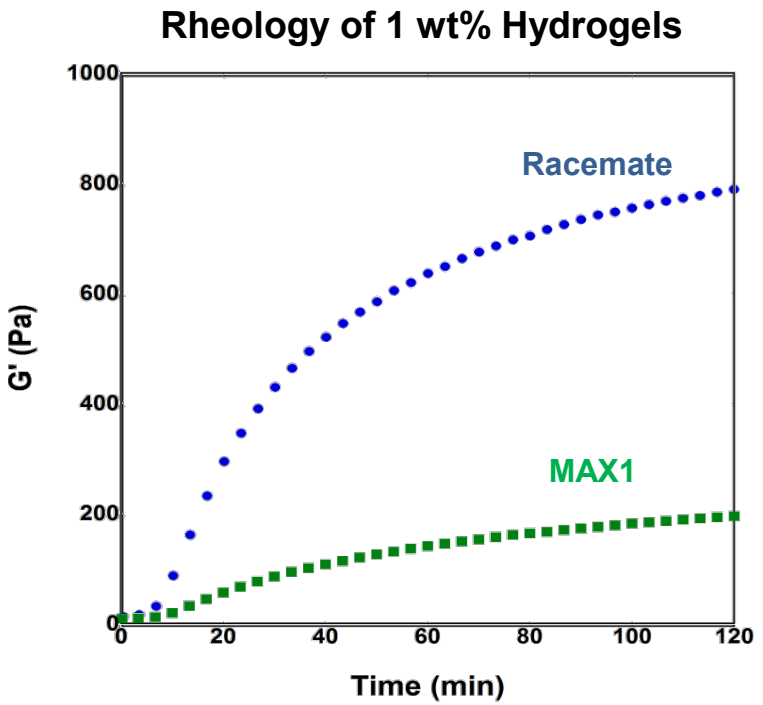
Racemic Gels are Stiffer because their Fibrils are Stiffer

$$G' = \frac{\kappa^2}{kT\xi^5}$$



Co-Assembled

Stiffer Fibrils



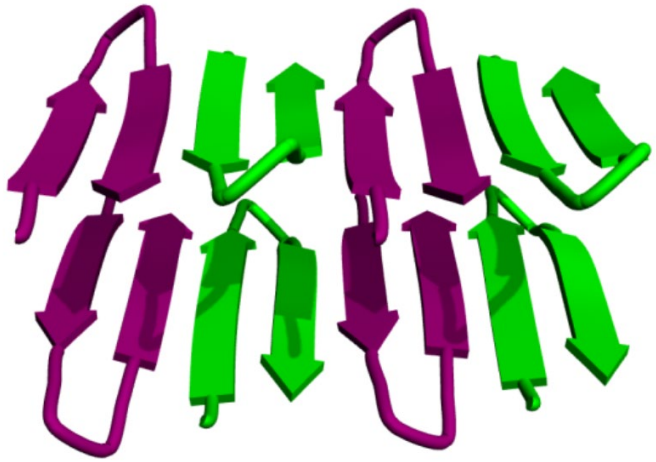
Sample	l_p (nm)	κ (pN-nm^2)
MAX1	7.5 ± 1.1	30.8
DMAX1	7.4 ± 0.8	30.4
Racemate	12.6 ± 0.8	51.8

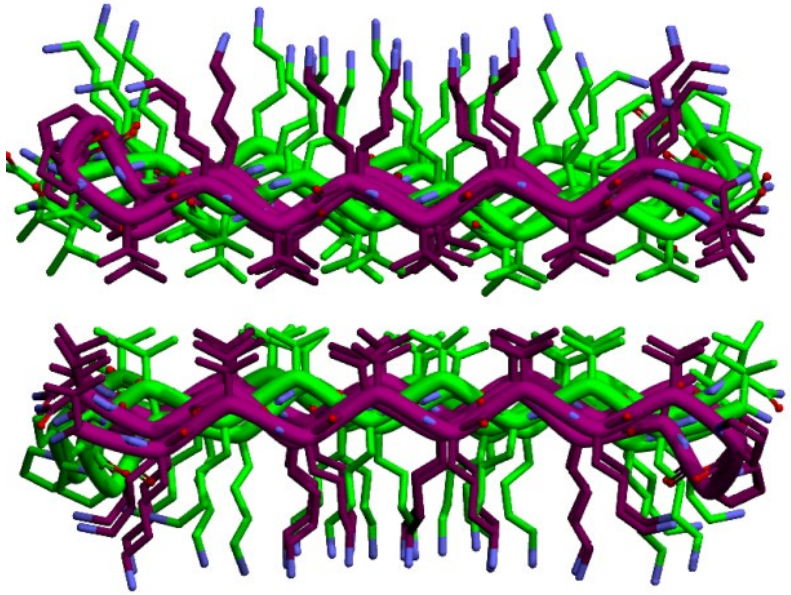
$$\kappa = l_p kT$$

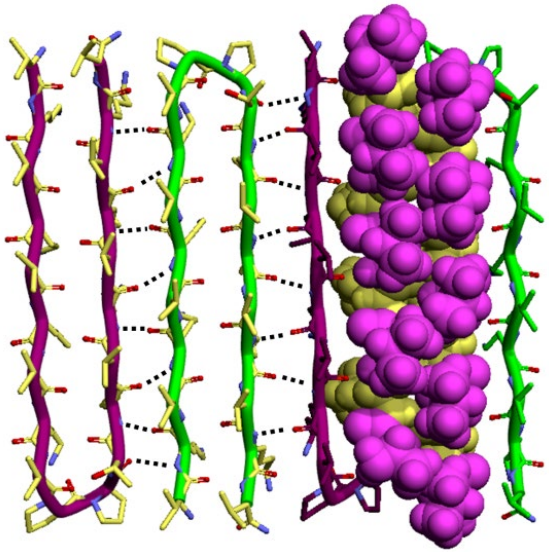
ACS Central Science, 2017

Rippled Sheets Facilitate the Formation of Nested Hydrophobic Interactions

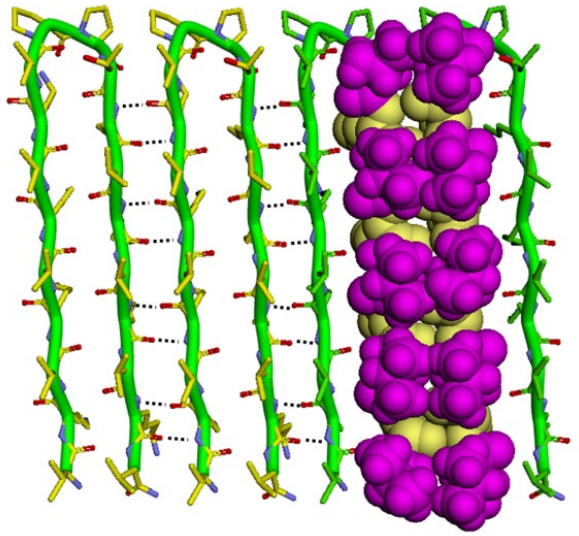
Racemic Fibrils Contain Rippled Sheets







Rippled Sheet



Pleated Sheet

J. Am Chem. Soc., 2011; ACS Central Science, 2017; Acc. Chem. Res., 2021; *J. Am Chem. Soc., 2025.*

Discussion Points

- **Impact of chirality on functional versus structural biomolecules.**
- **Impact of chirality on the extracellular matrix.**
- **Would ECM comprised of pure mirror image components be mechanically different? Probably not.**
- **However, the interplay of components of opposite chirality will likely have different mechanical properties. What impact would this have on an organism's fitness?**

Strain-relief mechanism of disassembly of AD-tau fibrils by D-TLKIVWX peptides

David Eisenberg, Nature, 2025