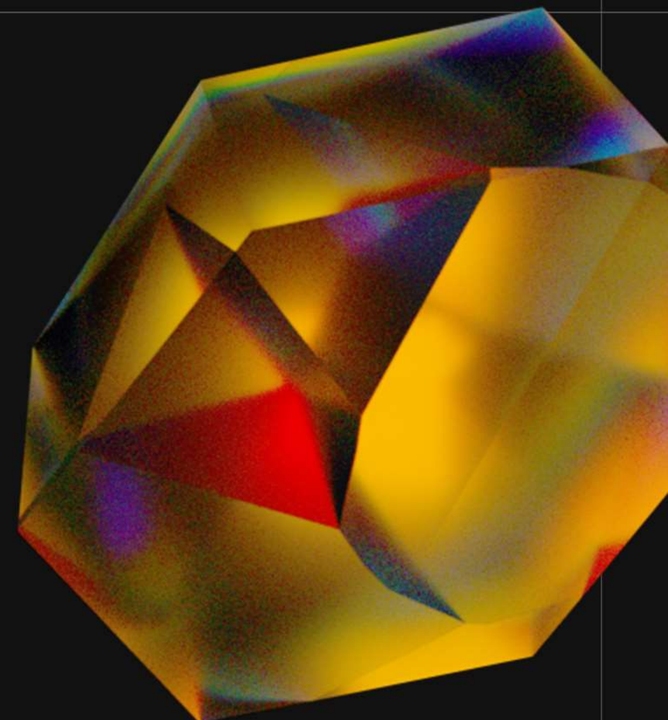
March 28, 2024

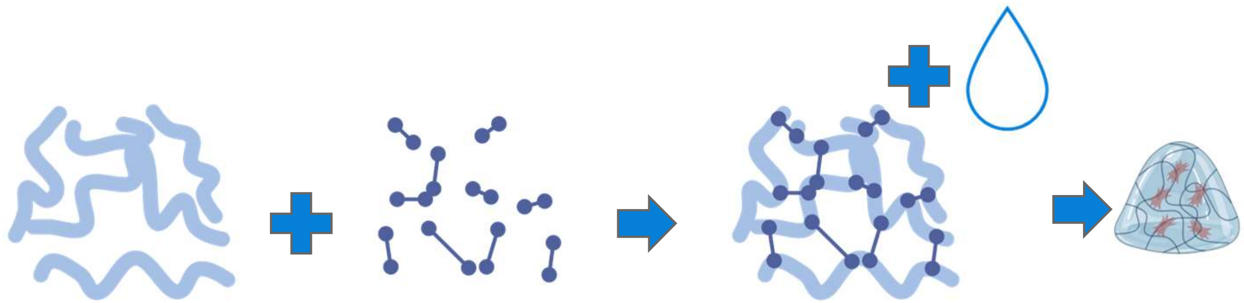
Closed-loop optimization of hydrogel formulations using dynamic light scattering



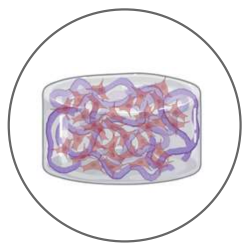
Acceleration Consortium Team:

Owen Melville, Ilya Yakavets, Yimu Zhao,
Nipun Gupta, Jeff Watchorn

Hydrogels are Awesome!



Polymer Chains | Crosslinkers | Polymer Network | Hydrogel



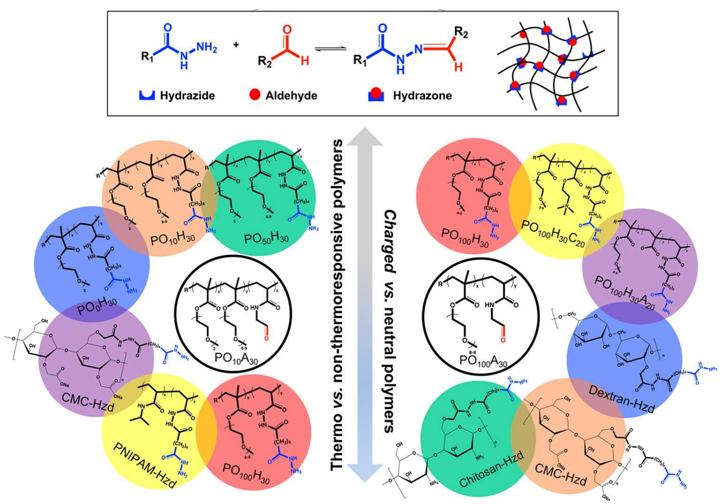
Cell culture

3D Printing

Drug Delivery

Hydrogels are Complicated!

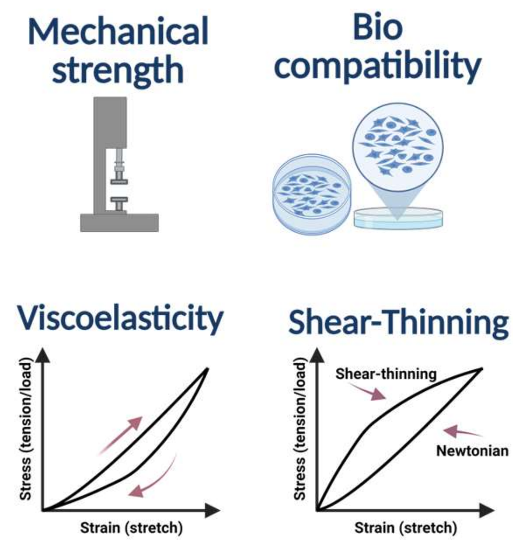
Complex Formulations



Ref: https://doi.org/10.1021/acs.biomac.9b01132

Xu et al. (2020). *Biomacromolecules*

Complex Properties



Li et al. (2020) Materials Science and Engineering

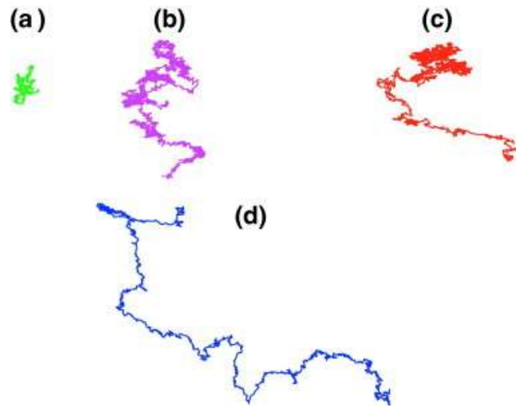
Measuring Hydrogel Properties

Rheology

Slow

Difficult to Automate

Video Particle Tracking



Ref: https://doi.org/10.1016/j.ymeth.2009.12.008

Data intensive

Finicky

Mao et al. (2022). *Front. Bioeng. Biotechnol.*

Dynamic Light Scattering

Well plate compatible

Fast measurements

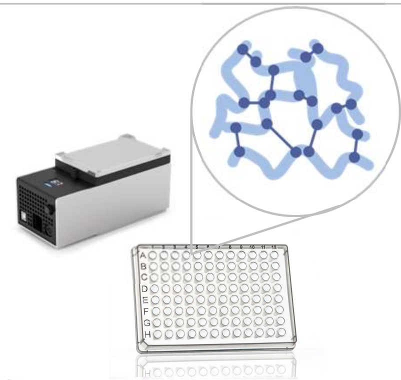
Krajina et al. (2017). *ACS Central Science*

A Hydrogel Self-Driving Lab!

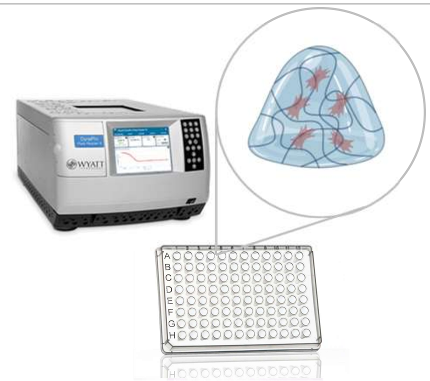
1 **Mixing hydrogel precursors**

Inputs:

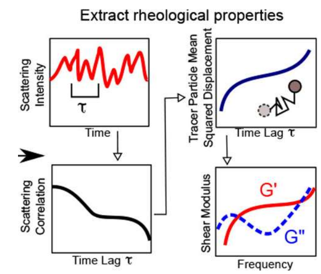
1. Precursor descriptors (substance)
2. Precursor concentrations (discrete)



2 **Crosslinking**



3 **Dynamic Light Scattering characterization**



DLSuR package

4 **Data analysis**

Outputs:

1. Relaxation time
2. Gelation time
3. Viscosity
4. Viscoelasticity (G' and G'')

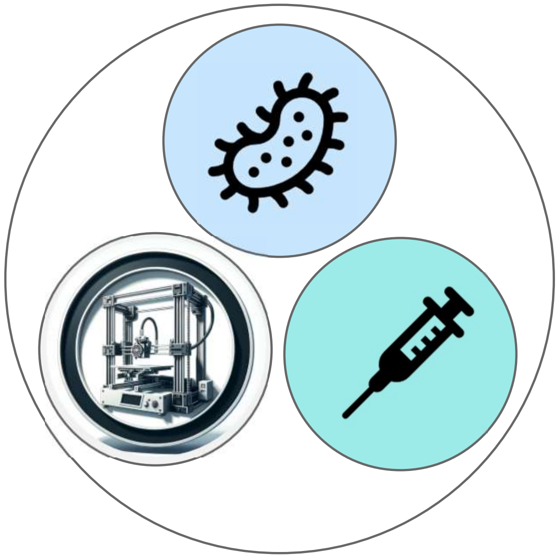
BO Features:

- Precursor representation (mixture constraints)
- Sequence optimization

BayBE package

5 **Bayesian Optimization**

The Future Needs Hydrogels!



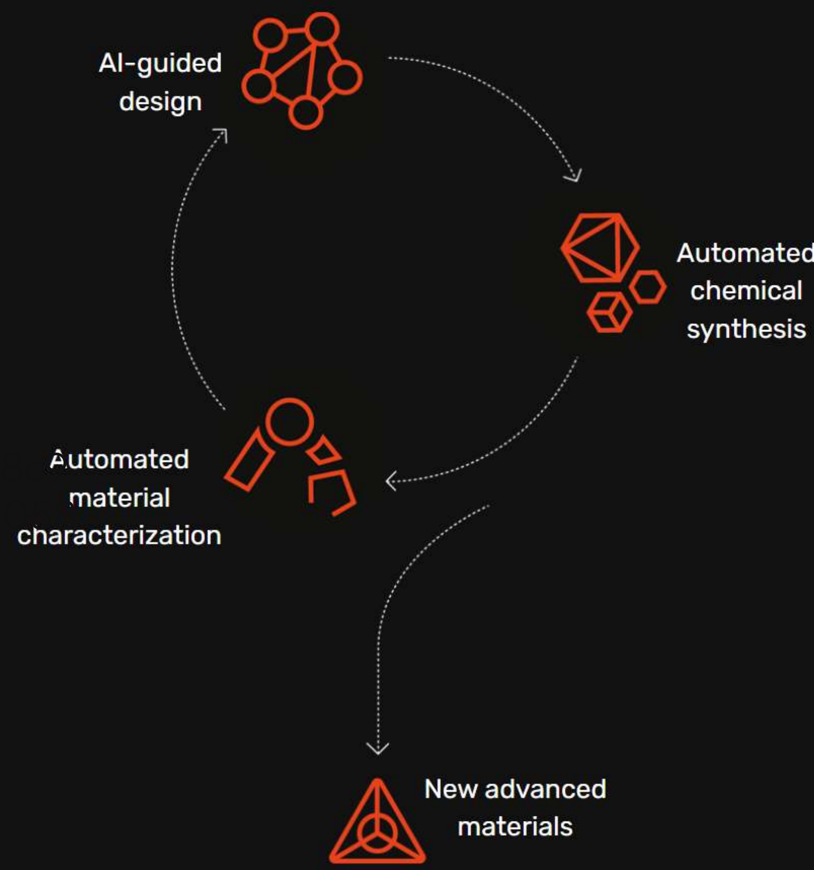
Cell culture
3D Printing
Drug Delivery

Faster Data
Reliable Data
Self-Driving Labs

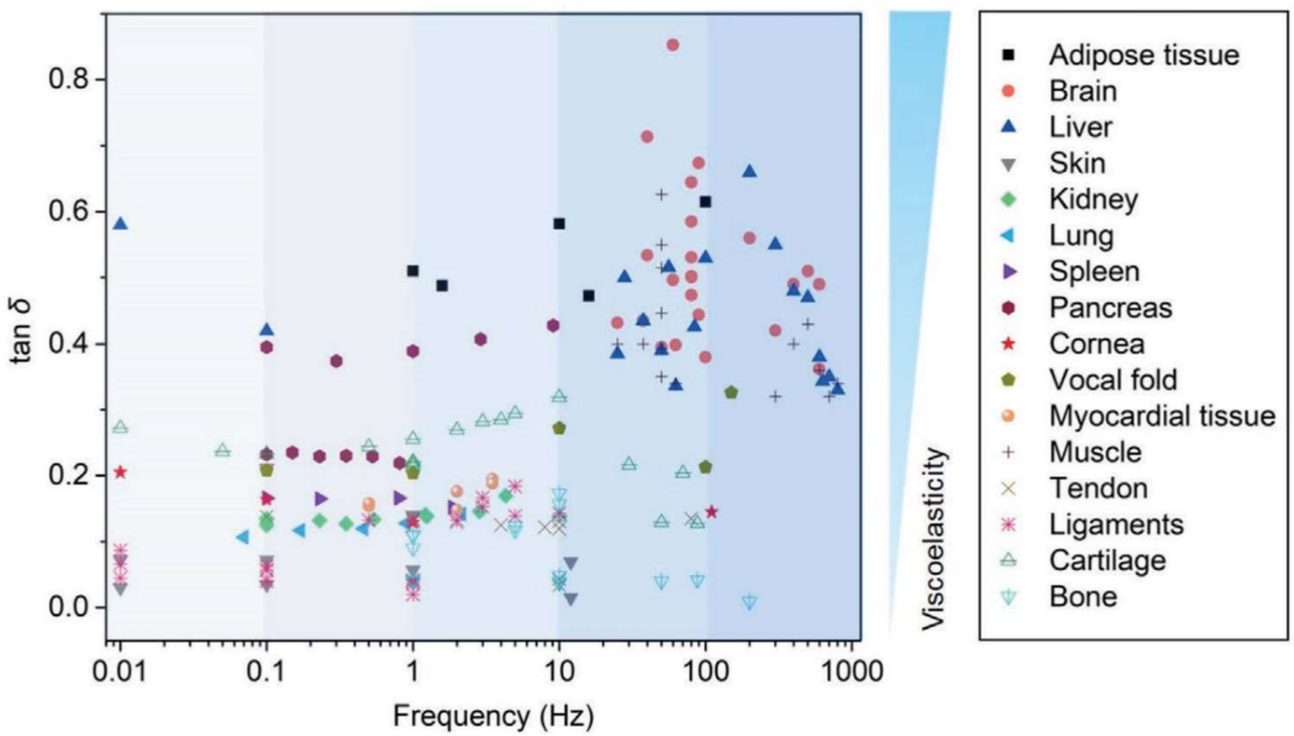
Healthy People
Happy Robots
Healthy Planet

Thanks for your attention

SELF-DRIVING LABS
ACCELERATING MATERIALS DISCOVERY



Various biological tissues show frequency-dependent viscoelastic features



Theory (Cai et al, 2021)

Incident light is scattered by embedded probe particles in a sample volume, and the scattering intensity is measured over time to derive the intensity autocorrelation function $g_2(\tau) = \langle I(t)I(t+\tau)\rangle\langle I(t)\rangle^{-2}$, where τ is the lag time between two time points and $\langle I(t)\rangle^{-2}$ is the normalization factor. This autocorrelation function relates to the mean-squared displacement $\Delta r^2(\tau)$ of the probe particles through the intermediate scattering function

$$g_1(\tau) = \exp\left(\frac{-q^2 \Delta r^2(\tau)}{6}\right), \tag{1}$$

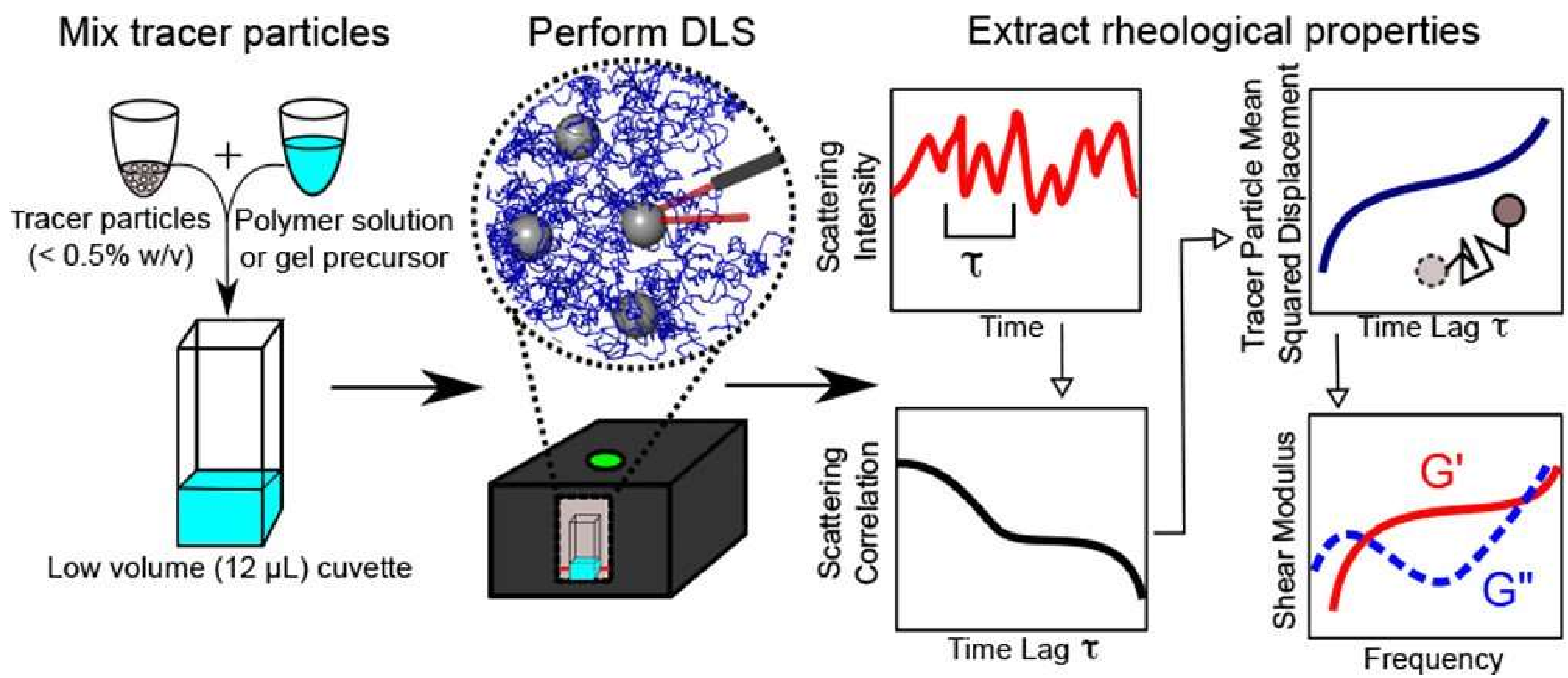
where the scattering vector $q = 4\pi n \sin(\theta/2)/\lambda$. The intermediate scattering function $g_1(\tau)$ for ergodic systems is derived from

$$g_2(\tau) = 1 + (g_0 - 1) \mid g_1(\tau) \mid^2, \tag{2}$$

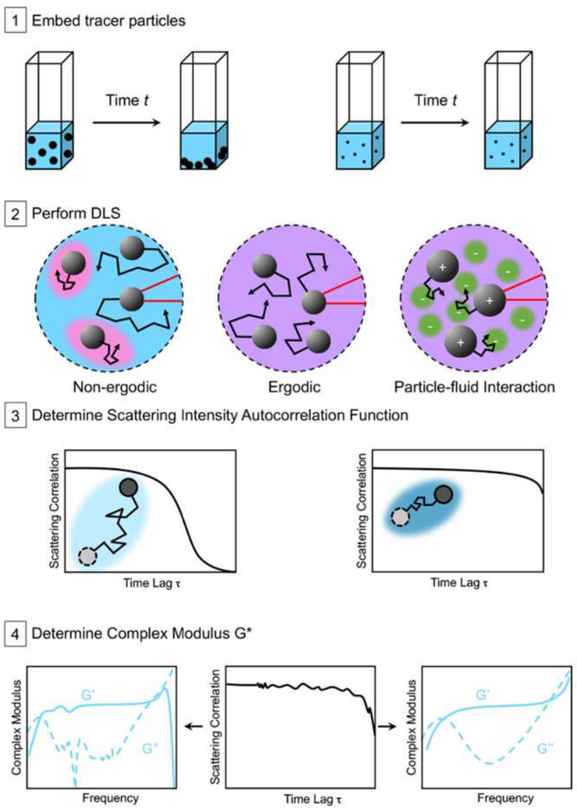
where $g_0 = g_2(0)$. From the mean-squared displacement, we then obtain the frequency-dependent complex modulus using the generalized Stokes-Einstein equation[21,22]

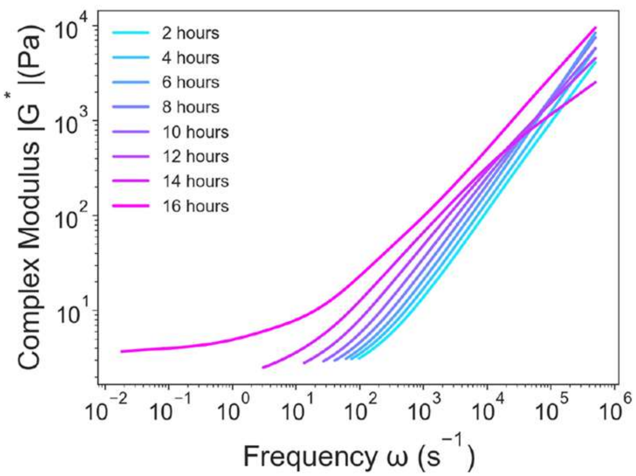
$$G^*(\omega) = \frac{k_B T}{\pi a (i\omega) \mathcal{F}_u\{\langle \Delta r^2(t)\rangle\}} \tag{3}$$

where $k_B T$ denotes the thermal energy, a is the particle radius, and $\mathcal{F}_u\{\langle \Delta r^2(r)\rangle\}$ is the unilateral Fourier transform of the mean-squared displacement. This relation is extended from the purely viscous regime to continuum viscoelastic fluids and connects macroscopic stress relaxations to microscopic stress relaxations.[23,35] Besides the complex modulus, another interesting and valuable interpretation of the mean-squared displacement is the creep compliance, which directly relates to the mean-squared displacement.[36] It should be noted that Equation 3 assumes that there is negligible impact from inertia of the probe, which is very sensitive to probe size and material properties of both the probe and the fluid. For a particle in a fluid, the timescale at which inertial effects are non-negligible can be estimated using the ratio of $m/\zeta = 2\rho_p a^2/9\eta_s$, where m is the mass of the particle, ζ is the drag coefficient, ρ_p is the density of the particle, a is the radius of the particle, and η_s is the viscosity of the fluid.[37] Particle sizes used in DLSμR are on the order of 1 μm, which requires a timescale of ~ 6×10^{-8} s for the inertia to dampen out in a material with a viscosity of 10^{-3} Pa·s. Thus, for the frequency range probed by DLSμR (up to 10^6 Hz), inertial effects can be neglected.[22]

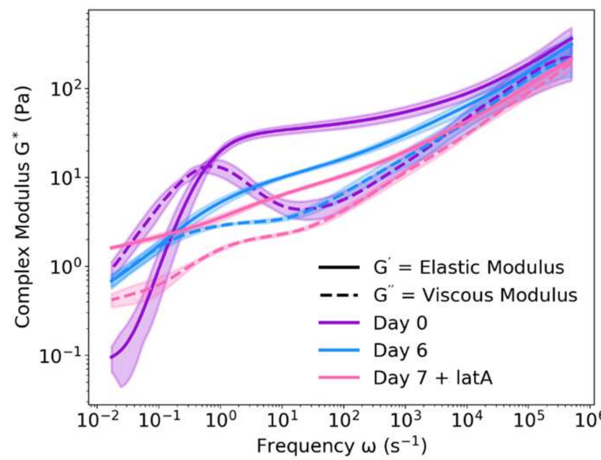

Mix tracer particles
Perform DLS
Extract rheological properties
+
Tracer particles
(< 0.5% w/v)
Polymer solution
or gel precursor
Low volume (12 µL) cuvette
Scattering Intensity
τ
Time
Scattering Correlation
Time Lag τ
Tracer Particle Mean Squared Displacement
Time Lag τ
Shear Modulus
G'
G"
Frequency

DLSµ R Workflow Scenarios Summary. (Cai et al, 2021)





Gelation Process of a Covalently Crosslinked PEG-based Gel.



Multi-day Rheology of a Living Composite of Human Breast Cancer Cells Encapsulated in Collagen I.

Relationship between Structure and Rheology of Hydrogels for Various Applications
Stojkov et al, 2021

Figure 5. Time sweep experiment shows the formation of the network structure of the hydrogel over time. The crossover point of G' and G" indicated the gelation point.

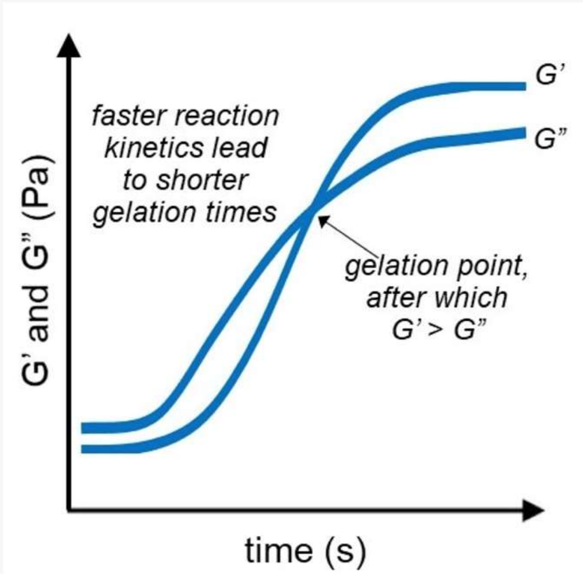
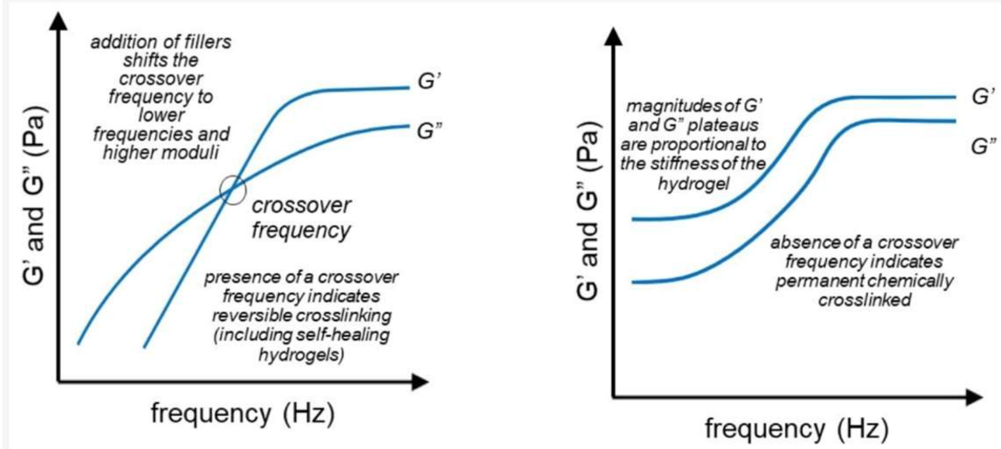


Figure 7. Frequency sweep experiments are a powerful tool in rheology of hydrogels which show the crosslinking behavior as well as the presence of a reversible network.



A Hydrogel Self-Driving Lab!

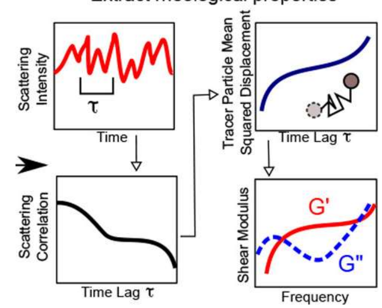
Preparation of hydrogel formulations → Shaking → Addition of beads → DLS measurements

Inputs:

1. Precursor descriptors (substance)
2. Precursor concentrations (discrete)

https://dlsur.readthedocs.io/

Extract rheological properties



Data analysis

Outputs:

1. Relaxation time
2. Gelation time
3. Viscosity
4. G' and G'' (Viscoelasticity)

BayBE
Bayesian Back End

Bayesian Optimization

Features:

- Precursor representation (mixture constraints)
- Sequence optimization