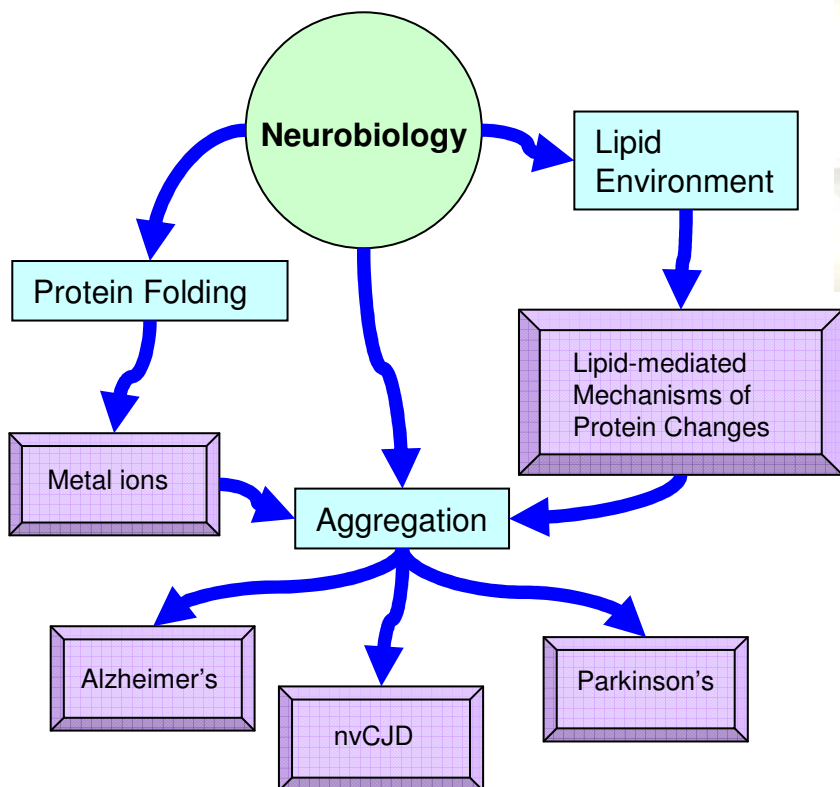


Applications of Dual Polarisation Interferometry in Neurobiology

Abnormal protein aggregation is associated with a number of neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Such changes are initiated by protein misfolding and play a pivotal role in the aetiology and pathogenesis of such disorders and have thus become major targets for drug discovery. Techniques to accurately measure protein misfolding therefore provide important insights into early changes in disease pathogenesis and as tools for the discovery of new medicines to slow, or even arrest, the progress of neurodegenerative change.

Dual Polarisation Interferometry (DPI) for the first time provides the ability to study the dynamic structurally-driven mechanisms behind protein misfolding and the earliest stages of aggregate nucleation and oligomerisation in neurodegenerative diseases.

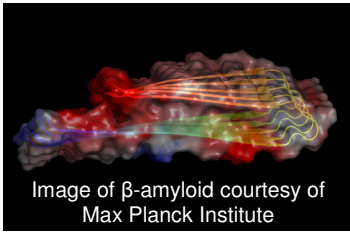


Automated biophysical screening for mechanisms of inhibition

- Intuitive icon driven assay scripting
- Remote operation and monitoring
- Candidate ranking in terms of kinetics,
- Affinity and structural relevance

DPI, embodied in the **AnaLight® 4D** from Farfield measures the size and density of protein assemblies at sub-atomic resolution. It can discriminate different folded states and monitor the transition between different isoforms (e.g. PrP and PrP^{Sc}) in real-time. Peptide association to and oligomerisation from lipid surfaces under differing conditions can be characterised, as can membrane disruption by insertion and micellisation. Metal-ion binding to proteins, their affinities, kinetics, stoichiometry, and associated conformational changes can be quantified. Also the inhibition of all of such processes by small molecule drug candidates can be modelled.

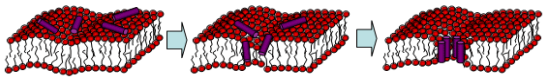
Insights into the molecular mechanisms of protein folding and aggregation associated with neurodegenerative diseases



Aggregation, nucleation & early-stage oligomerisation

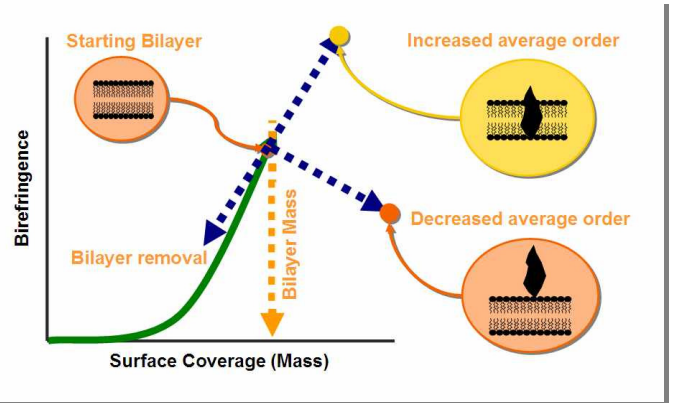
- Nucleation surfaces
- Mutant and wild type studies of aggregation mechanisms and their inhibition
- Protofibril detection and discrimination

Lipid-mediated interactions



Adsorption Absorption Micelle Formation

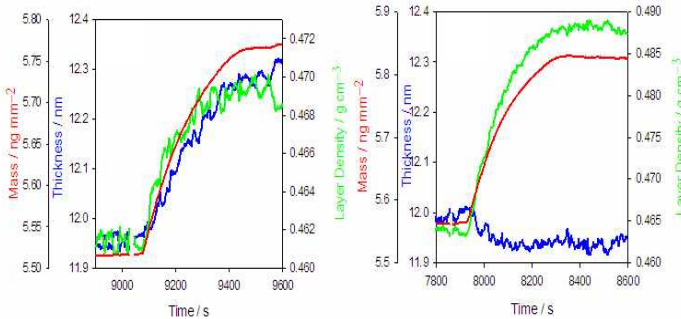
- Simple bilayer construction
- Fibril nucleation and growth
- Peptide adsorption and absorption



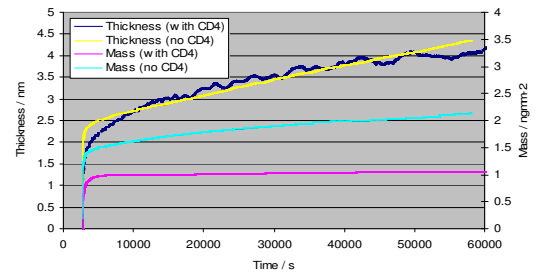
Monitor folding / misfolding transitions & aggregation on lipid surfaces

Monitor folding / misfolding & isoform transitions

- Environmental influences on folding
- Discriminate different isoforms

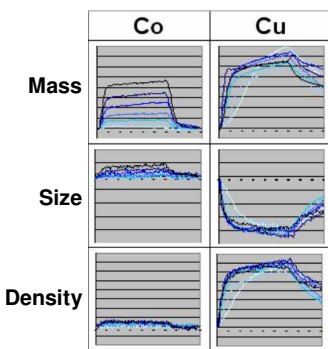


Clear discrimination between PrP and PrP^{Sc} isoforms



Mechanisms of Inhibition by CD4

- Inhibition of growth or nucleation
- Initiation, propagation or reversal of fibril growth
- Mechanisms of nucleation
- Mutation or genotype influence on mechanisms



Metal-ion peptide interaction & folding studies

- Concentration-dependent refolding
- Study effects of pH, temperature, ionic strength
- Affinities and kinetic responses
- Stoichiometry of interaction

Cu and Co binding to PrP

Note: Structural change only with Cu

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