Rheology Principles and Applications

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Supporting R&D thru Manufacture

► **(bio)pharmaceutical, materials, food, cosmetic, & others**

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

- **Physical stability**
- **Delivery**
- **Performance / Efficacy**
- **Sensory**
- **Regulatory considerations: macrostructure equivalence (Q3)**
- **Biotechnology (entanglement, aggregation, stability)**

Rheometer Overview

Upper Plate

- only moving part contacting sample
- different surfaces
  - -smooth
  - -rough
  - -serrated

Lower Plate

- does not move
- same surface as upper
- controls temperature (-5 to 180°C)

<u>Movements → torque</u>

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

Image from Malvern Pananalytical

By end of presentation…….

- What assay should I use?
- What experimental parameters should I consider?
- Which is more viscous – honey or mayonnaise? τ, γ, σ, η?
- Is silly putty viscoelastic solid or liquid? G', G", G*, δ, η*?

Some Basic Entrees

VISCOMETER

- Very good basic QC instrument
- Are batches generally similar?
- Generates a single value at defined temperature, spindle type & speed

RHEOMETER (characterizes sample in much more detail)

⇒ROTATIONAL

- Non-equilibrium (ramp) viscosity
- Equilibrium (step) viscosity
- Thixotropy
- Creep test
- Temperature sweep

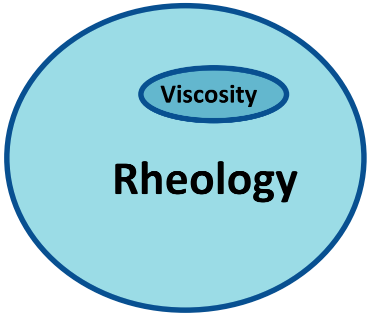
⇒OSCILLATIONAL

- Amplitude sweep
- Frequency sweep (single and ramp)
- Temperature sweep

⇒ VERTICAL

- Pull Away

Rheology is much more than just viscosity!



Regulatory Expectations

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

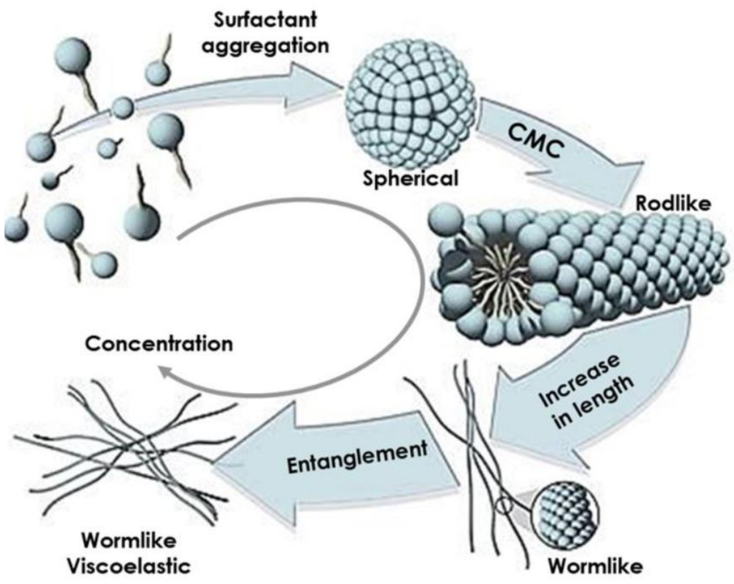
Q1: **Qualitative** ⇒Same components

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

Q3*: Microstructure

⇒ **Q1** + **Q2 + same arrangement of matter**

⇒ stability, batch-to-batch consistency



→ **Rheometer may discern among arrangements based on association energies**

→ **Rheological properties may affect biological activity**

* "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)

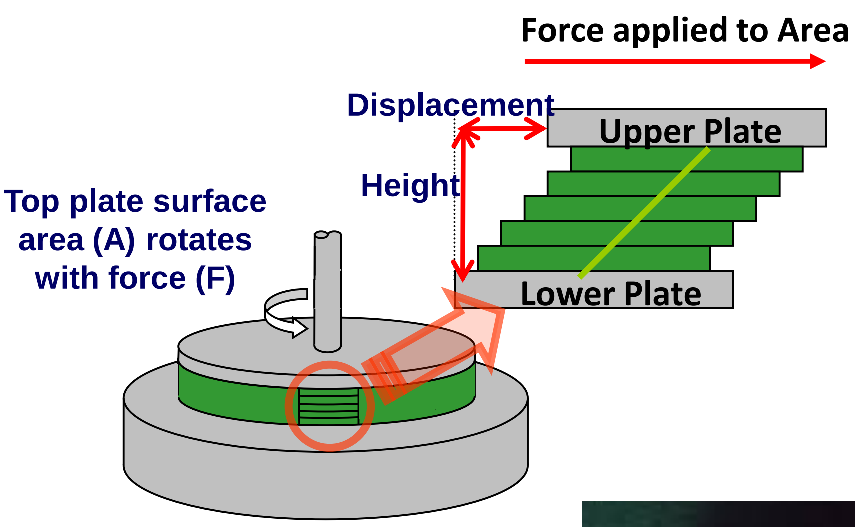
* "Generic Development of Topical Dermatologic Products: Formulation Development, Process Develoment, and Testing of Topical Dermatological Products" AAPS J. 2013 Jan; 15(1): 41-52 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3535108/)

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

Principle – Viscosity

Viscosity is "resistance to flow" under applied force

- Quantifies the <u>push</u> (stress) needed to get the material to <u>move</u> a certain speed (shear rate) and vice versa



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

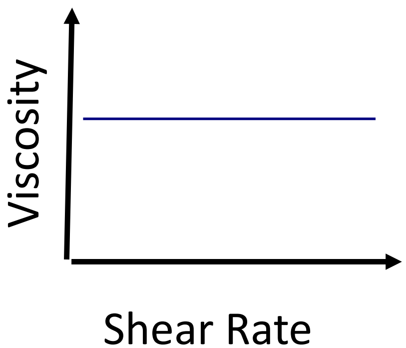
$$= \frac{\text{Force/Area}}{\text{Strain/Time}}$$

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

Image from Malvern Pananalytical

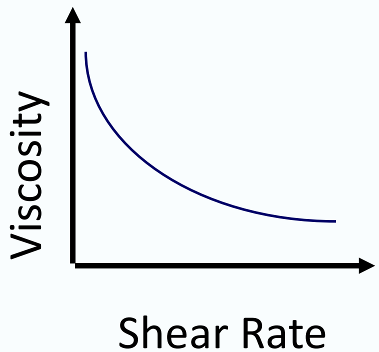
Flow Curves ⇒ Rotational Assay

Newtonian
measure with viscometer



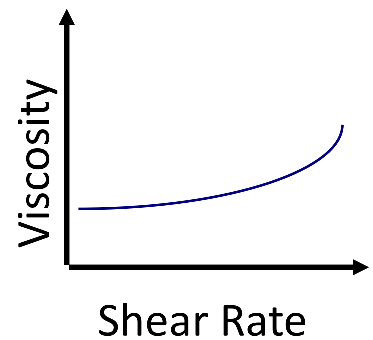
(silicon oil, water)

Shear-Thinning (non-Newtonian)
measure with rheometer



(most lotions, creams, ointments)

Shear-Thickening/Dilatant (non-Newtonian)
measure with rheometer

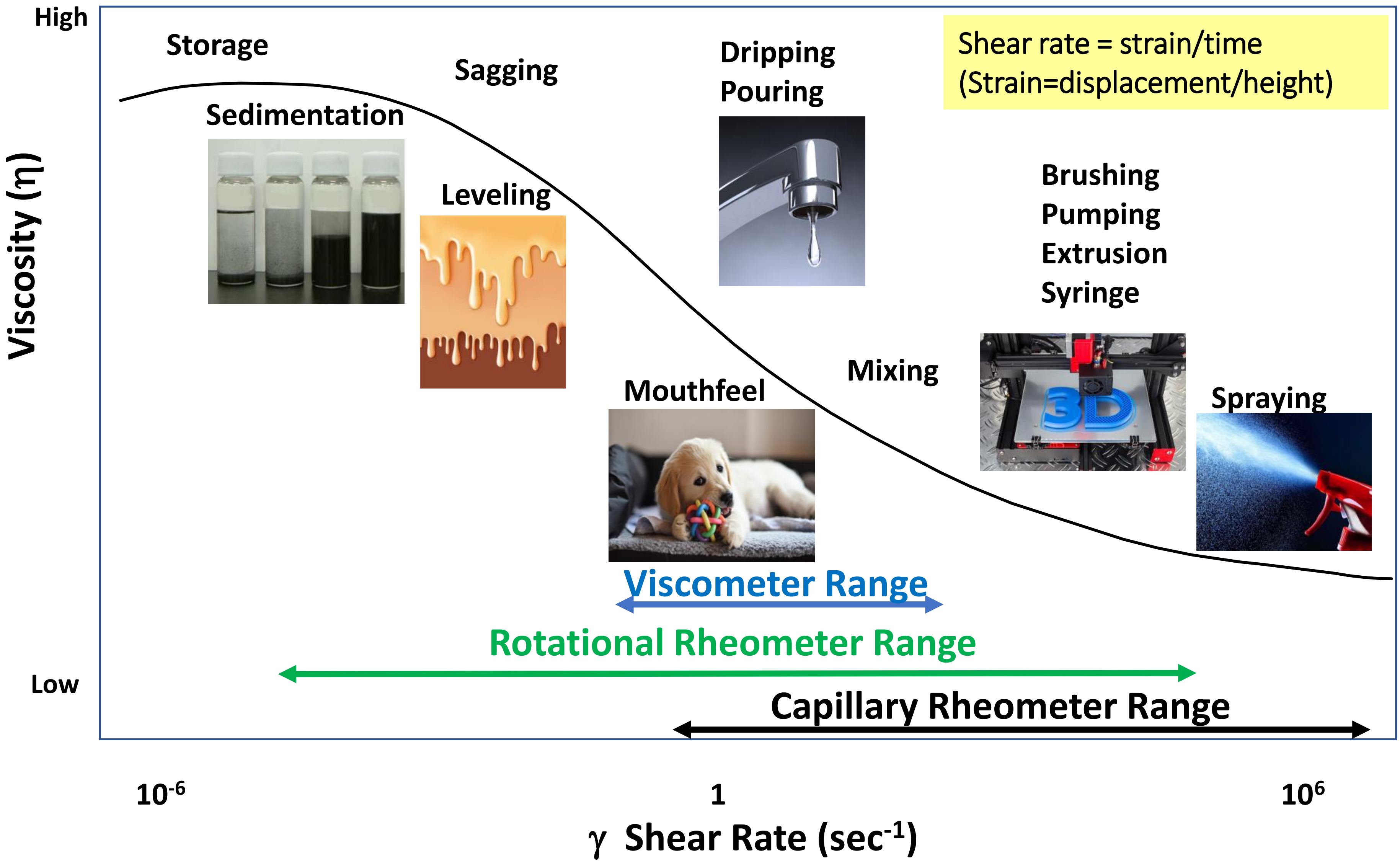


(corn starch)

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

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

Shear Rate of Processes (range 10^{12} (1 trillion))



Shear Rates of Common Processes (Continued)

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

Storage

End use

SAMPLE STORAGE

Very low shear rates: ~ 0.001s^{-1}

How stable is it (sedimentation, phase separation), sample quality…

SAMPLE DELIVERY

Medium shear rates: ~10s^{-1}

Pumpability? Scoopability?

SAMPLE APPLICATION 1

Low shear rates: ~1s^{-1}

Too thin? Flows off hand?

SAMPLE APPLICATION - 2

Higher shear rates: ~100s^{-1}

Too thick to spread? Nice feel?

Image from Malvern Panalytical

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

⇒biologicals, polymers, emulsions

Microstructure at Rest (Zero Shear)
(Disordered/Entangled)

Microstructure under Shear
(More ordered/aligned)

Polymer chains disentangle and stretch

Emulsion droplets reorganize and deform

Elongated particles align with flow (shear force)

Aggregates break down to primary particles

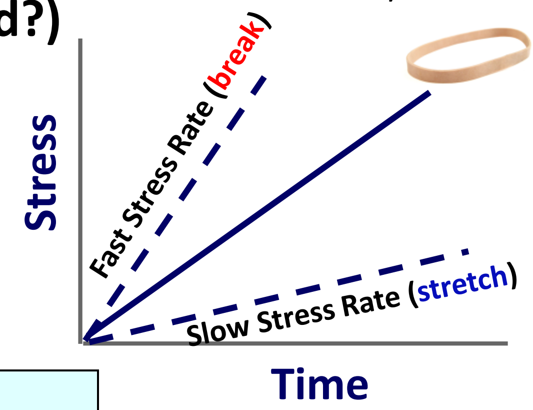
Image from Malvern Pananalytical

Yield Stress “Flow Curve”: non-equilibrium ramp

- **Primary Experimental Parameters**
  - ✓ geometry type (cone or plate; smooth, rough or serrated?)
  - ✓ stress ramp rate (slow → slow)?

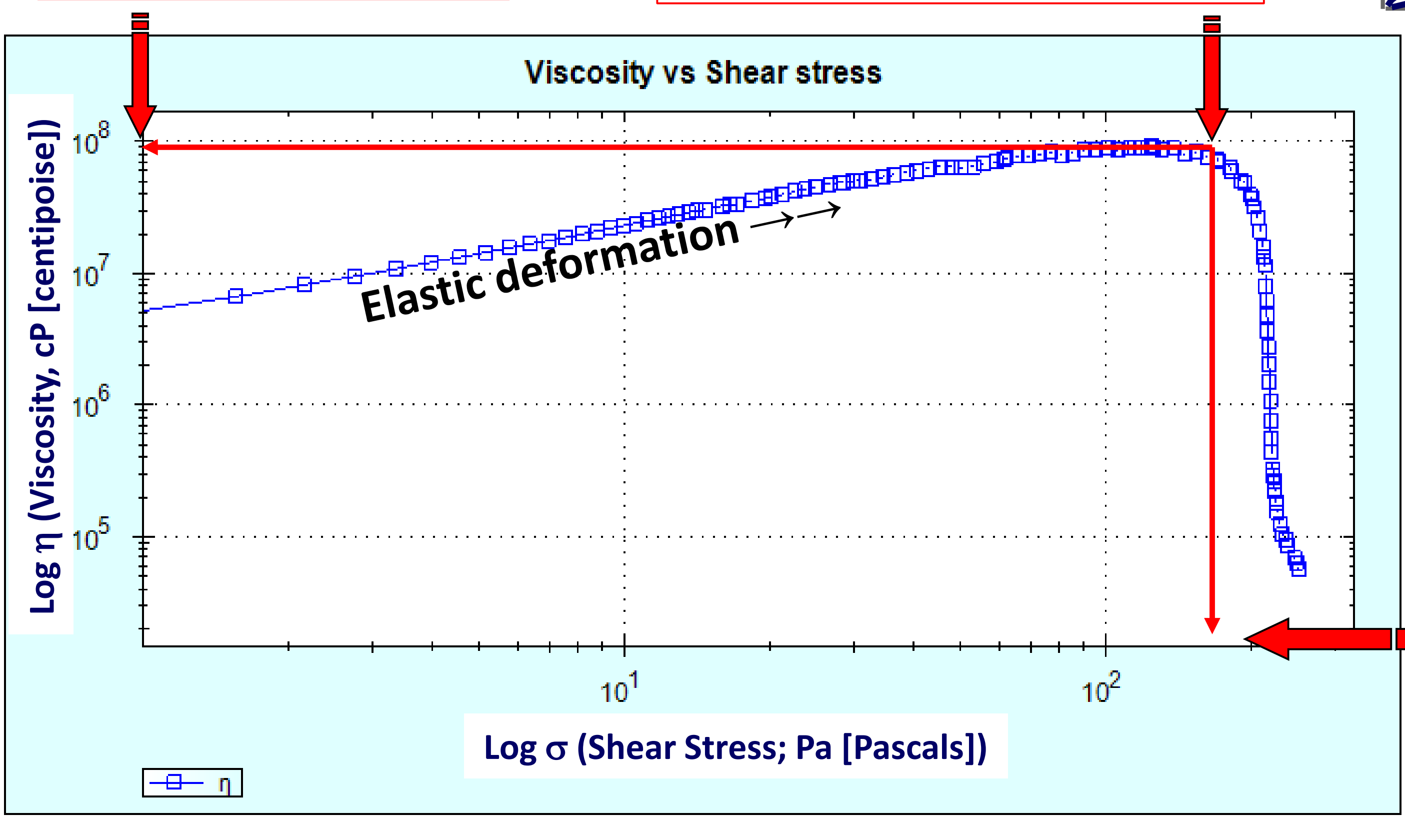
Rheometer Action

Stress = Force/Area



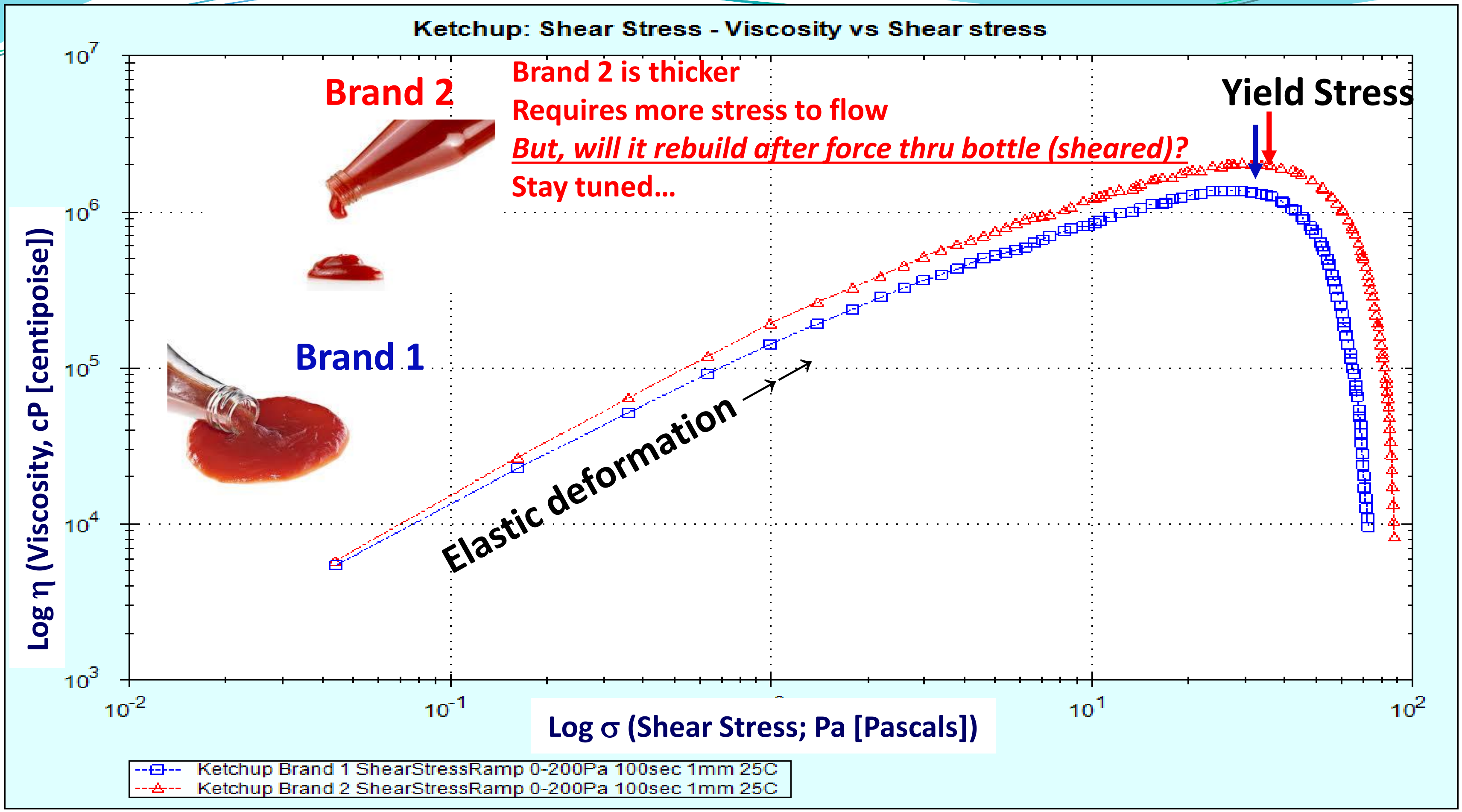
Report Yield Viscosity

Yield Stress
- “Break” structure,
- Flow begins, viscosity drops



Report Yield Stress

Yield Stress "Flow Curve" non-equilibrium ramp



- Model if sample likely to settle
  (Stoke's Law → can downward force of particles overcome media yield stress? → more next slide)
- Helpful model for difficult to pump or stir materials
- Formulation optimization (type and amount of thickeners, etc)
- Insight for manufacturing optimization
- Tune customer experience with sample – thicker, creamier

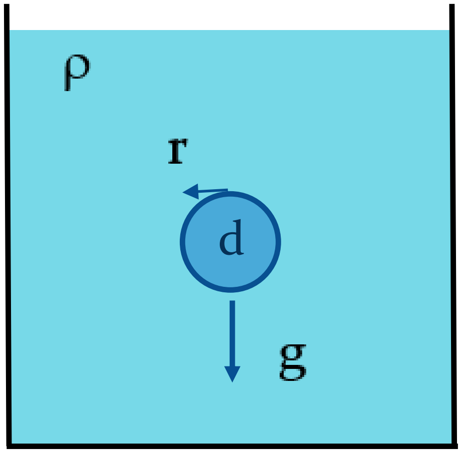
Application: Sedimentation using Yield Stress

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

non-Newtonian

$$\sigma_s = r * g(d - \rho)/3$$

σ_s = sedimentation stress on particle
r = particle radius
g = gravitational acceleration
d = particle density
ρ = fluid density
η_0 = zero shear viscosity

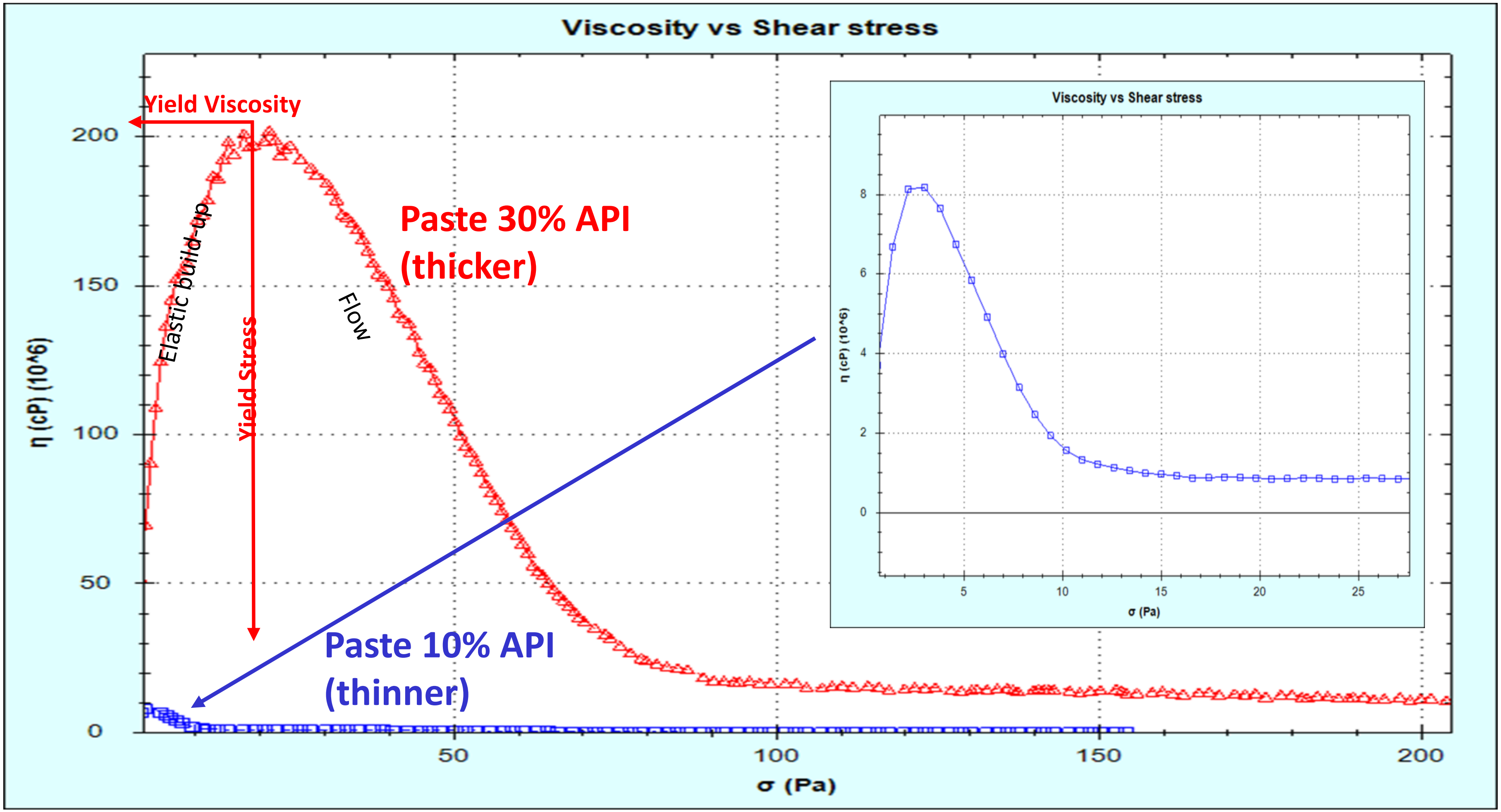


If sample's measured yield stress > σ_s, then sedimentation less likely assuming suspending media doesn't shear thin during transport and handling.

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

Application: Yield Stress "Flow Curve": non-equilibrium ramp

▶ **Issue:** Quantify pumpability impact of API loading in 2 pastes. Both visually similar.
Result: 30% API paste had <u>much</u> higher yield stress and yield viscosity →more difficult to pump



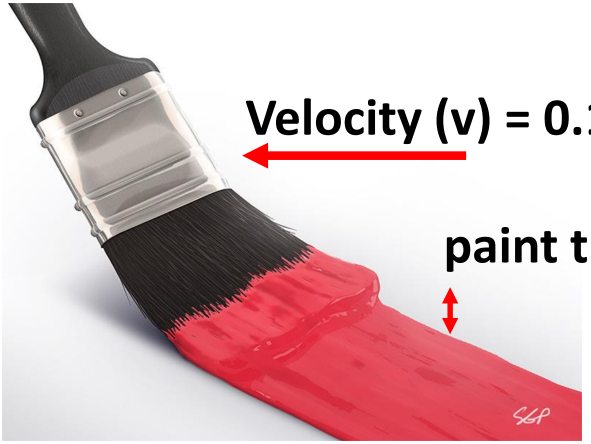
Calculation: Shear Rate Calculations of Common Processes

#1 Painting:

Shear rate γ = velocity / height

= 0.1m/sec / 0.0002m

= 500sec^{-1}



Velocity (v) = 0.1 m/sec (≈4 in/sec)

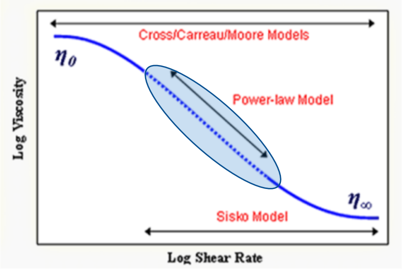
paint thickness (h) = 200µm = 0.0002m

#2 Flow in capillaries, tubes & pipes

Basic Poiseuille formula (modifications & corrections can be applied): $\gamma = V\cdot(3+1/n)/\ \pi\cdot r^3\cdot t$

To discharge material at 1cm^3/sec thru 10mm orifice

- n = Power law index (n=1 for Newtonian, 0 to <1 for shear-thinning non-Newtonian)
- V = volume dispensed (1 cm^3 = 10^{-6} m^3)
- t = dispensing time (1 sec)
- r = tube outlet radius = 0.5×10^{-2} m



For Newtonian (n=1*): $\gamma = (4\bullet10^{-6}\ m^3)\cdot 4\ /\ (\pi\cdot 1\times10^{-6} m^3\cdot 1sec) \approx$ 1.3sec^{-1}

For non-Newtonian (n=0 to <1; assume 0.4**): $\gamma = (5\bullet10^{-6}\ m^3)\cdot 5.5\ /\ (\pi\cdot 1\times10^{-6} m^3\cdot 1sec) \approx$ 1.8sec^{-1}

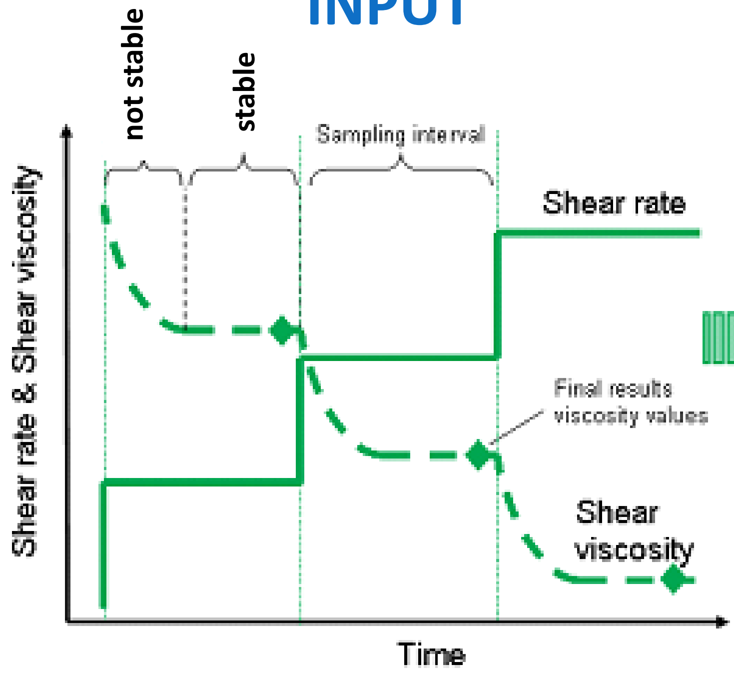
*water is Newtonian ** toothpaste in non-Newtonian (above calc used Rabinowitsch correction)

Viscosity – Shear Rate "Step" - Equilibrium

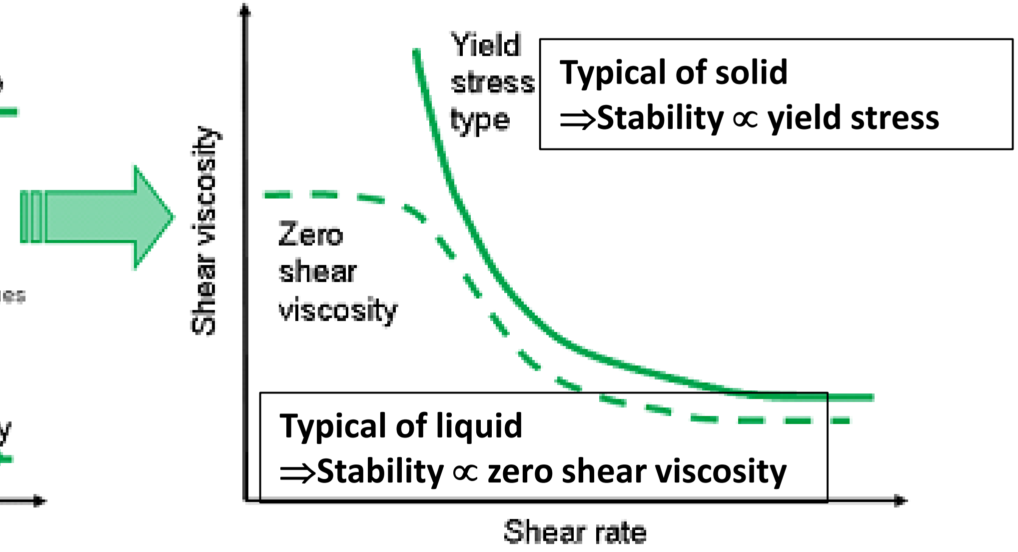
-Step thru range of shear rates

-Each step meeting viscosity equilibration or time criteria before stepping up to next shear rate.

INPUT



OUTPUT



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

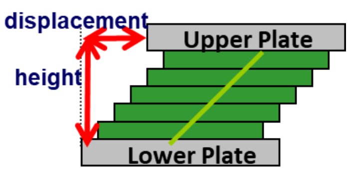
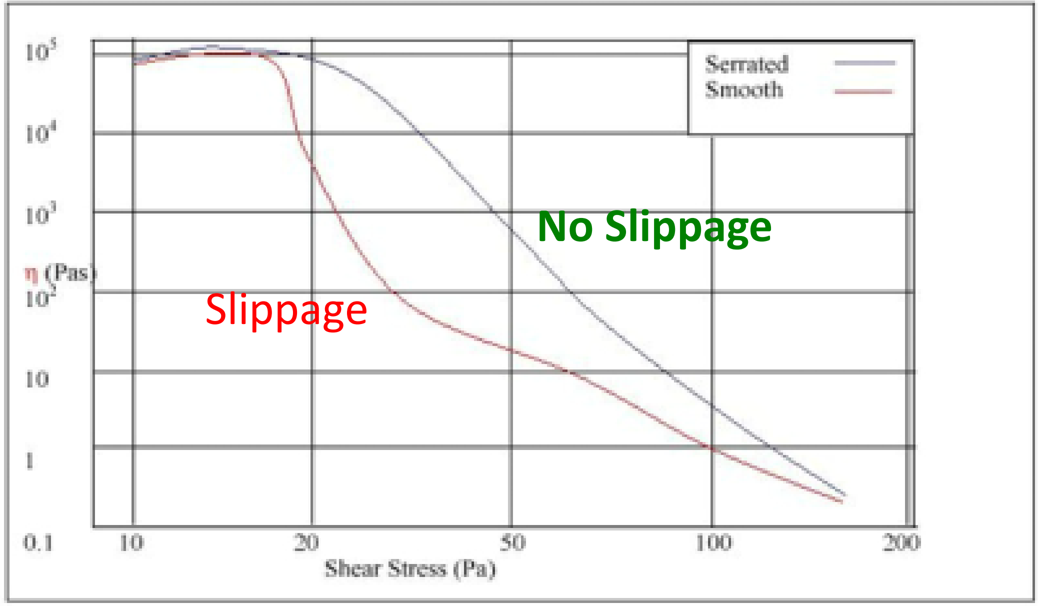


Image from Malvern Pananalytical

Mindful about slippage at plate-sample interface

- Plate must impart force <u>through</u> sample, not just at surface
- Slippage may lead to experimental error

►Use roughened or serrated plates to reduce potential for slippage



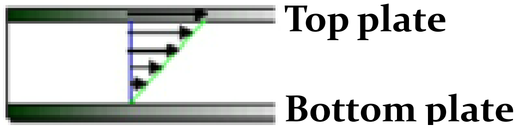


Fig 1. Laminar flow between plates

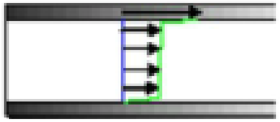


Fig 2. Slip flow between plates

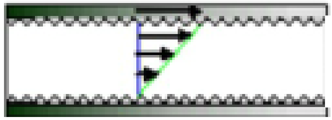


Fig 3. Rough or serrated plates can reduce or eliminate slip

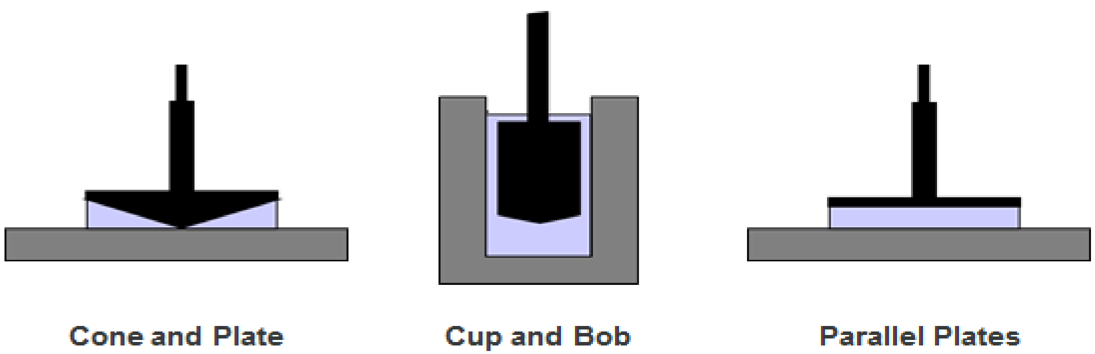
"Slippage" of top cards→

Images from Malvern Pananalytical

Other Experimental Considerations

- **Consistency is critical!**
  -Handling during loading (shear, bubbles)
  -Trimming to remove excess sample

- **Geometry: Cone, Plate or Cup & Bob, vane, etc etc**
  -Cone gives more consistent shear across sample. Few % better accuracy.
  -Cone <u>not</u> recommended for temperature sweeps if not compensated for thermal expansion



- **Plate/Cone Size**
  -Larger diameter better for less viscous samples. Requires more sample.

Other Experimental Considerations (continued)

- **Consistency is critical! …repeating**
  -Handling during loading (shear, bubbles)
  -Trimming to remove excess sample

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

- **Plate/Cone Gap**
  -Typically 0.2-1mm. Depends on sample and assay parameters.
  -Smaller gap requires less sample (200um gap with 25mm plate requires 200uL)
  -Smaller gap:
    -provides higher shear
    -reduces potential to lose sample from gap at high shear rate
    -more sensitive to gap inaccuracies

  -1/10 rule: gap > 10x largest particle/droplet. Default gap for cone = 150um.

  -Gap setting options:
    -<u>height</u> (typical)
    -<u>force</u> (polymeric samples with inconsistent thickness).
    ⇒Rheometer accurately tracks gap height and force 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!?!

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

  -BUT…….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

  -Perform <u>single</u> frequency vs time & monitor G' change

  what's a G'? Stay tuned……

  -Perform low single shear rate vs time & monitor viscosity

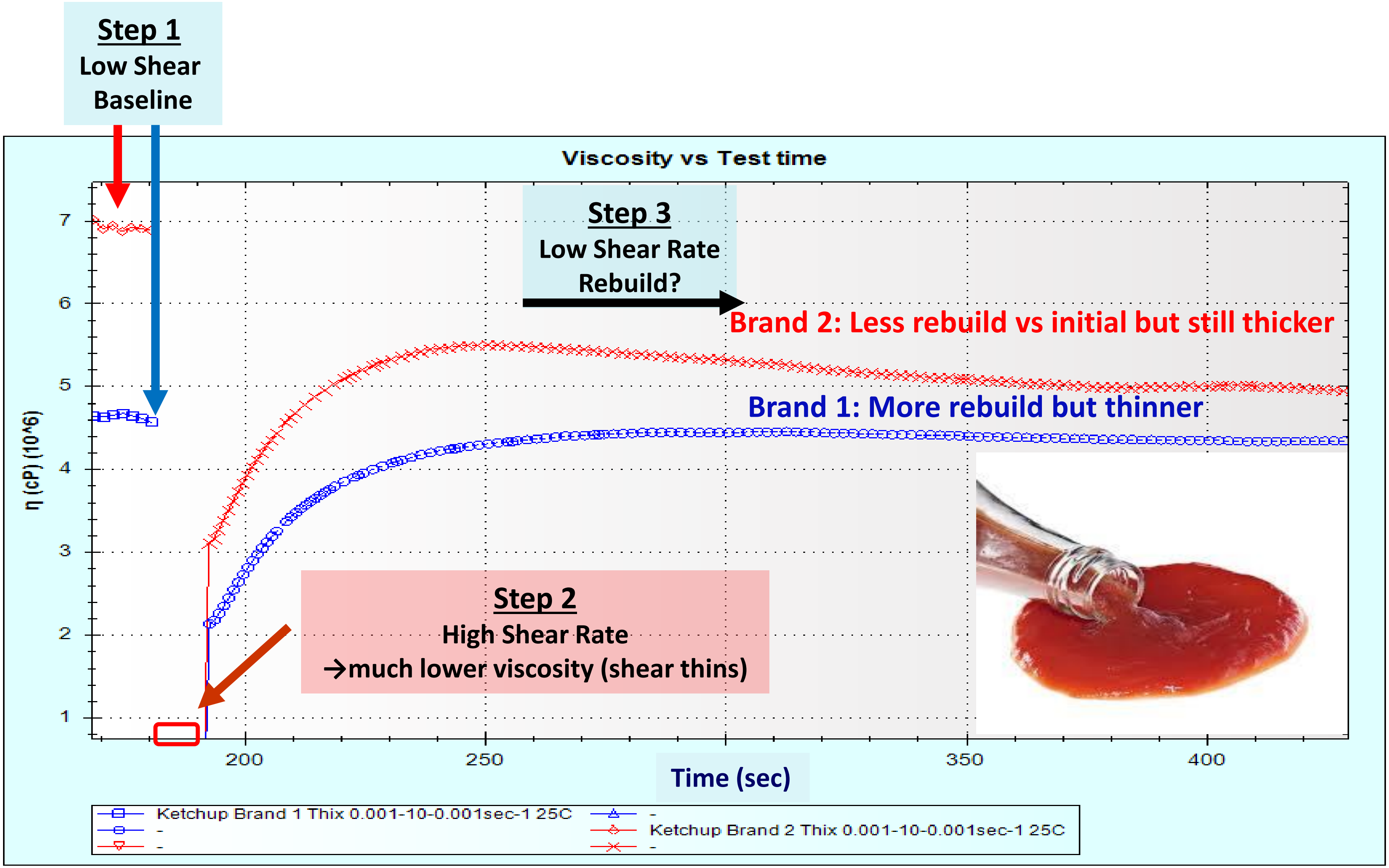
  -Got volatiles? Use a solvent trap

  -Maintain sample in enclosed volatiles saturated environment

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

Thixotropy (3-Step Rotational Shear)

-Determine rebuild extent and rate after higher shear



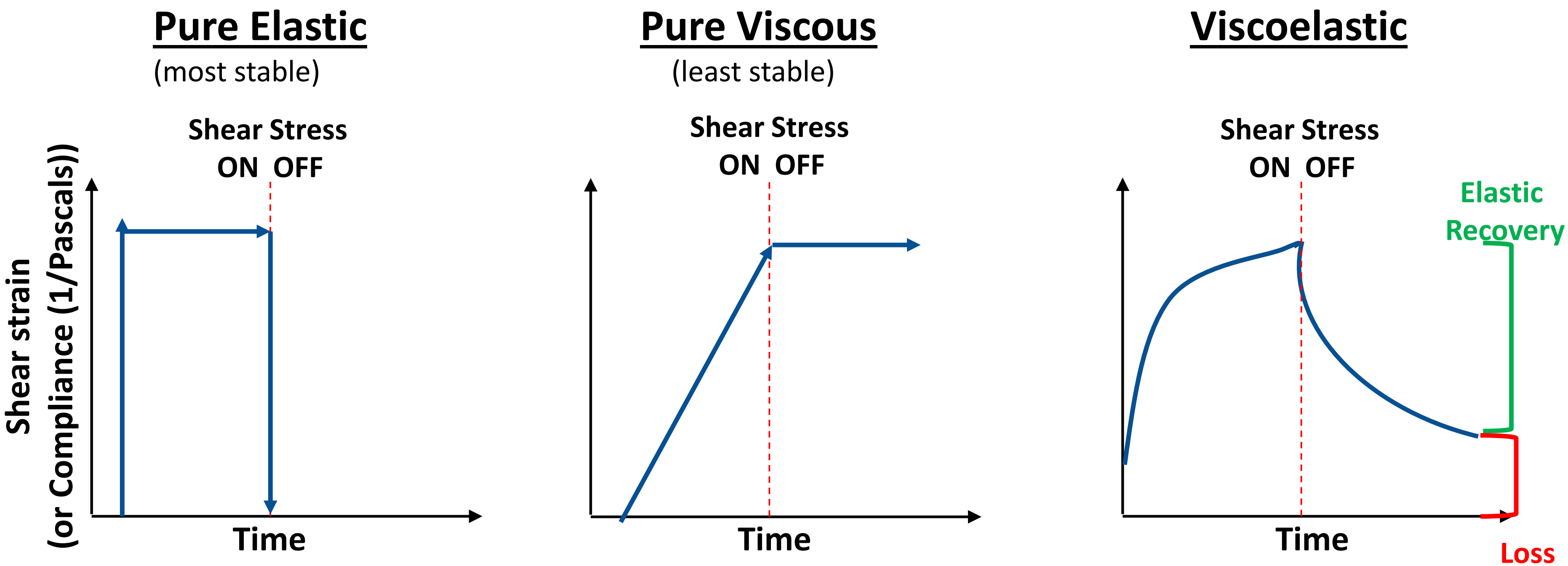
Creep-Recovery

Response to applied stress and release

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

⇒ **Used to determine zero-shear viscosity and evaluate suspension stability**

Squeeze/twist and release



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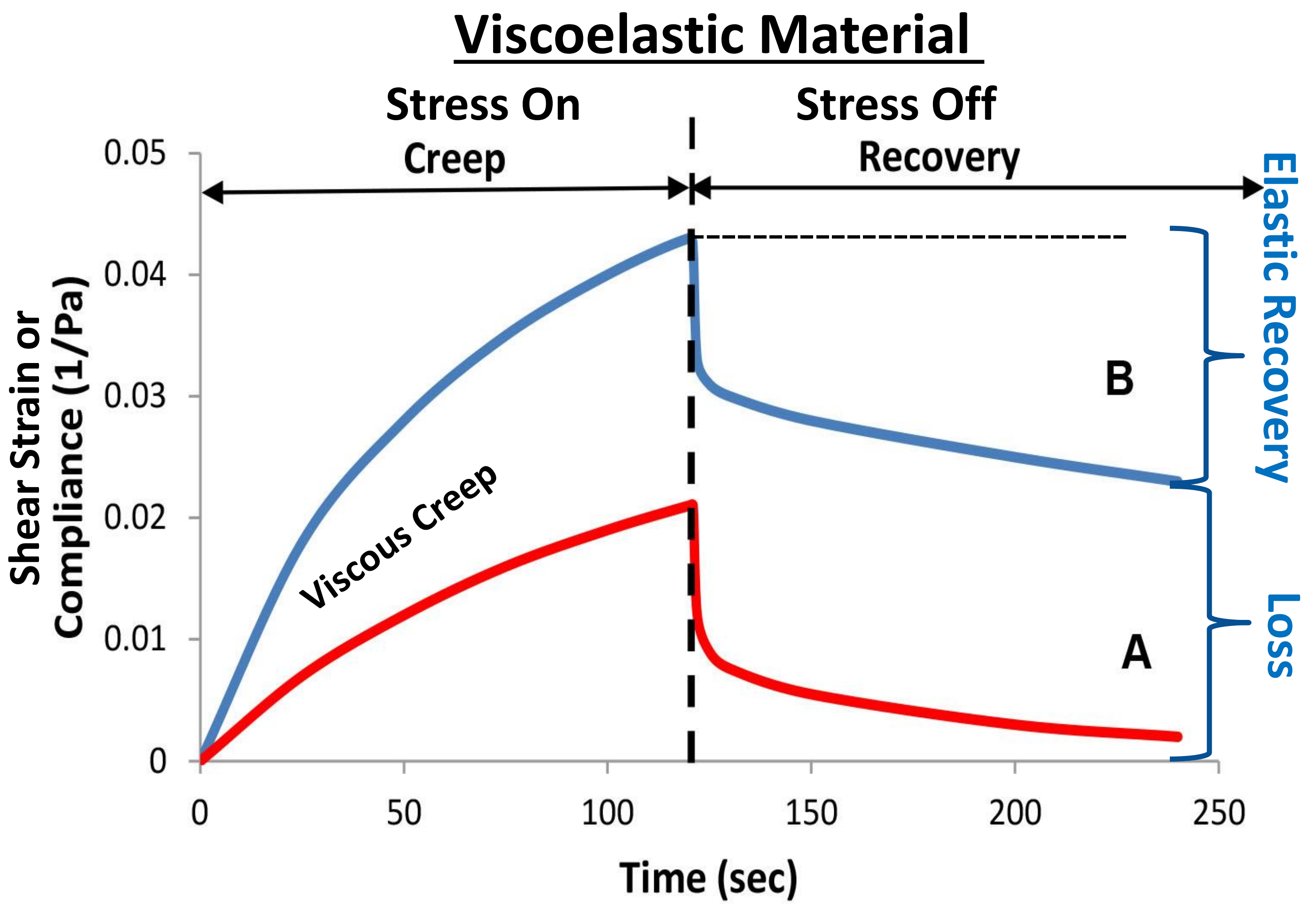


Oscillation ≈ washing machine agitator

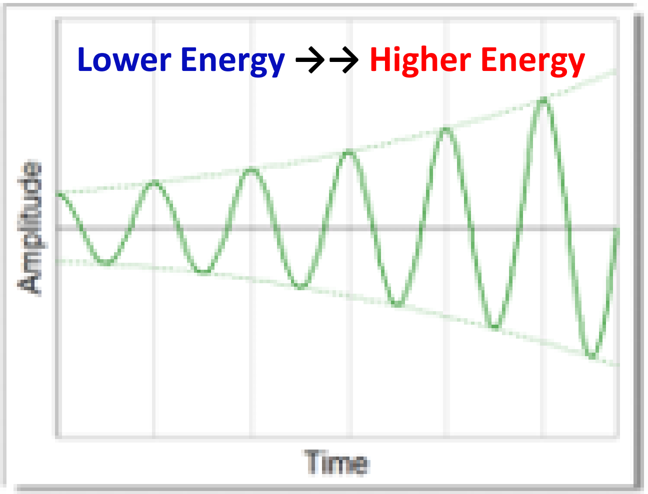
2 ways to modulate oscillation

1. Amplitude (destructive)

-Determine Linear Viscoelastic Region (LVER)

⇒"Breaking point" of structure ∝ stability

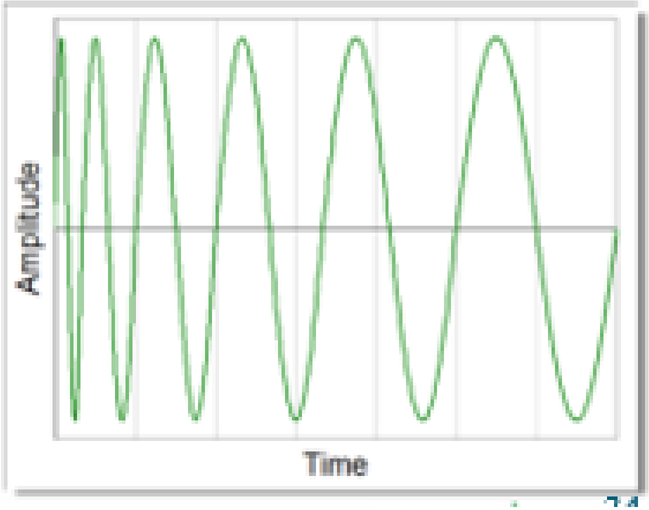
- Textural properties: stiffness, springiness, structural strength and brittleness



2. Frequency (not destructive)

-Measure response to event time =1/freq

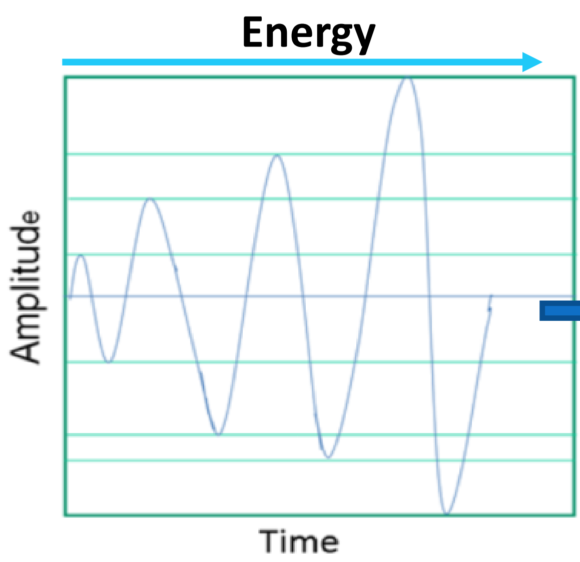
- Probe structural properties within LVER

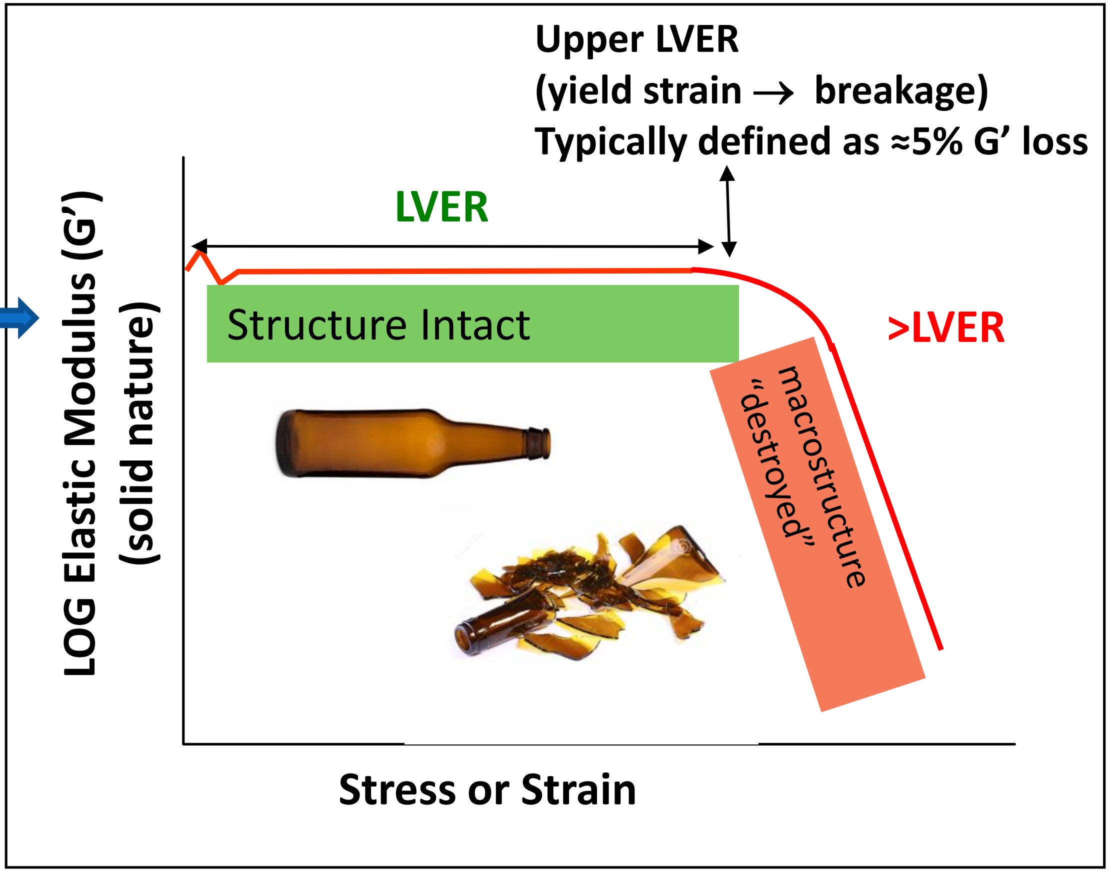


Oscillation - Amplitude Sweep

⇒ **Increase amplitude (energy) until "break" macrostructure**

⇒**Determine LVER before perform frequency sweep to ensure intact sample structure**

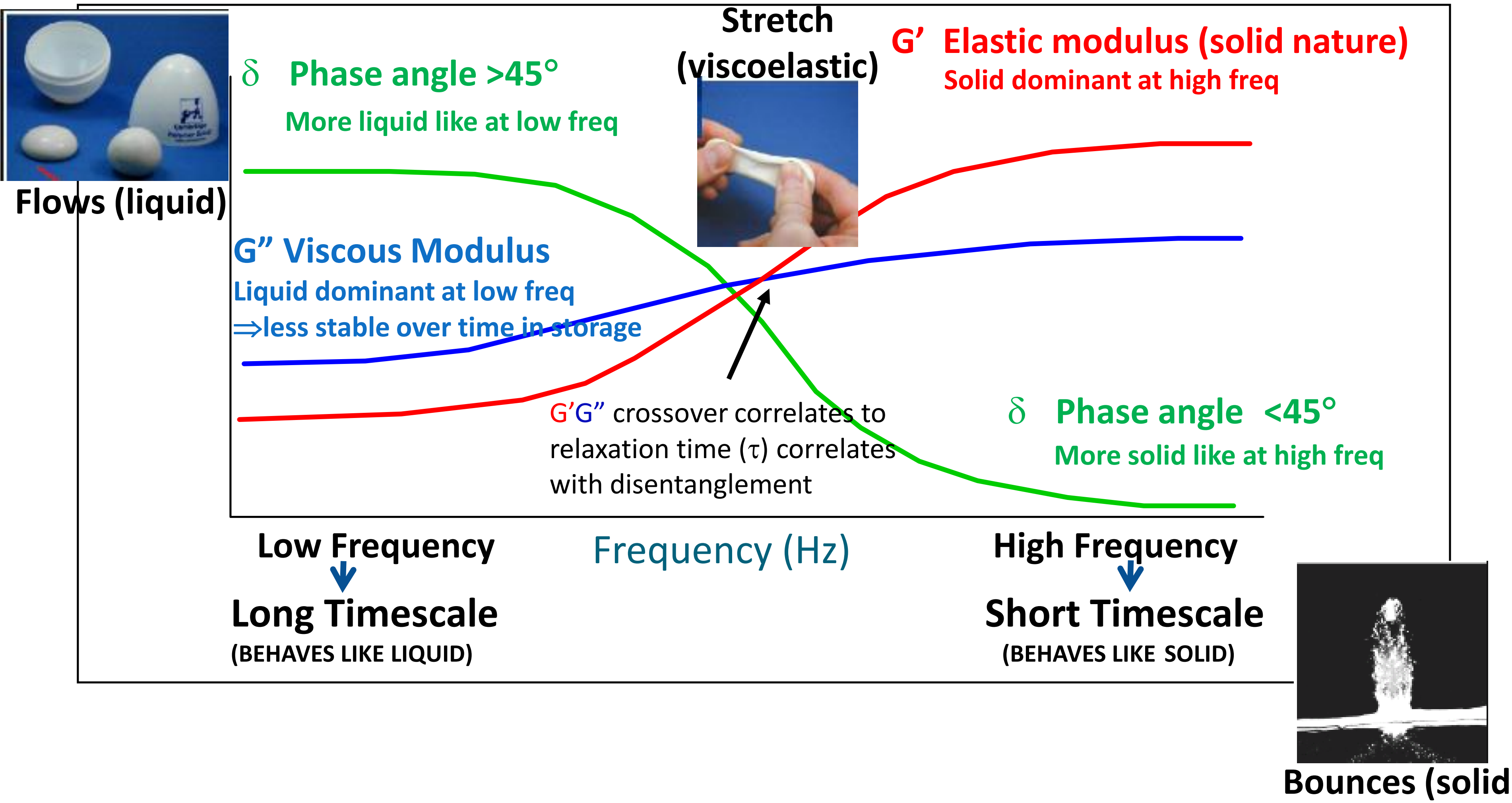




- **Determine LVER from data table, NOT visually with plot, esp <u>not</u> using log-log plot**

Frequency Sweep: Example Silly Putty

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



FREQUENCY SWEEP: Outputs G', G", δ and tan δ

- **G' (Pascals) = elastic or "storage" modulus ≈ solid nature**
- **G" (Pascals) = viscous or "loss" modulus ≈ liquid nature**
- **δ (degrees) = phase angle → increasingly solid 45° to 0°**
  → increasingly liquid 45° to 90°
- **tan δ = G" / G' = energy lost/energy stored during cyclic deformation**
  tan δ >100/1=100 is ideally liquid. tan δ < 1/100 = 0.01 ideally solid

$G' = \sigma_0 \bullet \cos\delta / \varepsilon_0$

$G'' = \sigma_0 \bullet \sin\delta / \varepsilon_0$

Where:

Strain: $\varepsilon = \varepsilon_0 \sin(\omega t)$

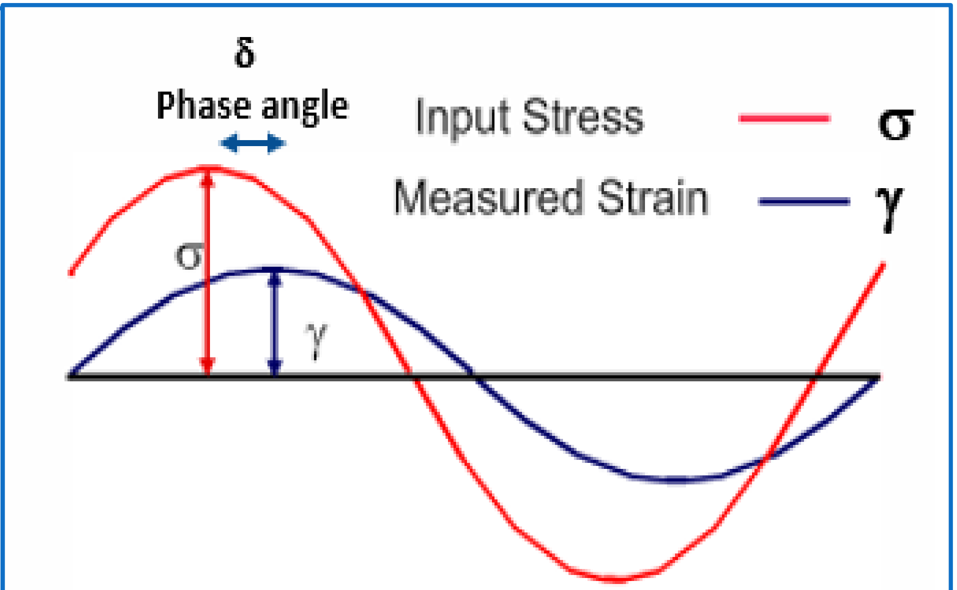
Stress: $\sigma = \sigma_0 \sin(\omega t + \delta)$

Where:

$\omega = 2\pi f$ f= freq of oscillation

t= time

δ = phase lag between stress and strain

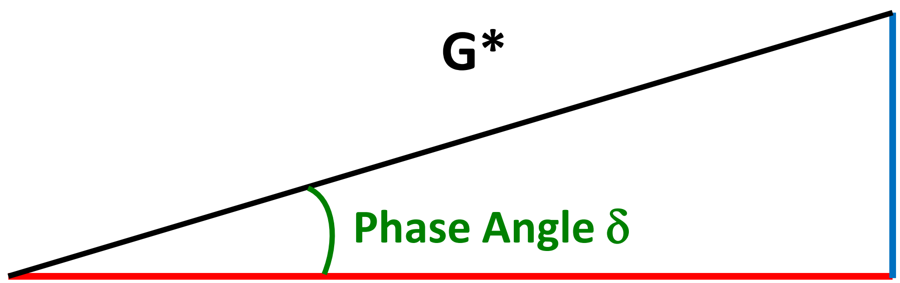


FREQUENCY SWEEP: G* and η*

- G^* (complex modulus) = $\text{Stress}_{(max)} / \text{Strain}_{(max)} \propto$ Stiffness

$$= G' + iG''$$

- η^* (complex viscosity) = $G^* / 2\pi f$ f= frequency

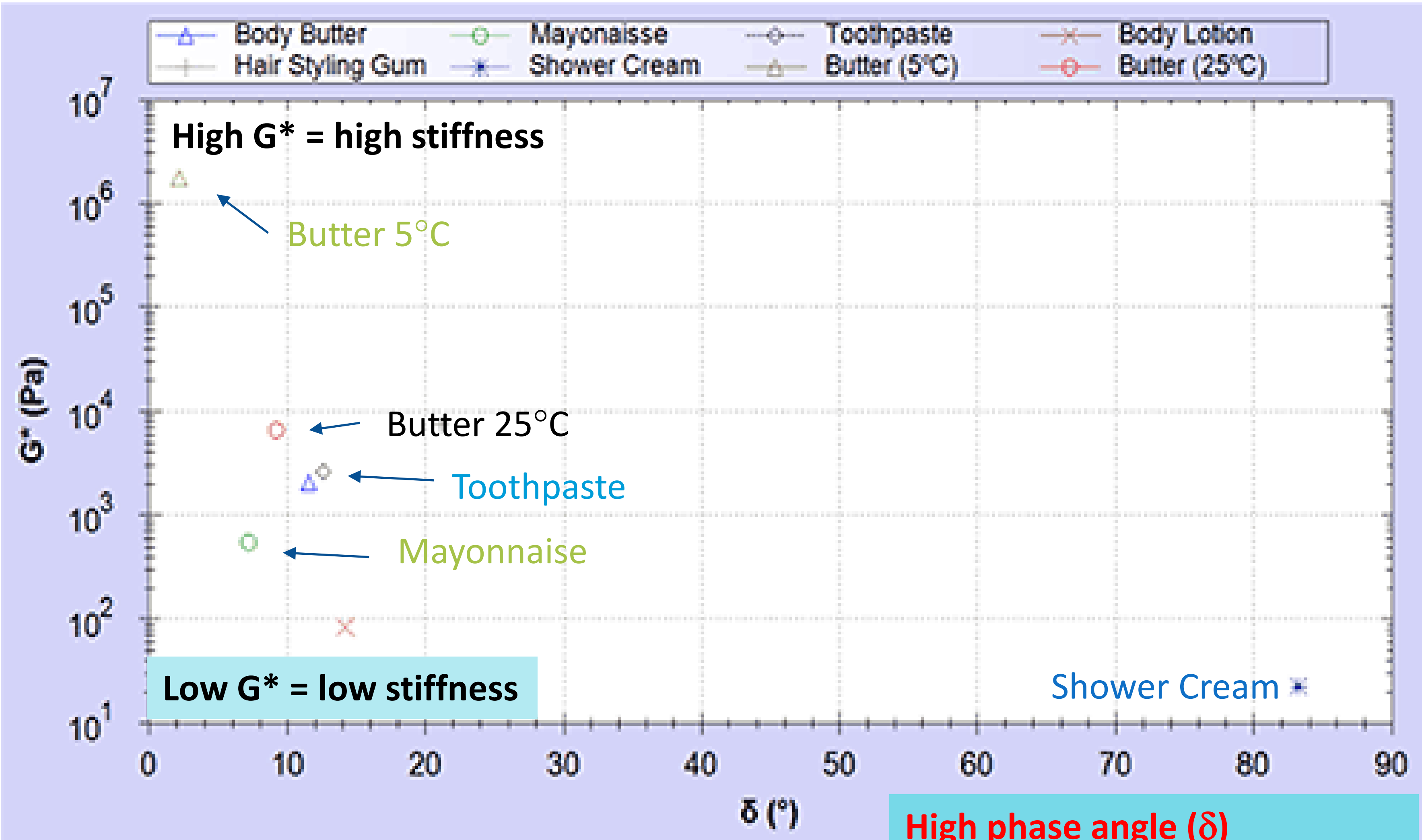


G”
-Viscous modulus
-Liquid nature
-Energy dissipation (loss)
-Weak forces

G’
-Elastic modulus
-Solid nature
-Deformation energy (storage)
-Strong forces

Amplitude Sweep: Quantifying Texture

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



High phase angle (δ)
= more liquid, less "springy"
= less elastic

Image from Malvern Pananalytical

FREQUENCY SWEEP

- pull-away assay also correlates with sensory

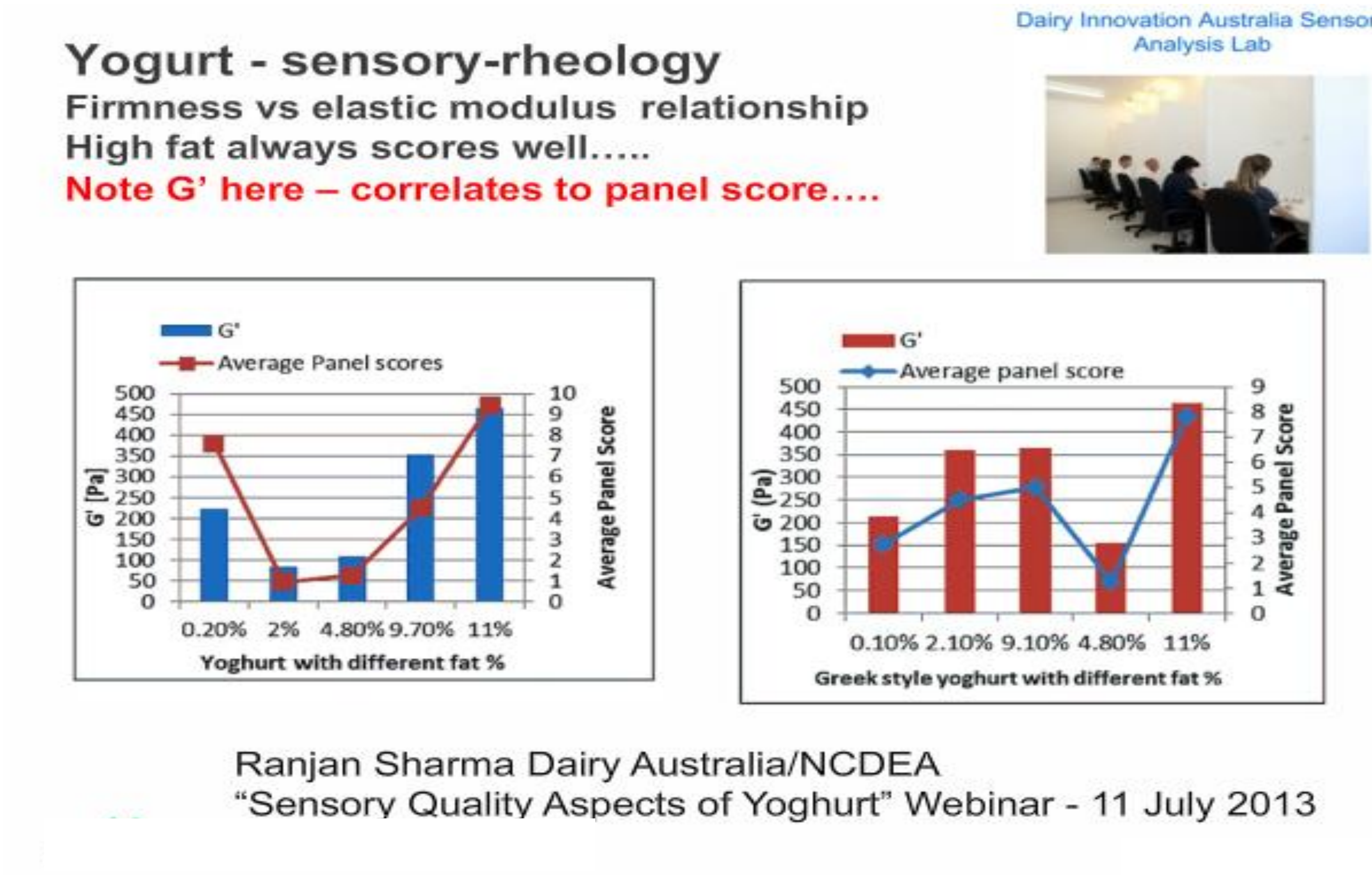


Image from Malvern Pananalytical

TEMPERATURE SWEEP – OSCILLATION MODE

G* ∝ stiffness

- Spreadable butter contains fats & oils that melt at lower temperatures making it easier to spread at lower temperature.

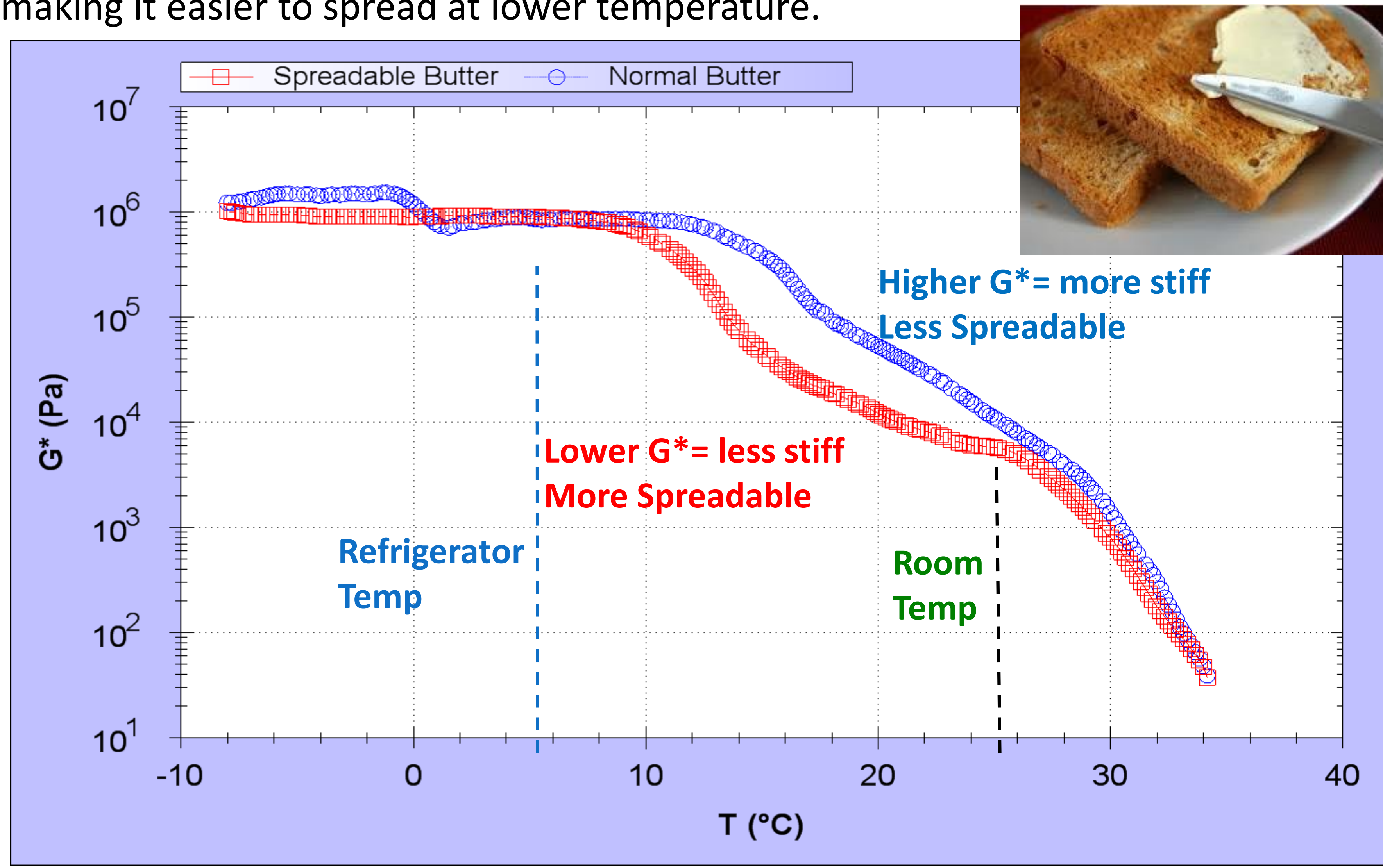
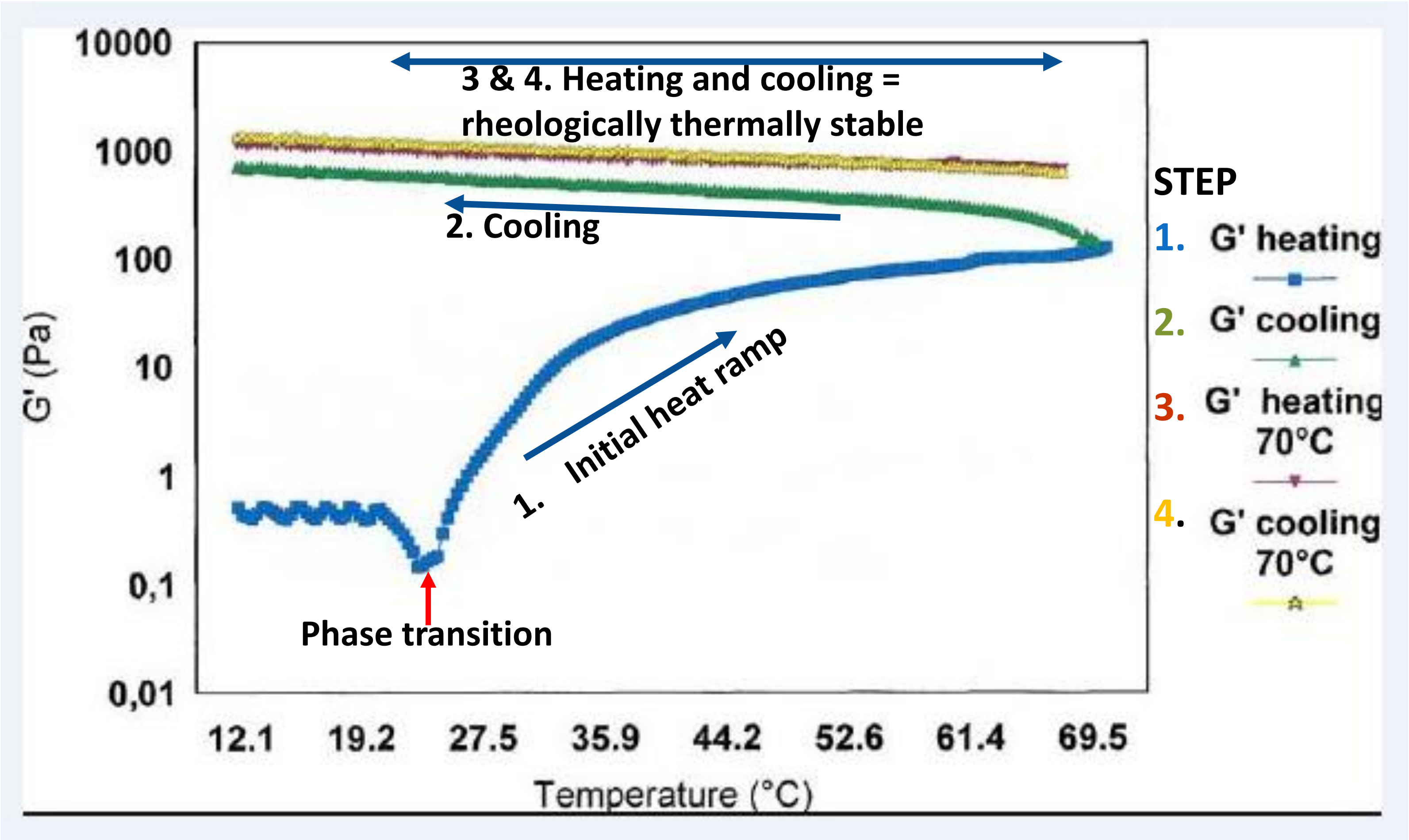


Image from Malvern Pananalytical

TEMPERATURE SWEEP

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

Example showing irreversible rheological change to more thermally stable material



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:

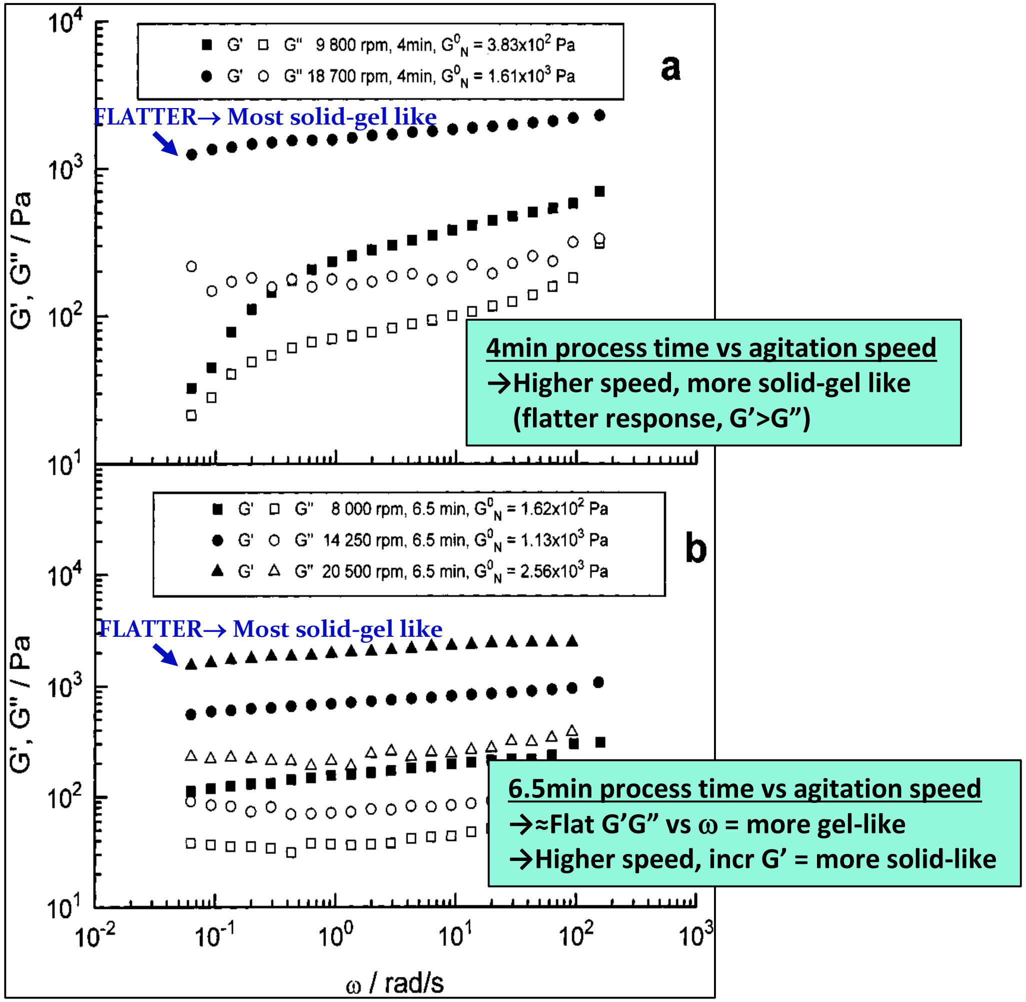
- Emulsion stability and physical properties improved by heating lupin solution prior to the addition of the oil phase or inducing a chemical or enzymatic reaction that increases the entanglement protein molecules along with hydrophobicity.

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

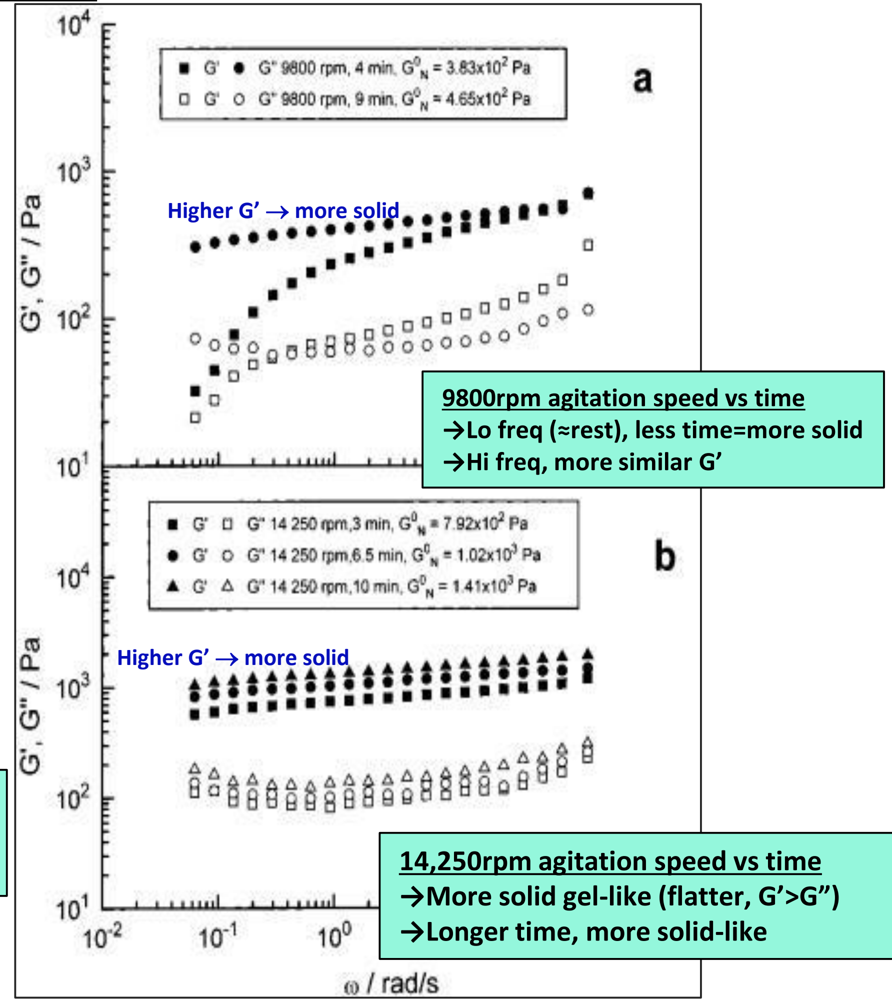
PROCESSING OF A PROTEIN-STABILIZIZED EMULSION

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



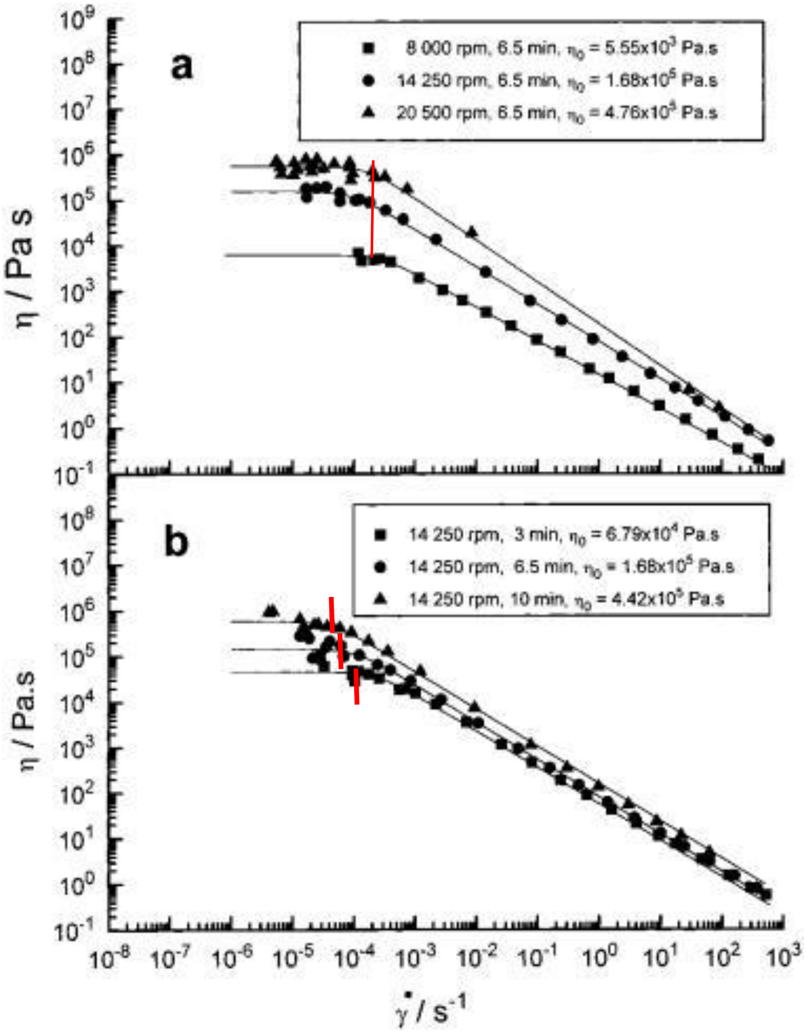
Freq Sweep: G' and G" of lupin protein-stabilized emulsions vs agitation speeds.



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.

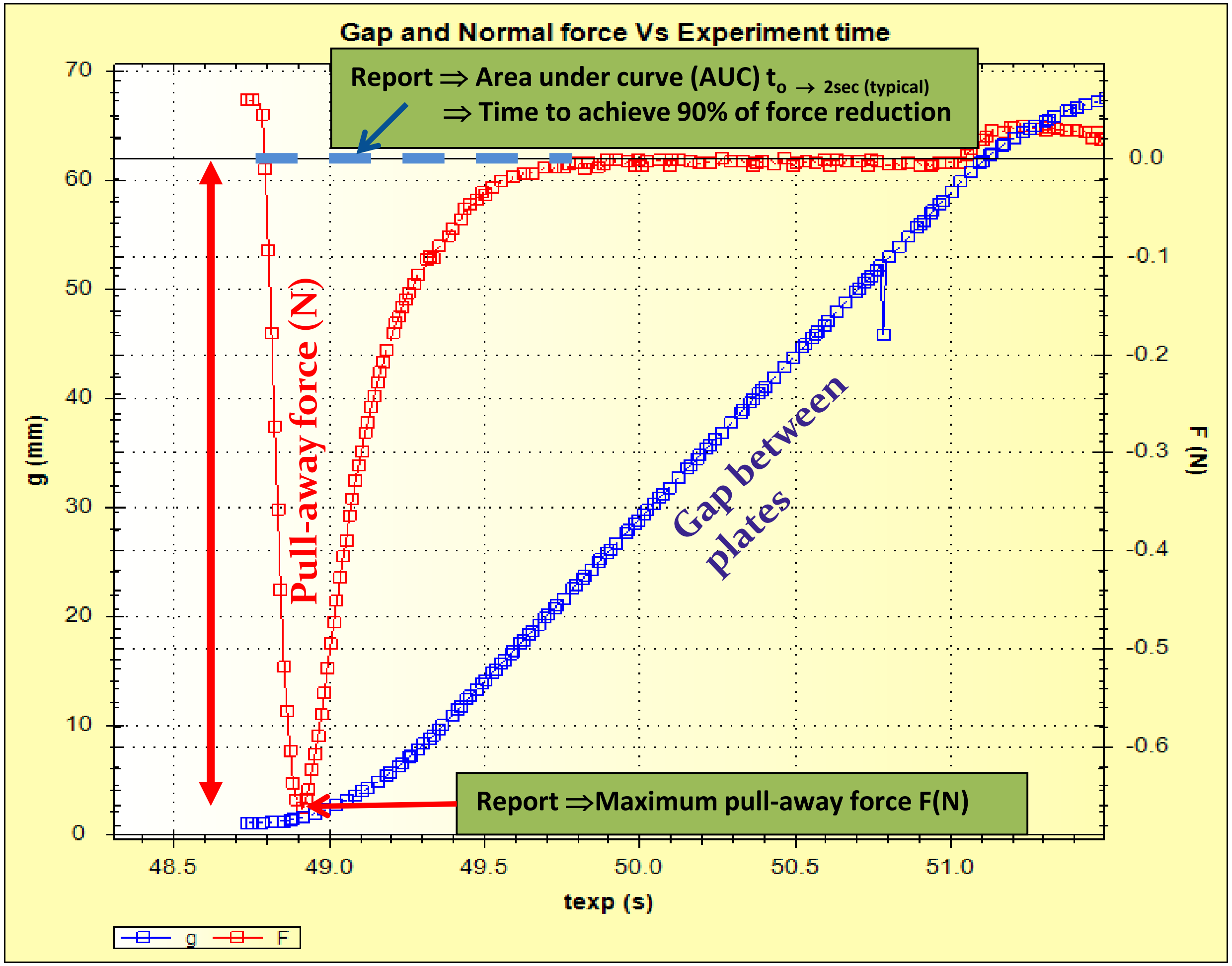
6.5min process time vs agitation speed
→Higher speed, more viscous
→All shear thin, with 20,500rpm more rapidly
→Generally, similar breakpoint

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

SQUEEZE PULL-AWAY

Experimental parameters: Plate, compression force, compression & pull-away time

→ models stickiness and tackiness



1. Compress
2. Pull-Away

Sample between plates experiences consistent gap, compression, and pull-away rate.

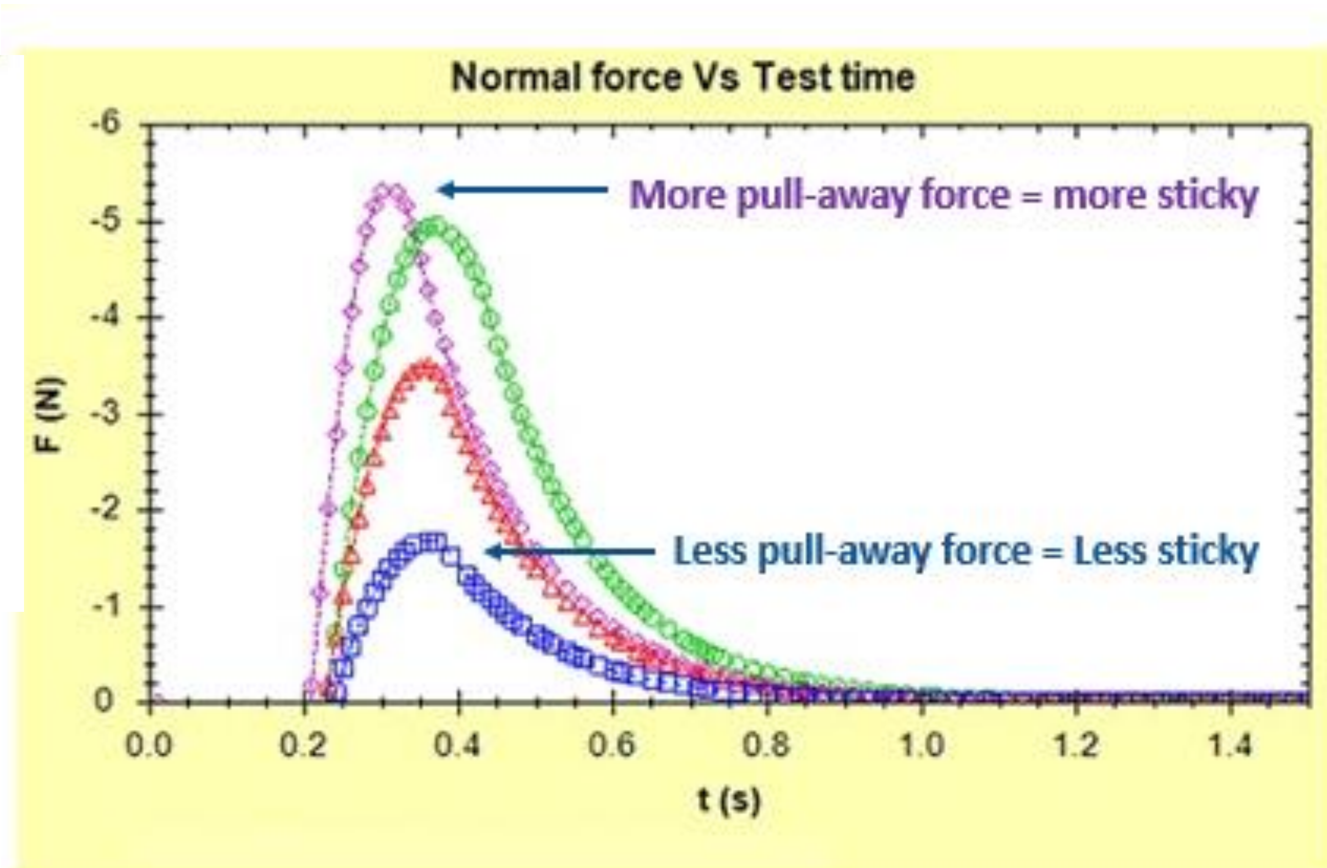
SQUEEZE PULL-AWAY

The following results are typically reported:

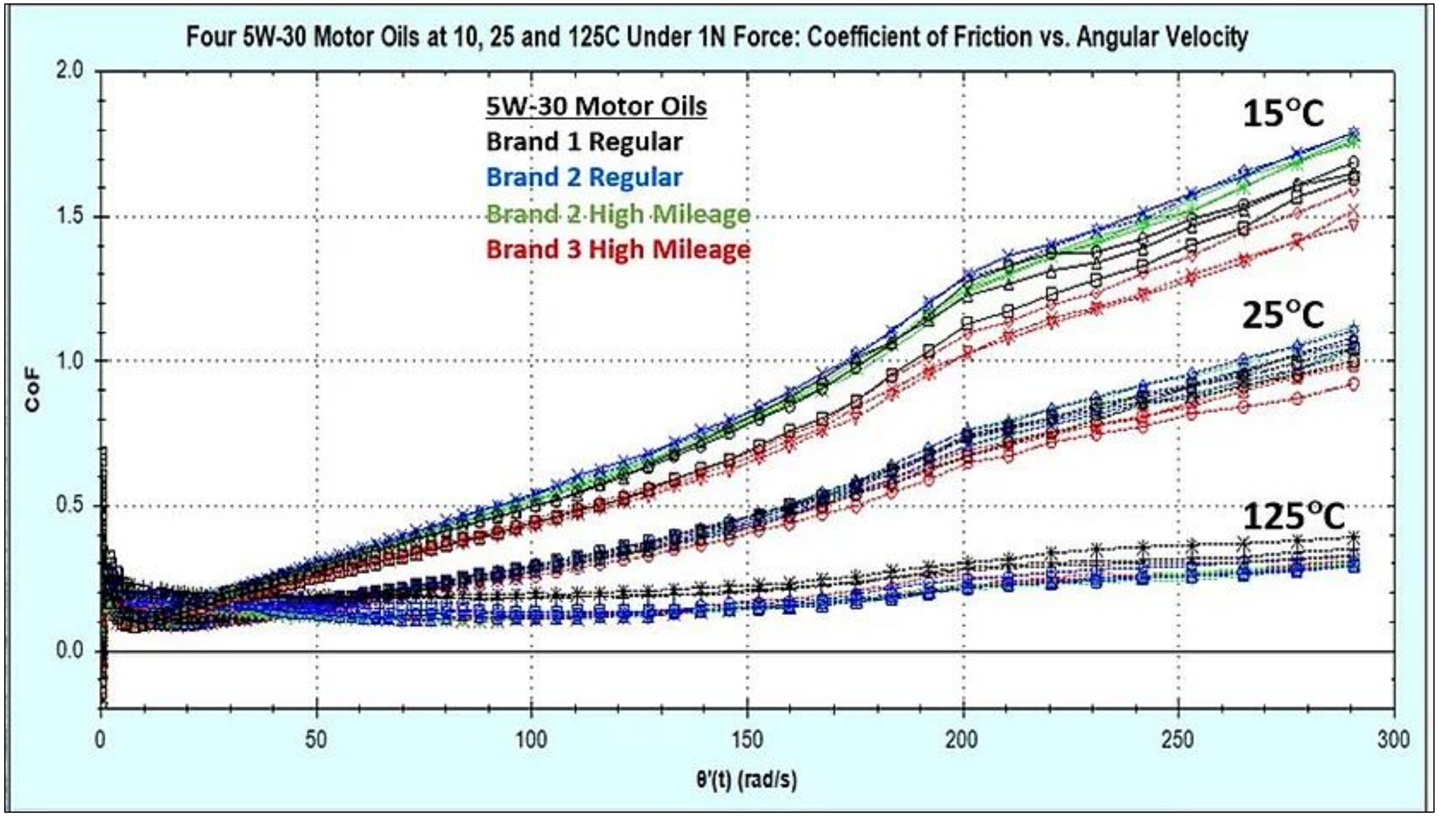
-peak pull-away force (Newtons) for tack

-area under the curve (N-sec) for adhesion/cohesion strength

-time (sec) for 90% of force reduction 90% for failure



APPLICATION: TRIBOLOGY (friction) OF MOTOR OILS AT 15, 25 & 125°C



Getting back to questions when we started…

→Which is more viscous – honey or mayonnaise?... careful

→Is silly putty a viscoelastic solid or liquid?

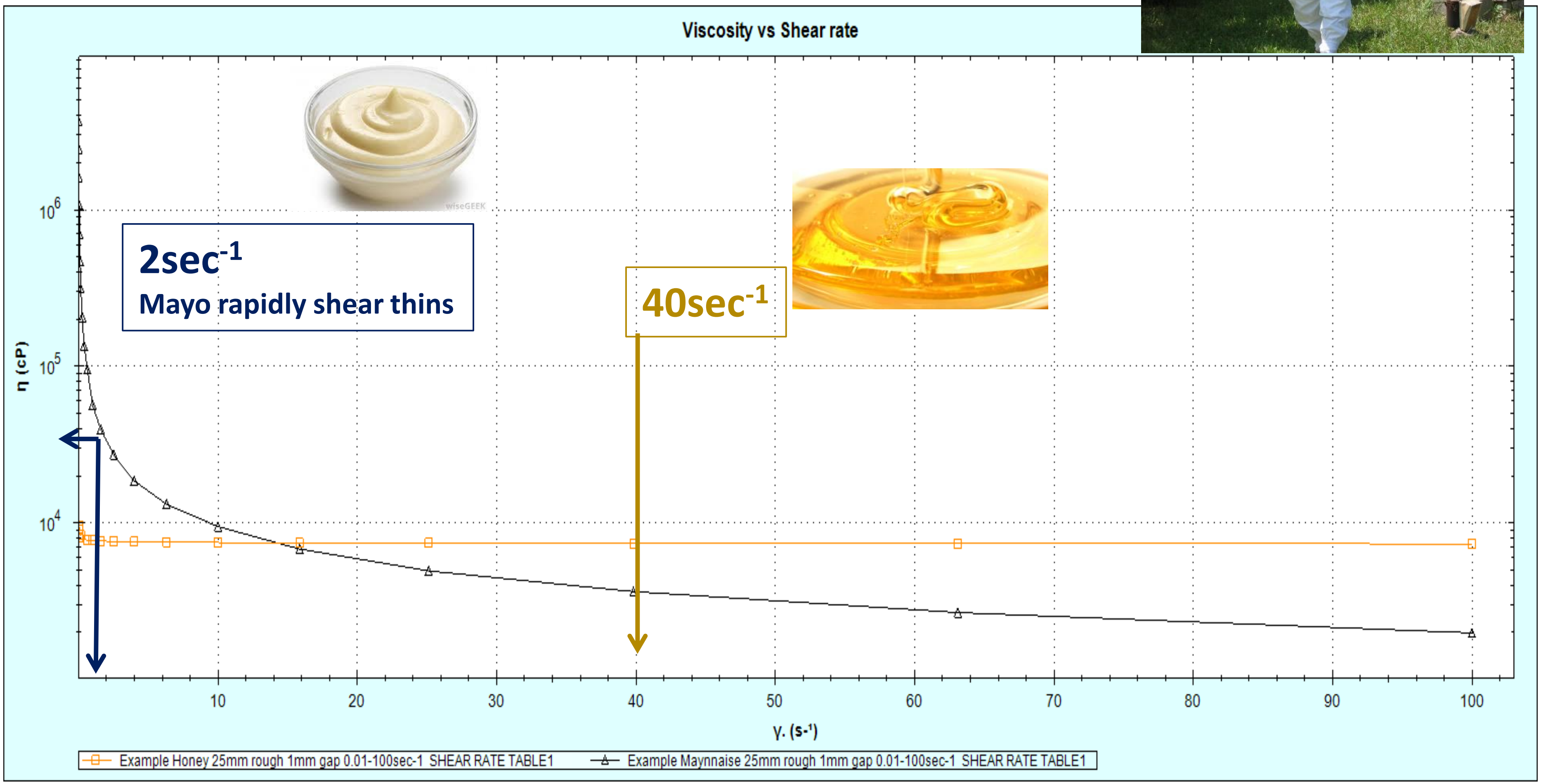
Which is more viscous – Honey or Mayonnaise?

⇒**Depends on shear rate……**

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

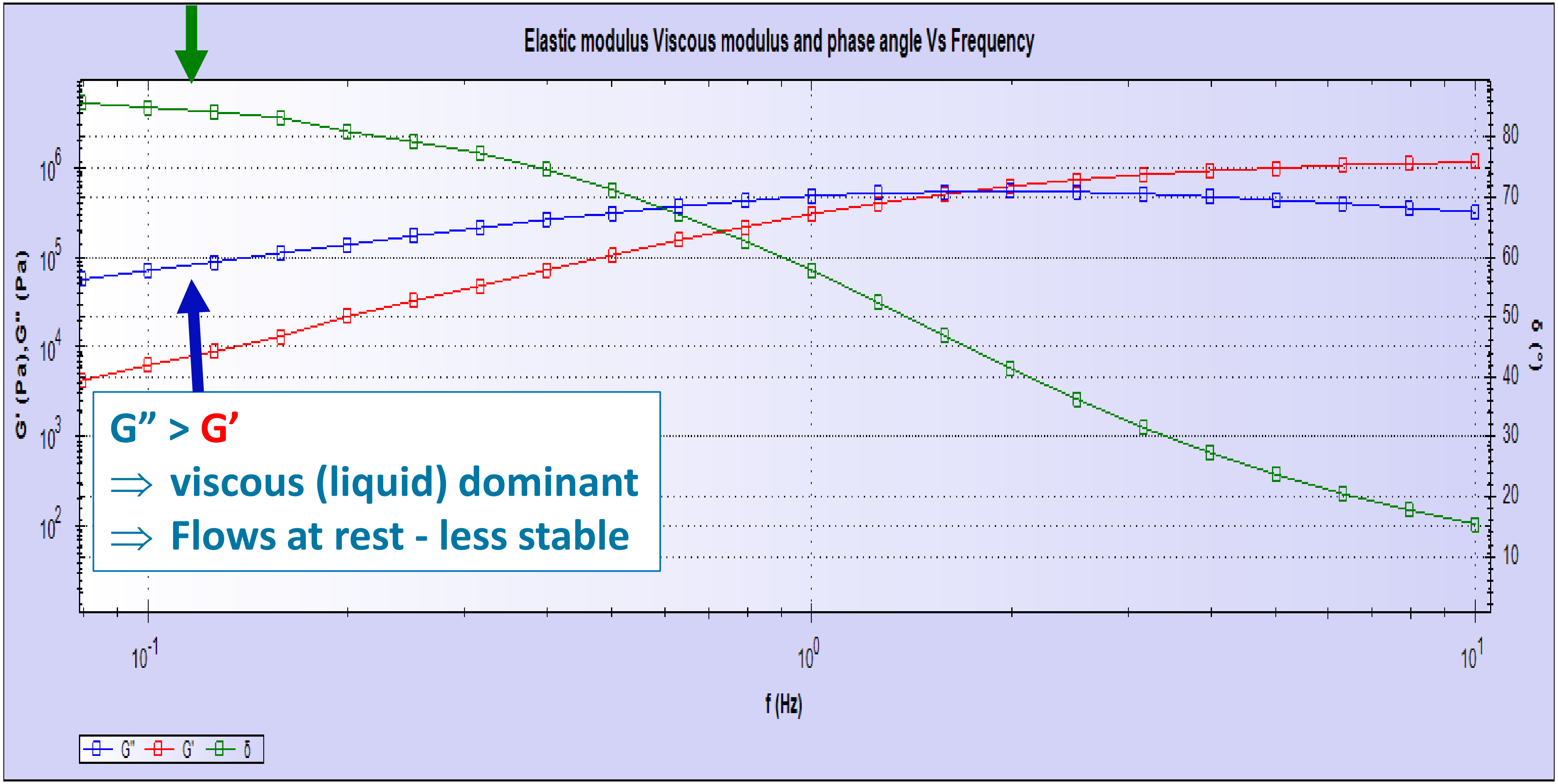
At 2sec^{-1} $\eta_{Mayonnaise} > \eta_{Honey}$

Yes, this is me



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

CONCLUSIONS

⇒ Which test is better?? Depends on the question to be answered

Mindful of experimental details! (handling, geometry, size, gap, sample change)

Viscometer - very good basic QC tool

- Value at single shear rate generated at defined parameters
  (spindle type, spindle rotation rate, temperature)

Rheometer characterizes sample in more detail

⇒ROTATION

- Flow Curve: Non-equilibrium shear stress ramp. Model spreadability, pumpability
- Equilibrium viscosity: Shear rate steps
- Thixotropy: Rebuild after shear thinning? Example: paint, ketchup, toothpaste
- Creep test: Response after release to stress. Example: Squeeze/release sponge
- Temperature sweep: Change with temperature, (ir)reversible?
- Tribology (friction)

⇒OSCILLATION

- Amplitude sweep: Define LVER = breaking point. Correlate stability, texture
- Frequency sweep: Rheological fingerprint across time domain. Example: silly putty
- Temperature sweep: Change with temperature, (ir)reversible?.Example: butter, stable solid

⇒ VERTICAL

- Pull Away (stickiness)

Thank you!

Questions?

Backup Slides

Applications

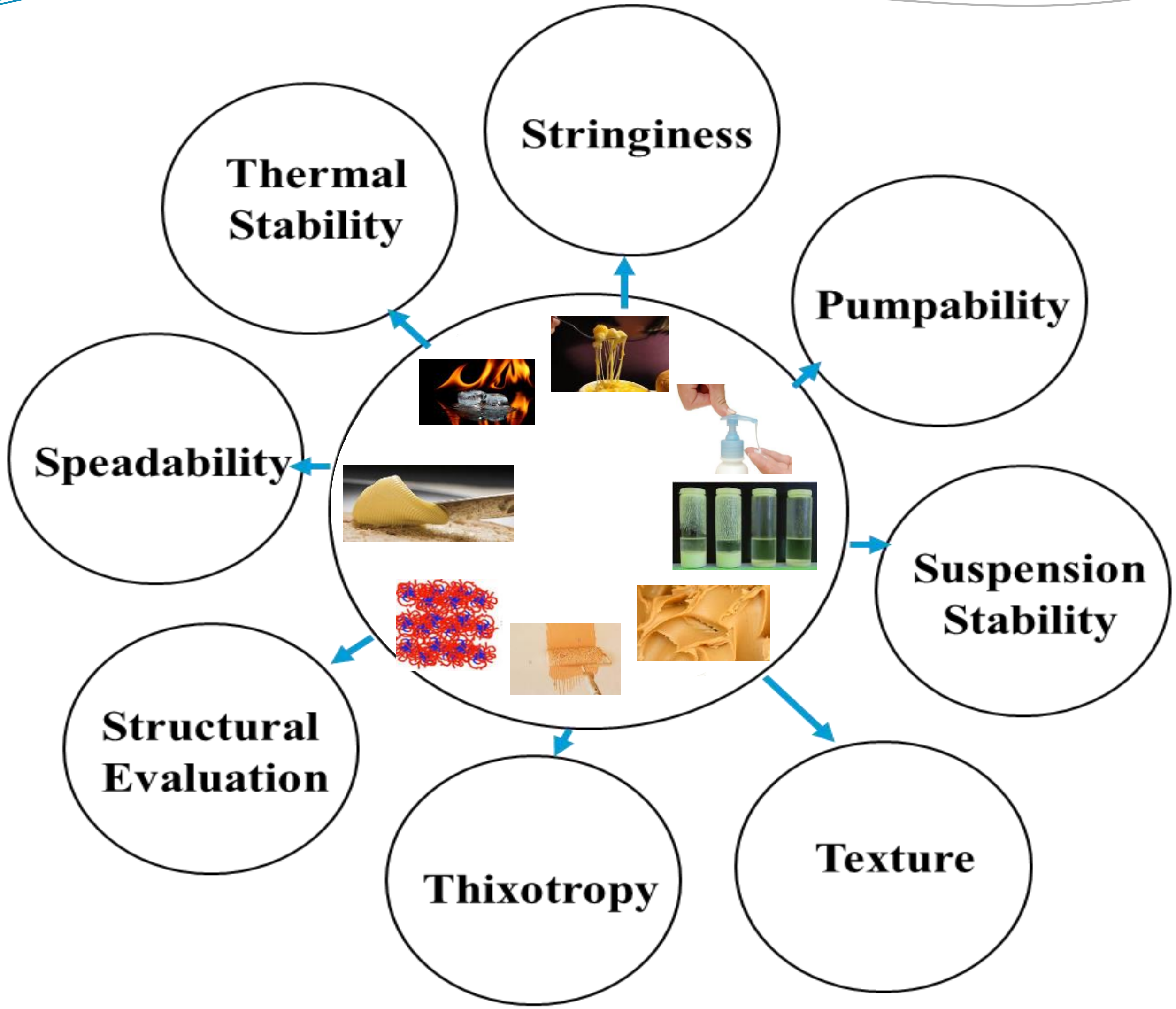


Plate Considerations

Geometry Size	Advantages	Disadvantages
Larger surface area	-Use for lower viscosity samples	-Requires more sample
Smaller surface area	-Use for higher viscosity samples -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 -May reduce potential for slippage	-May still give slippage
Serrated	-Most aggressive to reduce slippage	-May need brush to clean -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 -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 (η_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’ x γ^2)
Viscoelasticity	↓δ	-Viscoelastic liquids with high phase angle (δ) at low freq are less stable -Use structured gel having δ <45° and independent of freq -If heavy or large particles, decrease δ <45° at low freq

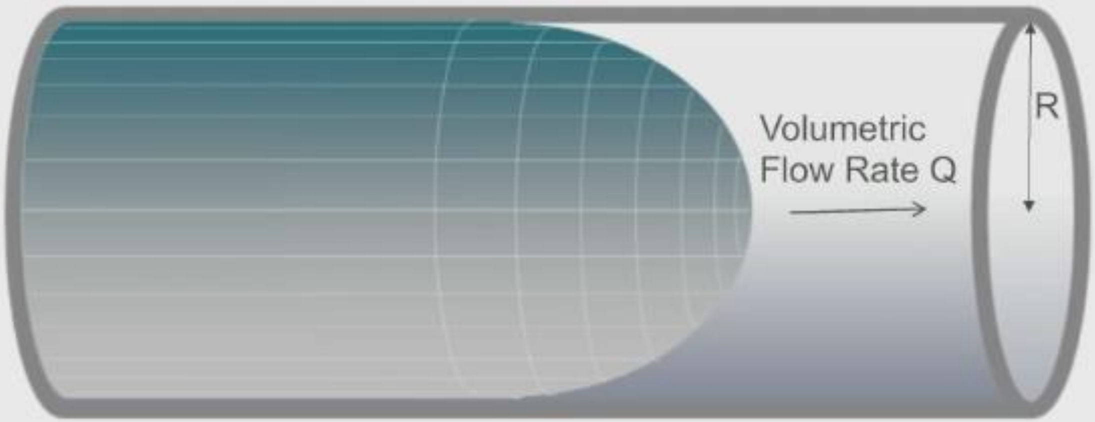
- Larger particles increase viscosity
- Irregular particles increase viscosity

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

Calculation of **Shear** rate – Pipe Flow

Poisellian Flow

Malvern Panalytical



Apparent shear rate
(Newtonian material)

$$\dot{\gamma}_a = \frac{4\,Q}{\pi R^3}$$

Corrected shear rate
(Rabinowitsch)

$$\dot{\gamma}_c = \frac{4\,Q}{\pi R^3}\,\frac{3n+1}{4n}$$

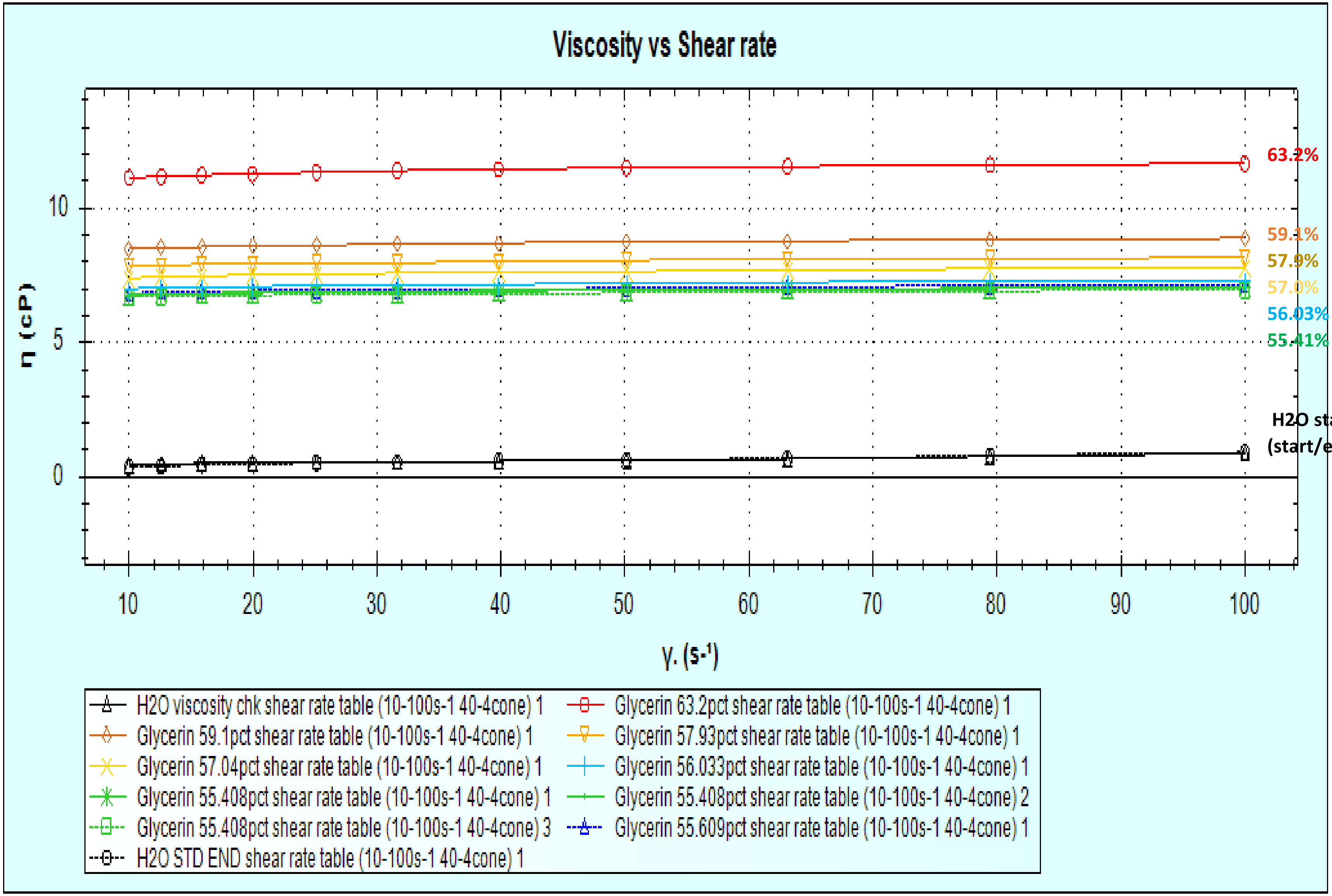
$$n = \frac{d\,(\log \tau)}{d\,(\log \dot{\gamma})}$$

If n = 0.5, $\dot{\gamma}_c = 1.25 * \dot{\gamma}_a$

Example of Equilibrium (Table) Viscosity: Aqueous Glycerol Mixtures (55-63%)

-Consistent viscosity increase with increasing glycerol of relatively narrow range

-Essentially no viscosity change across shear rate = Newtonian.



FREQUENCY SWEEP