ΛPOHΛ

Case study

See how your formulation behaves under stress — directly

Non-Newtonian dynamics under multiple concurrent stresses, captured as a standardised, microlitre-scale readout of formulation behaviour — on Apoha's Liquid State Intelligence (LSI).

At a glance

This note reports Liquid State Intelligence (LSI) measurements of antibody formulations. The physical basis for the measurement draws from our previous reports (St John et al., 2026; Thomas et al., 2026) and the wider rheology literature. Beyond the reported measurements, we present some ongoing interpretational work on the microstructural identity of the LSI response.

What is measured

LSI dispenses formulation droplets, one at a time, into a trough of engineered sensing liquid and records the liquid bridge as it pinches off. A single coalescence event applies three stress classes in sequence: interfacial (adsorption to the air–liquid interface), mechanical (extensional flow, in-plane compression, Marangoni flow at the thinning neck), and chemical (ion gradients and surfactant exchange) — so one measurement probes behavior under multiple simultaneous stresses (St John *et al*., 2026).

The reported quantity, the VIBE feature (VIBE1 in St John *et al*., 2026; formally, the per-titration kurtosis of the interfacial (SY) waveform in a fixed window), increases with the amplitude and the drop-to-drop variability (roughness) of the post-pinch-off signal (Figure 1). Across a 1,182-titration reference dataset, the drop-to-drop standard deviation of pinch-off time accounts for R^2 = 0.92 of the VIBE feature (St John *et al*., 2026). The VIBE feature identifies antibodies carrying multiple biophysical liabilities and enriches for clinical failure across a 235-antibody clinical-stage dataset (Thomas *et al*., 2026).

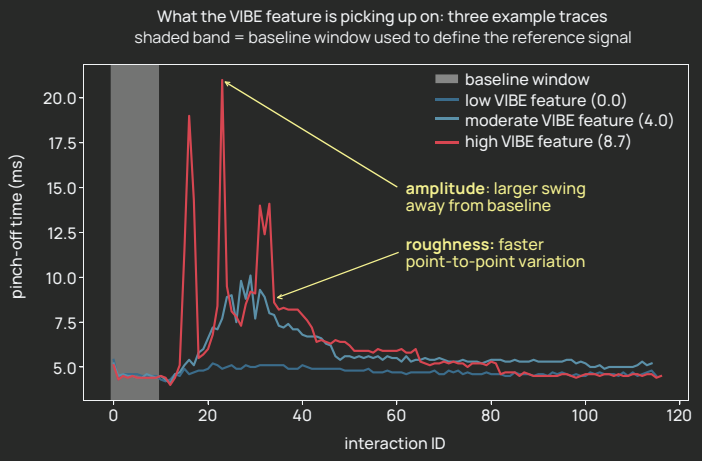

Figure 1: Three example pinch-off traces at low, moderate and high VIBE-feature values. Shaded band marks the baseline window; annotations mark the amplitude and roughness components from which the feature is computed.

What the signal is

High-speed imaging at 10,000 frames per second resolves the coalescence directly (St John *et al*., 2026). Every droplet — water and antibody — thins at the same Newtonian capillary–inertial rate while the neck is wide. For some antibodies, the bridge thinning decelerates as internal strain builds, following an elasto-capillary (viscoelastic) trajectory, with a deceleration timescale that tracks pinch-off time inversely. In the strongest cases, the merged droplet does not relax into a sphere within 50 ms, which a homogeneous viscous fluid at any plausible IgG-formulation viscosity would in under 5 ms. The measured feature in Liquid State Intelligence is therefore a direct, observational readout of non-Newtonian, viscoelastic behavior during coalescence.

In protein solutions, non-Newtonian behavior is a signature of intermolecular association. Concentrated antibody solutions become non-Newtonian (shear-thinning, viscoelastic) when molecules form transient, reversible clusters and networks, while non-associating solutions remain Newtonian. The strength of the response scales with the strength of self-association, so the critical shear stress at which shear-thinning begins is a measure of equilibrium cluster strength. Antibodies differing only in their CDRs can differ in whether they are non-Newtonian at all (Zarraga *et al*., 2013). In extensional flow, as in a thinning coalescence neck, an elasto-capillary signature likewise requires an extensible, connected microstructure absent in a simple liquid (Anna & McKinley, 2001; Tirtaatmadja *et al*., 2006). The feature therefore reflects the degree of stress-induced intermolecular association — the collective mechanical consequence of those interactions, not a single association constant. Interfacial and mechanical stress, and the self-association they probe, are recognised drivers of antibody aggregation and particle formation (Li *et al*., 2019).

Running a formulation study

A molecule is measured across a panel of formulation conditions. Each condition returns one VIBE-feature value; the set of values across the panel is that molecule's behavioral fingerprint. Parameters used in this study:

Molecule concentration	0.2 mg/mL (antibodies)	**Trastuzumab panel**	24 conditions (buffer × excipient × pH)
Sample per measurement	microlitre-scale, from ~8 µg	**Cross-protein set**	8 conditions common to all six proteins
Buffers	20 mM		
Amino-acid excipients	150 mM	**Reported feature**	VIBE feature — kurtosis of the post-pinch-off SY waveform
Sugars (sucrose / sorbitol)	300 mM	**Variability**	SEM shown; per-condition one-way ANOVA (Figure 3)

Observation 1 — one antibody across 24 formulations

Trastuzumab at 0.2 mg/mL was measured in triplicate across a 24-condition panel (buffer × excipient × pH), designed to match the excipient-compatibility matrix of Xin *et al*. (2024). Across these conditions, the VIBE feature spanned approximately two orders of magnitude. The highest-ranked conditions were glycine-containing (Figure 2).

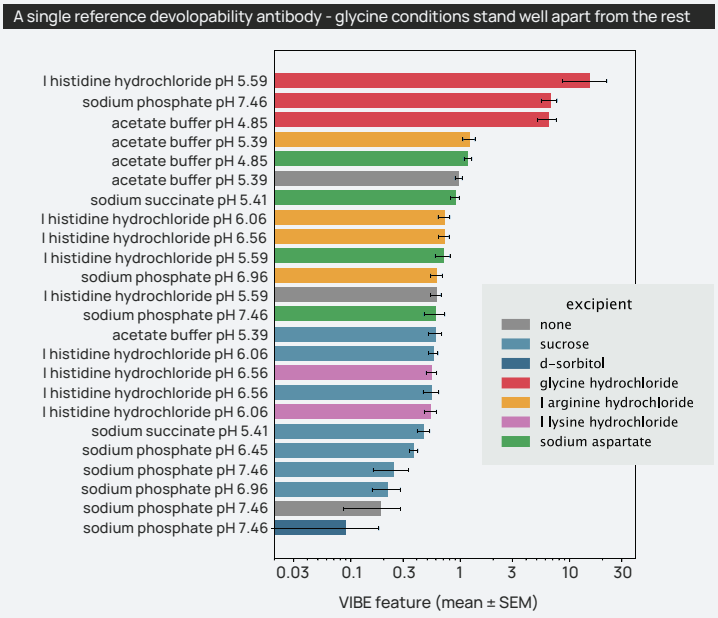

Figure 2: Trastuzumab VIBE feature across the 24-condition panel, ranked and coloured by excipient. Glycine-containing conditions rank apart from the rest.

Observation 2 — six proteins across shared conditions

Four antibodies (adalimumab, trastuzumab, carlumab, omalizumab) and two non-therapeutic model proteins (BSA, ovalbumin) were measured in triplicate across the eight conditions common to all six. The four antibodies show elevated VIBE-feature values on glycine conditions and lower values elsewhere; BSA and ovalbumin show a flatter profile across the same conditions (Figure 3) — consistent with the antibody-specific, BSA-negative response established in the reference dataset (St John *et al*., 2026). Within the four antibodies, the rank order is consistent across conditions (adalimumab highest, trastuzumab lowest on almost every condition). Per-condition standard errors and one-way ANOVA F-statistics are shown on the figure.

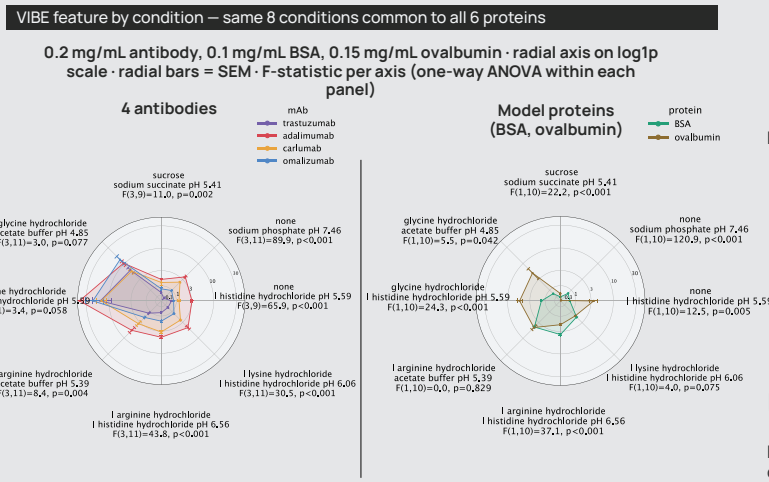

Figure 3: VIBE feature by condition. Left: four antibodies; right: two model proteins from the albumin family (heterologous to antibodies). Radial axis log1p-scaled; radial bars = SEM (n = 3); F-statistic per axis from one-way ANOVA within each panel.

What these observations establish

Established by the measurements and the cited record:

- **Reproducible separation.** With triplicate titrations, differences between conditions exceed within-condition variability (SEM and per-condition ANOVA, Figure 3).
- **Formulation-resolved, molecule-specific fingerprint.** A molecule returns a distinct VIBE-feature value per condition (Figure 2); fingerprints differ between molecules in a consistent rank order and differ between antibodies and model proteins in overall shape (Figure 3).
- **A physically grounded readout.** The feature is a direct readout of non-Newtonian, viscoelastic behavior during coalescence (imaging; St John *et al*., 2026), which in protein solutions reflects the degree of intermolecular association (Zarraga *et al*., 2013; Anna & McKinley, 2001), under the multiple simultaneous stresses of the event.

Reserved (not required by these results):

- **Microstructural identity.** St John *et al*. (2026) interpret the response as a transient gel-like transition; the observations above do not depend on that identification.
- **Quantitative endpoint mapping.** Relating a fingerprint to a specific numerical endpoint — a viscosity value, an aggregation rate, a shelf-life — for a given formulation is established per study; these data demonstrate the readout and its reproducibility.

Using a fingerprint

Because each condition yields an independent value, a fingerprint supports two direct comparisons: across conditions — which formulations shift a molecule's non-Newtonian behavior — and across molecules — how candidates rank under identical conditions. Both are read directly from the measured feature, from microlitre samples, without titration to high concentration.

References

St John A.N., Holland J., Lam E.S.-H., Lee S., Caramazza P., Thomas A.N., Shrivastava S. (2026). Millisecond nonlinear state changes during droplet coalescence identify therapeutic-antibody developability liabilities. bioRxiv 2026.05.06.723251.

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About Apoha

Apoha has invented the world's first technology platform to understand the behaviour of molecules. It does so by resolving States: a new fundamental data class of molecular science, alongside Sequences and Structures. Sequences told us what a molecule is. Structures showed us what it looks like. But molecular behaviour — the layer that determines whether a drug works, a formulation holds, or a material performs — is determined by a molecule's thermodynamic state and has remained elusive. Until now.

We call this new paradigm Liquid State Intelligence: the ability of machines to unlock complex molecular behaviour under real-world conditions, generating data no simulation or model can reproduce. As this data layer grows, it gives humanity the power not just to analyse the physical world, but to redesign it.