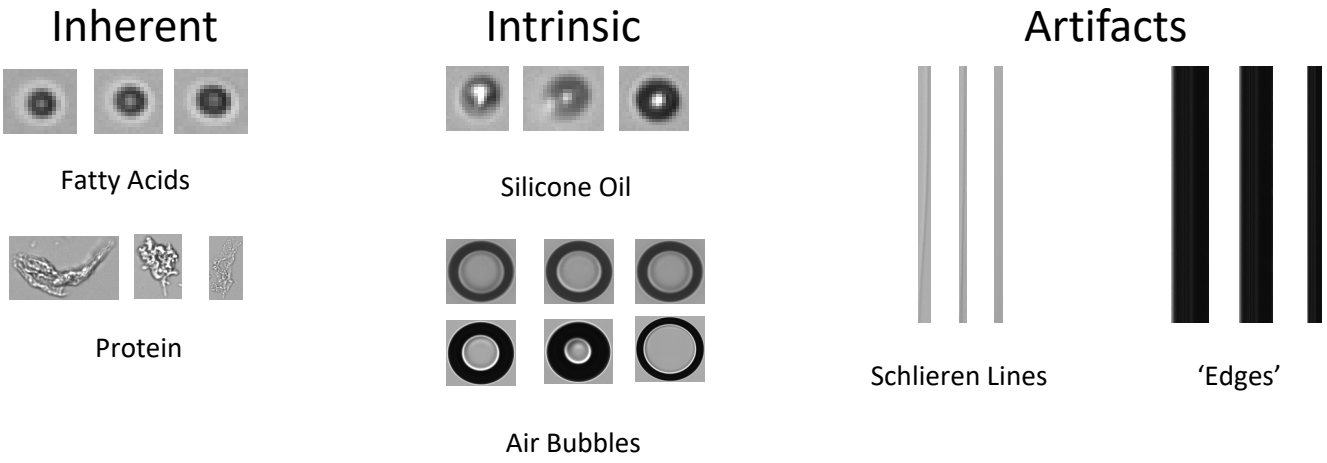
Detection and Diagnosis of Biologic Product Instability using LINK, Machine Learning, and Morphology Fingerprints

STABILITY-INDICATING PARTICLE POPULATIONS IN BIOLOGICS

It is critical during formulation development to understand the types of particles that may be present in the formulation and their impact on drug product safety and efficacy. And to identify the 'stability-indicating' particle populations that must be monitored on an ongoing basis to ensure product safety and compliance (e.g., protein aggregates, excipient degradation particulate, aggregation-inducing particulate).

However, there is often a complex mixture of particles present in high (and varying) concentrations that can mask the populations of interest and obscure their detection (e.g., silicone oil droplets, air bubbles, measurement artifacts such as schlieren lines). It therefore becomes necessary to use sophisticated particle classification algorithms to identify and report on each individual population throughout development and the product life cycle.



LINK and MACHINE LEARNING – ISOLATE, MONITOR, AND DIAGNOSE CHANGES TO PARTICLE POPULATIONS OF INTEREST

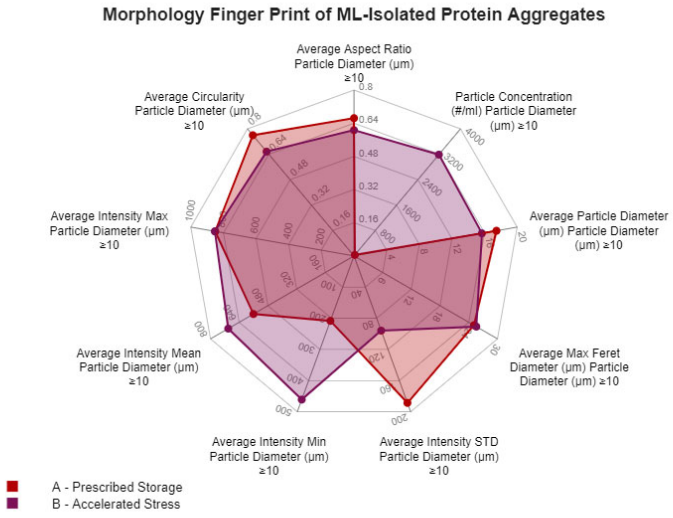
Lumetics LINK™ combined with machine learning capabilities for particle classification, quickly, easily and accurately permits isolation of particle populations in complex mixtures. This aids in both identifying and monitoring stability-indicating particle populations. Additionally, LINK™ supports morphology fingerprints, which may aid in identifying the root cause of the change in the particle population, e.g., protein aggregates under freeze/thaw stress or heat stress have a specific morphology signature, LINK may be used to not only detect early protein aggregate formation, but also the mechanism by which this has occurred.

HOW DOES LINK DO THIS…?

- Automated data and imaging parsing directly from imaging instrumentation (MFI/FlowCAM/Halo)
- Classify particles using one or more machine learning models
- Assess product safety/efficacy by isolating particle populations of interest (e.g., protein aggregates, silicone oil, polysorbate)
- Assess formulation stability by isolating stability-indicating particle populations of interest (e.g., protein aggregates vs fatty acids)

- Characterize stress conditions by isolating stability-indicating populations (e.g., protein aggregates) and producing morphological parameter fingerprints for relevant conditions (e.g., stress, storage)
- Monitor stability-indicating populations and using LINK tabular summaries, identify statistically significant change
- Visual detection of statistically significant change in sample populations with the LINK radar chart
- Predict the root cause and source of a particle event long before outright USP failures arise

EXAMPLE – Detect Change and Correlate ML-derived morphology fingerprint to a stress mechanism



LINK PROCESS:

1 - ISOLATE AND MONITOR THE PROTEIN AGGREGATE POPULATION, USING MACHINE LEARNING MODELS

2 - VERIFY STATISTICALLY SIGNIFICANT CHANGE USING THE LINK MORPHOLOGICAL PARAMETER TABULAR SUMMARY

3 – USING A LINK RADAR CHART, REVIEW THE MORPHOLOGY FINGERPRINT AND CORRELATE CHANGE TO THE ASSOCIATED DEGRADATION MECHANISM

Condition	# Meas	Aspect Ratio >=10	Aspect Ratio >=10, CI(z,0.05)	Circ >=10	Circ >=10, CI(z,0.05)	Intensity Max >=10	Intensity Max >=10, CI(z,0.05)	Intensity Mean >=10	Intensity Mean >=10, CI(z,0.05)	Intensity Min >=10	Intensity Min >=10, CI(z,0.05)	Intensity STD >=10	Intensity STD >=10, CI(z,0.05)	Max Feret >=10	Max Feret >=10, CI(z,0.05)	ECD >=10	ECD >=10, CI(z,0.05)
A - Prescribed Storage	8	0.66	0.06	0.76	0.05	850.14	9.71	560.67	30.04	208.36	41.63	188.60	14.51	25.07	5.70	17.46	3.03
B - Accelerated Stress	9	0.61	0.04	0.66	0.04	852.80	9.29	701.13	18.02	460.95	31.32	95.88	11.39	25.57	2.31	15.68	0.93

A - Prescribed Storage

B - Accelerated Stress