Modelling Liquid-Liquid Phase Separation

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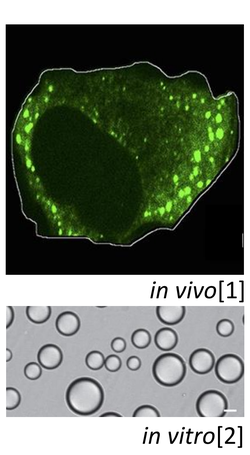
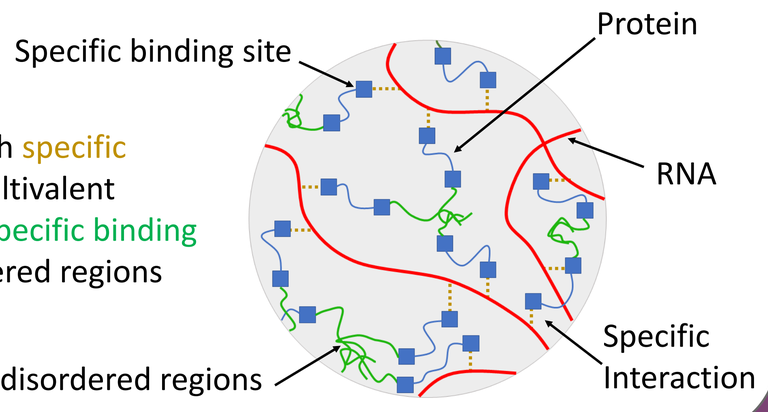
Liquid-Liquid Phase Separation in Cells



in vivo[1]

in vitro[2]

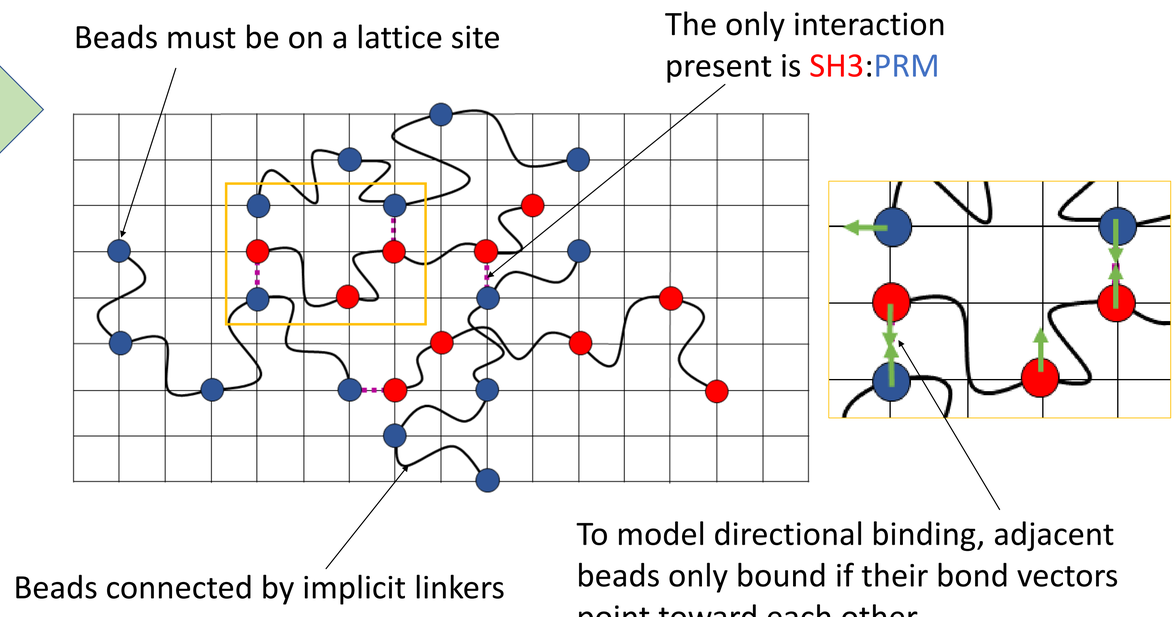
- Membraneless organelles, consisting of RNA and proteins, found in cells
- Many have liquid like properties whilst still being distinct from the cytoplasm, therefore their formation is described as liquid-liquid phase separation
- Solidified compartments associated with degenerative disease



Phase separation due to both specific protein binding between multivalent Proteins and RNA and non-specific binding between intrinsically disordered regions (IDRs)

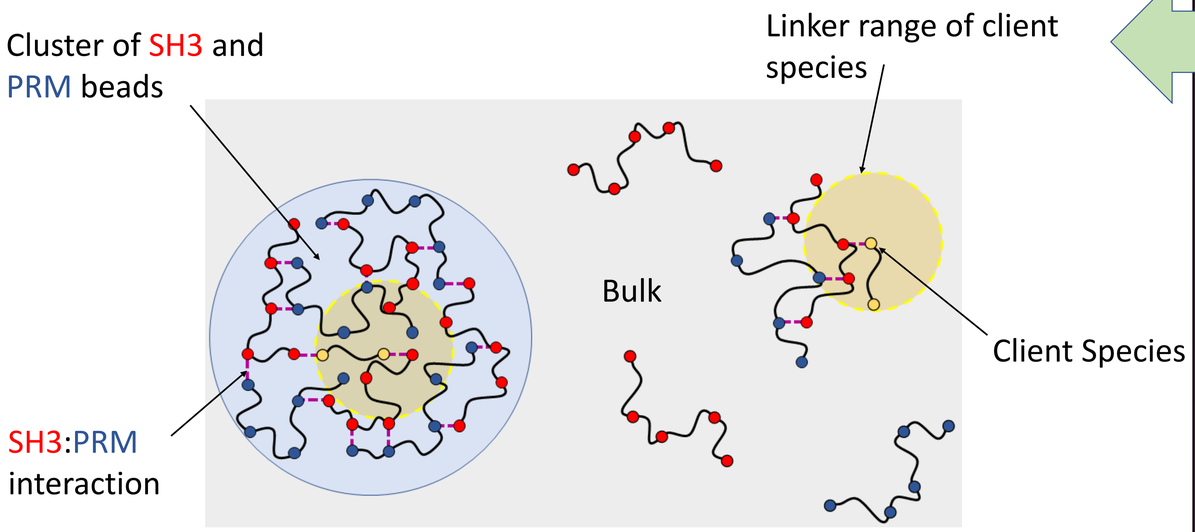
Model

In vitro system too expensive to study so simple experimental model consisting of segments of two multivalent proteins (SH3 and PRM) was used as inspiration [2]. A 2D representation of the 3D model system of two protein types is shown below. Configurational space is explored through Monte Carlo moves



Client Scaffold Model

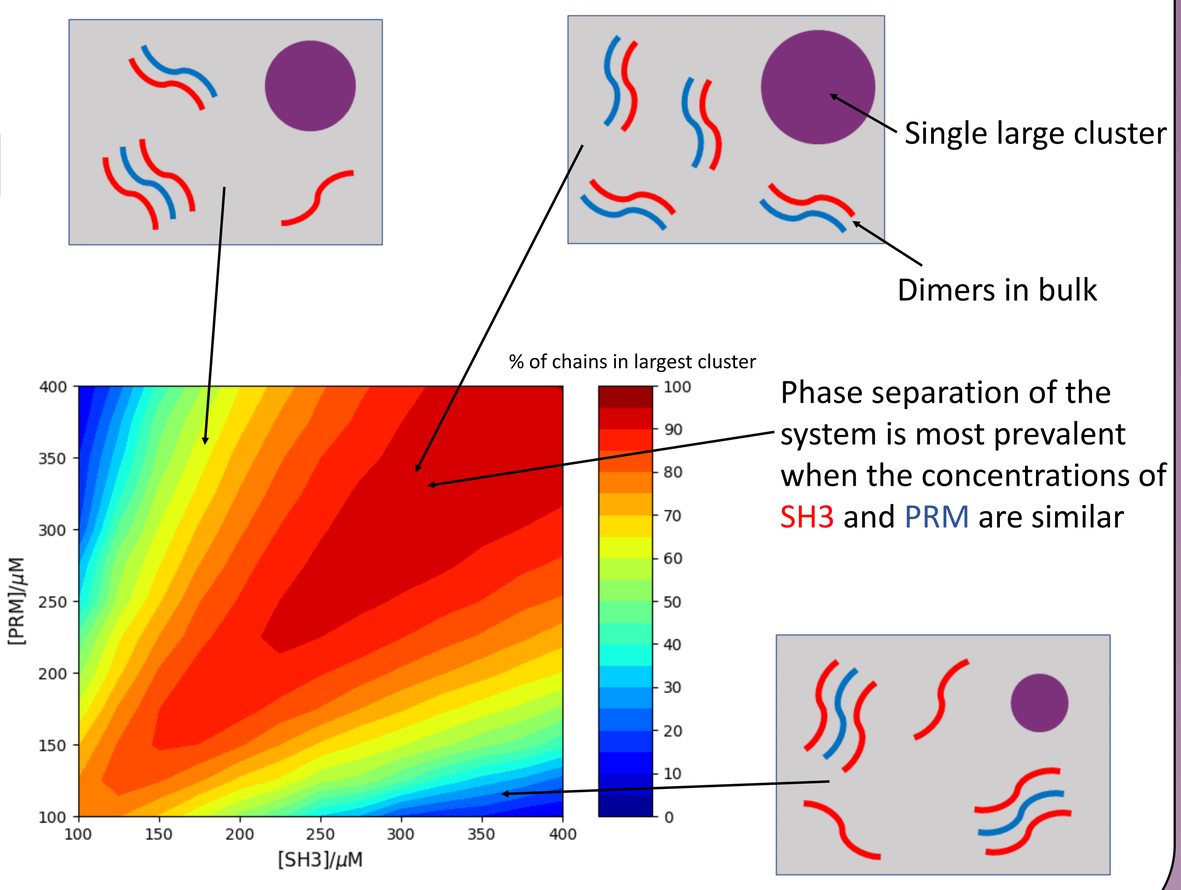
- Proposed that certain proteins and RNA form ‘scaffold’ structures that ‘client’ proteins can then bind to. The scaffold gives the membraneless organelle (granule) its structure whist allowing rapid movement of client thought droplet. [3]
- Explains why many of the proteins often found in membraneless organelles are not required for their formation
- It also gives mechanism for sequestering non-essential enzymes and proteins during stress, which is believed to be one of the key functions stress granules [3]



- Client species are preferentially recruited to the cluster compared to the bulk, in qualitative agreement with experimental work [4]
- We believe this is due to the greater availability of free scaffold sites (within client linker range) in the cluster

Simulated Phase Separation

- Generally a single large cluster forms with the surrounding bulk being made up of monomers, dimers and trimers of proteins
- Phase separation propensity increases with protein valency and interaction strength, in agreement with experimental results [2]



Future Work

Further study into the behaviour of clients in the system will give us greater insight into why clients with a high valency are non-monotonically drawn preferentially to the cluster as opposed to the bulk solution

Investigations into the fundamental protein properties that allow granule formation and granule property modification will be carried out using our adapted model

Simulation of more complex chains, where the interaction strengths between different beads varies, in order to more realistically represent proteins that are observed in membraneless organelles found within cells

References

[1] Wheeler *et al*., eLife, 2016, **5**, 5
[2] Li *et al*., Nature, 2012**, 483**, 336-340
[3] Boeynaems *et al*., Trends in Cell Biology, 2018, **28**, 420-435
[4] Banani *et al*., Cell, 2016, **166**, 651–663