# Rheology Principles and Applications

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| OVERVIEW | ROTATIONAL ASSAYS | OSCILLATORY ASSAYS | VERTICAL ASSAYS | OTHER |
|---|---|---|---|---|
| • Applications<br>• Rheometer Mechanics<br>• Q3 for IP & Regulatory | • Basic Principles<br>• Shear Stress Ramp<br>• Shear Rate Ramp<br>• Thixotropy<br>• Time Sweep (stability)<br>• Temperature Sweep (stability, melting)<br>• Creep-Recovery<br>• Tribology (friction) | • Basic Principles<br>• Amplitude Sweep<br>• Frequency Sweep<br>• Time Sweep (stability)<br>• Temperature Sweep (stability, melting) | • Squeeze-Pull Away (stickiness)<br>• Model Chewing<br>• Surface Tension | • General Experimental Considerations<br>• Plate & Cone Considerations<br>• Optimizing Dispersion, Colloidal & Emulsion Stability<br>• Literature Example: Influence of Processing Variables on Rheological & Textural Properties of Lupin Protein-Stabilized Emulsions<br>• Conclusions |

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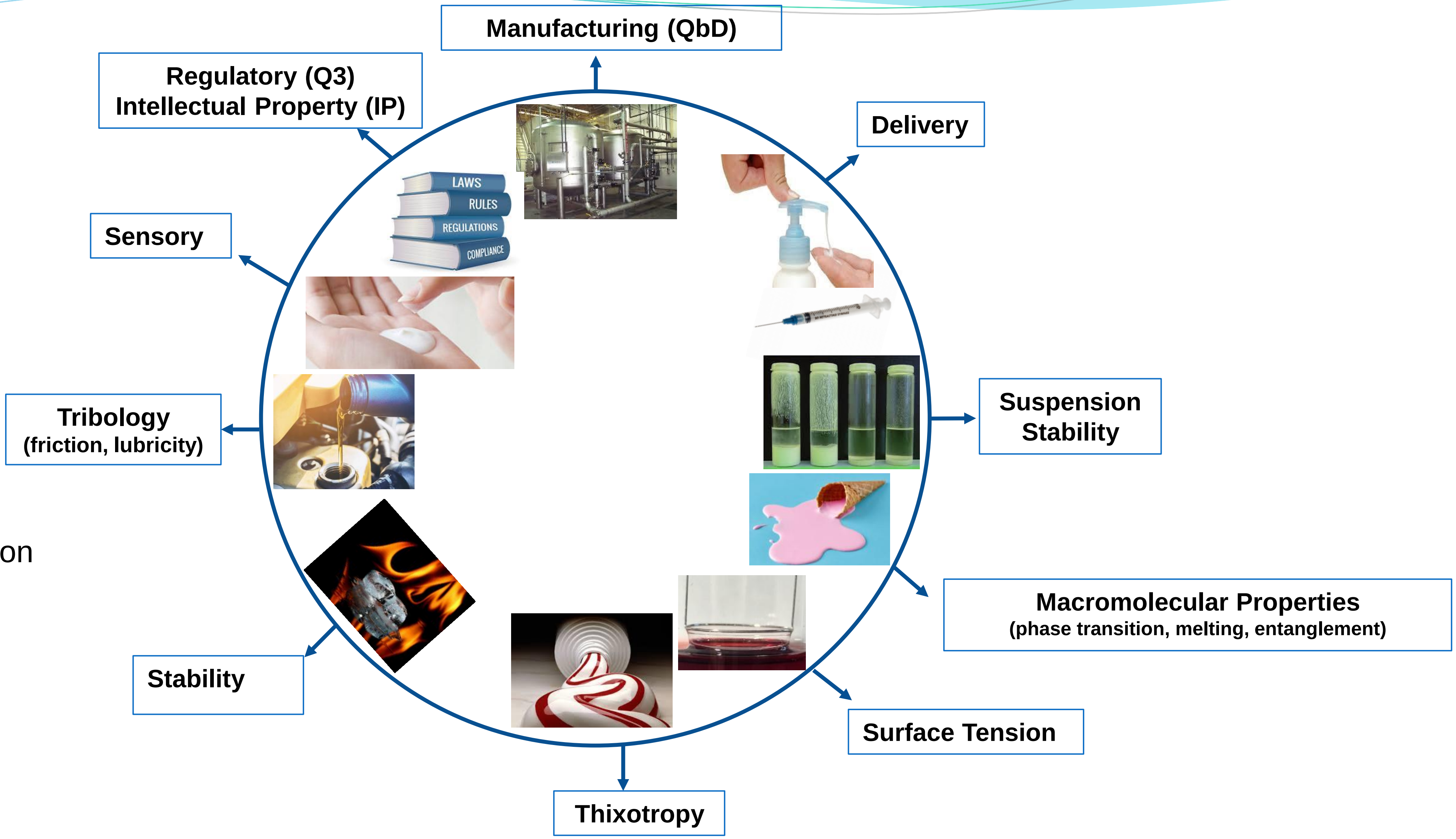
# Rheology Applications - R&D to Manufacturing

**Industries**
- Pharmaceutical
- Biopharmaceutical
- Bioengineering
- Food
- Cosmetic
- Plastics
- Many others

**Materials**
- Polymer
- Cream
- Emulsion/Suspension
- Gel
- Lotion
- Oil
- Ointment
- Solution
- Many others



# Rheology Applications - R&D to Manufacturing (CON'T)

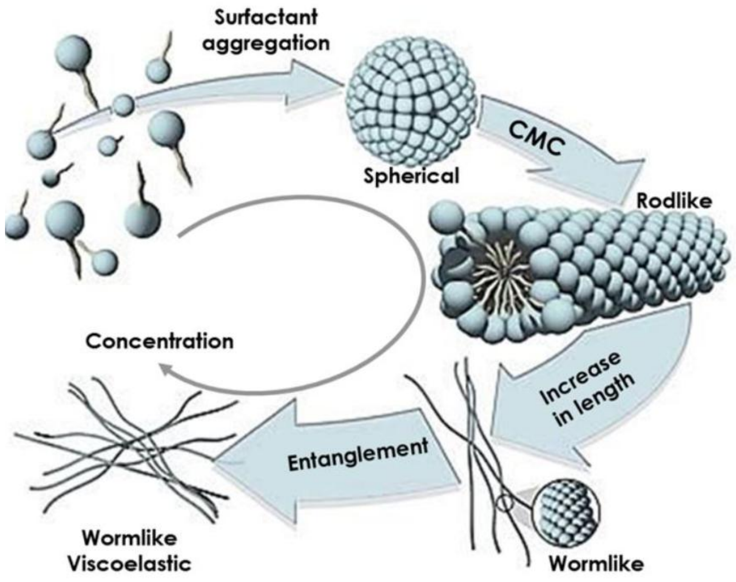
- **Product development, optimization & in-process control (Quality by Design (QbD))**
  - batch consistency
  - addition order & rate
  - mixing time & speed
  - temperature (heating/cooling range & rate)
  - bulk transfer (shear thinning, rebuilding)
  - equipment type & size (scale-up, pumps, pipes)
  - transport (sedimentation, phase separation)
  - stability

# Regulatory & Intellectual Property (IP)

## Confirm Product (Dis)Similarity to RLD (Reference Listed Drug) for ANDA

**Q1**: **Qualitative** ⇒Same components

**Q2**: **Quantitative** ⇒Q1 & same amount




Q3*: Microstructure

⇒ Q1 + Q2 + same arrangement of matter

⇒ Performance, efficacy, stability, batch-to-batch consistency

**→ Rheometer may discern among arrangements based on association (entanglements) and their relaxation time**

**→ Rheological properties may affect biological activity**

- Fulfilling the FDA's Rheology Testing Requirements for Abbreviated New Drug Applications (ANDA) for Topical Creams – Netzsch (https://analyzing-testing.netzsch.com/en-US/application-literature/fulfulling-the-fdas-rheology-testing-requirements-for-abbreviated-new-drug-applications-anda-for-topical-creams)

* "Draft Guideline on Quality and Equivalence of Topical Products" European Medicines Agency (18Oct2018) (https://www.ema.europa.eu/en/quality-equivalence-topical-products#current-version-section)

* "Generic Development of Topical Dermatologic Products: Formulation Development, Process Development, and Testing of Topical Dermatological Products" AAPS J. 2013 Jan; 15(1): 41-52 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3535108/)

* "Testing Topicals: Analytical Strategies for the In-Vitro Demonstration of Bioequivalence" Pharm Tech Sept 2018 (http://www.pharmtech.com/testing-topicals-analytical-strategies-vitro-demonstration-bioequivalence?pageID=1)

# Rheometer Overview

## Upper Plate

- only <u>moving</u> part contacting sample
- different surfaces
  - -smooth
  - -rough
  - -serrated
- many other attachments

## Lower Plate

- does not move
- same surface options as upper plate
- controls temperature (-5 to 200°C)*

*Options to extend temperature ranges are available.

Images from Netzsch

## <u>Movements → torque</u>

- Rotational (1 direction)
- Oscillational (bi-directional)
- Vertical

# By end of presentation…….

- What assay should I use?
- What experimental parameters should I consider?
- Appreciate which is more viscous – honey or mayonnaise? What are these? $\tau$, $\sigma$, $\gamma$, $\eta$
- Is silly putty viscoelastic solid or liquid?  What are these? G’, G”, G*, $\delta$,  $\eta$*, tan delta

# SOME BASIC RHEOLOGY ASSAYS ENTRÉES

***…many side options available***

**⇒ ROTATIONAL → measure flow**

- Shear Rate Ramp (shear thinning)
- Shear Stress Ramp (yield stress, start of flow)
- *Thixotropy (rebuilding after shear thinning)*
- *Time Sweep (stability)*
- *Temperature Ramp (stability, phase transitions, melting)*
- *Creep-Recovery (yield stress, rebuilding)*
- Tribology (friction, lubricity)

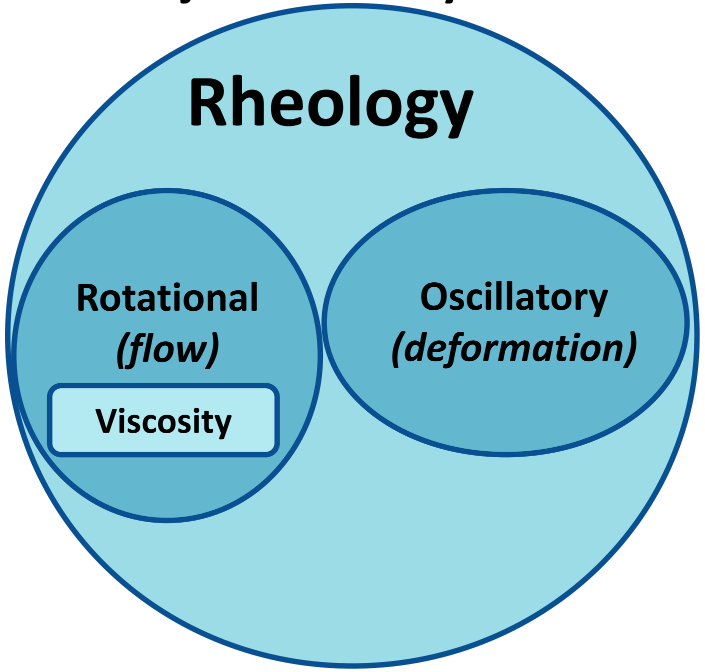
**⇒ OSCILLATORY → measure deformation**

- Amplitude Sweep (LVER, stability)
- Frequency Sweep (viscoelasticity)
- *Thixotropy (rebuilding after thinning)*
- *Time Sweep (stability)*
- *Temperature Ramp (stability, phase transitions, melting)*
- Creep-Recovery (yield stress, rebuilding)

**⇒ VERTICAL**

- Squeeze-Pull Away (stickiness, model chewing)
- Surface Tension

**Rheology is much more than just viscosity!**



# Viscosity → Resistance to Flow

**Viscosity(η; cP or Pa-sec) = Shear Stress / Shear Rate = σ (Pa or N/m²) / γ (sec⁻¹)**

$$\text{Viscosity}(\eta;\ \text{cP or Pa-sec}) = \frac{\text{Shear Stress}}{\text{Shear Rate}} = \frac{\sigma\ (\text{Pa or N/m}^2)}{\gamma\ (\text{sec}^{-1})}$$

1000cP=1Pa-sec

$$= \frac{\text{Force (N) /Area (m}^2)}{\text{Strain (unitless) / Time (sec)}}$$

$$= \frac{\text{Force (N) /Area (m}^2)}{(\text{Displacement (m) /Height (m)) /Time (sec)}}$$

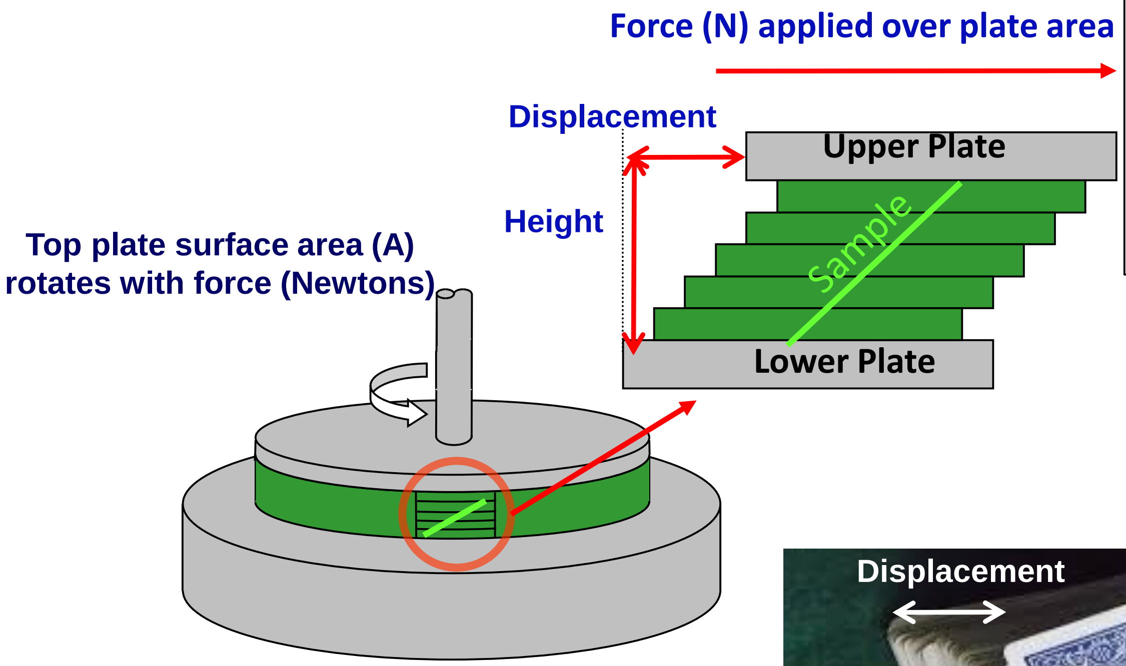
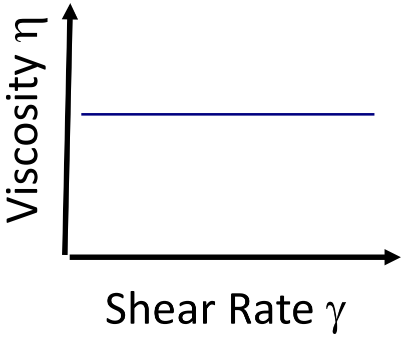



Image from Netzsch


*Problem with 2 top cards…more later*

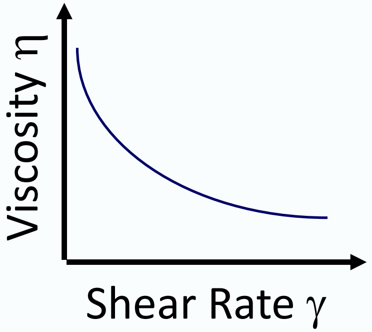
# Rotational - Measure flow *(as torque)* with applied force & movement

**Newtonian**



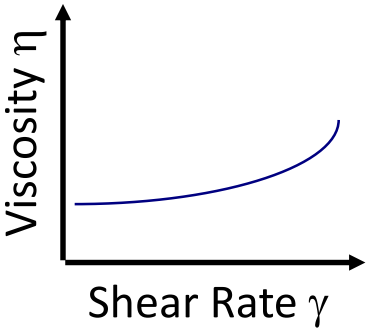

**(silicon oil, water)**

**Shear-Thinning**
**non-Newtonian**




**(most lotions, creams, ointments)**

**Shear-Thickening**
**(Dilatant, Rheopectic)**
**non-Newtonian**




**(corn starch, whipping cream, egg whites)**

- **Most semisolids shear thin (non-Newtonian)**
- **Helpful to model processes (spreading, pumping, syringability, feel)**

Shear rate = strain/time
(Strain=displacement/height)

# Effect of Shear on Microstructure.. “go with the flow”

⇒ Biologicals, polymers, emulsions
⇒ Larger & irregular particles tend to increase viscosity
⇒ Mixtures having more polydisperse particles tend to have lower viscosity

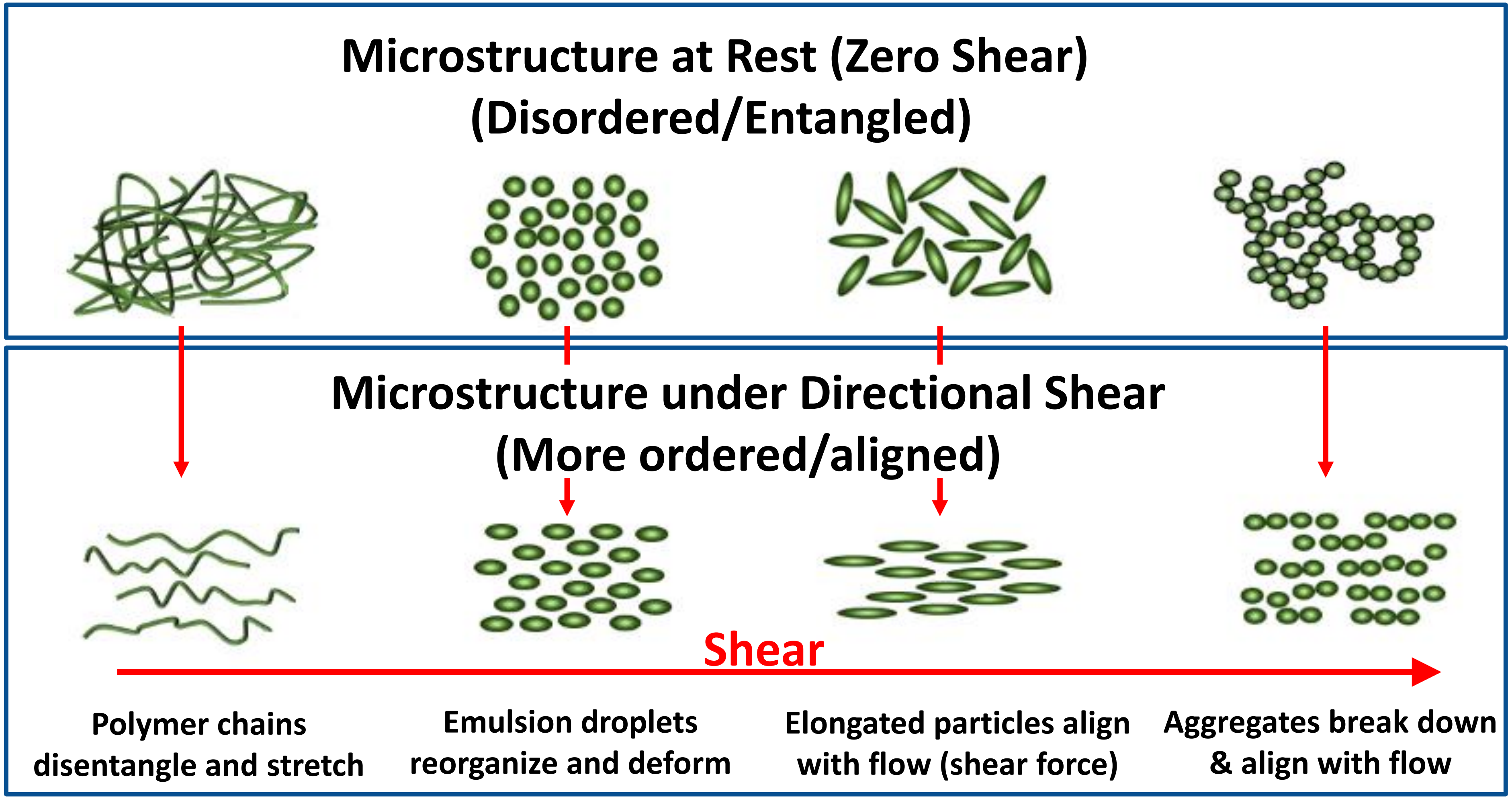
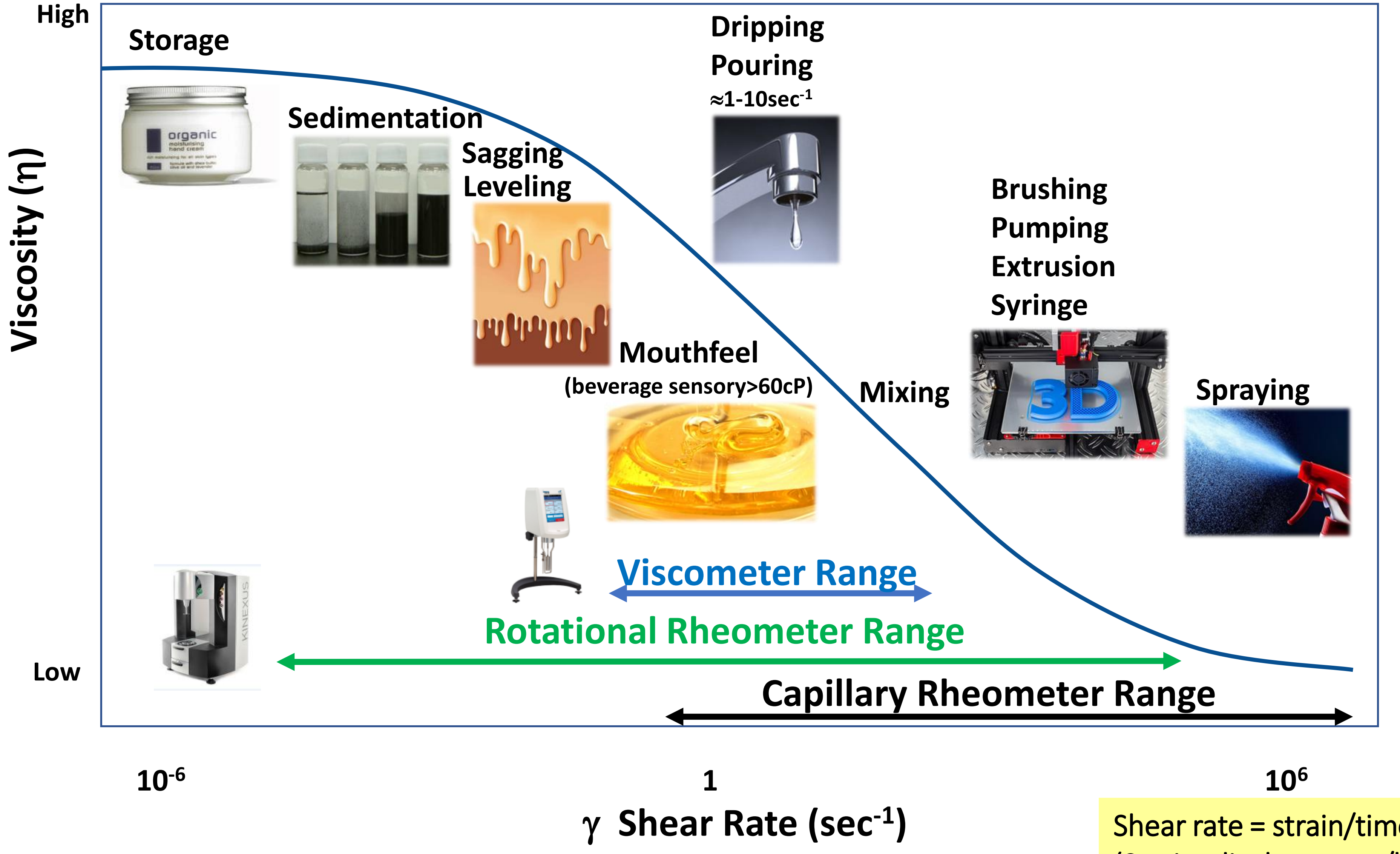



Image from Netzsch

# Shear Rate of Processes - range $10^{10}$ (10 billion)




Shear rate = strain/time
(Strain=displacement/height)

# Shear Rates of Common Processes


**SAMPLE STORAGE**

Very low shear rates: $\leq 0.001 s^{-1}$

Stability (sedimentation, phase separation)

**SAMPLE DELIVERY**

Medium shear rates: $\sim 10 s^{-1}$

Pumpability? Scoopability?

**SAMPLE APPLICATION**

Low shear rates: $\sim 1 s^{-1}$

Too thin? Flows off hand?

**SAMPLE APPLICATION**

Higher shear rates: $\sim 100 s^{-1}$

Too thick to spread? Nice feel?

Image from Netzsch

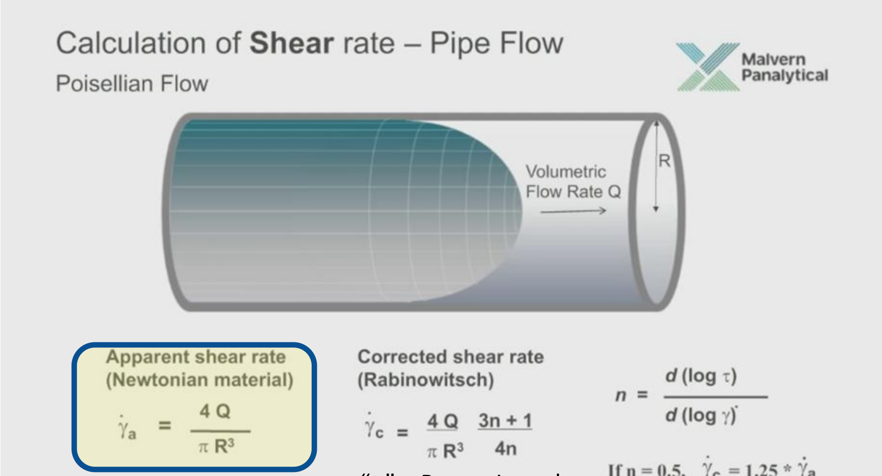
# Calculations: Shear Rate Calculations of Common Processes

## #1 Painting

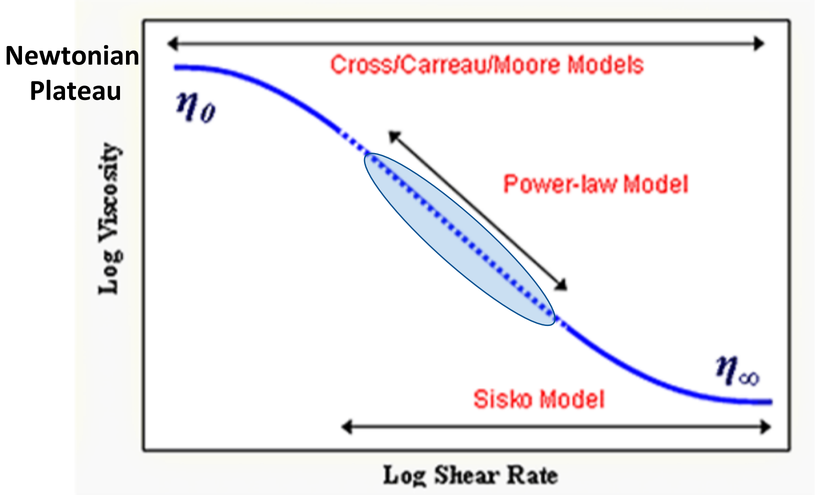
Shear rate $\gamma$ = velocity / height
= 0.1m/sec / 0.0002m
= 500sec$^{-1}$

Brush velocity = 0.1 m/sec (≈4 in/sec)
Paint thickness = 200µm = 0.0002m (≈ 0.008in)

## #2 Flow in capillaries, tube, pipe, syringe & needle - Poiseuille's Law




"n" = Power Law slope




Many more curve fitting models available

*water is Newtonian
** toothpaste is non-Newtonian

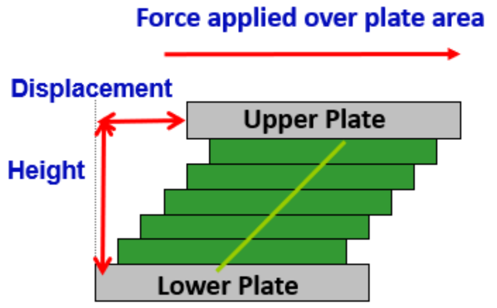
# Switching gears ⇒ Rotational Methods

## SHEAR STRESS RAMP ASSAY

**Analogous to moving revolving door**

- **Start Applying Force:** Initially door does not move
  - →**Yield Stress**: Force required to start moving door (yield point→flow)
  - →**Yield Viscosity**: Viscosity at yield point

- **Note**: *Very small initial movement (shear rate) at yield point can give very high yield viscosity.*

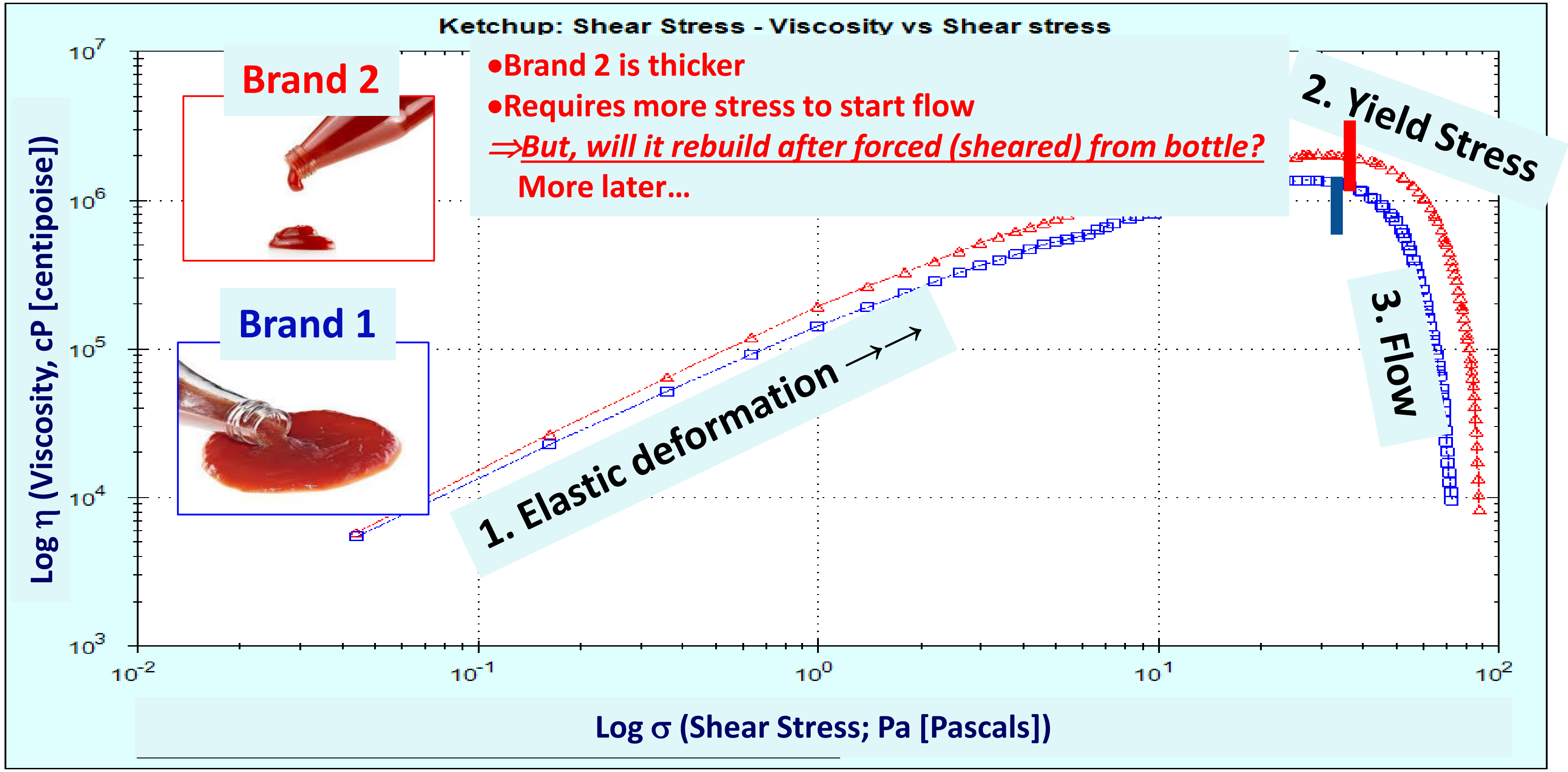



$$\text{Viscosity}(\eta) = \frac{\text{Shear Stress}}{\text{Shear Rate}} = \frac{\sigma}{\gamma}$$

$$= \frac{\text{Force/Area}}{(\text{Displacement/Height})/\text{Time}}$$

# Application: Yield Stress Ramp "Flow Curve" - Ketchup

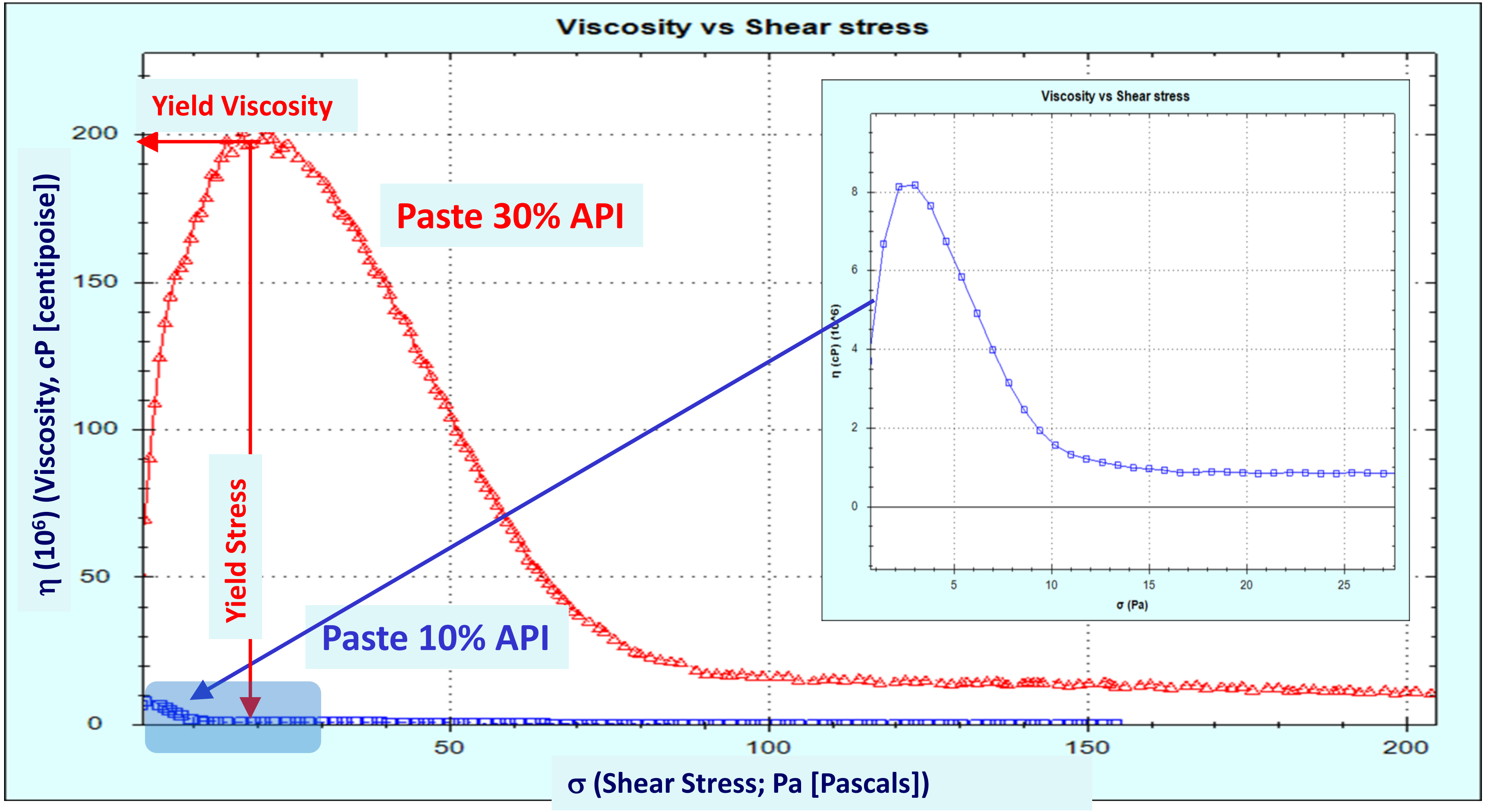
► **Purpose:** Client (engineers) needed data for process modelling




- Helpful model for difficult to pump or stir materials → start up force >> maintain flow force due to shear thinning
- Formulation optimization - type and amount of thickeners, excipients
- Insight for manufacturing optimization – pump capacity, transfer pipe dimensions, temperature
- Refine customer experience – thicker, creamier
- Model if sample is likely to settle. Stokes Law → is downward force on particles > media yield stress?

# Application: Yield Stress Ramp - Pharmaceutical Paste

- **Purpose:** Client needed to quantify impact of % API on processing & application
- **Result**: 30% API paste has much higher yield stress & yield viscosity → difficult to initiate movement

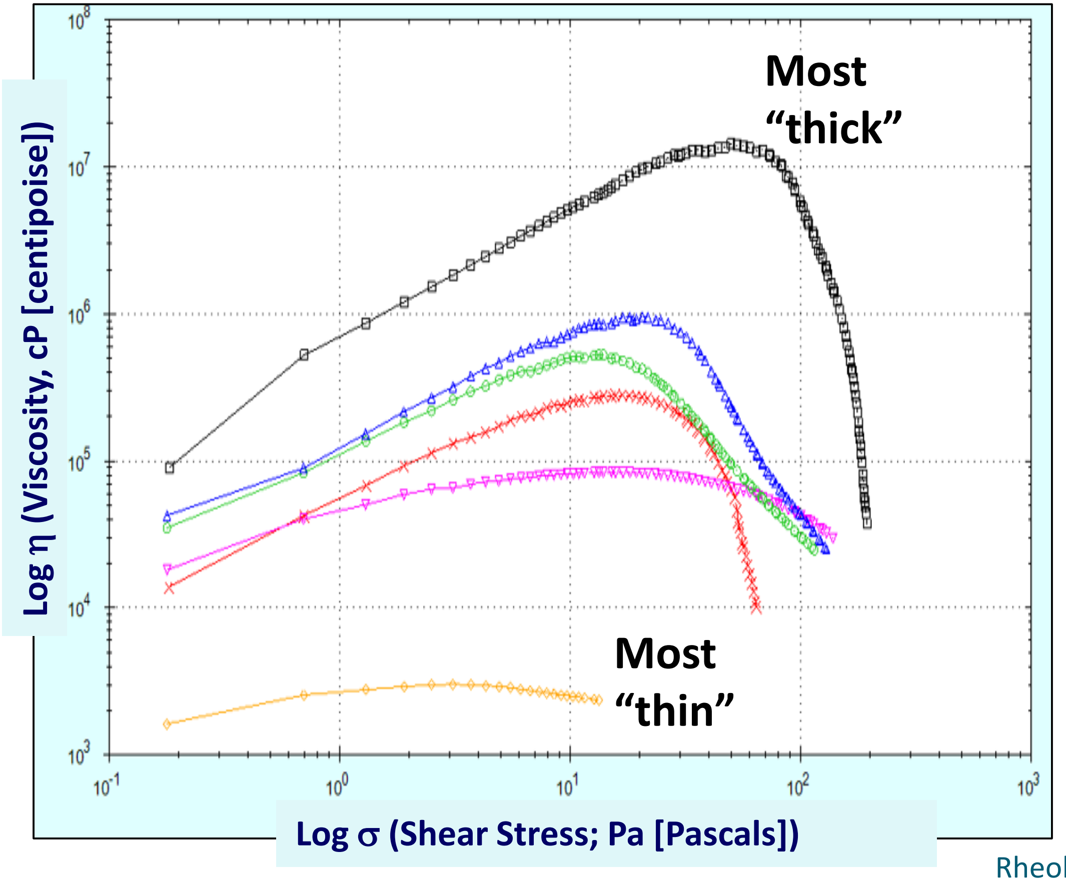



**Stress = Force/Area**

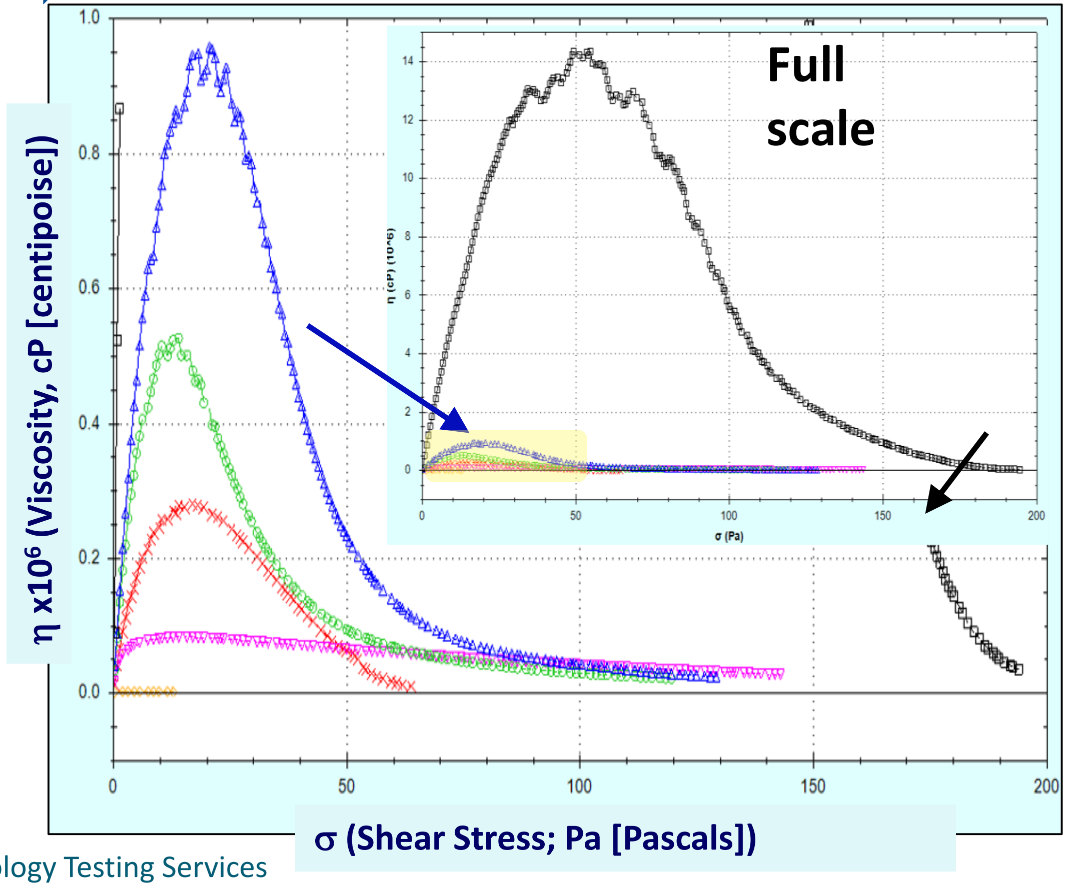
# Application: Yield Stress Ramp - Arthritis products

- ▸ **Purpose:** Client requested side-by-side rheological profiles for 6 products
- ▸ **Results:** Orders of magnitude difference!
  - **Experimental**: 25mm rough parallel plate, 200um gap (100uL sample), 0 to 300Pa over 300sec
  - **Note:** Yield response is rate dependent. Values vary with experimental parameters. *Example: Pull rubber band slow vs fast.*

## Log-Log Plot




## Linear-Linear Plot



# Application: Using Yield Stress to Screen Sedimentation

**Downward stress from gravity on a spherical particle in dilute suspension is estimated by Stokes' Law**

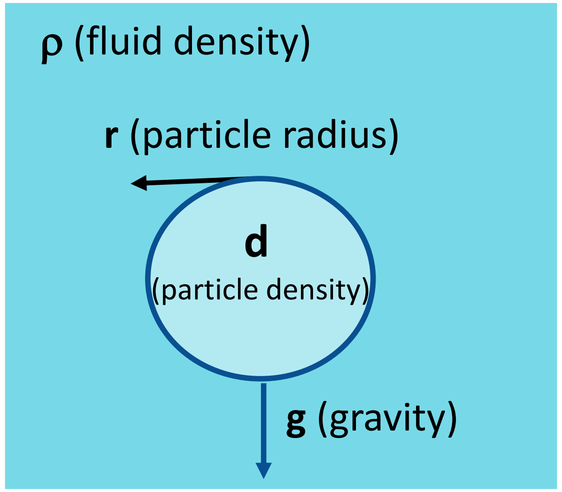
$$\sigma_s = r * g * \frac{d - \rho}{3}$$

Stress ($\sigma_s$); Particle radius ($r$); Gravitational acceleration ($g$); Particle density ($d$); Fluid density ($\rho$)

$$V_s = 2\, r^2 * g * \frac{(d\text{-}\rho)}{9\eta_0}$$

Sedimentation velocity ($V_s$); Zero shear viscosity ($\eta_0$)

**Vodka with suspended gold flakes (non-Newtonian)**




- **If sample yield stress > $\sigma_s$, then sedimentation less likely assuming suspending media doesn't shear thin during transport and handling.**
- **Can also determine with amplitude sweep (cohesion energy density).**

Ref: azom.com/article.aspx?ArticleID=2885

# Switching gears ⇒ Rotational methods

## SHEAR RATE RAMP ASSAY

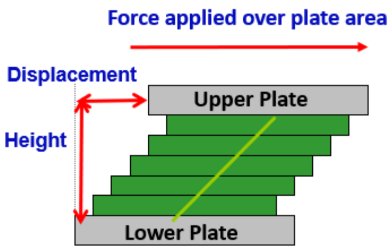
-Continuous ramp (most requested)

-Stepwise ramp

Viscosity(η) = Shear Stress / Shear Rate = σ / γ

= Force/Area / Strain/Time

= Force/Area / (Displacement/Height)/Time



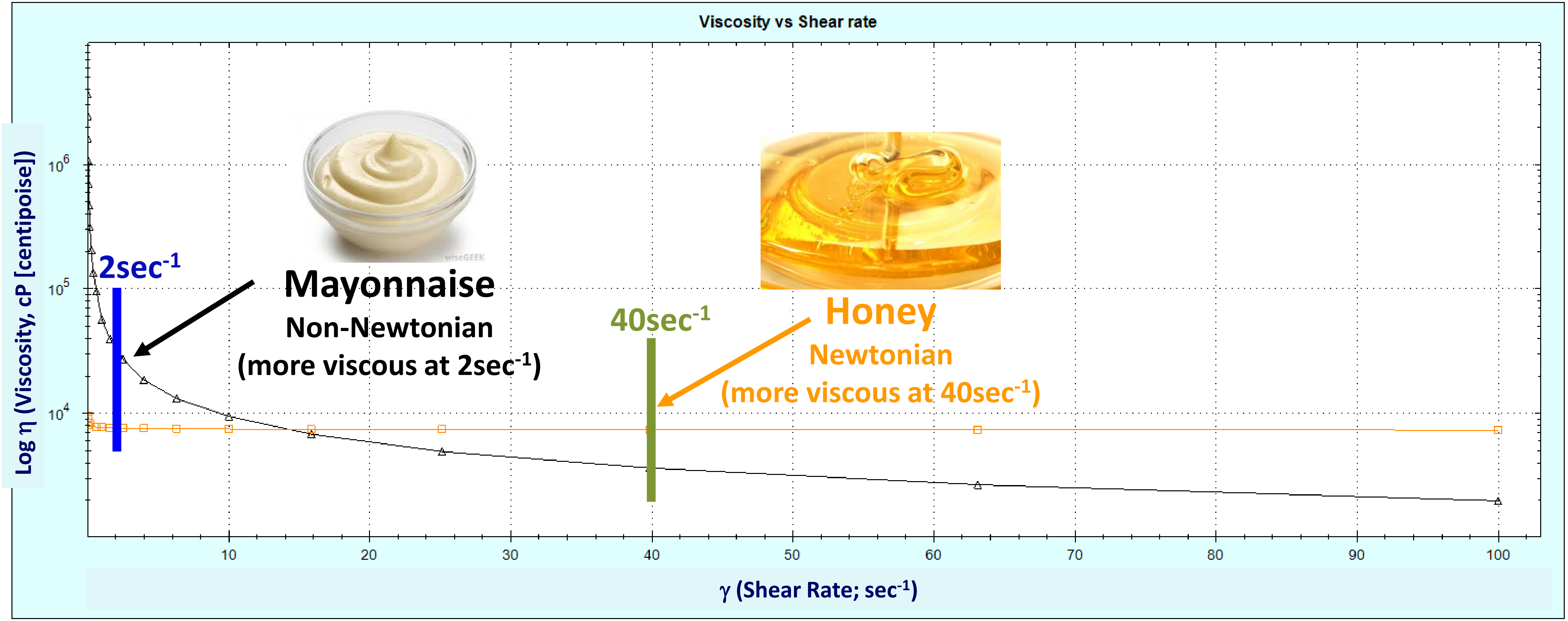

# Shear Rate Ramp (Continuous)

## Which is more viscous – honey or mayonnaise?

**Depends on shear rate…… CRITICAL CONSIDERATION WHEN COMPARING VISCOSITIES**

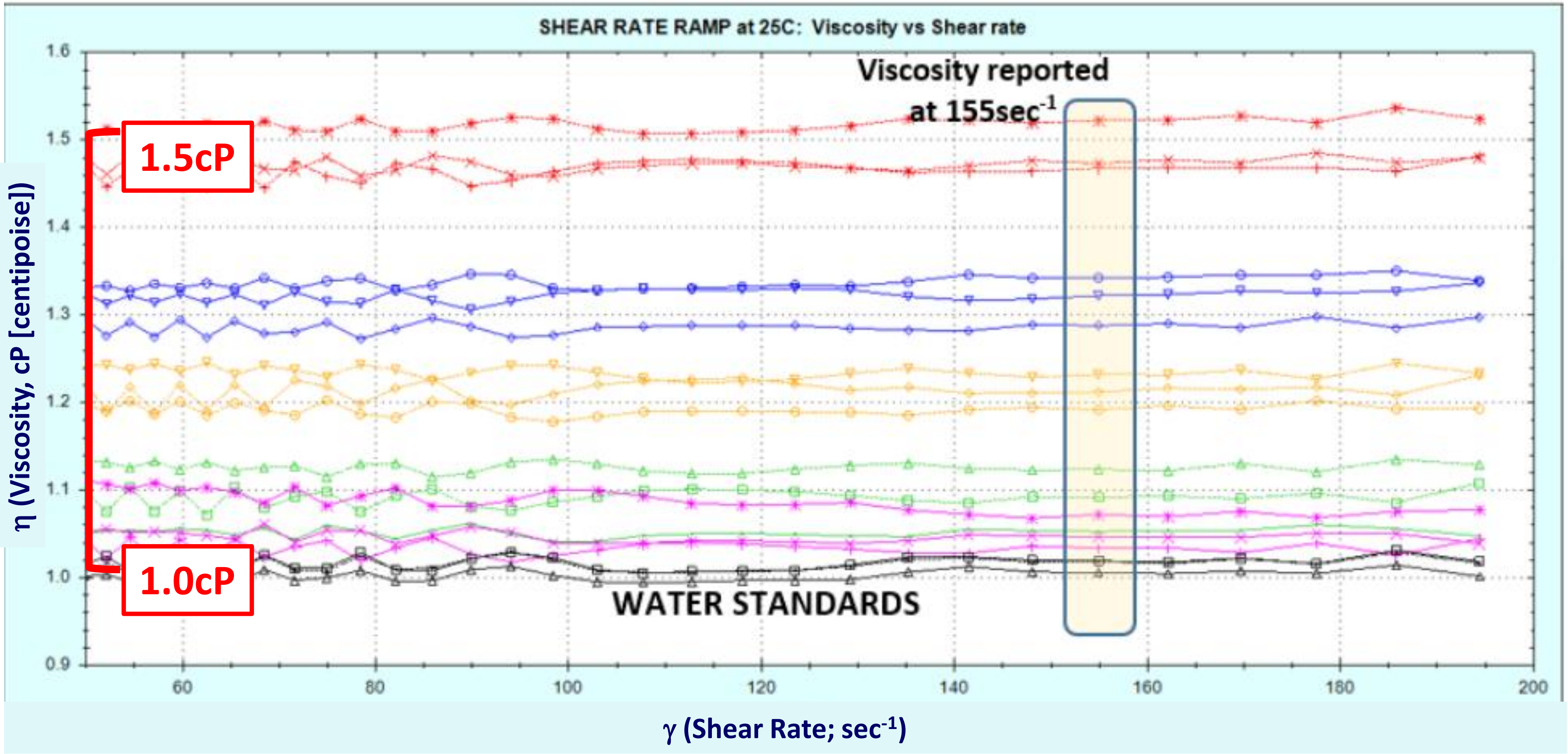
→At 2sec$^{-1}$ $\eta_{Mayonnaise} > \eta_{Honey}$

→At 40sec$^{-1}$ $\eta_{Honey} > \eta_{Mayonnaise}$



# Shear Rate Ramp (Continuous) – Low Viscosity Samples → Sensitivity

- **Purpose**: Client needed to compare viscosity for 5 aqueous formulations vs water
- **Result:** Resolved water stds & 5 very low viscosity samples within 0.5cP range with good reproducibility
- Experimental: 40mm smooth upper parallel plate, 300uL gap (380uL sample) at 25°C over 50-200sec$^{-1}$




Sample 1 (RSD 1.6%)

Sample 2 (RSD 2.3%)

Sample 3 (RSD 1.4%)

Sample 4 (RSD 2.7%)

Sample 5 (RSD 1.5%)

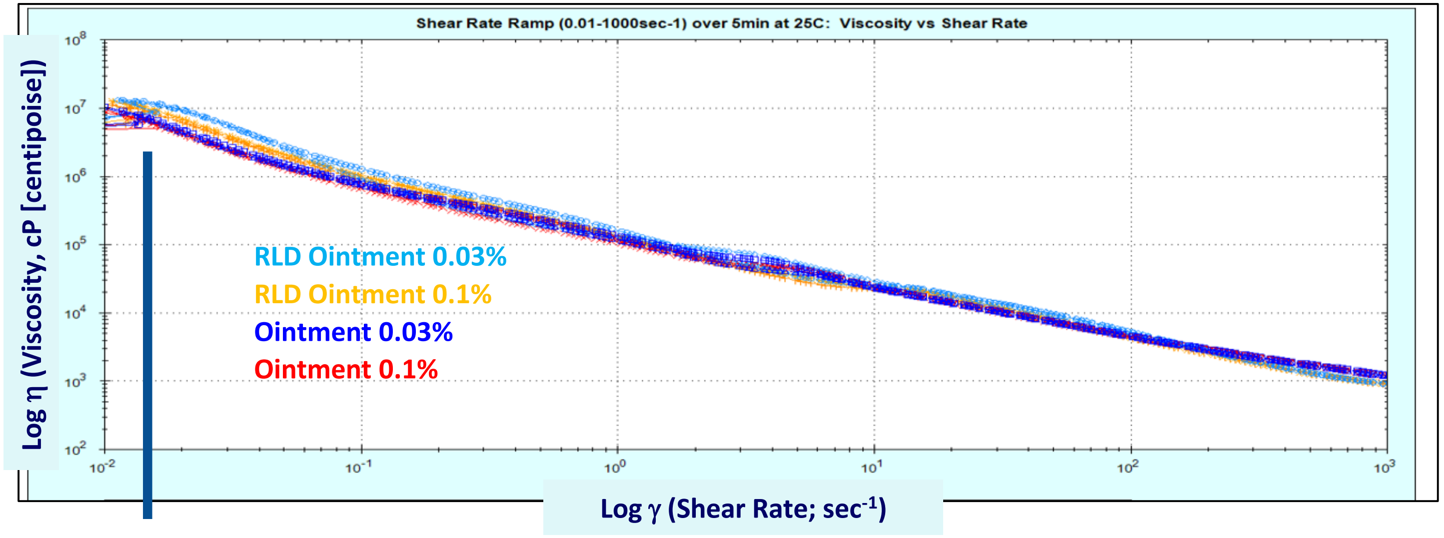
Water Std (RSD 1.1%)

# Shear Rate Ramp (Continuous) – 2 RLD vs 2 Generic Ointments

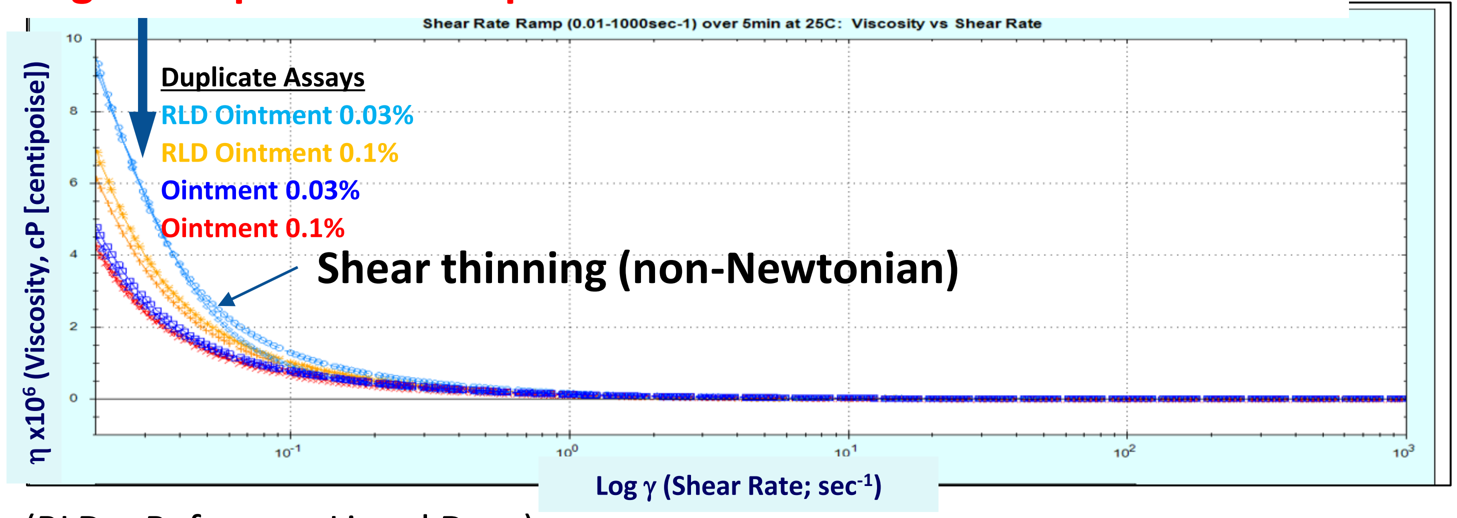
**Experimental:** Shear rate ramp (0.01-1000sec$^{-1}$) over 5min at 25°C, 25mm rough upper plate

**Conclusion:** 0.03% > 0.01% for both RLD and Generic ointments with good reproducibility (n=2**)**

## log-log plot → Samples look reasonably similar




## log-linear plot → See reproducible differences at low shear rates!



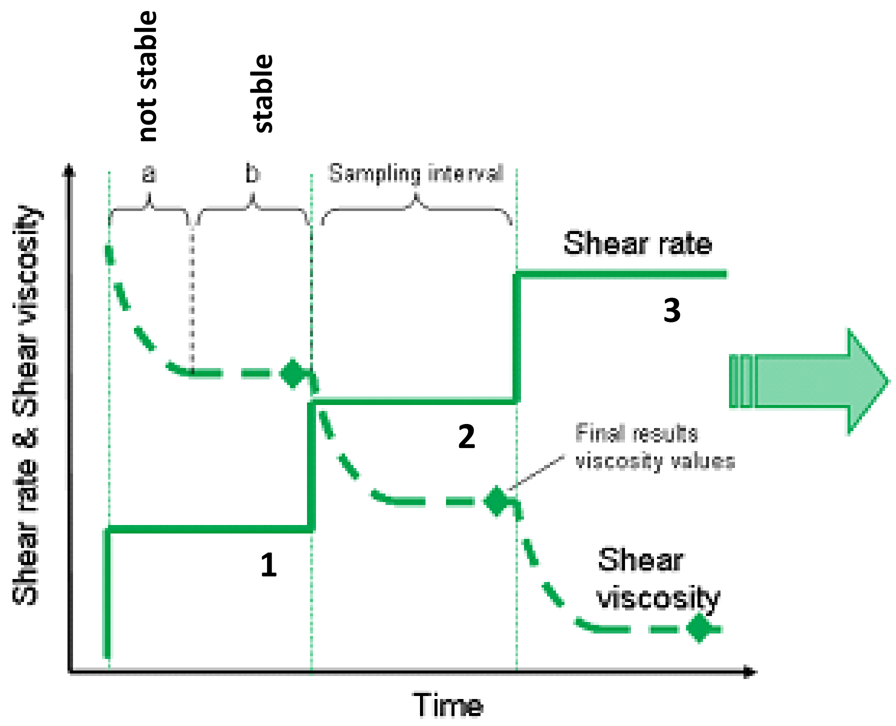

(RLD = Reference Listed Drug)

# Viscosity – Stepwise Shear Rate Ramp

- Incrementally step shear rates up/down.
- Can define viscosity stabilization criteria (i.e. 5% change/5sec) or timeout (i.e. 30sec) before next step.
- Helpful to model manufacturing processes, quantify post-shear thinning (ir)reversibility (hysteresis).

## APPLIED MOVEMENTS

**(for 3 increments)**




## OUTPUT PLOT

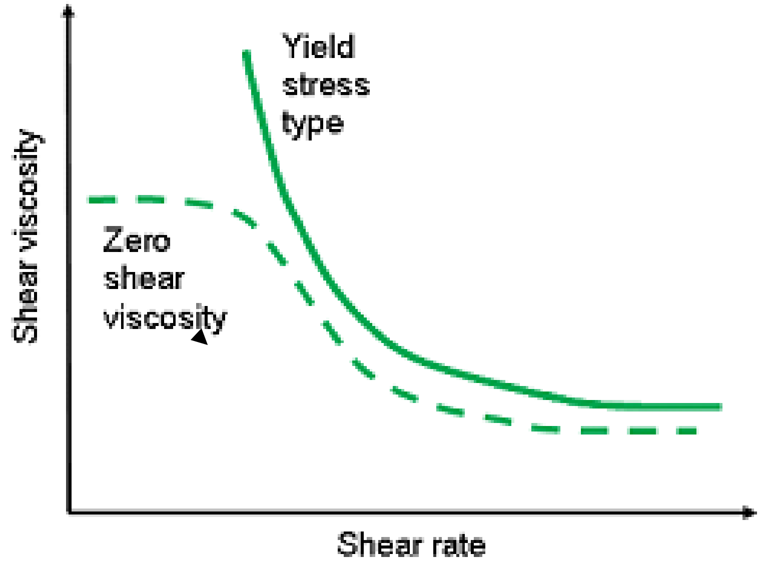


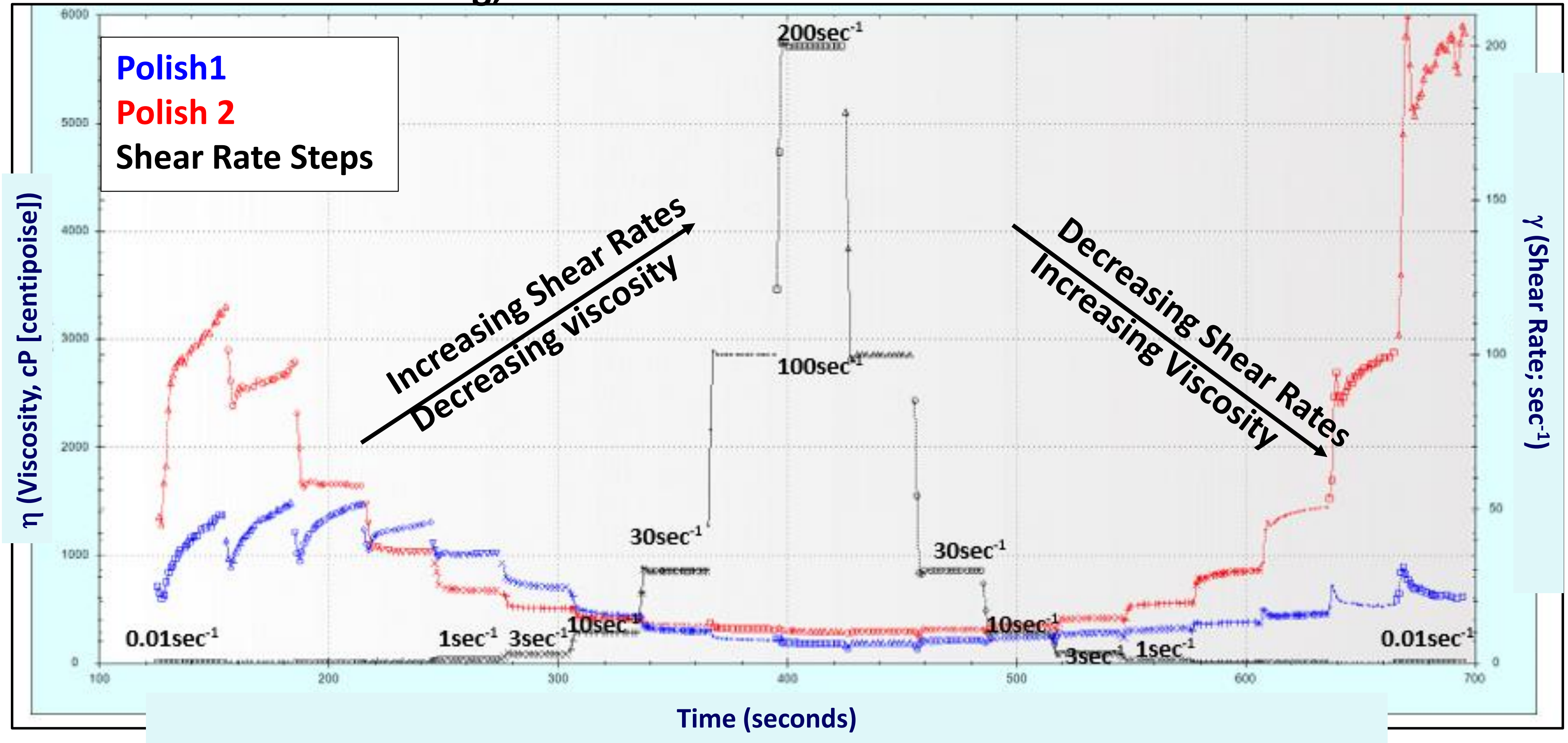

Image from Netzsch

# Stepwise Shear Rate with Increasing/Decreasing Ramps for 2 Polishes

- Experimental: 25mm rough plate, 300um gap (150uL), 0.01 → 200 → 0.01$sec^{-1}$
- 30 seconds hold at each step (10 steps up / 9 steps down)

**Results: -Samples thinned with increasing shear rate, then differed extent of rebuilding with decreasing shear.**

**-After shear thinning, Polish 1 *under*-rebuilt 0.53-fold & Polish 2 *over*-rebuilt 1.86-fold vs initial.**



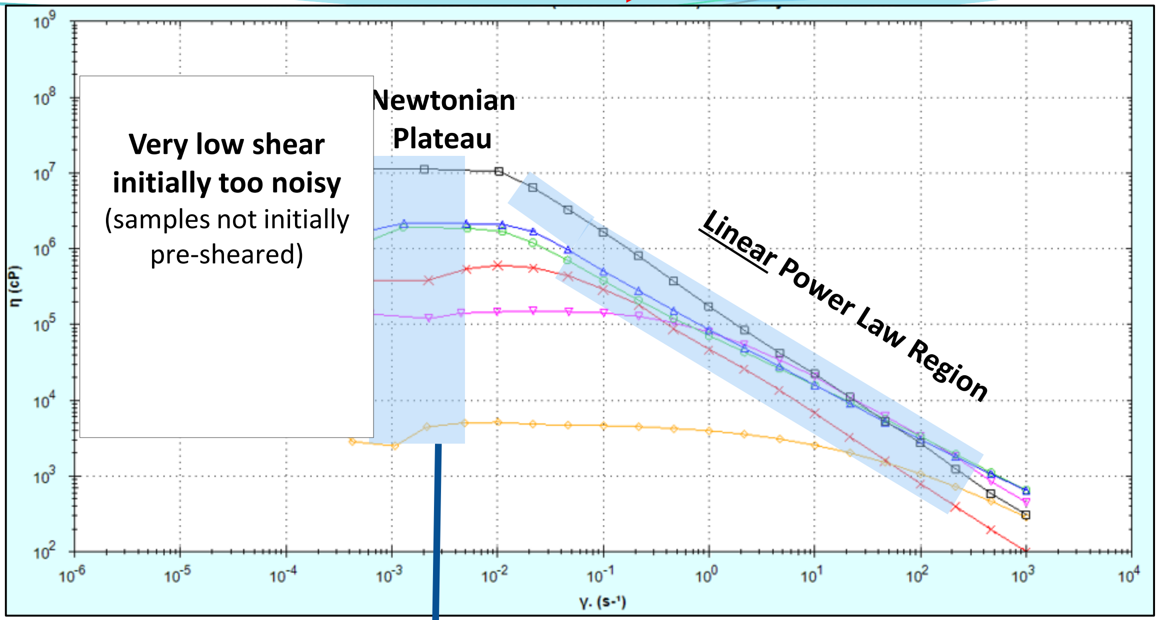
# Application: Stepwise Shear Rate for Arthritis Products

- Move to next step after stability criteria met (5%)

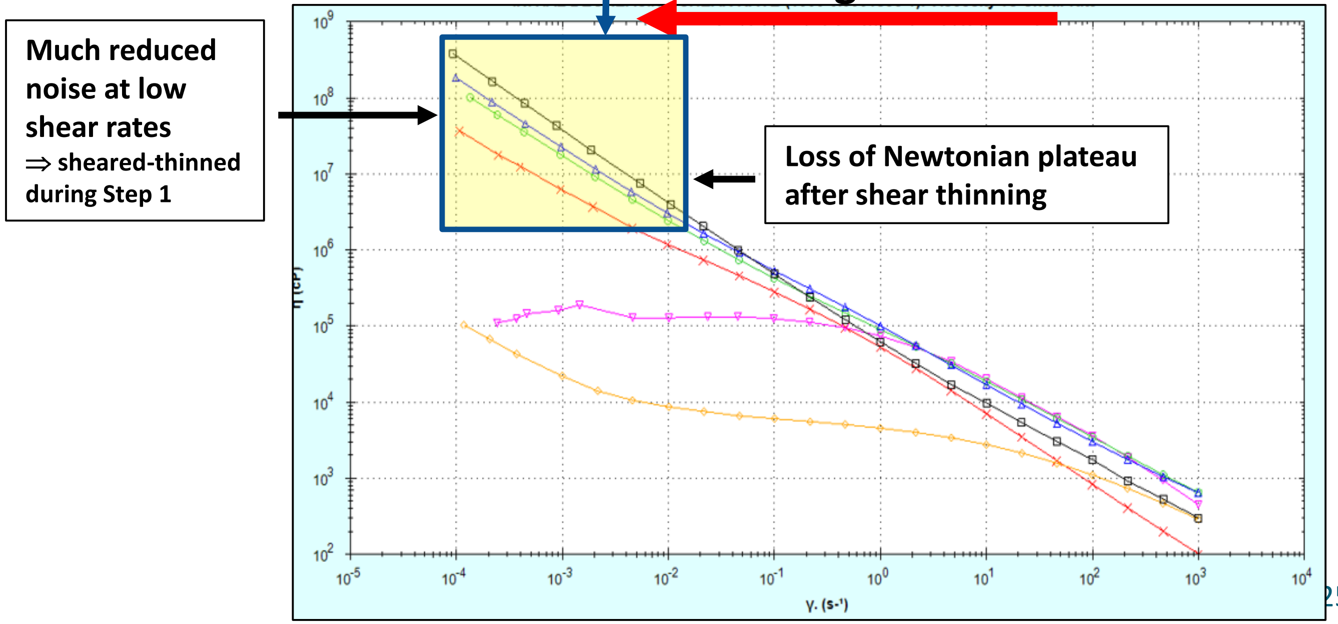
▶ **Purpose:** Client requested side-by-side comparison.
▶ **Results**
 **-**Very different among samples.
 -Increasing vs decreasing shear rate results different showing loss of Newtonian plateau

- **Experimental**: 25mm rough plate, 200um gap (100uL), 0.0001-1000sec$^{-1}$

STEP 1 - Increasing Shear Rate




STEP 2 - Decreasing Shear Rate



# Application: Stepwise Shear Rate - Rank order macromolecule MW ∝ "zero" shear rate

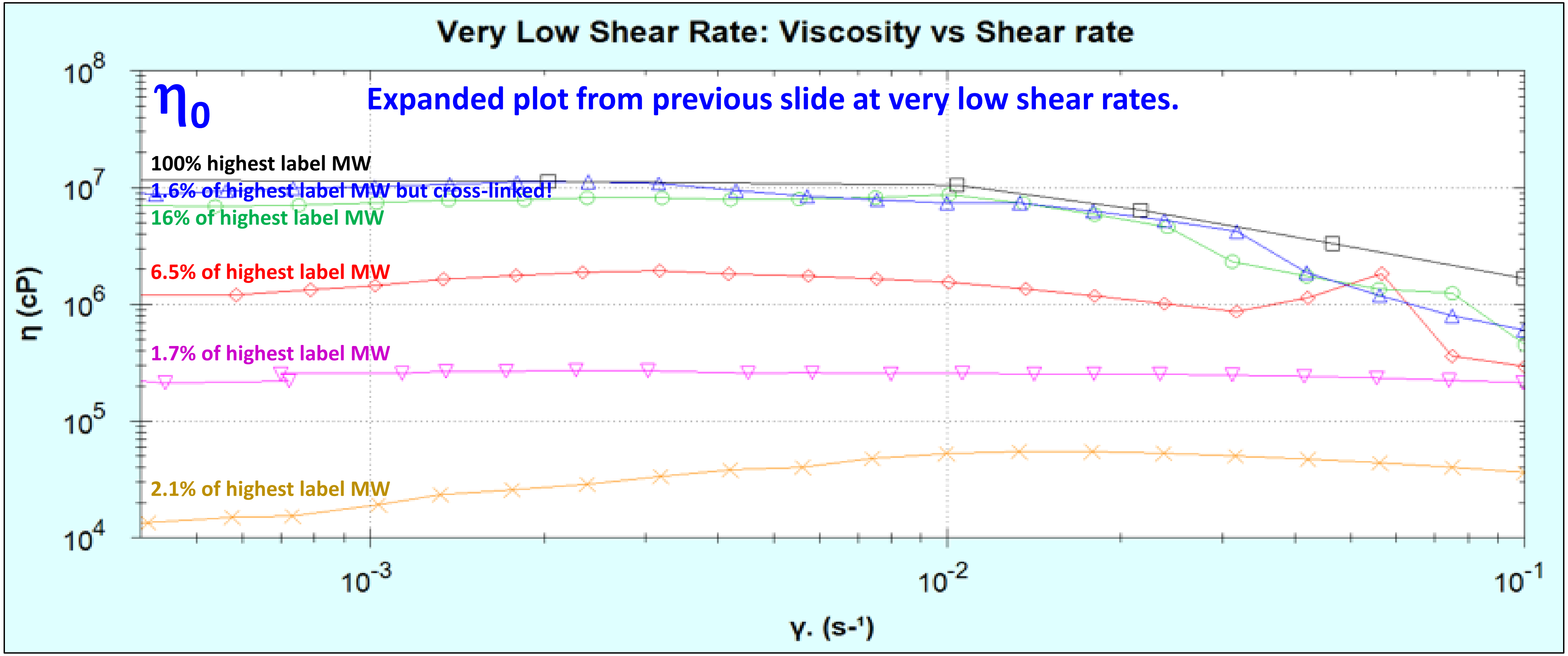
► **Purpose:** Client requested side-by-side rheological profile for several products.

► **Results:** Viscosity at Newtonian Plateau correlate with molecular weight (MW).

→ **General Rule of Thumb:** Polymer having same $\eta_0$ with broad MW distribution (less ordered) starts shear thinning at lower shear vs narrow MWD (more ordered).

→ **General Rule of Thumb:** Correlation with η* (complex viscosity) can also determined with low frequency (oscillatory) assay.

G' & G" shift to ↓freq with ↑MW. ↑G'G" crossover frequency→ ↓ MW. ↑ G'G" crossover modulus → more narrow MWD….*MORE LATER*.



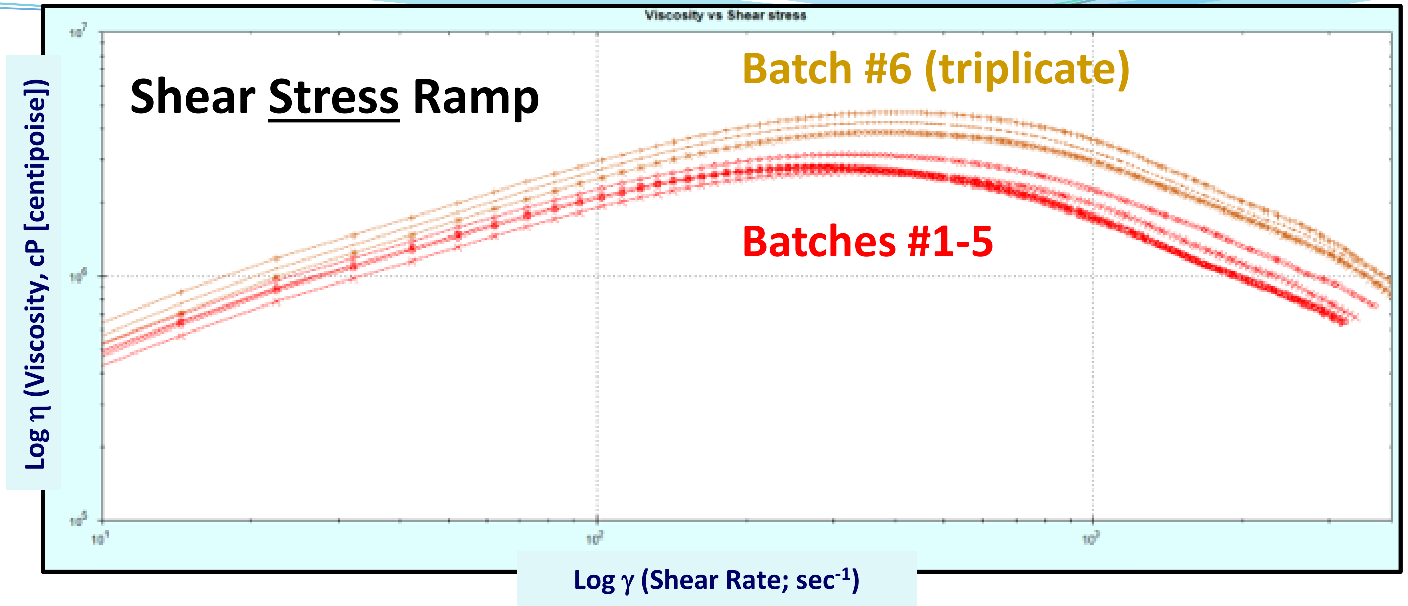
# Application: Batch (In)Consistency using Shear Stress & Shear Rate Ramp Assays

**Conclusion: Both shear stress ramp & shear rate ramp assays confirm Batch #6 differs.**

**SHEAR STRESS RAMP**

Batches #1-5 → Similar

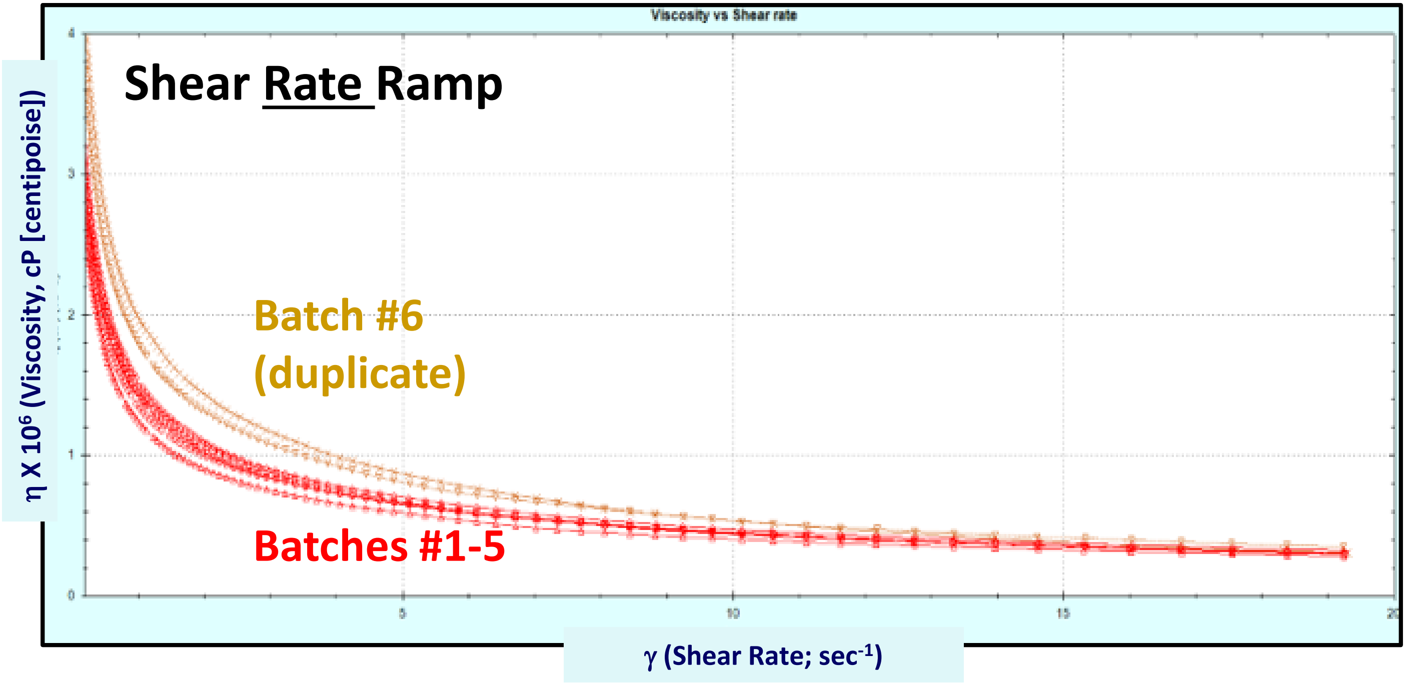
Batch #6 (triplicate) → Higher yield stress & yield viscosity → more stiff




**SHEAR RATE RAMP**

Batches #1-5 → Similar

Batch #6 (duplicate) → Higher viscosity at low shear rate (1-10sec$^{-1}$)

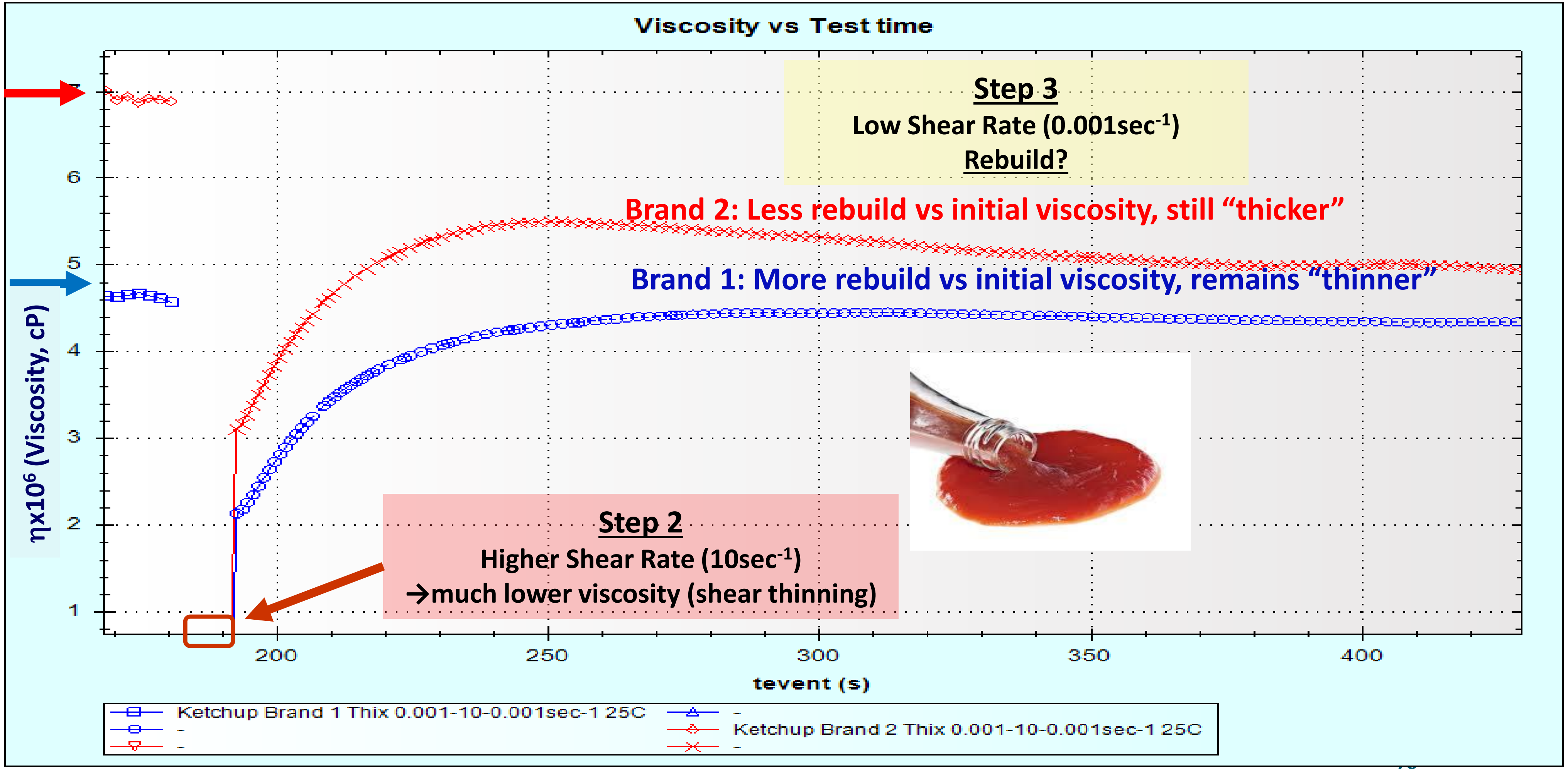


# Application: Thixotropy (3-Step) – Ketchup…again

▸**Purpose:** Client (engineers) requested ketchup data for process modelling.
Determine rebuild extent and rate after exposure to higher shear (i.e. shear thinning).

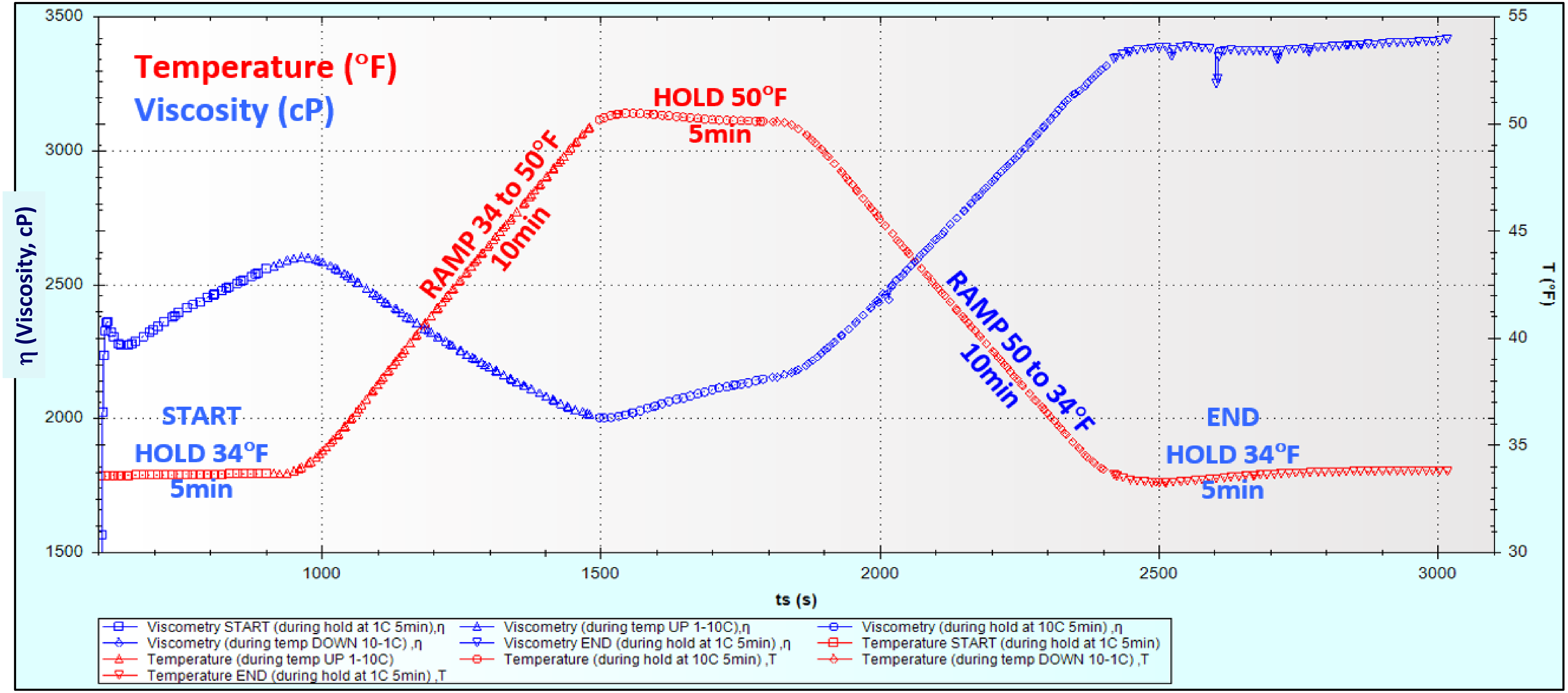
→→**CAREFUL! Assay parameters, esp Step 2 depend on question seeking to answer…….**

**Step 1**
**Low Shear Rate ($0.001 sec^{-1}$)**
**Baseline**



# Application: Temperature Cycling with Single Shear RATE - Food

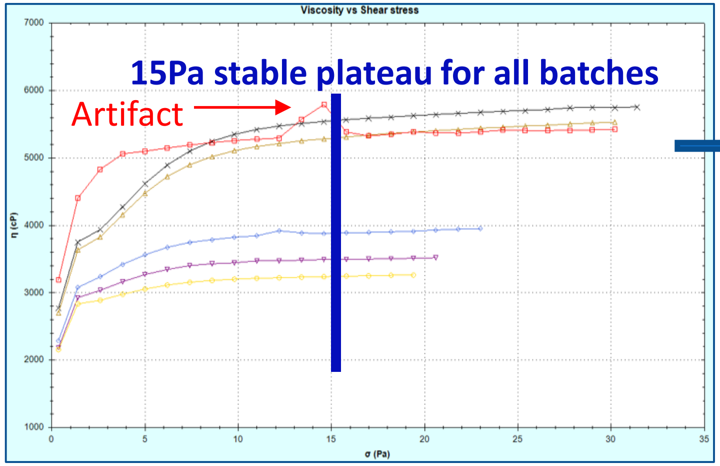
- Investigate irreversibility of food product viscosity with temperature cycles 34 → 50 → 34°F
- Used solvent trap to increase humidity in assay chamber to reduce moisture loss
- Sample assayed at low shear rate of 0.1sec$^{-1}$



# Application: Temperature Ramp with Single Shear STRESS - 6 dispersed polymers

- ▶ **Purpose**: Client requested screen for rheological differences & stability with brief exposure to at 90°C.
- ▶ **Result:** Batches differed (Fig 2). All appeared to be rheologically stable with brief heating (Fig 3).
- **Experimental**: 25mm rough parallel plate, 0.2mm gap, 15Pa over 5→ 90 →5°C (5°C/min)

**Fig 1. Preliminary yield stress screen at 25°C IDed stable stress input (15Pa) for subsequent temperature ramps (Figs 2-3)**



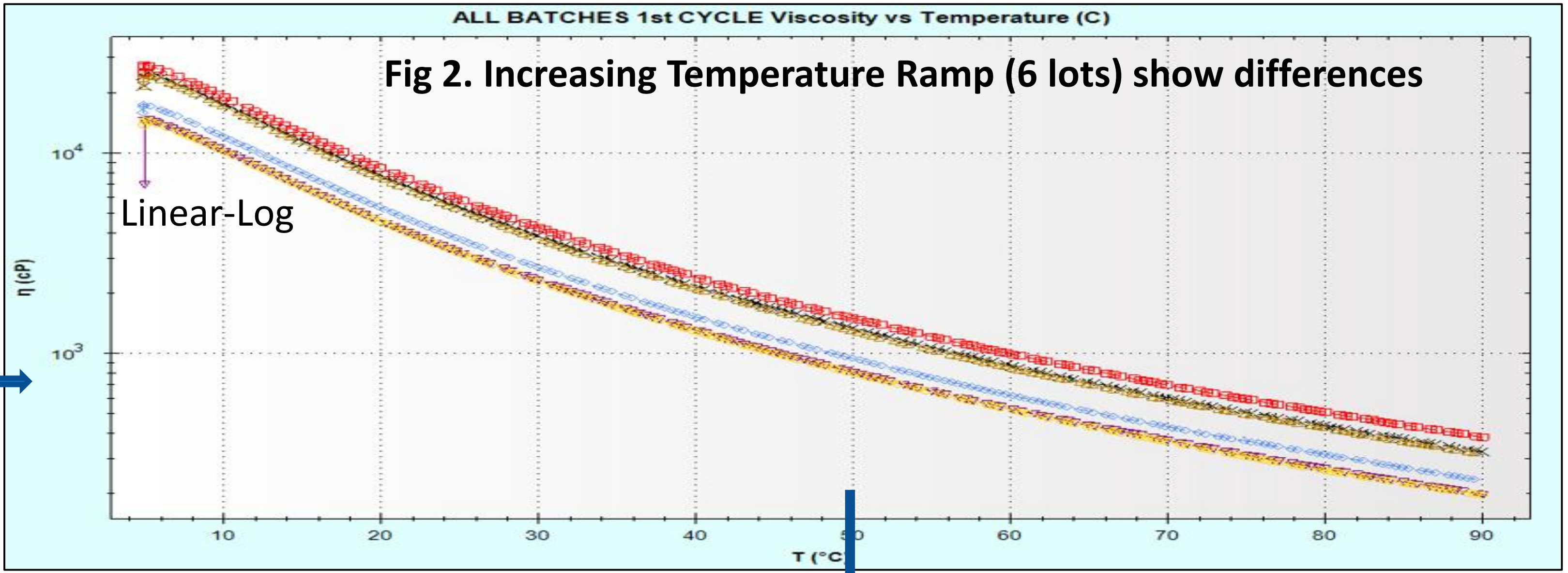




**Fig 2. Increasing Temperature Ramp (6 lots) show differences**

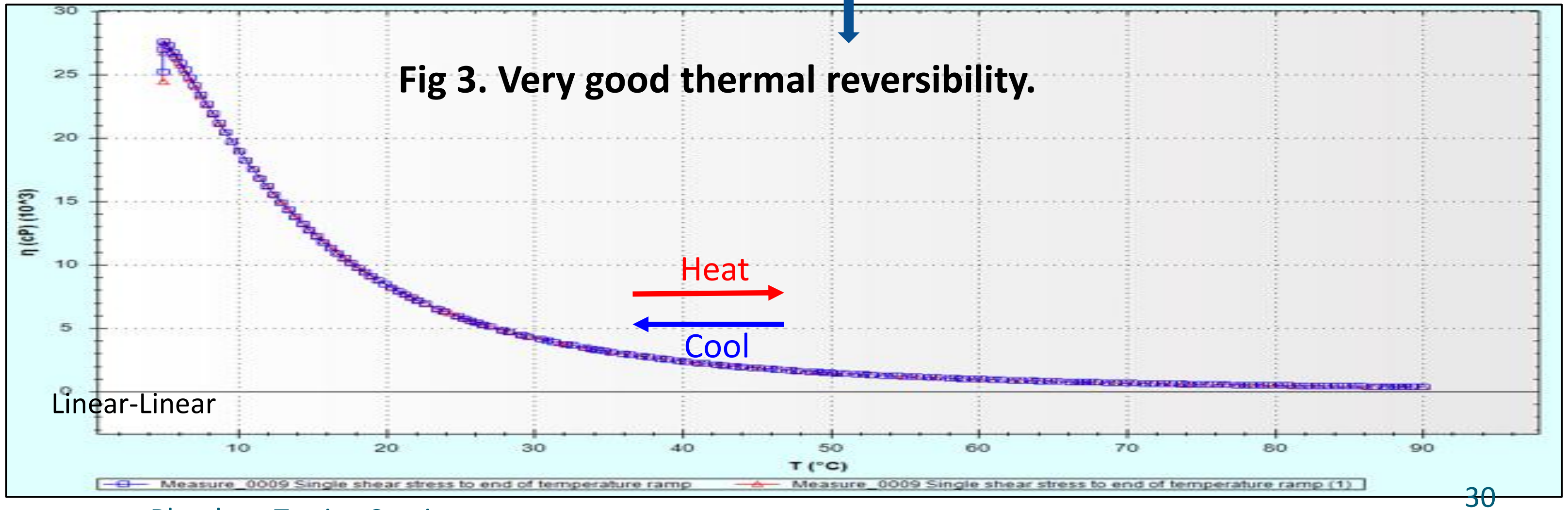



**Fig 3. Very good thermal reversibility.**

# Creep-Recovery for Yield Stress & Elasticity

*Squeeze/twist and release.*
*Quantify responses.*

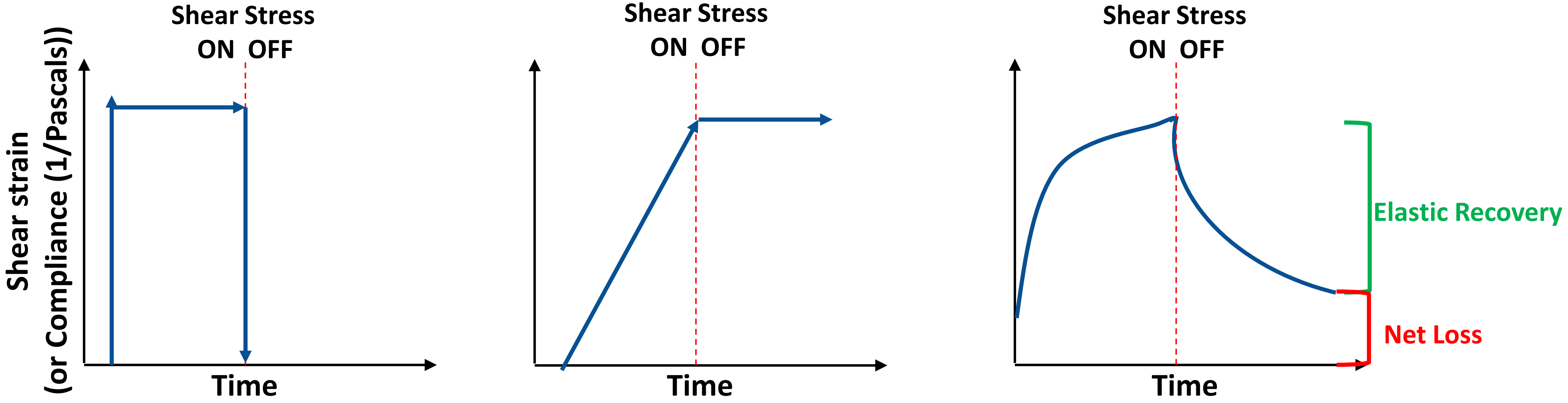
**Response to applied stress and release**

- ⇒ Quantitate net loss of elasticity (fatigue) following stress or strain
- ⇒ Used to determine zero-shear viscosity and evaluate suspension stability

**Pure Elastic**
Most stable
Bounces 100% of initial height

**Pure Viscous**
Least stable
No bounce

**Viscoelastic**
Mix of Viscous & Elastic

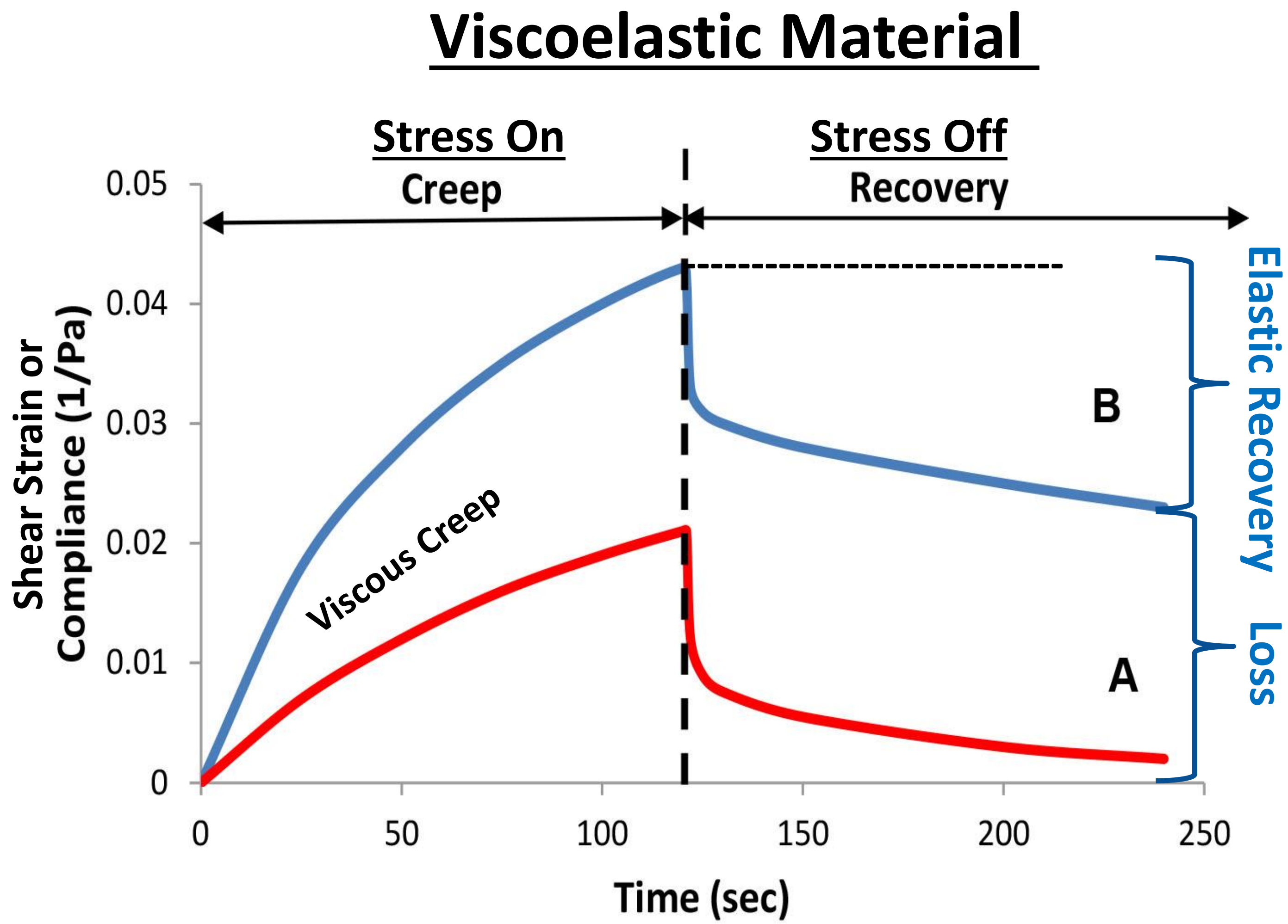


# Creep-Recovery

**Response to applied stress and release**

**⇒ Quantitate net loss of elasticity following stress**

*Squeeze/twist and release.*
*Quantify responses.*



# Application: Tribology (friction) of 4 common 5W-30 motor oils at 15, 25 & 125°C

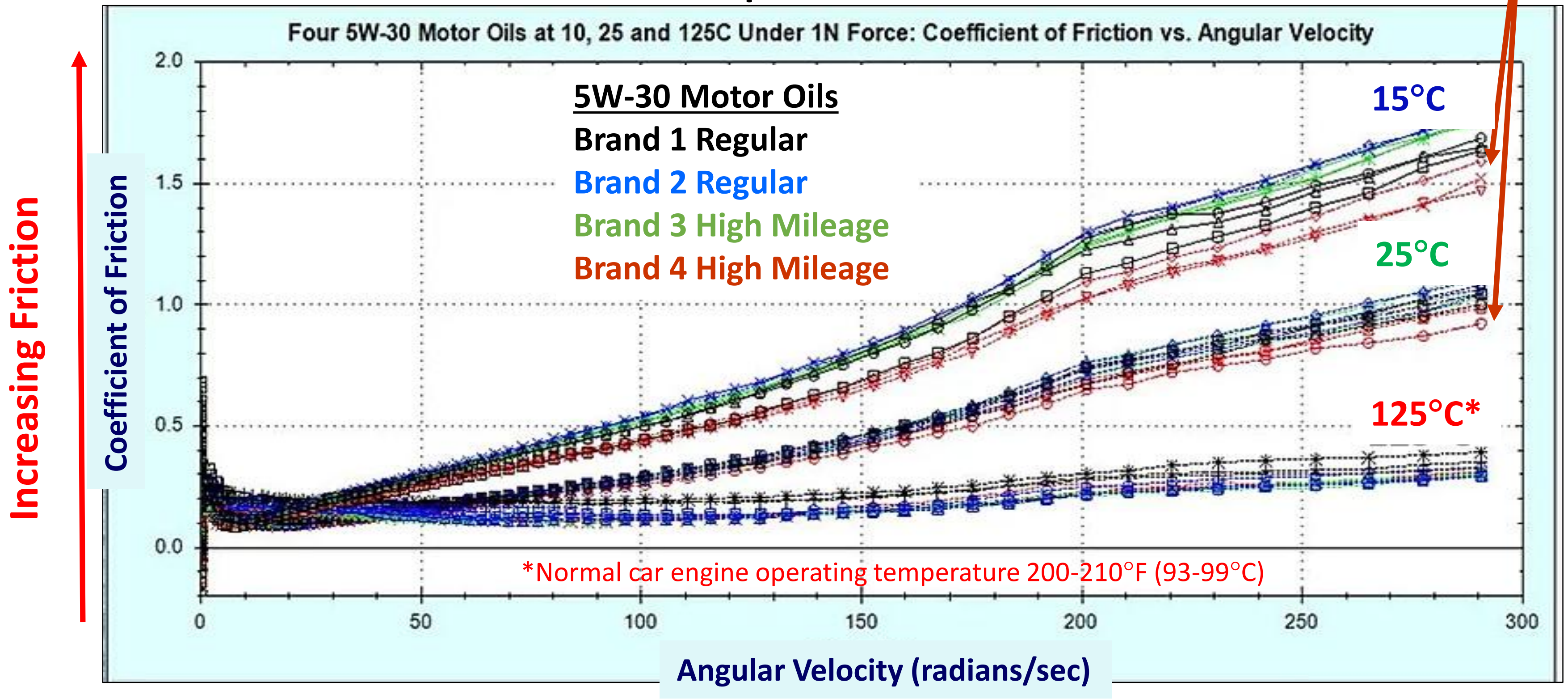
►**Result:** Differences among oils decrease with increasing temperature and decreasing shear

⇒ food and cosmetics applications

**per ISO7148**

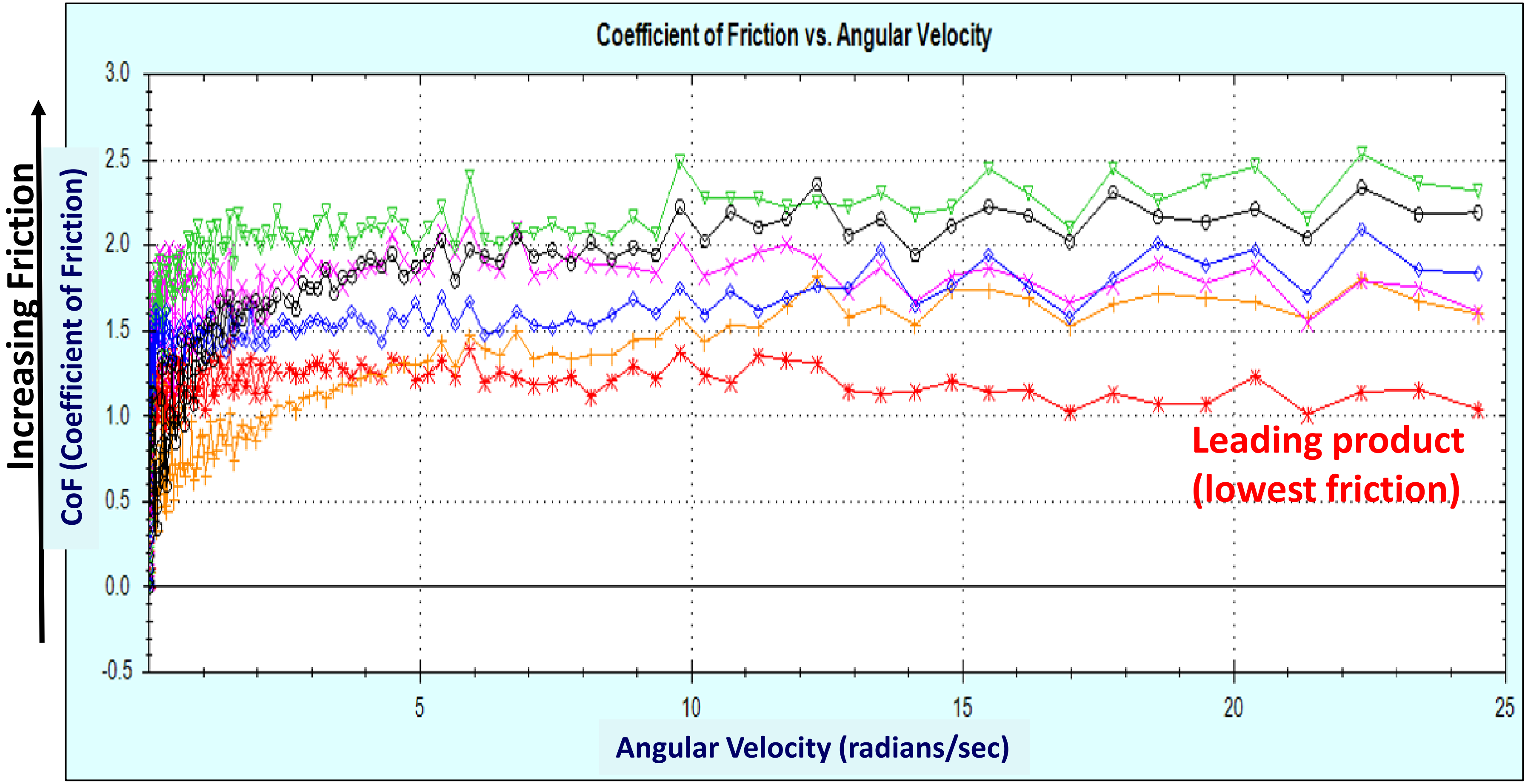
Brand 4 (high mileage oil) has lowest friction (CoF) at lower temperatures as ↑shear.

**Stribeck Curves**



# Application: Tribology (friction) for arthritis products

- ▶ **Purpose**: Client wanted to compare friction properties across 6 products
- ▶ **Result:** Observed ≈2-fold difference among samples with leading product having least friction (lowest CofF).
- **Experimental:** 36°C, 0.2N downward force over 0.0001 to 100 radians/sec. Requires ≈300uL sample.



Now that we've looked at some examples, some experimental considerations….

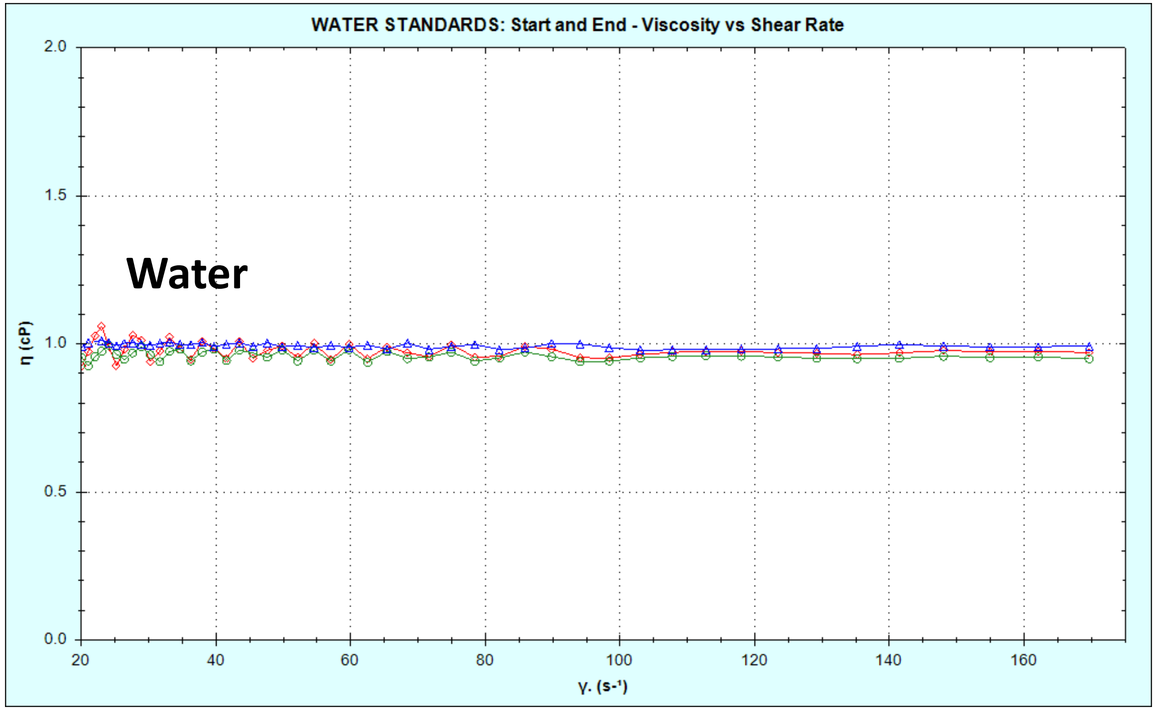
# Preliminaries to Ensure & Confirm Rheometer Performance

- Motor Warmup, Torque Mapping, Geometry Inertia
- Performance standards: start & end bracketing water or silicone oil for rotational assays and PDMS for oscillatory assays

**For Rotational Assays: Shear Rate Ramp (same used for samples)**

**• Water for highly aqueous, low viscosity samples**

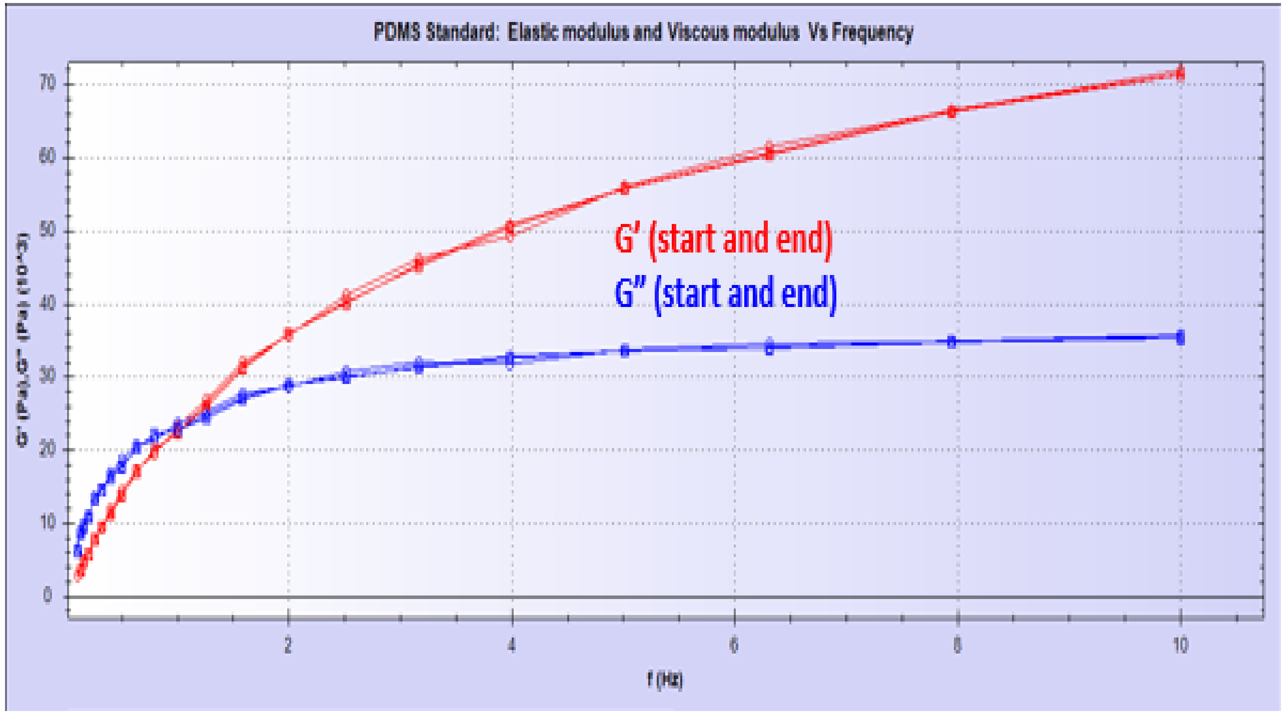
**• Certified silicone oil standards for higher viscosity samples**




**For Oscillatory Assays: Frequency Sweep**

**• PDMS Std**

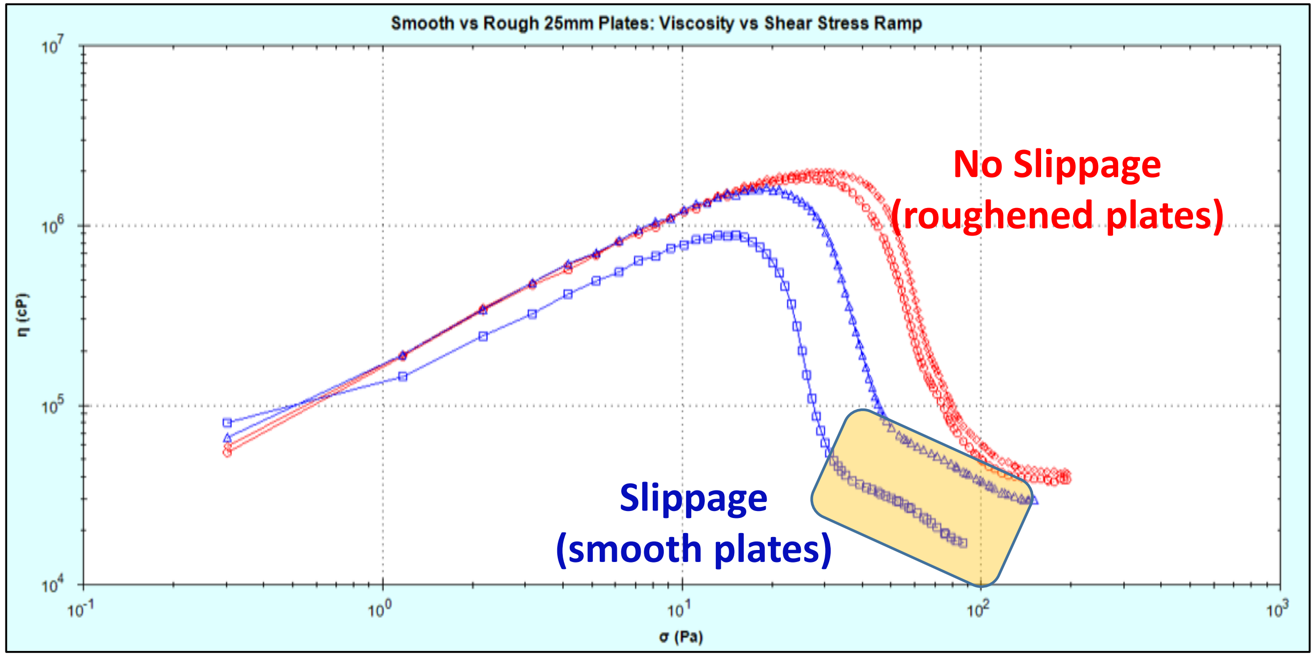
**(10→0.1Hz at 25°C, 0.5% strain, 0.5mm gap with 25mm rough plate vs label claim)**

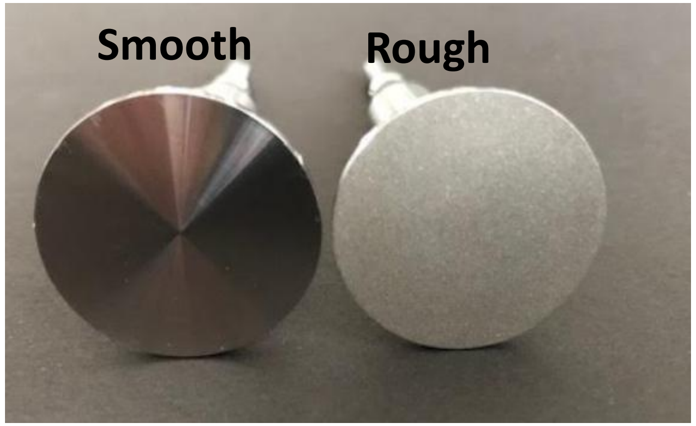


# Mindful about slippage at plate-sample interface

- Plate must impart force through sample, not just at plate-sample interface
- Slippage leads to experimental error, variability and conclusions
- If sample not prone to slippage, results should be similar with different gaps (i.e. sample height)

► Use roughened or serrated plates to reduce potential for slippage




**Example of "Slippage" at of top cards→**

Top 2 cards "slip" further than others

# Other Experimental Considerations

- **Consistency is critical!**

  -Handling during loading (minimize shear, bubbles, volatiles loss (more later))

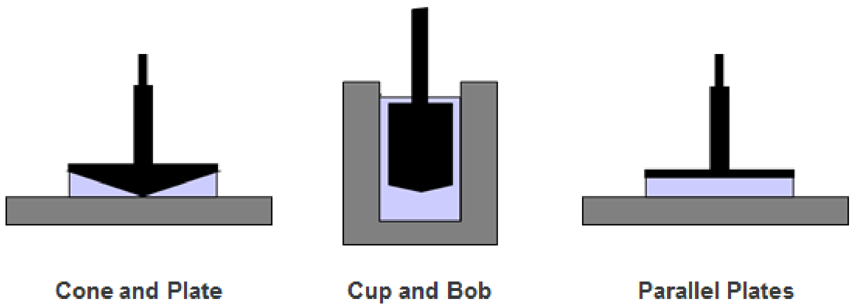
  -Trim to remove excess sample

- **Geometry: Cone, Plate or Cup & Bob, vane, many options**

  -Cone gives more consistent shear across sample vs parallel plate.

  -Cone not recommended for temperature sweeps if not compensate for thermal expansion.

  -Plate allows flexible and smaller gap to assay with higher shear rate without losing sample.  Cone has default gap.




- **Plate/Cone Size**

  -Larger diameter provides more sample contact to provide more torque, hence more sensitivity; but requires more sample.

  -Larger diameter is more sensitive for less viscous samples and achieves smaller strain amplitudes for oscillatory assays.

  -Larger diameter can generate higher shear rate

  -Larger diameter, having more oscillating mass gives “inertia flag” at higher frequency, esp for lower viscosity samples.

  -Smaller diameter better for more viscous and viscoelastic samples.  Also uses less sample.

  -Smaller cone angles achieve higher shear rates.

# Other Experimental Considerations (continued)

- **Consistency is critical! …repeating**

**Shear rate = strain/time**
**(Strain=displacement/height)**

- **Gap (sample height)**

-Typically 0.2-1mm. Depends on sample and assay parameters. (human hair ≈70+/-20um)

-Smaller gap requires less sample (100ul for 25mm plate with 200um gap)
-Smaller gap:
  -Generates higher shear rate.
  -Reduces potential to lose sample from gap at high shear rate. Observe stress ↓↓ with ↑ shear rate if sample displaced.
  -Small gap inaccuracies may lead to modest % assay error.
-Larger gap facilitates smaller strain amplitude

-1/10 rule: plate-plate or plate cone gap $\geq$ 10x largest particle or droplet. Cones have fixed default gaps.

-Gap setting options to provide consistent sample loading:
  -height controlled → For most samples. Typically 200-1,000um.
  -force controlled → For samples with inconsistent thickness (i.e. cheese), rigid &difficult to compress (polymer films). Rheometer software accounts for sample height throughout assay to calc outputs.

⇒Kinexus rheometer tracks both gap height and force for each datapoint throughout assay.

# Other Experimental Considerations (continued)

- **Pre-Shear or not to pre-shear…..**

  **-**Depends on question to be answered

  -Any sample movement (loading) may irreversibly shear thin sample, maybe not!?! Screen with thixotropy assay (later)

  -Can apply very low pre-shear to "normalize" for handling effects

  ***BUT****… pre-shear can "erase" other rheological properties especially if sample easily shear thins with poor rebuilding.*

- **Sample change during handling and analysis**

  **-Curing, degradation, rebuilding, cross-linking, volatiles loss, etc**

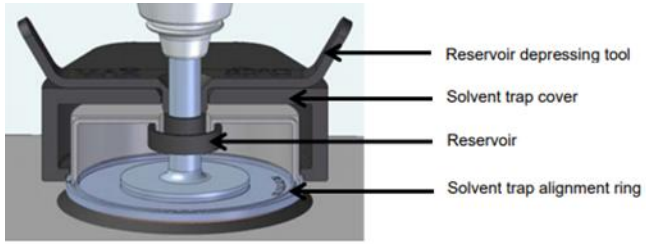
  -Rotational: Screen with <u>single</u> shear rate or shear stress vs time at assay temperature(s) and monitor viscosity

  -Oscillatory: Screen with <u>single</u> frequency vs time & monitor G', G", $\delta$, G* changes.

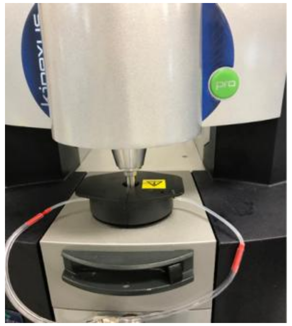
  *What are* G', G", $\delta$, G* *? Stay tuned……*

  **-Got volatiles? Use a solvent trap**

  -Maintain sample in enclosed volatiles saturated environment (i.e. humidity)




  **-Sensitivity to oxidation at elevated temperature →** enclosed, low $N_2$ flow



# Switching gears from rotational to oscillatory assays → DEFORMATION

**Movements → torque**

- Rotational (1 direction)
- **Oscillatory (bi-directional)**
- Vertical


# Oscillation ≈ washing machine agitator…sort of

<u>**2 Ways to Modulate Oscillation:**</u>

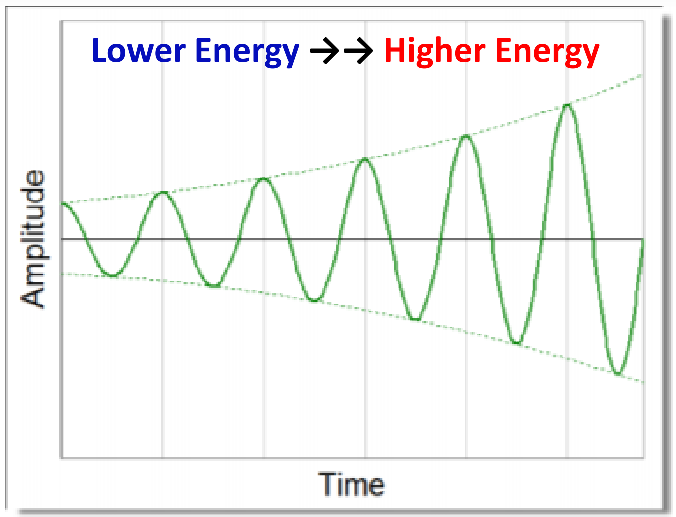
## 1. Amplitude (destructive)

- Determine <u>L</u>inear <u>V</u>iscoelastic <u>R</u>egion (LVER)
  ⇒"Breaking point" of structure ∝ stability

- Quantify textural properties: stiffness, springiness, structural strength, brittleness

## 2. Frequency (non-destructive)

- Measure response to event time =1/freq
  -Probe structural properties <u>within LVER</u> to maintain rheological integrity during assay



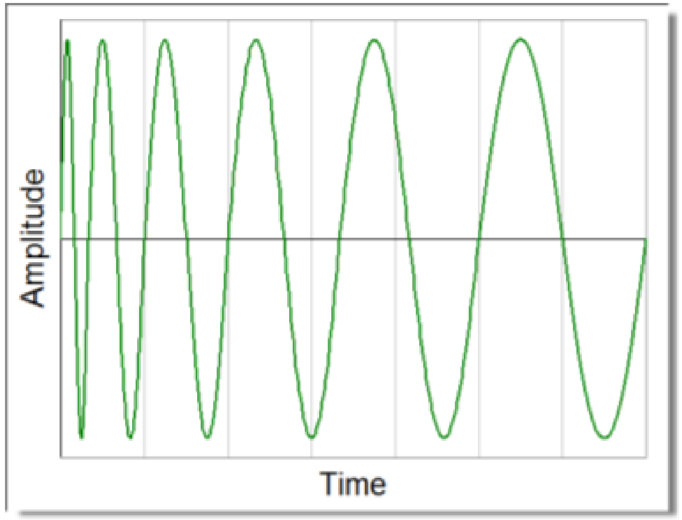




Image from Netzsch

# Oscillation - Amplitude Sweep

⇒ Increase amplitude (back-forth movement) until "break" macrostructure

⇒ Prelimary assay to determine LVER before perform frequency modulated assays to ensure sample integrity.

⇒ LVER can decrease with increasing frequency. Typically perform assays at 1Hz.

⇒ G' (elastic modulus; solid-nature) tends to increase with increasing frequency

⇒ LVER tends to decrease with increasing solid form (i.e. temperature dependence). LVER $_{melted}$ > LVER $_{not\ melted}$

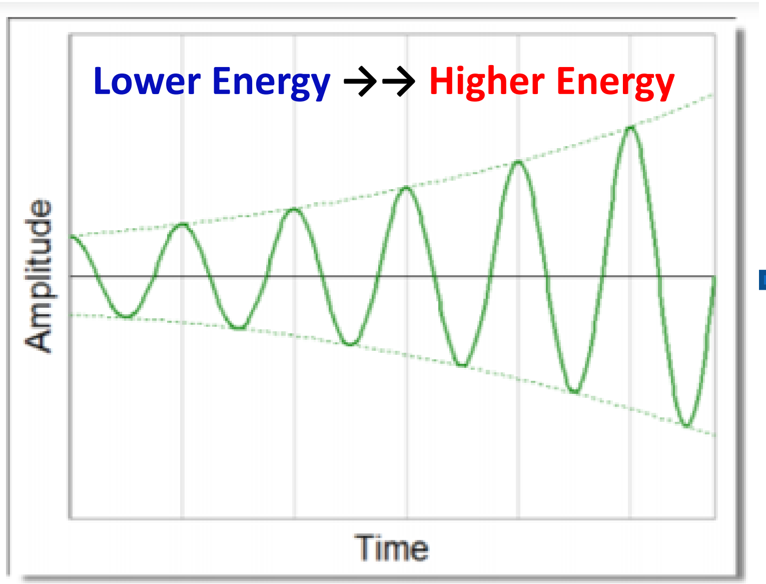
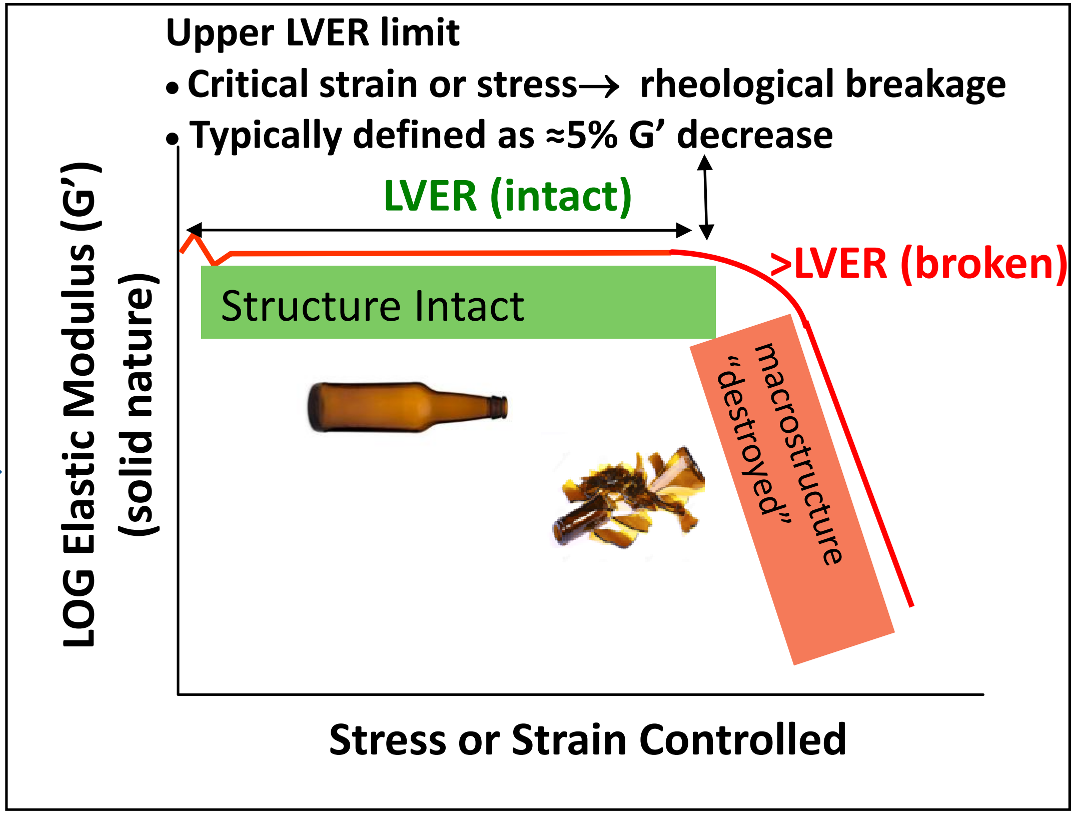
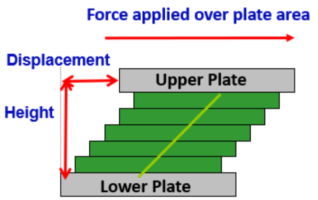



Image from Netzsch




**Stress controlled:** Measure sample movement from defined applied force (stress=F/A).
**Strain controlled:** Measure torque required to move sample defined displacement.



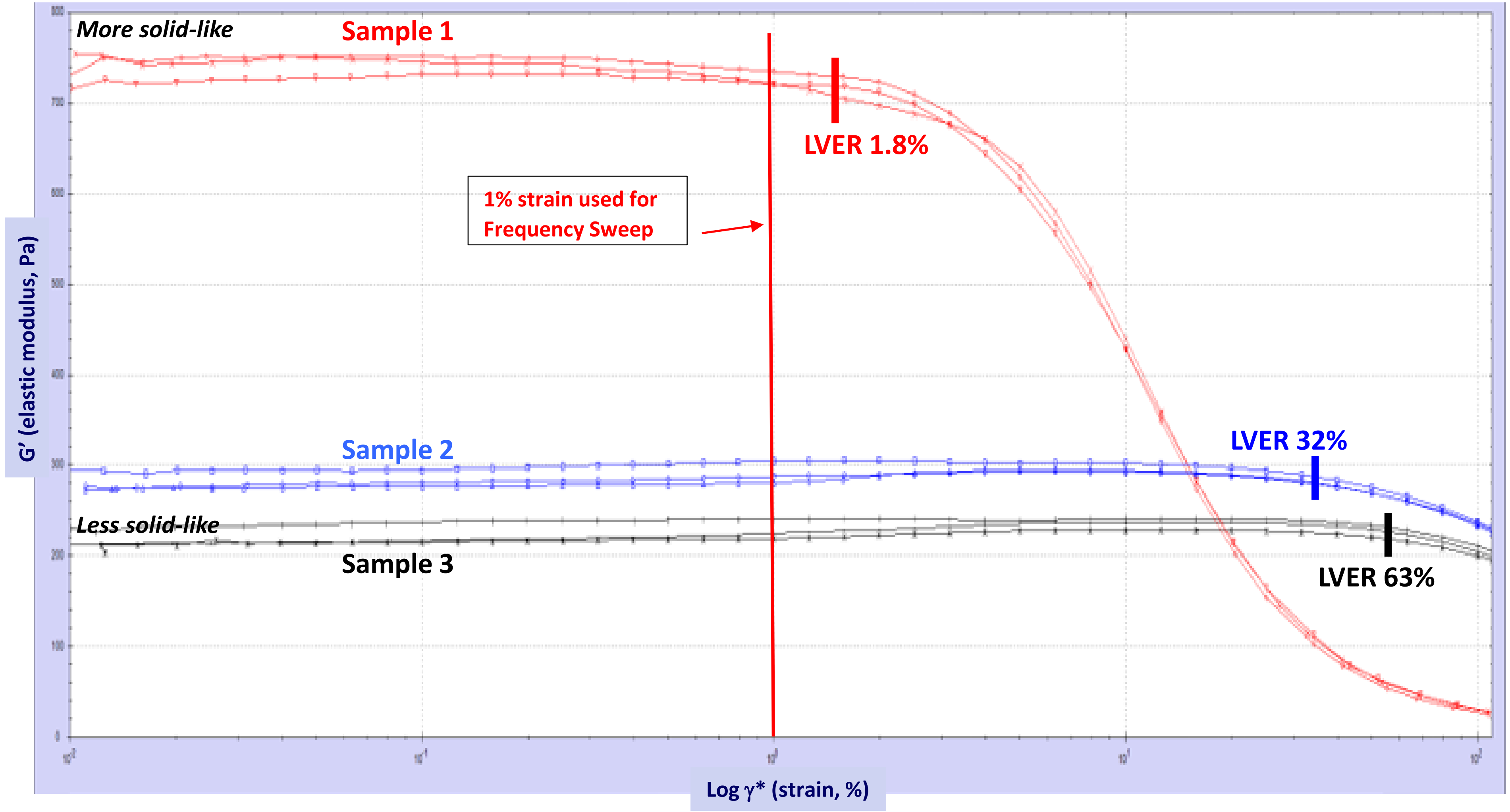
# Application: Amplitude Sweep: G' vs % strain to determine LVER for gels containing hyaluronic acid

→ strain = extent of sample deformation relative to sample height

► **Purpose**: Compare properties. <u>ALSO</u> need LVER from this assay to define %strain (within LVER) input for subsequent frequency sweeps.

► **Result:** Observed large LVER and G' differences. Determined input %strain for subsequent frequency sweeps.

**Note**: LVER typically defined as 5% G' decrease. Determined from data tables, <u>not</u> visually from plots.



# Interpretation of Amplitude Sweeps: Shelf Life of Dispersions

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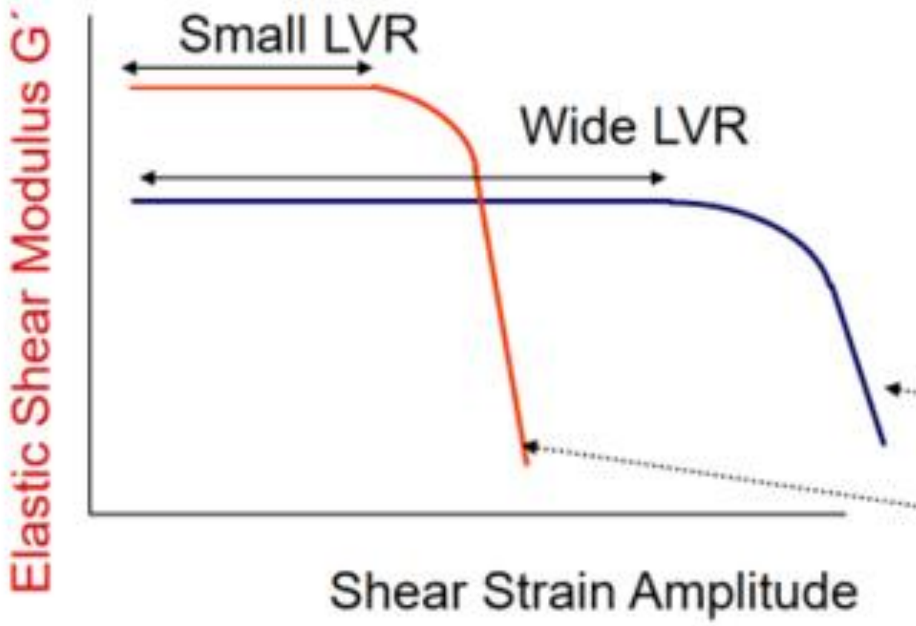
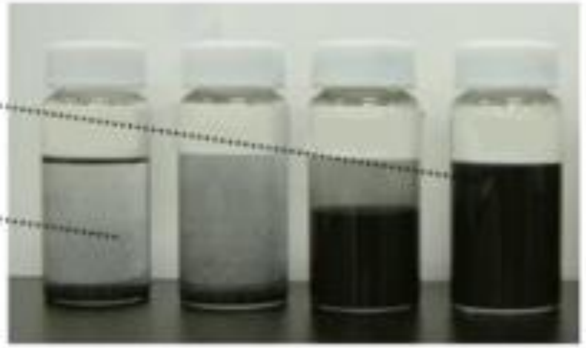
## Quick Check of Shelf Life without Prediction of Timescale!




**Cohesion Energy Density**

$$E/V = \tfrac{1}{2}\, G' \times \gamma_{kr}^{2}$$

Units: $\frac{J}{m^3} = \frac{kg \cdot m^2}{s^2} \cdot \frac{1}{m^3} = \frac{kg}{m \cdot s^2} = \frac{N}{m^2} = Pa$



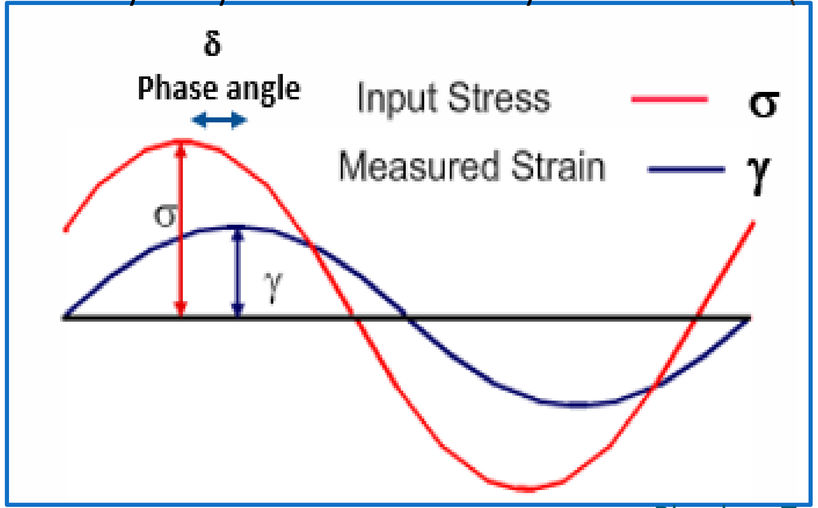
Long-Range Interactions increase the Cohesion Energy by enlarging the LVR.

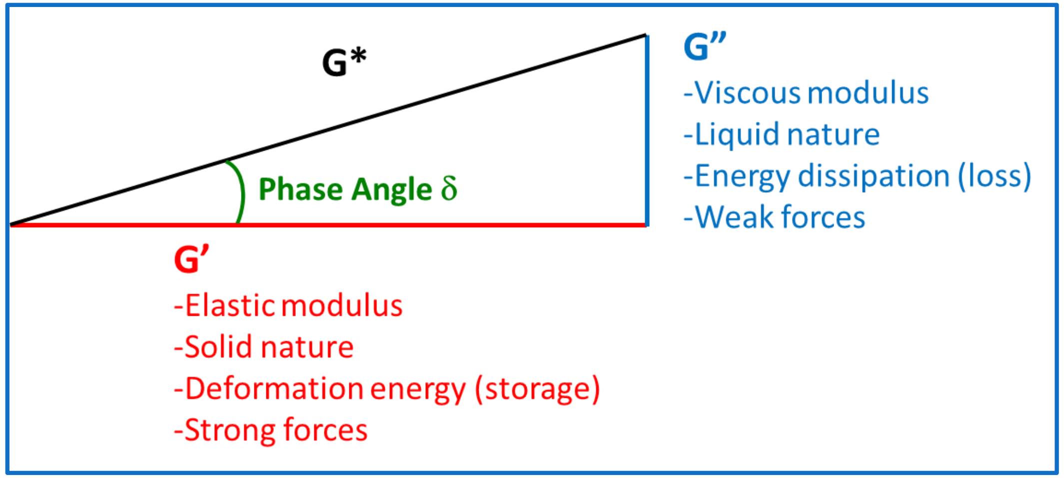
Slide from Netzsch

# Oscillatory Assay Output Summary: G’, G”, δ, G*, η* and tan delta to Quantify Viscoelastic Deformation

- **G’ (Pascals; Pa) :** Elastic or “storage” modulus ∝ solid nature
- **G” (Pascals; Pa) :** Viscous or “loss” modulus ∝ liquid nature
- **δ (degrees):** Phase angle 45° → 0° increasingly solid
  45° → 90° increasingly liquid
- **tan δ (unitless): =** G”/G’ ∝ ability to store (solid-like) and release (liquid-like) energy.
  - With decreasing tan delta, particles increasingly associated due to colloidal forces, sedimentation could occur
  - The lower the frequency of G’G” crossover, the higher the molecular mass.
  - <1 increasingly solid-like; >1 increasingly liquid like; = 1 is G’G” crossover (phase transition, melting pt, gel pt)
- **G* (complex modulus; Pa)** = $\text{Stress}_{(max)} / \text{Strain}_{(max)}$ ∝ Stiffness
- **η* (complex viscosity; cP or Pa-sec)** = G*/ 2πf where f= angular frequency that must be units of radians/second

⇒Depending on sample properties, it is important to note that "η viscosity" obtained with rotational assays and "η* complex viscosity" determined with oscillatory assays are not necessarily the same value (see references about "Cox-Merz Rule-Netzsch" and "Cox-Merz Rule-TA").

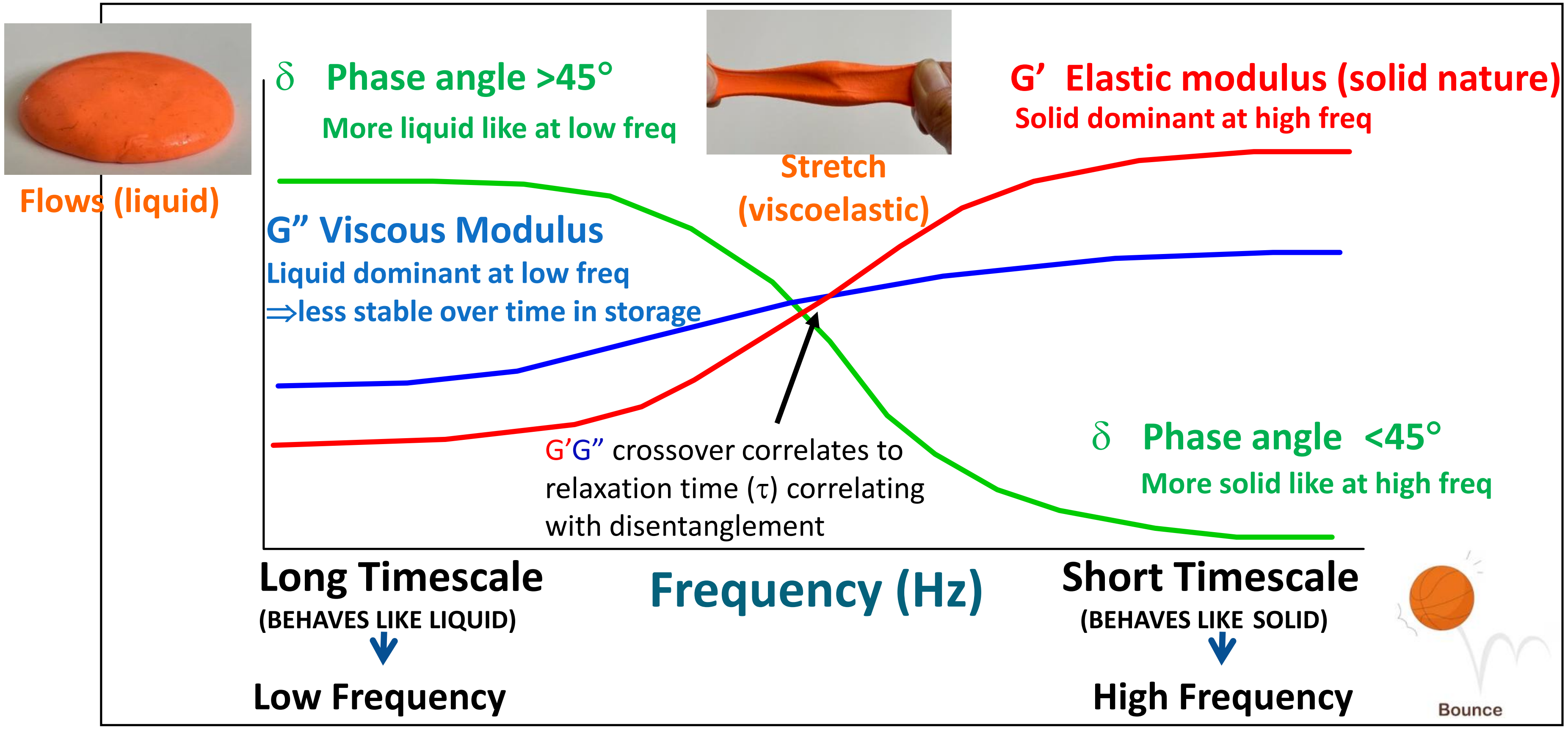


# Frequency Sweep: Example Silly Putty → Viscoelastic Liquid or Solid?

- Probe properties across a time domain.  Frequency = 1/time (sec)
- Generates rheological “fingerprint” or “spectrum”
- Use % strain as assay input within LVER determined with amplitude sweep

At lower Hz, sample molecular relaxation time is shorter than applied test freq, more liquid-like with G” > G’ ⇒ flows.




At higher Hz, sample molecular relaxation is longer than test freq, more solid-like with G’ >G” ⇒bounces.

Bounces (solid)

# Application: Frequency Sweep - Quantify Texture

## Complex modulus (G*) vs Phase Angle (δ) at 1Hz and consistent %strain

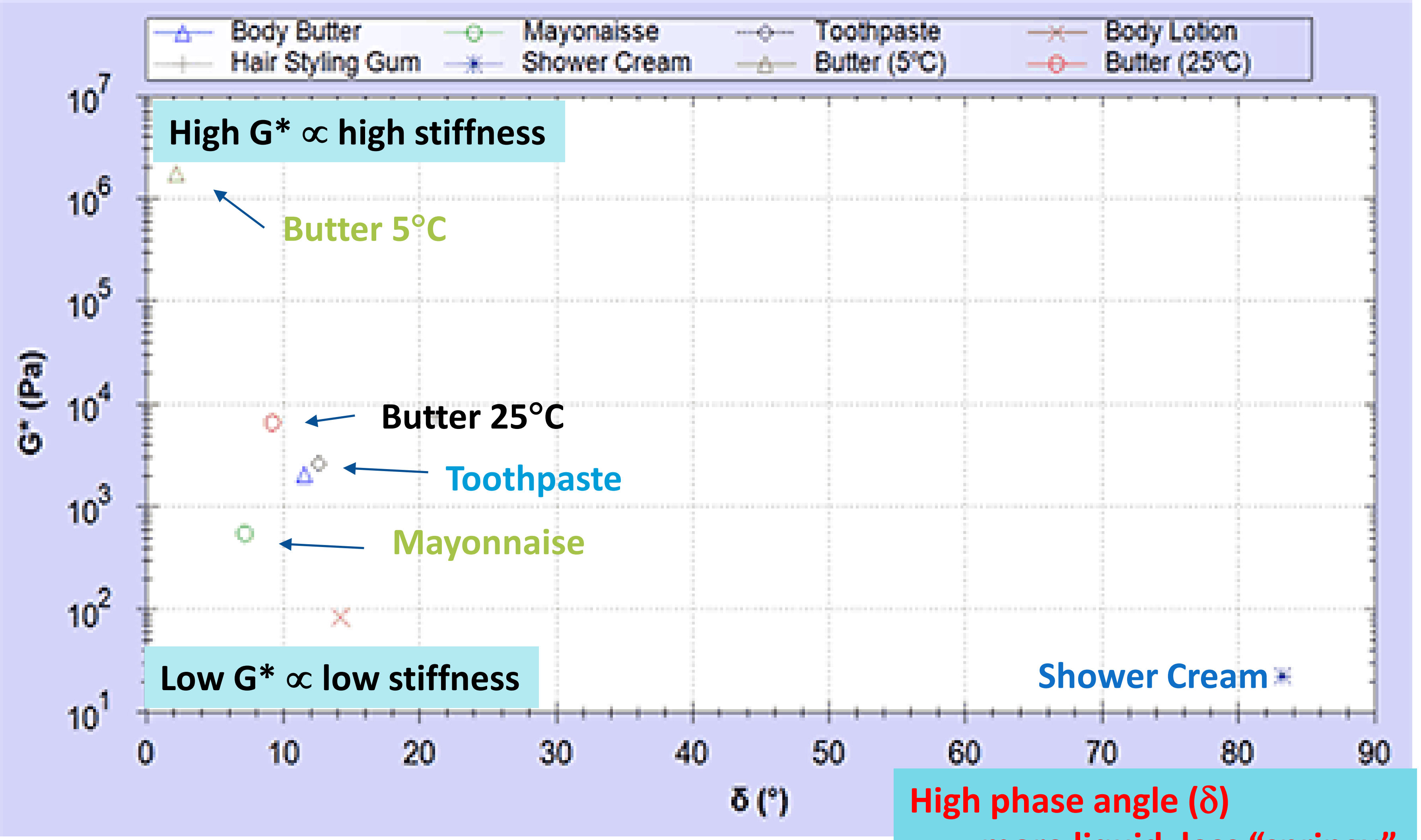
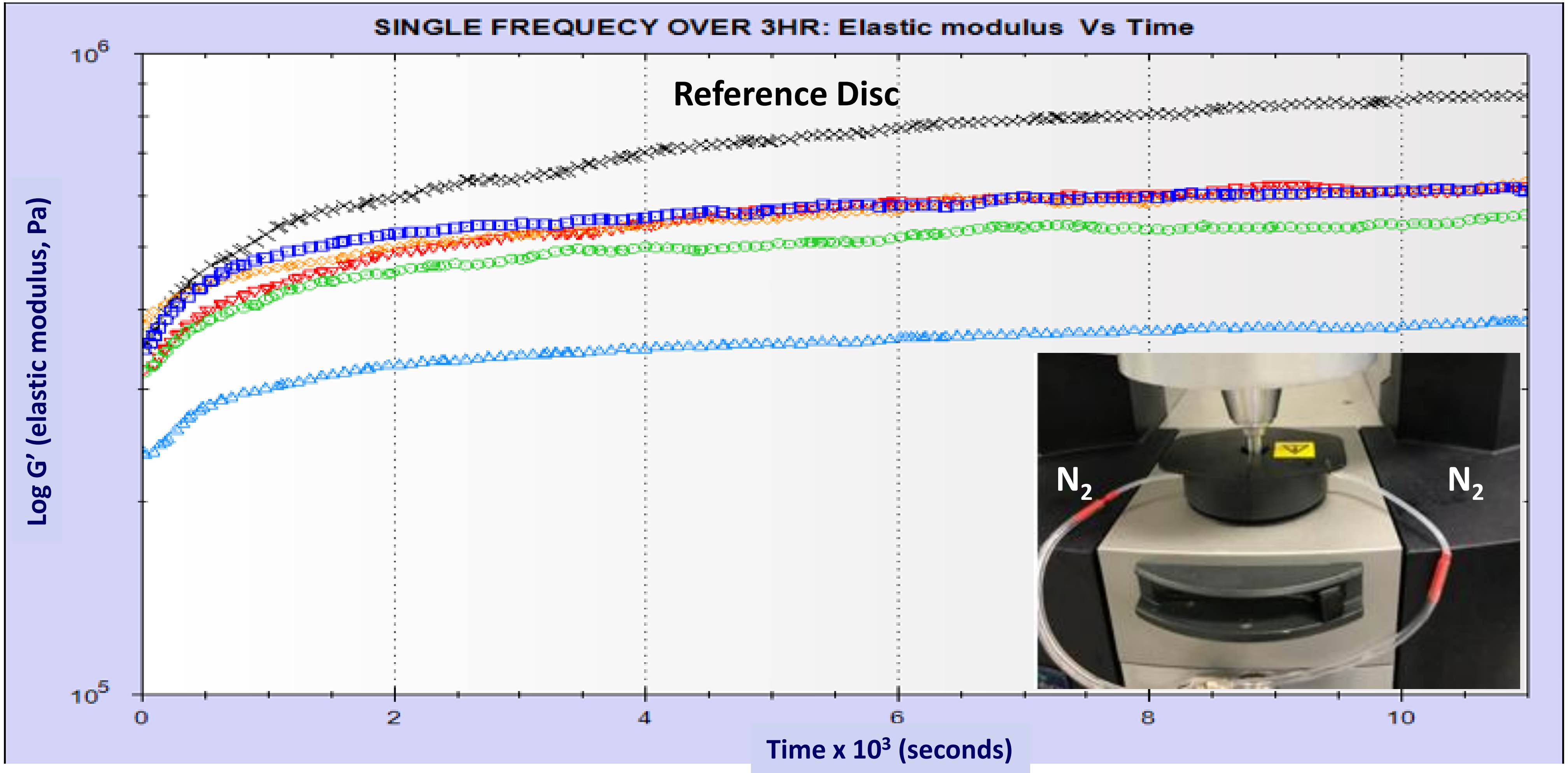



Image from Malvern Pananalytical /Netzsch

# Application: Stability - Single Frequency and %Strain for Polymer Discs

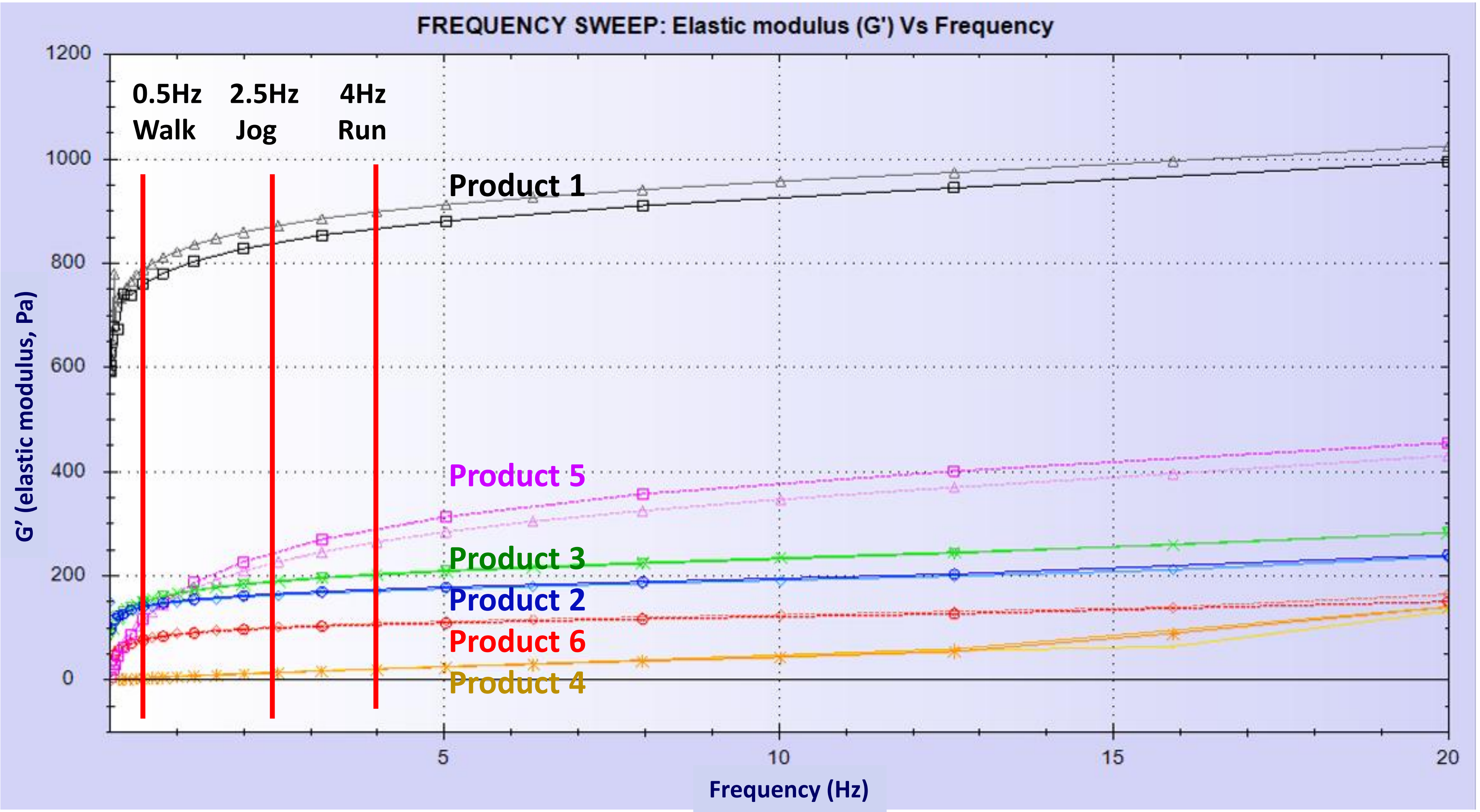
- ► **Purpose**: Compare thermal stability of discs vs % anti-oxidant relative to Reference Disc
- ► **Result:** Samples show different G’$_{(plateau)}$ and stabilization rate
- ► **Experimental**: Gap discs with 4N downward force, assayed 3hrs at 180°C under $N_2$ with 1.59Hz at 0.5% strain



# Application: Frequency sweep G' 20-0.01Hz, 3% strain* for 6 Arthritis products

**⇒ID products that stiffen more than others with increasing frequency (∝ exercise) as shown in results**

- ► **Purpose:** Client requested detailed comparison for rheological of 6 products. Assayed in duplicate.
- ► **Results:** Significant differences. Helpful for Q3 (ANDA) pharma, ID counterfeit and adulterated products




* 3% strain obtained from literature and also confirmed with amplitude sweep

# Application: FREQUENCY SWEEP – Sensory Screen

- **Pull-away assay also correlates well with sensory panel results**

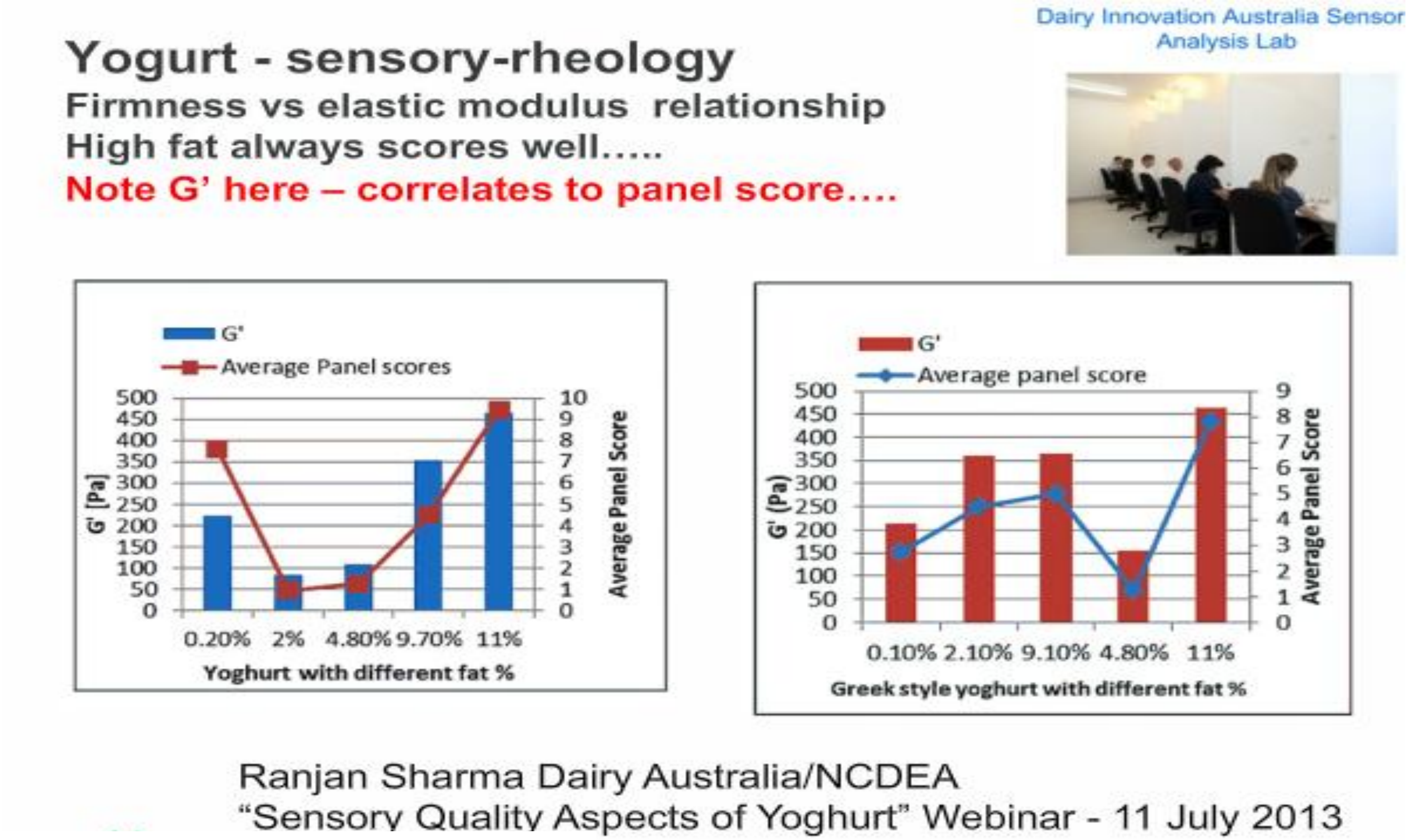
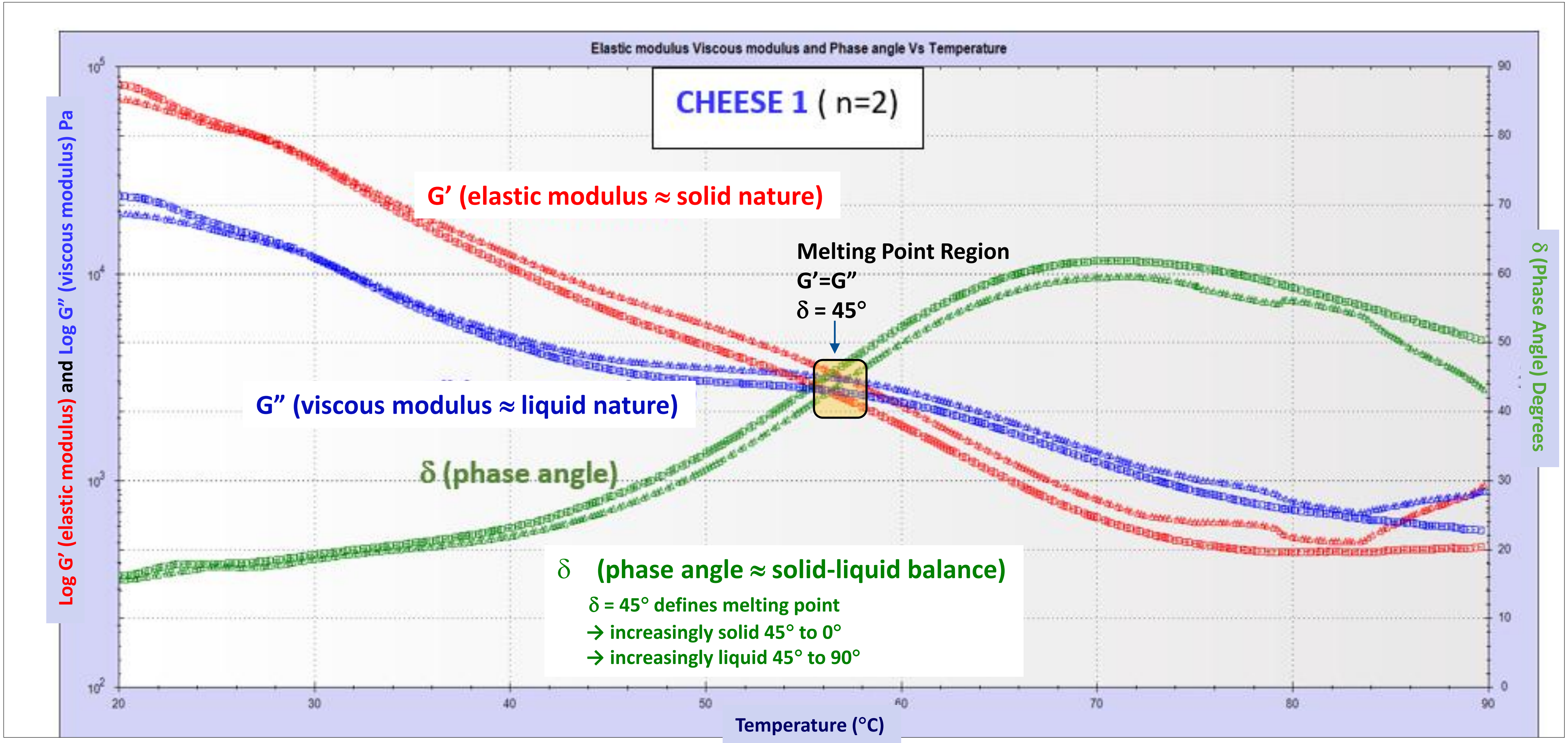



Image from Malvern Pananalytical/ Netzsch

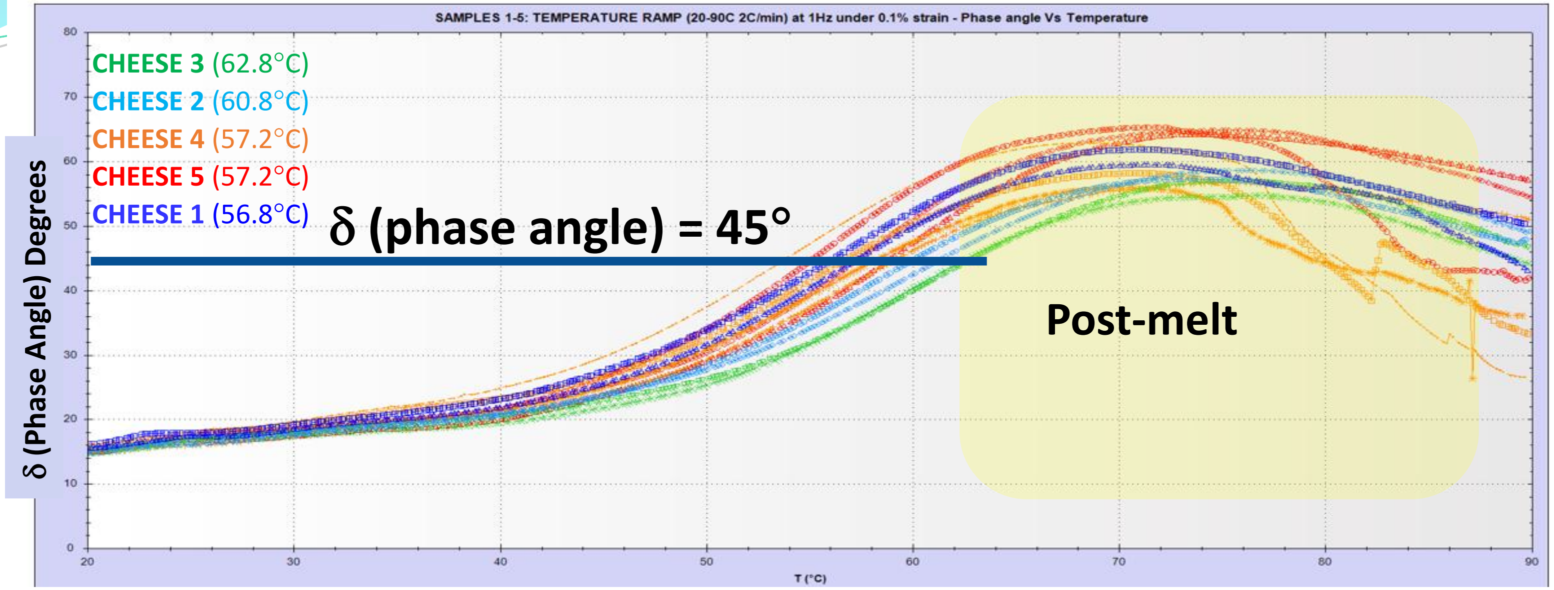
# Application: Oscillatory Single Frequency Temperature Sweep - Melting Point of Cheese

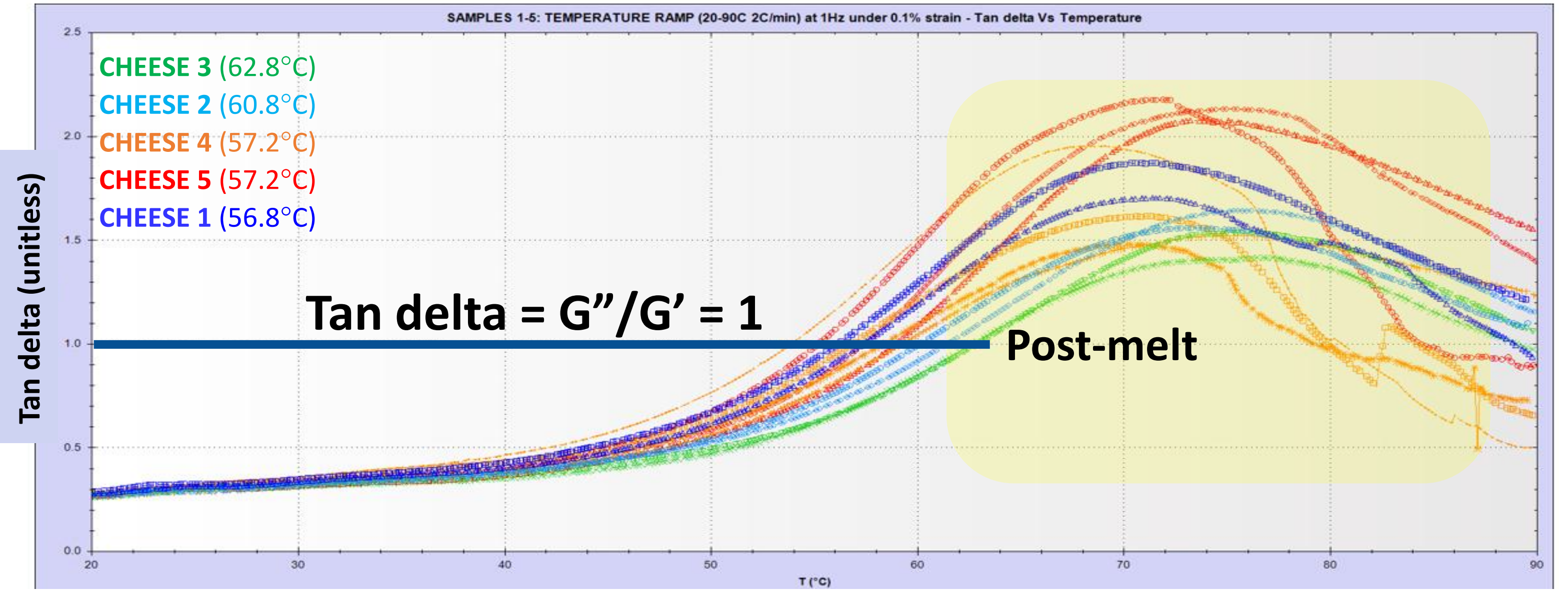
- **Quantify melting pt with G'G"- crossover and phase angle (δ=45°))**



# Application: Oscillatory Single Frequency Temperature Sweep - Melting Point of Cheese

- **Quantify melting pt with phase angle (δ=45°) and Tan delta (G"/G'=1)**




| REPRODUCIBILITY* | |
|---|---|
| **Sample** | **Melt Point °C** |
| **CHEESE 1** | 56.28 |
| | 57.35 |
| **AVG** | **56.8** |
| **CHEESE 2** | 60.21 |
| | 61.41 |
| **AVG** | **60.8** |
| **CHEESE 3** | 62.93 |
| | 62.69 |
| **AVG** | **62.8** |
| **CHEESE 4** | 59.39 |
| | 58.46 |
| | ~~53.95~~ |
| | 56.96 |
| **AVG** | **57.2** |
| **CHEESE 5** | 58.93 |
| | 55.32 |
| | 57.49 |
| **AVG** | **57.2** |

*Values determined directly from data files not from figures.

Apparent outlier

# Application: Oscillatory Single Frequency Temperature Sweep – Butter Spreadability

- G* ∝ stiffness
- Spreadable butter contains fats & oils that melt and more spreadable at lower temperatures.

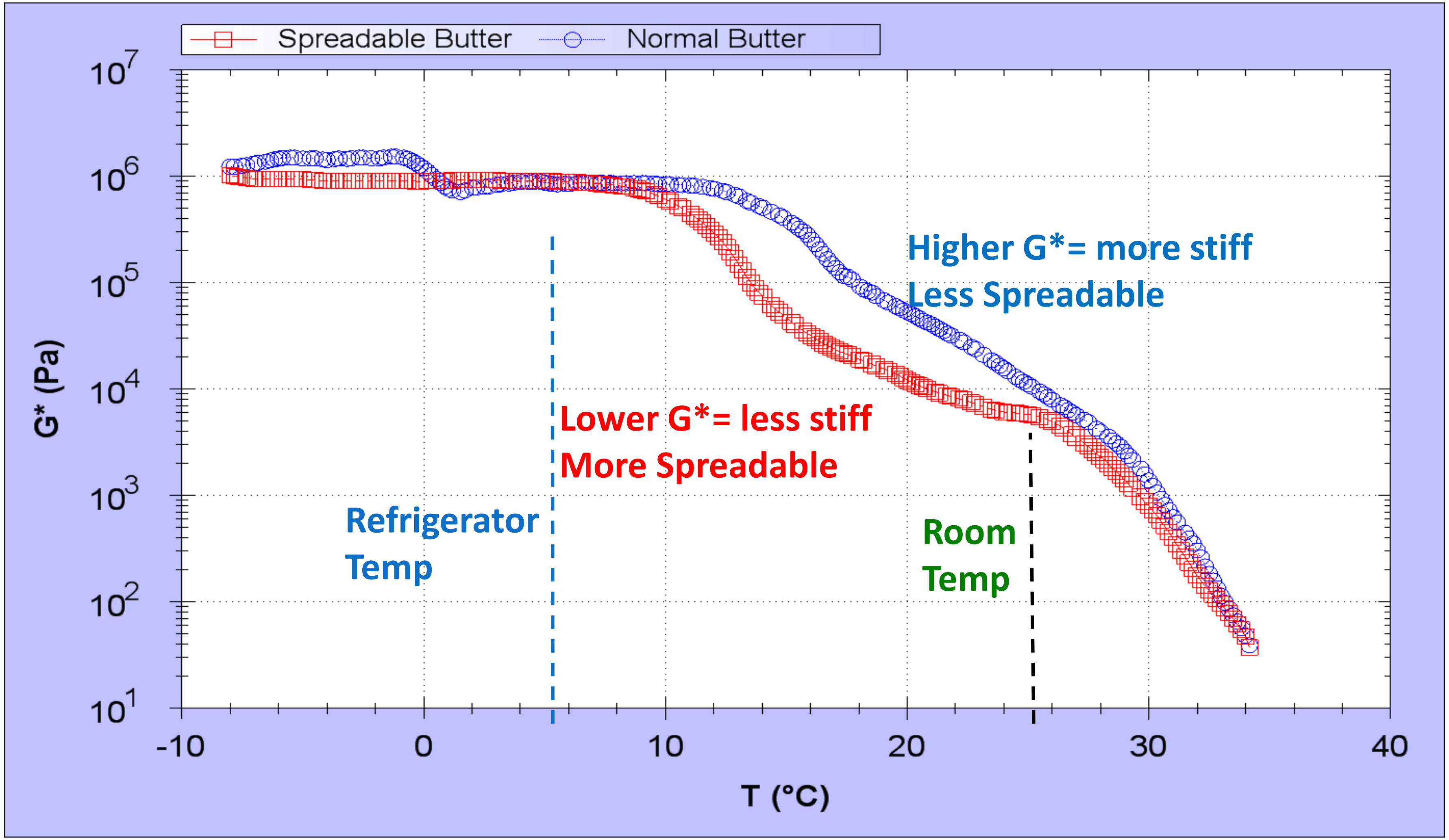
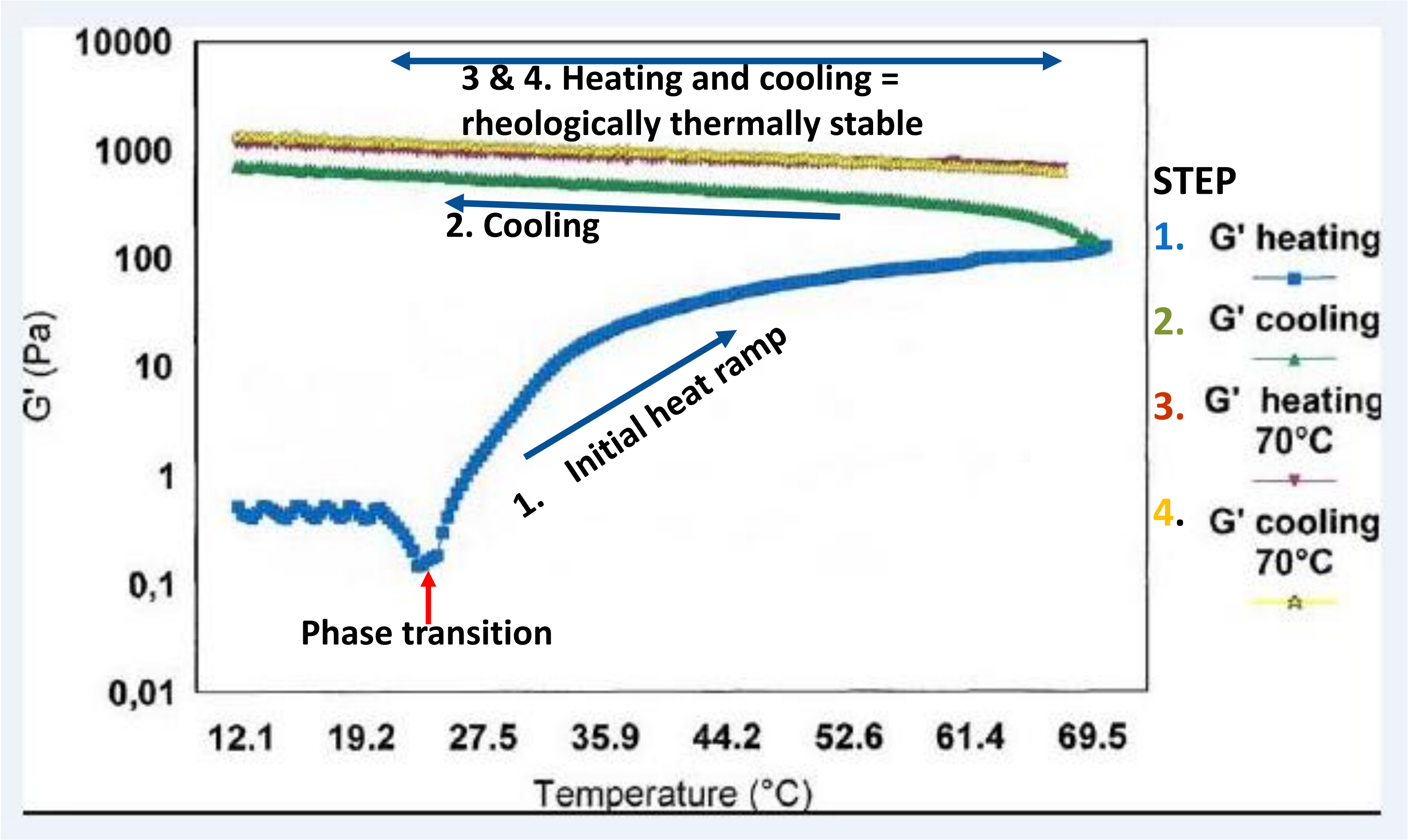



Image from Malvern Pananalytical/Netzsch

# TEMPERATURE SWEEP TO PROBE THERMAL (IR)REVERSIBILITY

- Can do in either rotational or oscillatory mode
- Probe properties with multiple temperature up/down ramps
- Important for manufacturing and low/high temperature exposure (winter/summer)

<u>Example showing irreversible rheological change to more thermally stable material</u>



# Switching gears to vertical assays

- Pull away
- Model chewing
- Surface tension

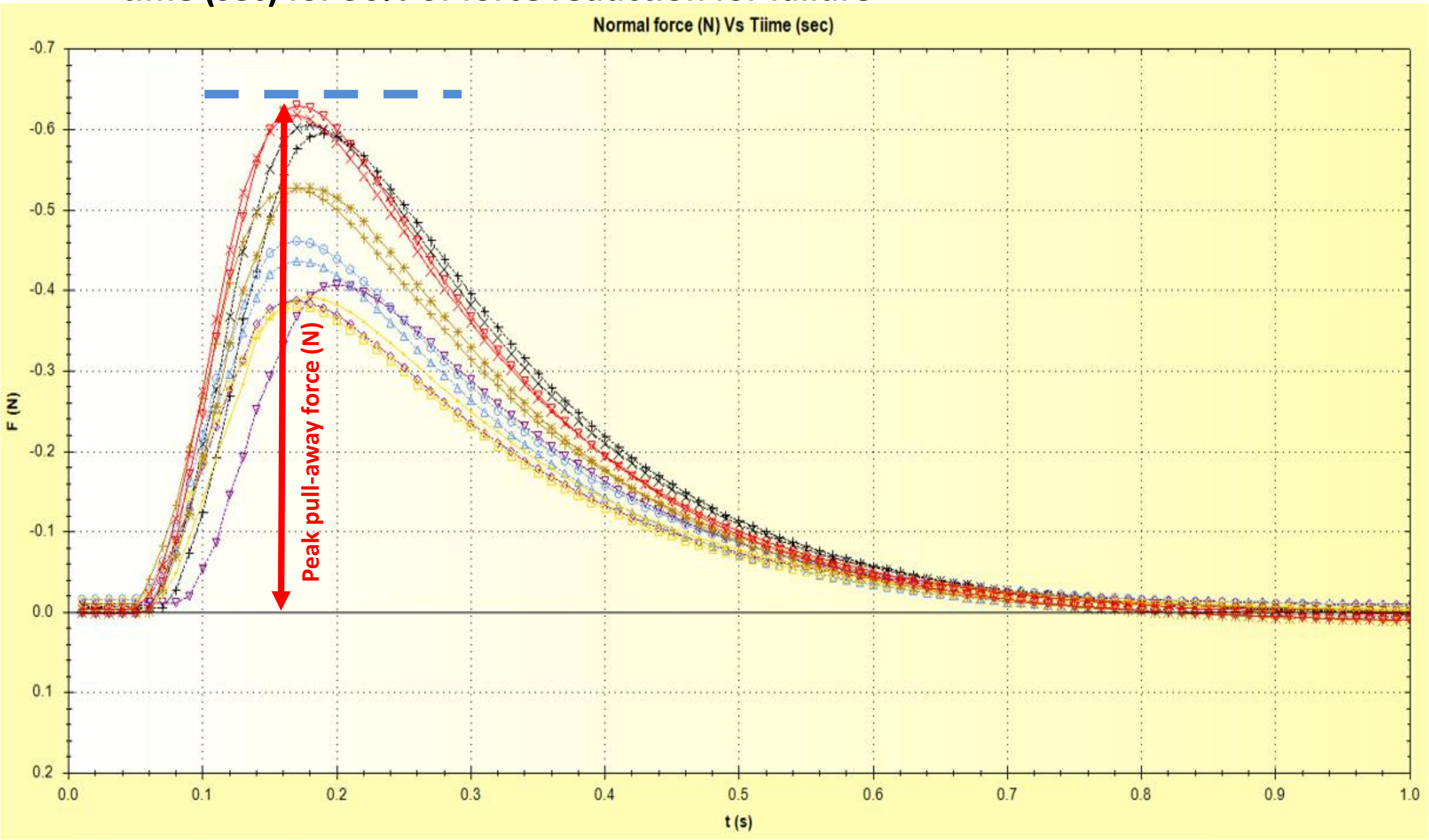
**Movements → torque**

- Rotational (1 direction)
- Oscillational (bi-directional)
- **Vertical**

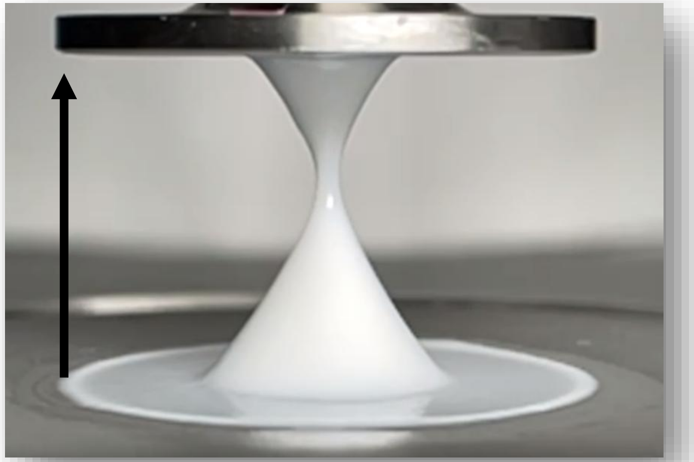

# Squeeze-Pull Away for Several Manufacturing Sources

## Model adhesion/cohesion, stickiness, mastication (chewing)

- peak pull-away force (N; Newtons) for tack
- area under the curve (N-sec) for adhesion/cohesion strength
- time (sec) for 90% of force reduction for failure




Tack test method: ASTM D2979



# Application: Axial Testing to Quantify Texture with Heating- Chocolate

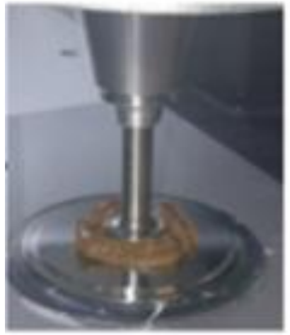
## Chocolate

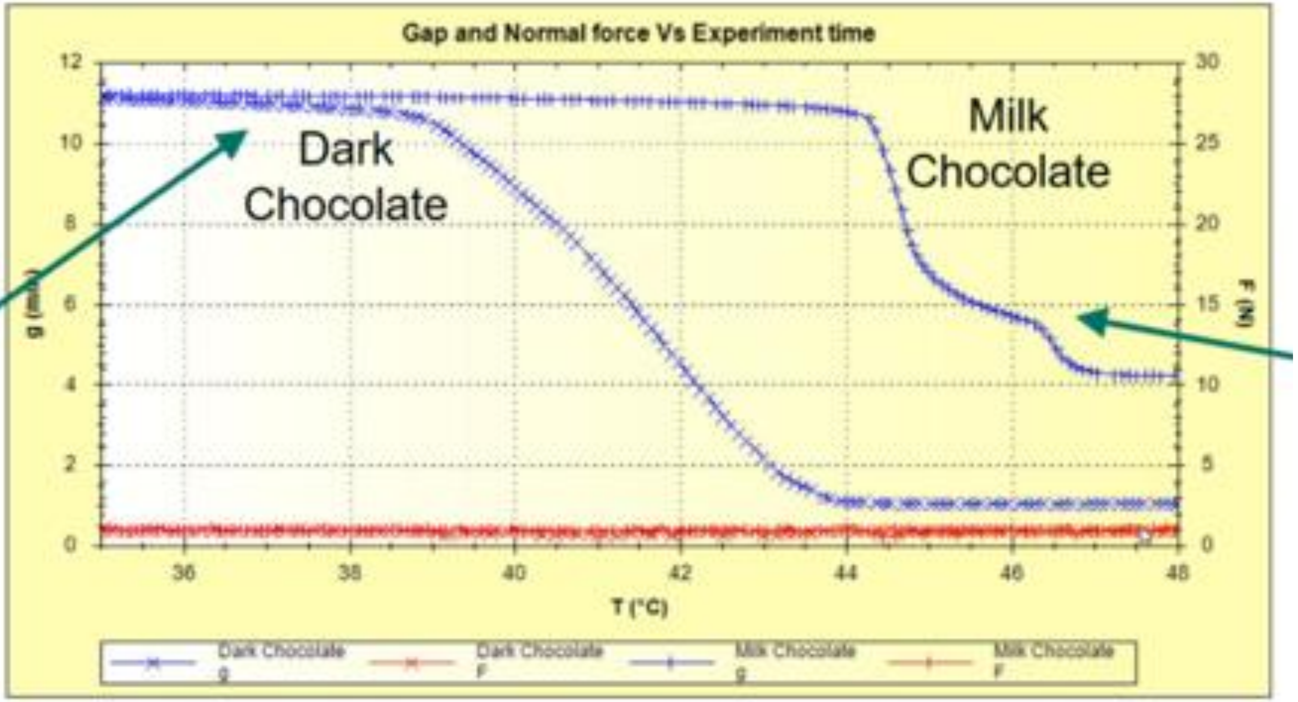
### Rheometry Axial Testing Results

NETZSCH

- These relative tests allow for a close correlation, under more scientific control, of properties that we “feel” and know

**Softening at 42°C**






**Still solid at 42°C**

Slide from Netzsch

# Application: Squeeze-Pull Away Cycling to Model Chewing

Food Research International 49 (2012) 161–169

Contents lists available at SciVerse ScienceDirect

Food Research International

journal homepage: www.elsevier.com/locate/foodres

Instrumental mastication assay for texture assessment of semi-solid foods: Combined cyclic squeezing flow and shear viscometry

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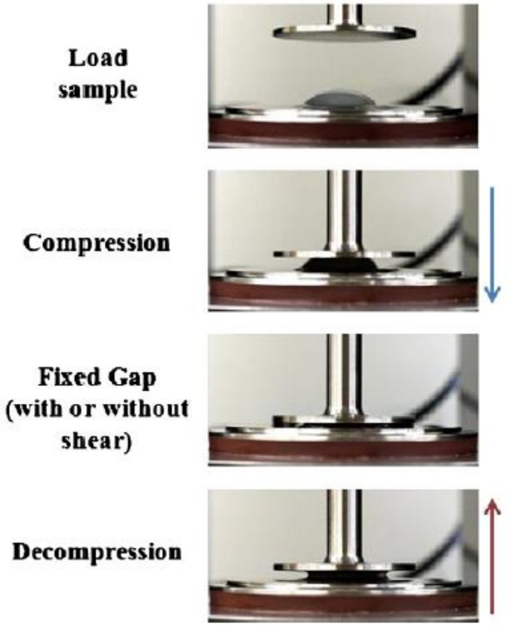
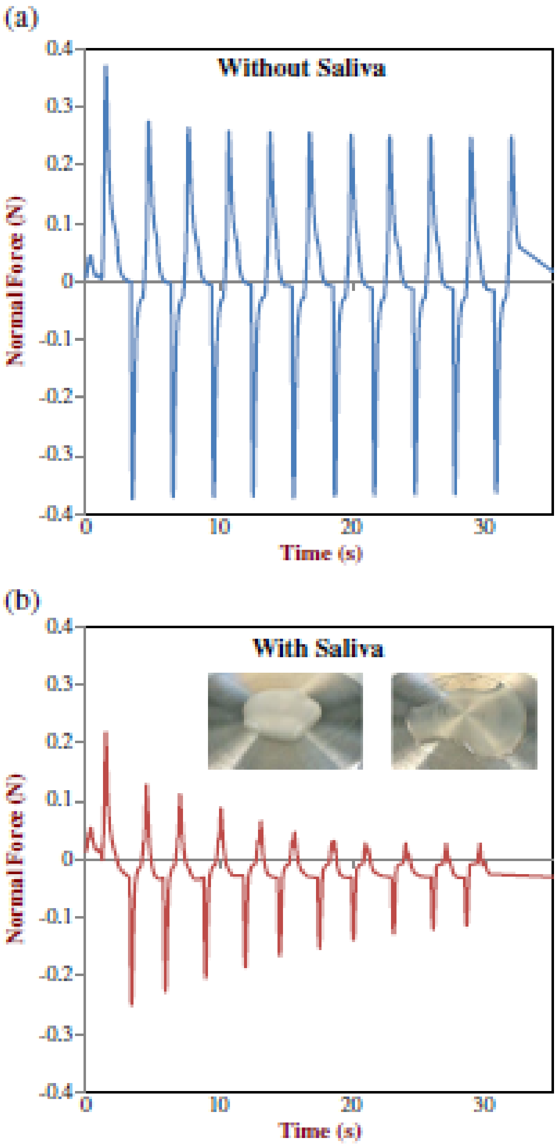
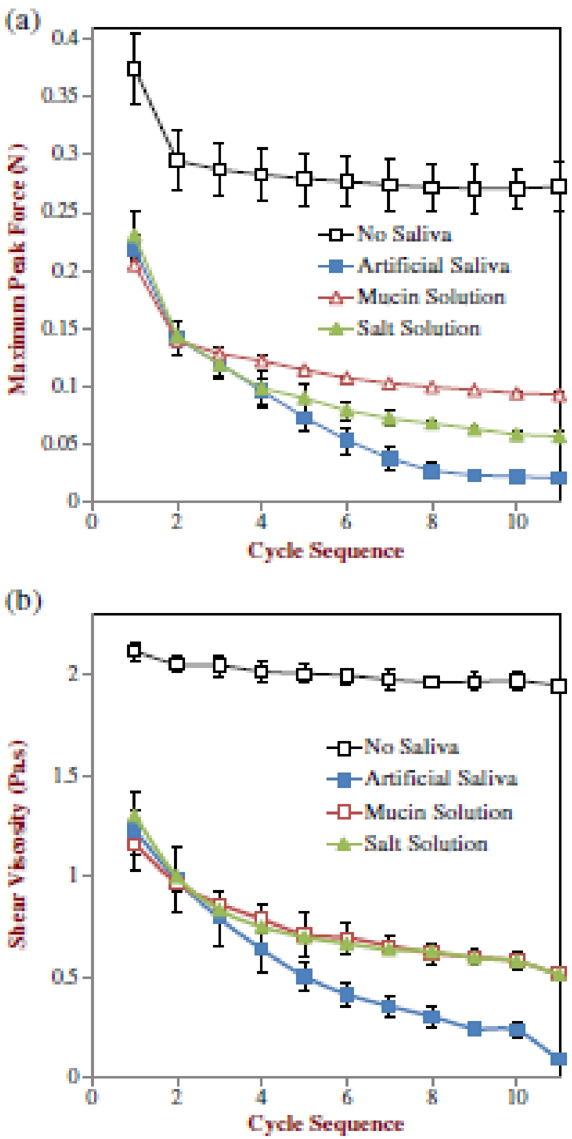



**Table 1**
Chemical composition of artificial saliva (Mandel et al., 2010; Sarkar et al., 2009).

| Chemical type | Concentration (g/L) or activity (units/mL) |
|---|---|
| Sodium chloride | 1.594 |
| Ammonium nitrate | 0.328 |
| Potassium phosphate | 0.636 |
| Potassium chloride | 0.202 |
| Potassium citrate | 0.308 |
| Uric acid sodium salt | 0.021 |
| Urea | 0.198 |
| Sodium DL-lactate/lactic acid sodium salt | 0.146 |
| Mucin from porcine stomach, type II | 30 |
| Alpha amylase activity | 93 units/mL |

168 C. Chung et al. / Food Research International 49 (2012) 161–169

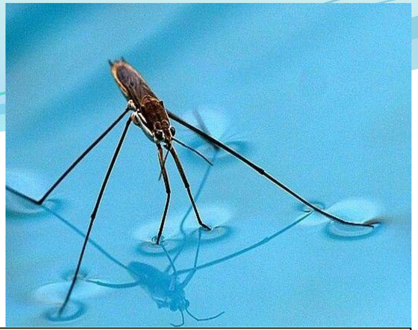


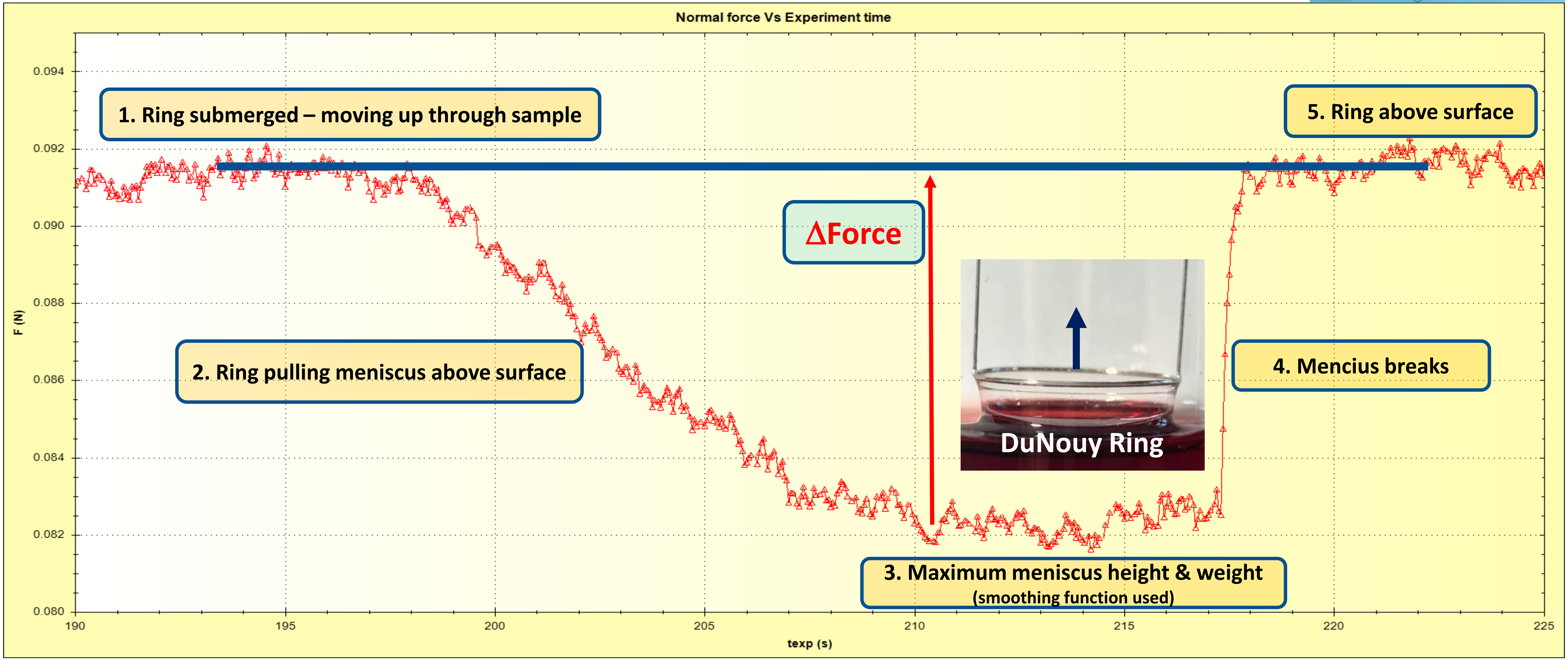



# Application: Interfacial surface tension (liquid-air, liquid-liquid)

- Applications in  pharmaceutical, cosmetics, paint, food industries
- Surface Tension (milliNewton/meter) = ΔForce * Ring factor

Ring factor is normalized to bracketing water standards 71.99mN/meter for assays at 25°C.  Adjust for assays at other temperatures.





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## Example Results

| Sample Description | # Pulls | Average Surface Tension (milliNewton/meter) | %RSD |
|---|---|---|---|
| HPLC grade water START | 12 | 71.99 | 5.3 |
| 1mg/mL SET 1 | 6 | **72.99** | 4.4 |
| 1mg/mL SET 2 | 6 | **72.90** | 3.6 |
| HPLC grade water INTERIM 2 | 6 | 71.99 | 4.6 |
| 10mg/mL SET 1 | 6 | **63.84** | 3.4 |
| 10mg/mL SET 2 | 6 | **63.89** | 5.1 |
| HPLC grade water END | 6 | 71.99 | 1.8 |

# CONCLUSIONS

√ **Rheology is <u>much</u> more than viscosity!**
√ **Many approaches to characterize materials.  Depends on the questions to be answered.**
√ **Viscosity will often decrease with increasing shear rate → shear thinning (non-Newtonian).**
**→Very important to report viscosity with associated shear rate.**
√ **Regulatory considerations! Q3**
√ **Numerous experimental considerations**

**⇒ROTATION**

- Shear stress ramp and stepwise: "Flow curve". Model delivery, performance & processes.
- Shear rate ramp and stepwise: Compare products.  Shear thinning profile.
- Thixotropy: Extent & rate of rebuild after shear thinning. Ketchup, paint, toothpaste
- Single shear rate or stress over time: Stability
- Temperature sweep: Change with temperature, model processes
- Creep-Recovery
- Tribology (friction, lubricity): motor oil, arthritis products

**⇒OSCILLATORY**

- Amplitude sweep: Define LVER ∝ breaking point ∝ rheological stability.  Critical input for frequency assays.
- Frequency sweep: Rheological fingerprint across frequency (1/time) domain.  Silly putty example. Model arthritis products. Texture.
- Temperature sweep and cycling: Thermal (ir)reversibility, melting point. Cheese melting point, polymer disc examples.

**⇒ VERTICAL**

- Squeeze - Pull Away: stickiness, model chewing, texture
- Surface Tension

# Backup Slides

# Plate & Cone Considerations

| Geometry Size | Advantages | Disadvantages |
|---|---|---|
| Larger surface area | -Use for lower viscosity samples | -Requires more sample |
| Smaller surface area | -Use for higher viscosity samples<br>-Requires less sample | -May not provide adequate response since less sample area |

| Geometry Surface | Advantages | Disadvantages |
|---|---|---|
| Smooth | -Easy to clean | -May give slippage |
| Roughened | -Easy to clean<br>-May reduce potential for slippage | -May still give slippage |
| Serrated | -Most aggressive to reduce slippage | -May need brush to clean<br>-May "gouge" sample surface |

| Geometry Type | Advantages | Disadvantages |
|---|---|---|
| Flat (parallel) | -Good for high viscosity fluids | -Variable shear rate across radius. Sample may yield at edge before center. |
| Cone (2 & 4°) | -Good for low viscosity fluids<br>-Constant shear rate in gap | Don't use for temperature sweeps unless rheometer compensates for thermal expansion |

# Optimizing Dispersion, Colloidal and Emulsion Stability

**(dispersed phase <1mm)**

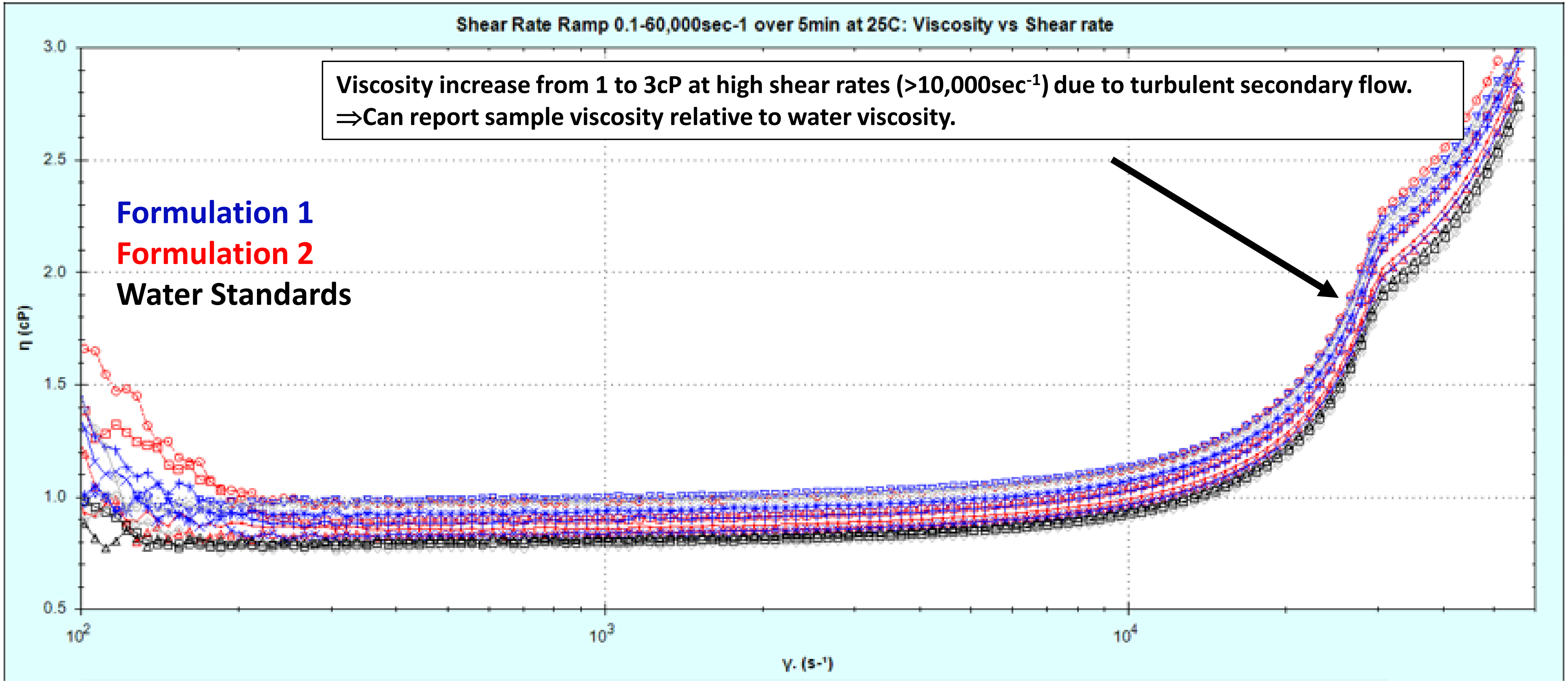
| Property | To Improve Stability | How | |
|---|---|---|---|
| Zero Shear Viscosity ($\eta_0$) | ↑ | Add thickeners to prevent particles from settling | |
| Yield Stress | ↑ | Provides high resistance to sedimentation. | |
| Thixotropy | ↓ | Decrease rebuild time to near pre-shear value | |
| Cohesive Energy | ↑ | Determine with strain controlled amplitude sweep ($CE=1/2G' \times \gamma^2$) | |
| Viscoelasticity | ↓$\delta$ | -Viscoelastic liquids with high phase angle ($\delta$) at low freq are less stable<br>-Use structured gel having $\delta$ <45° and independent of freq<br>-If heavy or large particles, decrease $\delta$ <45° at low freq | |

- Larger particles increase viscosity
- Irregular particles increase viscosity

https://www.azom.com/article.aspx?ArticleID=11442

# Shear Rate Ramp: Low viscosity formulations with high shear rate

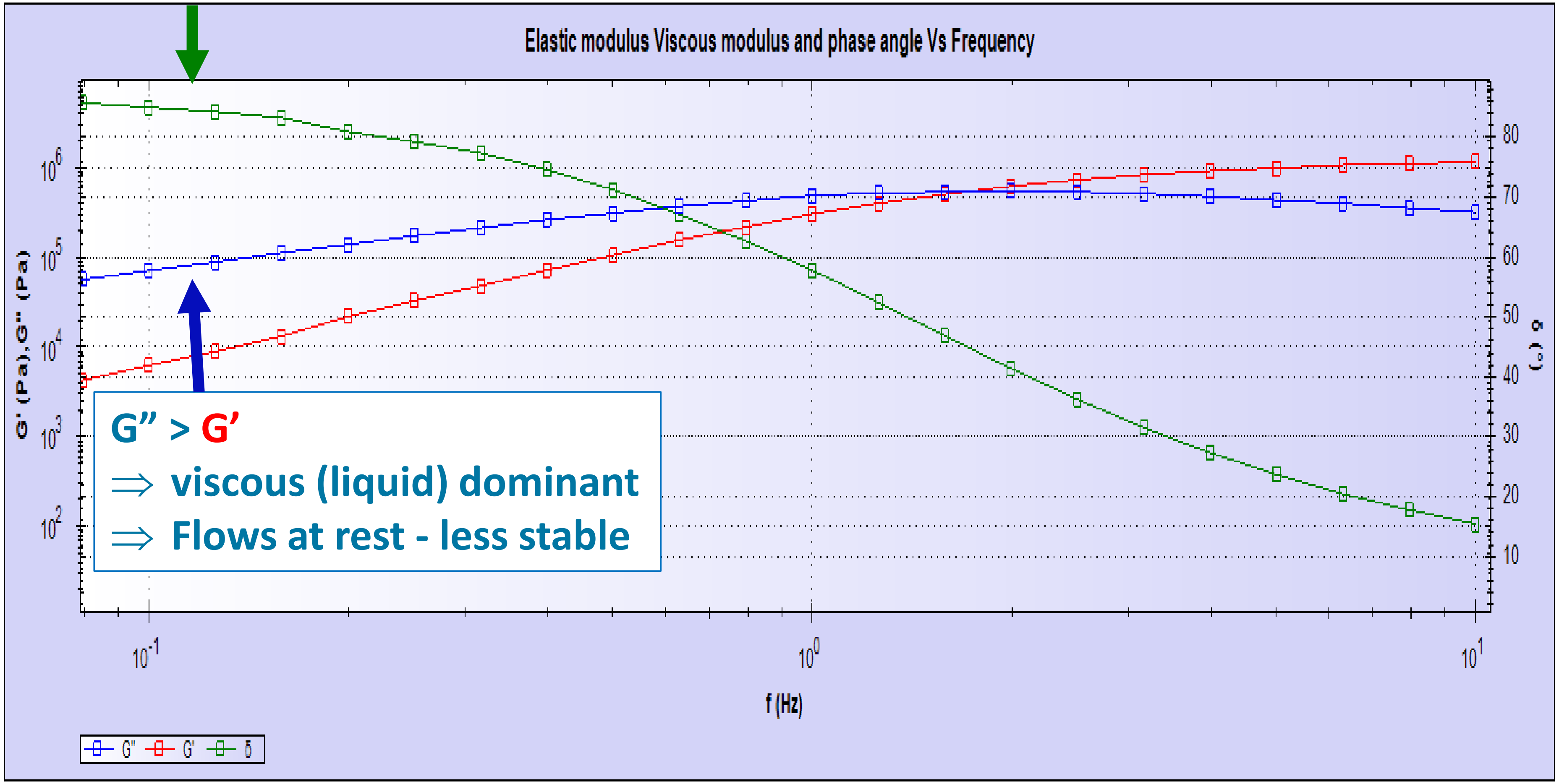
- Experimental: 40mm smooth parallel plate, 100uL gap* (130uL sample), 25°C, 0.1-60,000$sec^{-1}$ over 5min




* Small gap (100um) is required to retain sample within plates at high shear. Human hair is 70+/-20um.

# Is Silly Putty a viscoelastic solid or liquid at rest?

phase angle starts >45°
⇒ liquid dominant




G'' > G'
⇒ viscous (liquid) dominant
⇒ Flows at rest - less stable

# PROCESSING OF A PROTEIN-STABILIZIZED EMULSION

## Influence of Processing Variables on Rheological & Textural Properties of Lupin Protein-Stabilized Emulsions

J. M. Franco, A. Raymundo, I. Sousa, and C. Gallegos J. Agric. Food Chem. 1998, 46, 3109−3115

### PURPOSE

- Mayonnaise and salad dressing-type emulsions are stabilized by an adsorbed layer of protein at the oil-water interface.
- Previous studies show poorer gelation and thickening properties of lupin protein compared to commercially used soy protein.

### EXPERIMENTAL (rheology only)

- **Steady-state flow curves (rotational)**: Serrated plate (20 mm) to prevent wall-slip.
- **Frequency Sweep (oscillational):** Within LVER, using a cone/plate (35 mm, 2°) across 0.05-200 rad/s (0.01-31.8Hz).

### CONCLUSION:

- Emulsion stability and physical properties improved by heating lupin solution prior to the addition of the oil phase or inducing a chemical or enzymatic reaction that increases the entanglement protein molecules along with hydrophobicity.

- Processing variables (temp, time, impeller/stir type & speed) affect viscous and viscoelastic behavior by droplet size distribution, interdroplet interactions and entanglement.

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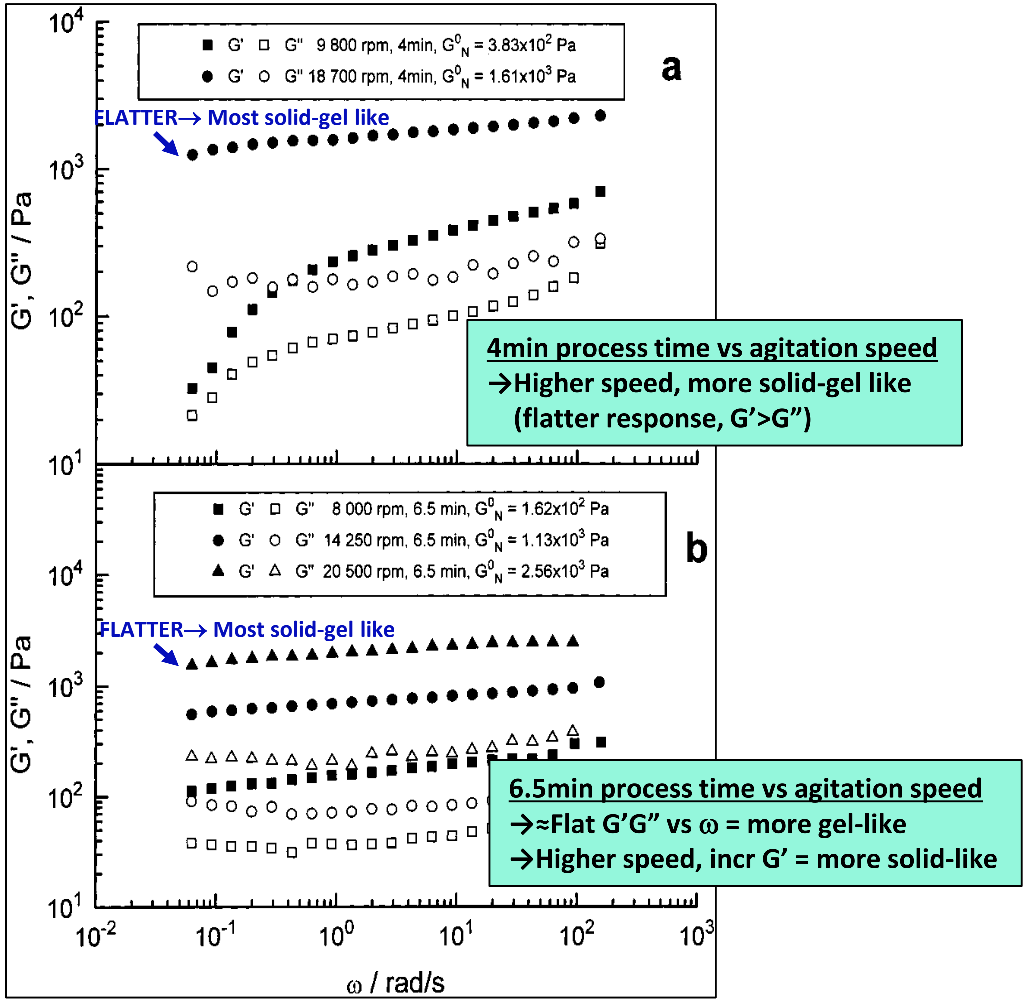
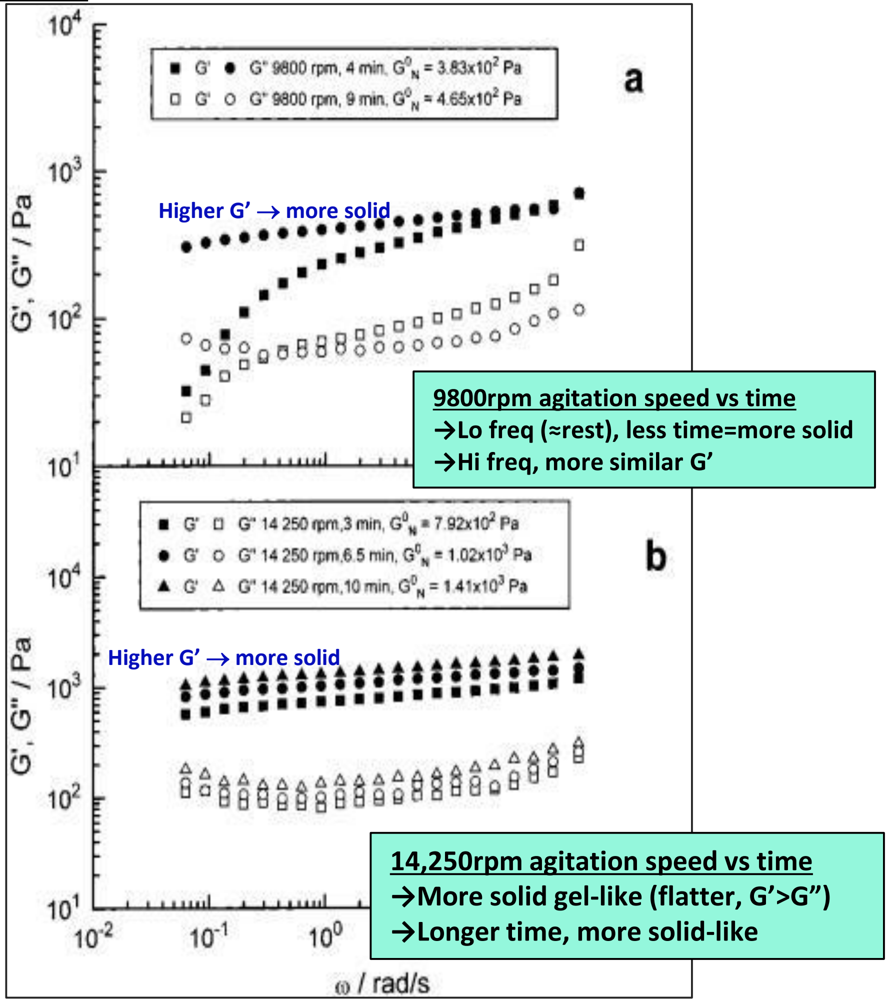


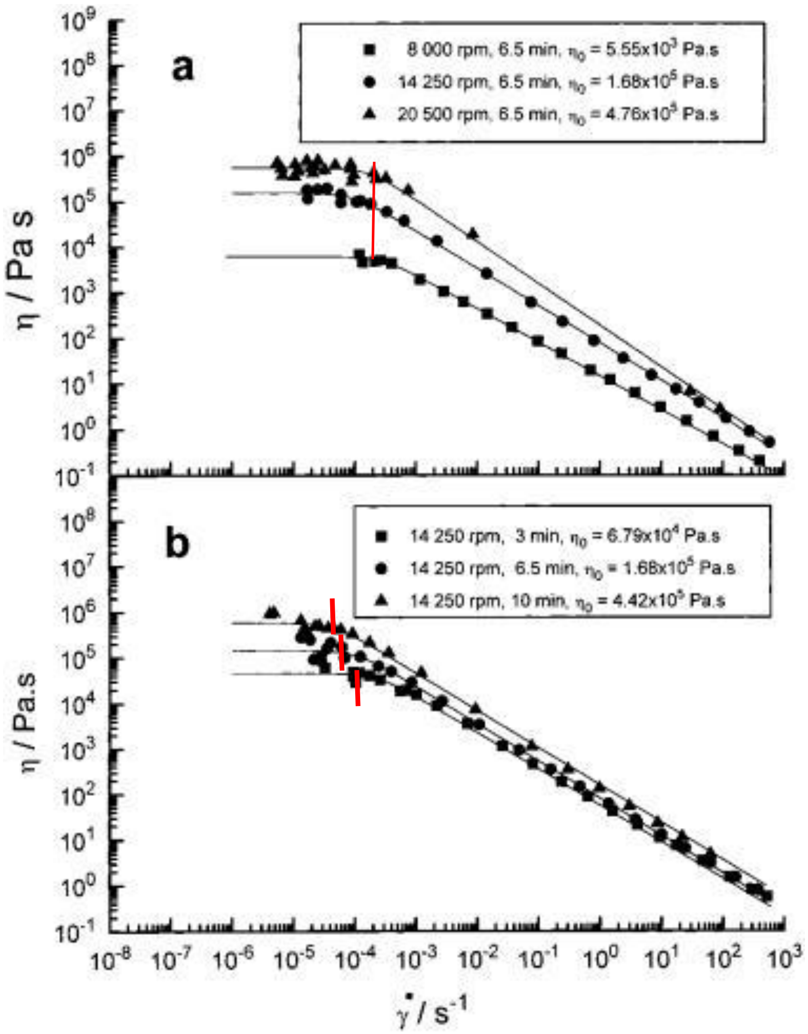

**Freq Sweep:** G' and G" of lupin protein-stabilized emulsions vs agitation speeds.




**Freq Sweep**: G' and G" for lupin protein-stabilized emulsions prepared vs emulsification times

# PROCESSING OF A PROTEIN-STABILIZIZED EMULSION (con’t)

J. M. Franco, A. Raymundo, I. Sousa, and C. Gallegos J. Agric. Food Chem. 1998, 46, 3109−3115




**Steady-state flow curves**: (a) agitation speed and (b) emulsification time for lupin protein stabilized emulsions.

**6.5min process time vs agitation speed**
**→Higher speed, more viscous**
**→All shear thin, with 20,500rpm more rapidly**
**→Generally, similar breakpoint**

**Agitation speed (14,250rpm) vs time**
**→Longer time, more viscous**
**→Shorter time, later breakpoint**