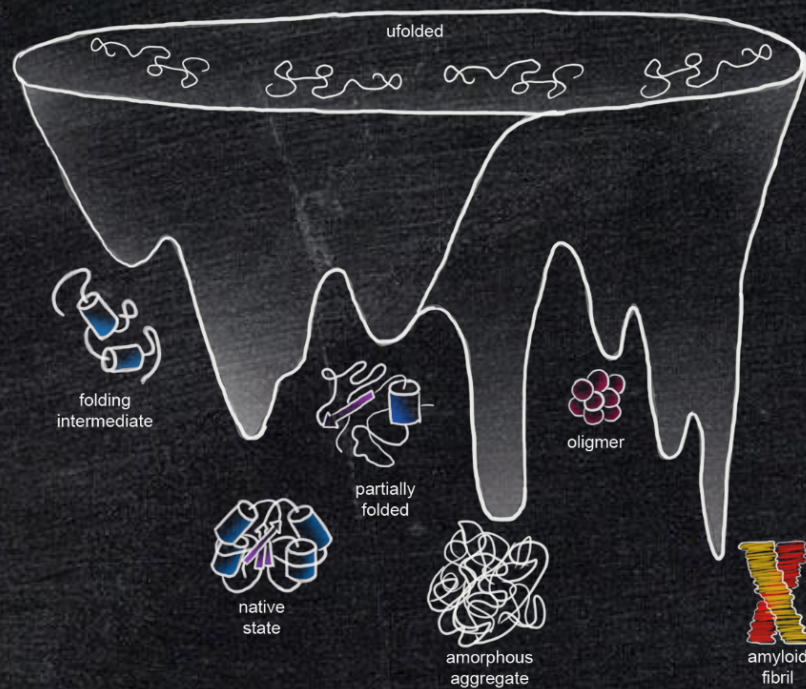


Physiological consequences of protein aggregation

Liliana Malinovska
18.12.2017

The aggregation propensity of a protein is determined by different factors



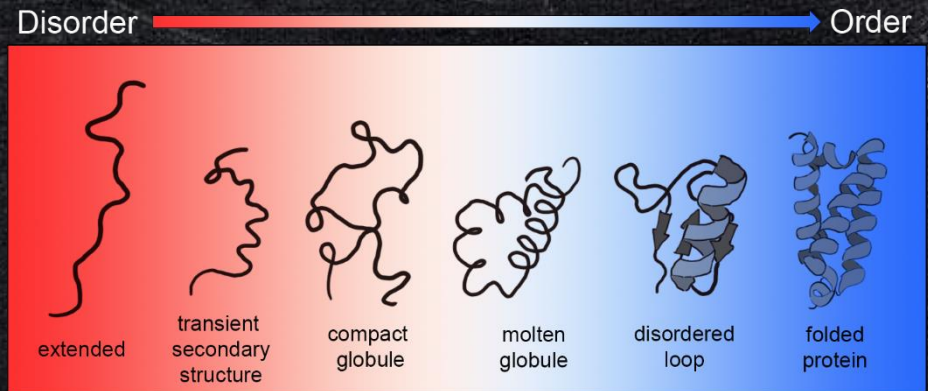
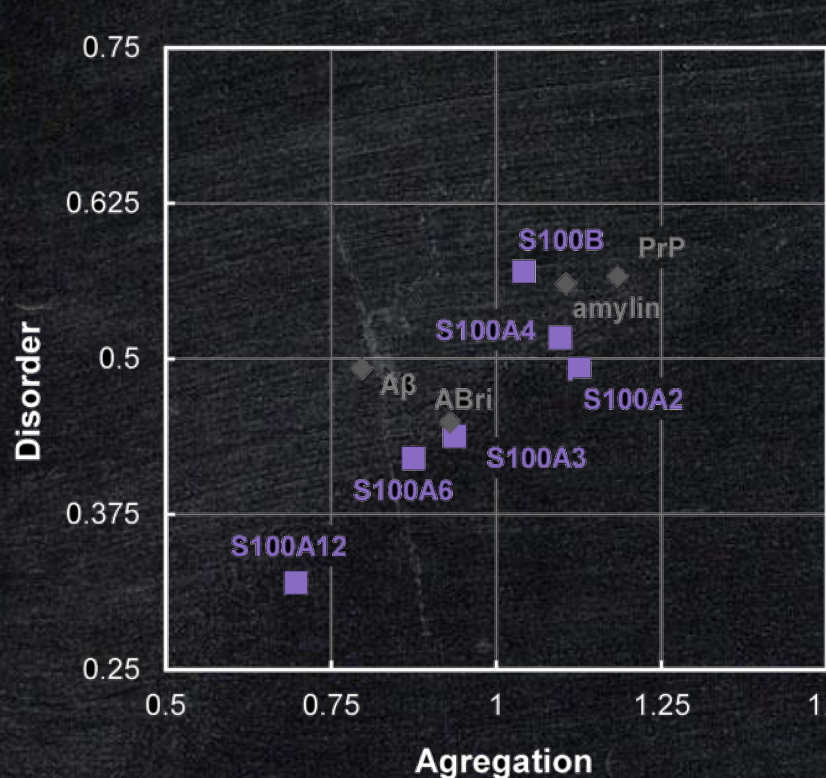
Extrinsic factors

- interactions with cellular components
- physico-chemical properties of the environment

Intrinsic factors

- charge
- hydrophobicity
- polar residues
- secondary structure preferences

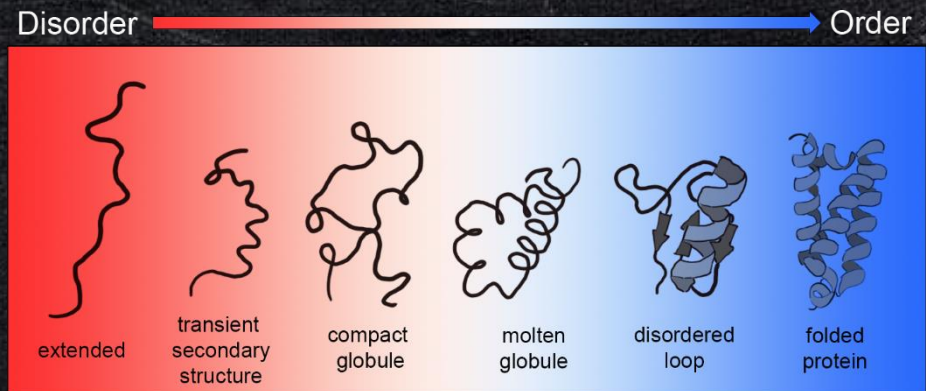
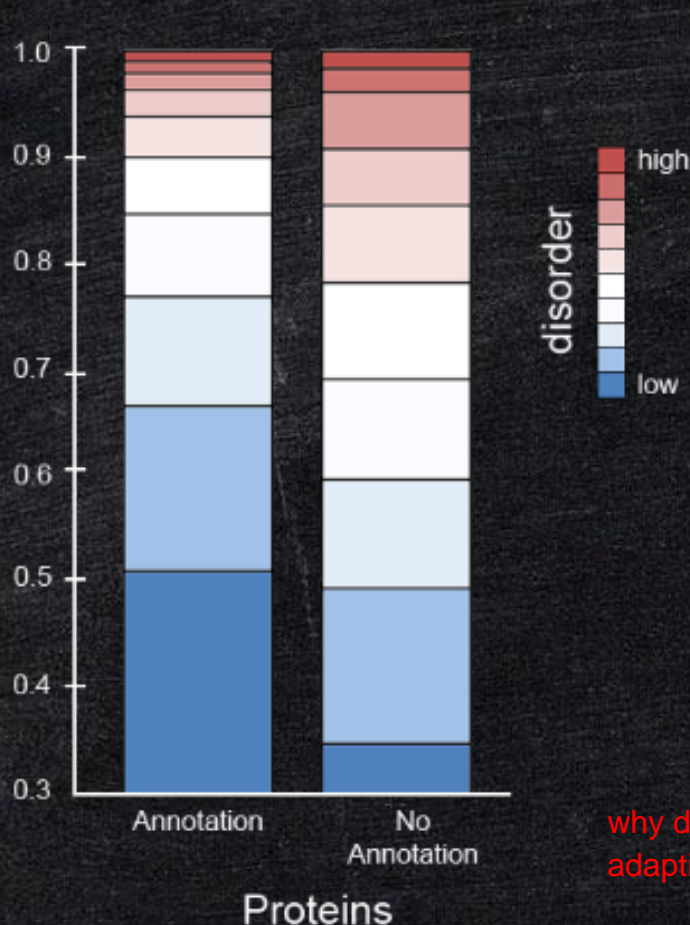
Disorder promotes aggregation propensity



Intrinsic factors

- charge
- hydrophobicity
- polar residues
- secondary structure preferences

Over 40% of any eukaryotic proteome contains disorderd regions (IDR)



Intrinsic factors

- charge
- hydrophobicity
- polar residues
- secondary structure preferences

why do organism tolerate a high number of aggreation prone porteins:
adapional advantage; another level of protein regulation.

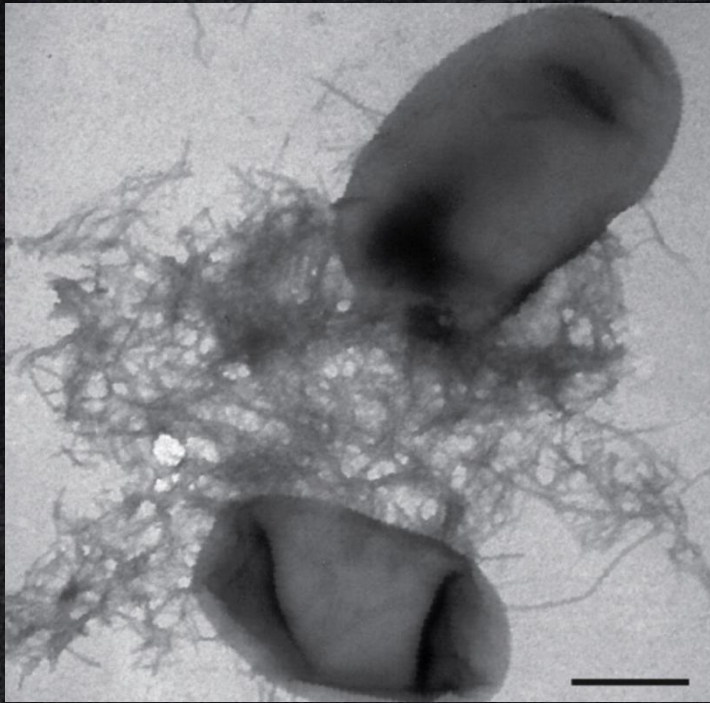
protein stability is tightly maintained and aggregation is controlled for
aggregates can exert function in the cell
IDRs exert additional functions in the cell

Functional aggregates in different organisms

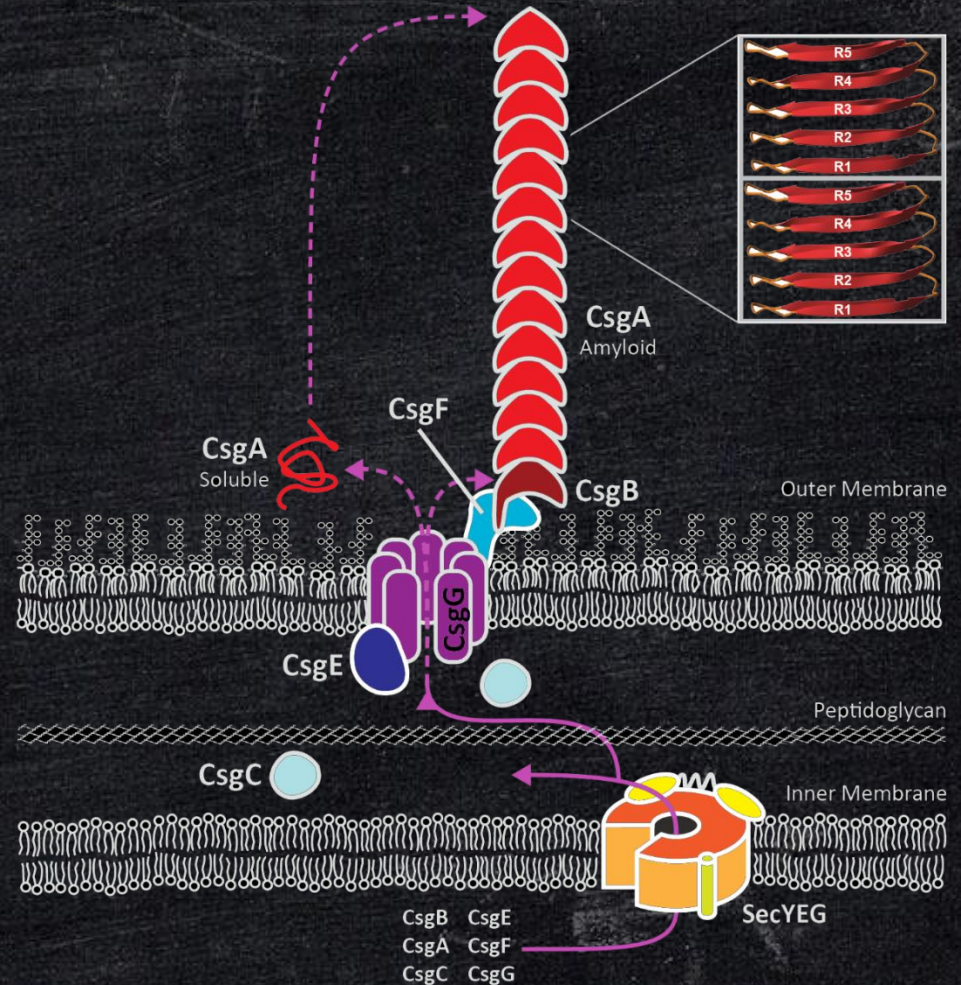
	Amyloid	Function
Bacteria	Curli	Component of extracellular matrix involved in adhesion, aggregation, invasion and biofilm formation
	Microcin E492	Bacteriocin, membrane pore-forming peptide, amyloid form is inactive
	Chaplins	Assisting aerial hyphae formation in Streptomyces
	Harpins	Secreted by plant pathogenic bacteria, destabilize plant membranes, induce cell death
Fungi	Sup35a	Translation termination, prion form is inactive
	Ure2pa	Regulatory function in the nitrogen catabolite repression pathway, prion form inactive
	Rnq1pa	Enhances the inducibility of other prions
	Swi1pa	Chromatin remodeling factor, prion form inactive
	Mot3a	Transcriptional regulator of cell wall remodeling genes, prion form is inactive
	Hydrophobins	Surface attachment and aerial hyphae formation
	HET-s	Heterokaryon incompatibility
	Whi3	
A	CPEB	Cytoplasmic polyadenylation element-binding protein regulates mRNA translation
D	Orb2	Long-term plasticity of neurons
Human	Pmel17	Templates the synthesis of melanin
	Peptide hormones	Sorting, storage, and release of diverse hormones
	RIP1/RIP3	mediate the tumor necrosis factor-induced programmed cell necrosis
	prostatic acid phosphatase and semenogelins	exploited by the HIV virus for infection

Functional aggregates in different organisms

E. coli

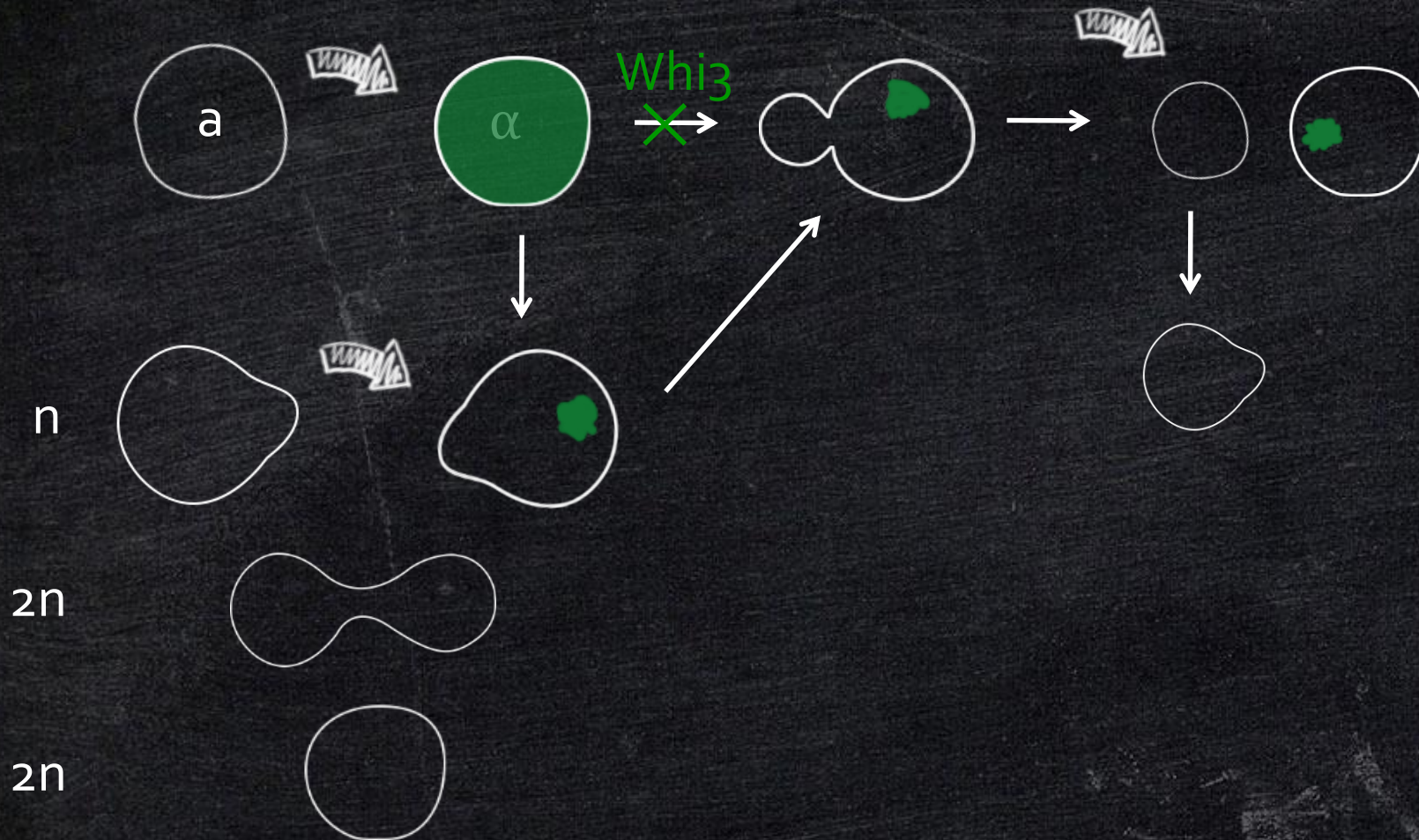


Curli are the major protein component of *E. coli* biofilms



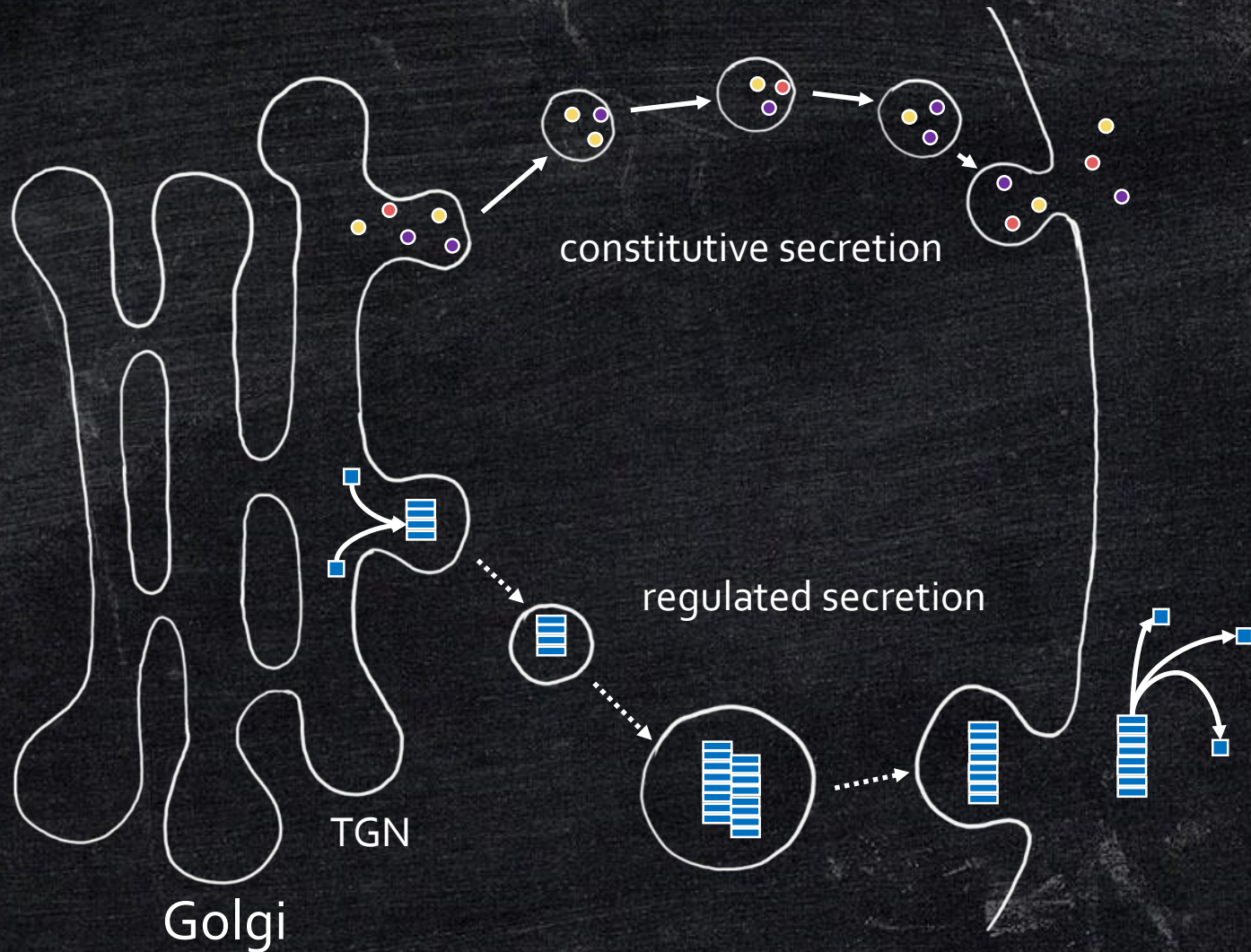
Functional aggregates in different organisms

S. cerevisiae



Functional aggregates in different organisms

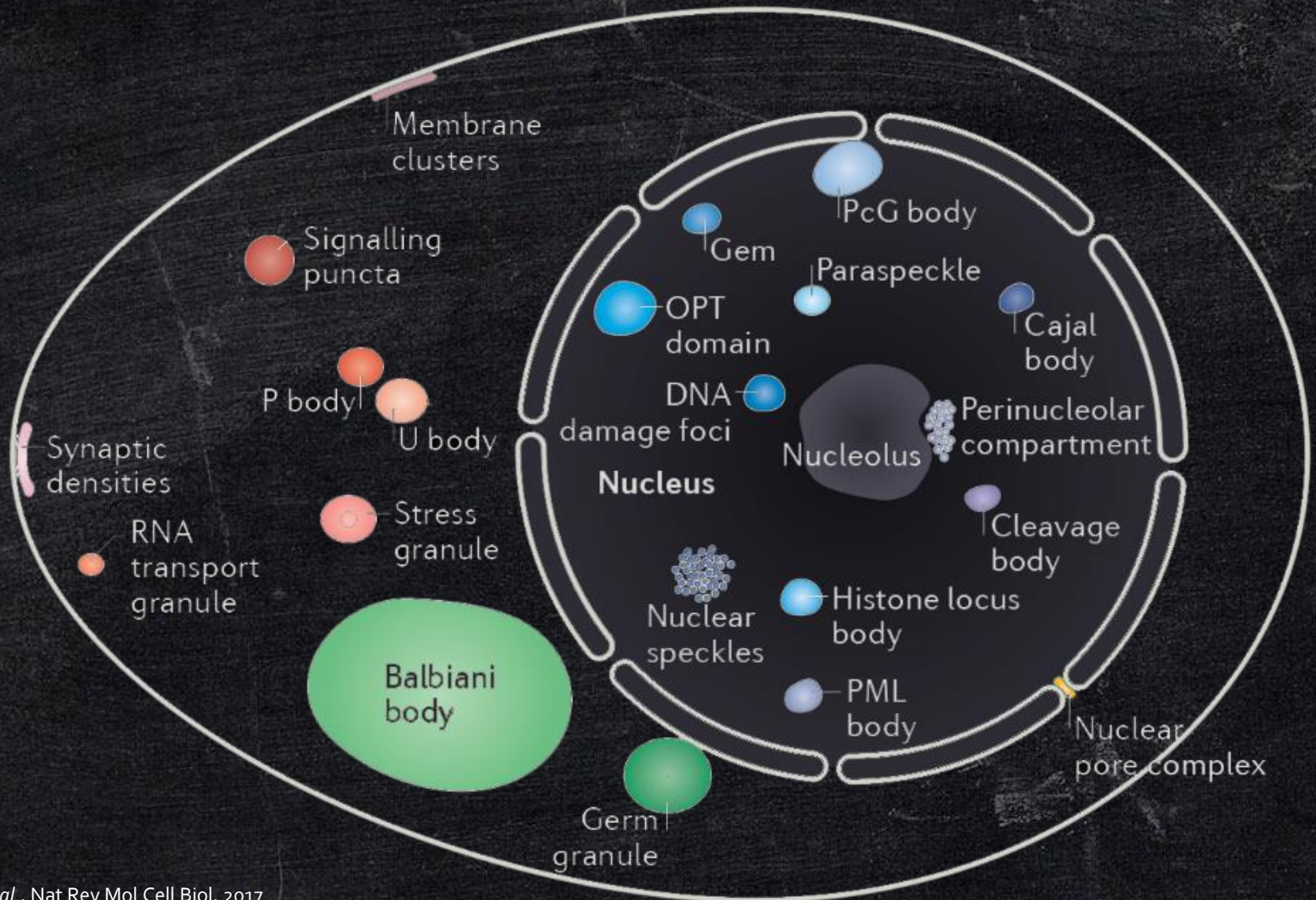
H. sapiens



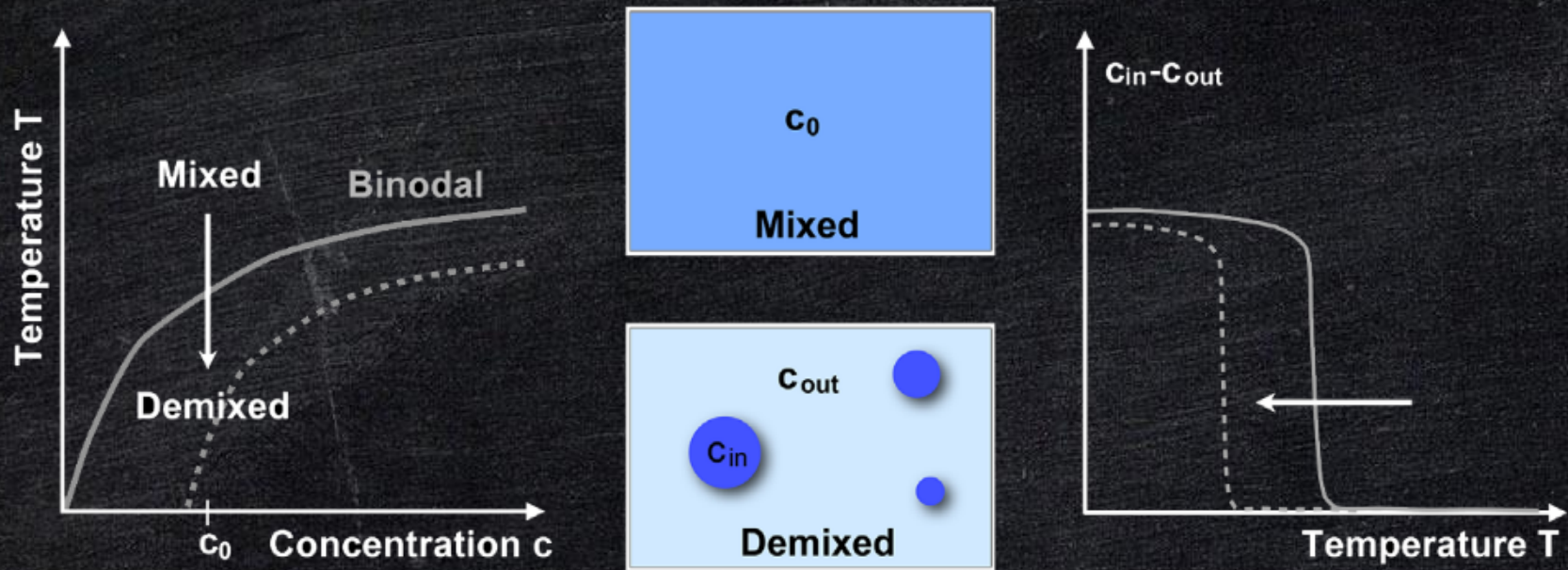
Functional aggregates in different organisms

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IDPs participate in the self-assembly of membrane-less organelles

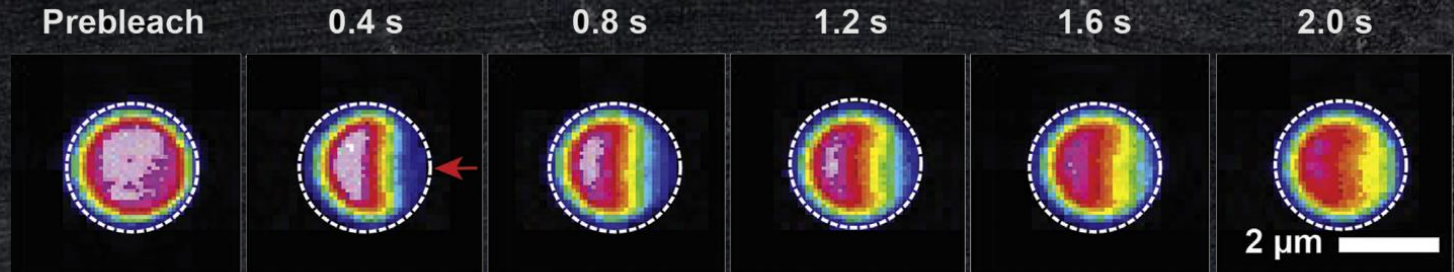


Liquid-liquid phase transitions are sensitive to changes in physico-chemical conditions

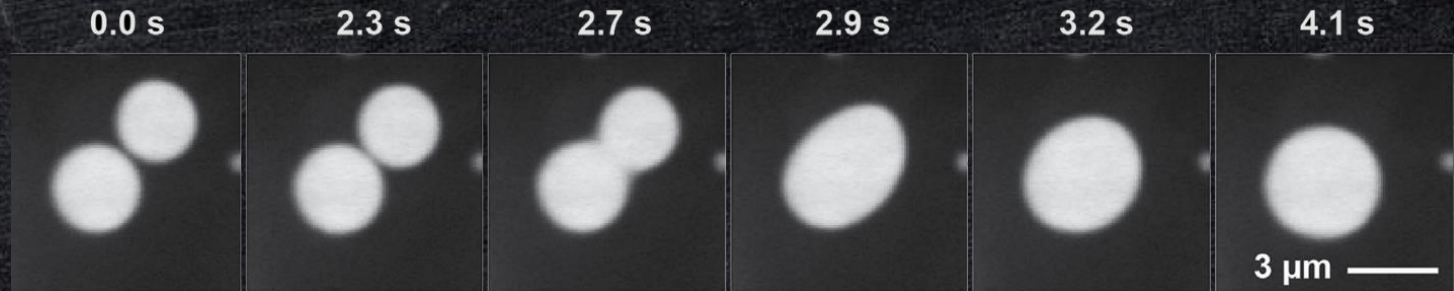


IDPs form dynamic liquid-like assemblies that can solidify over time

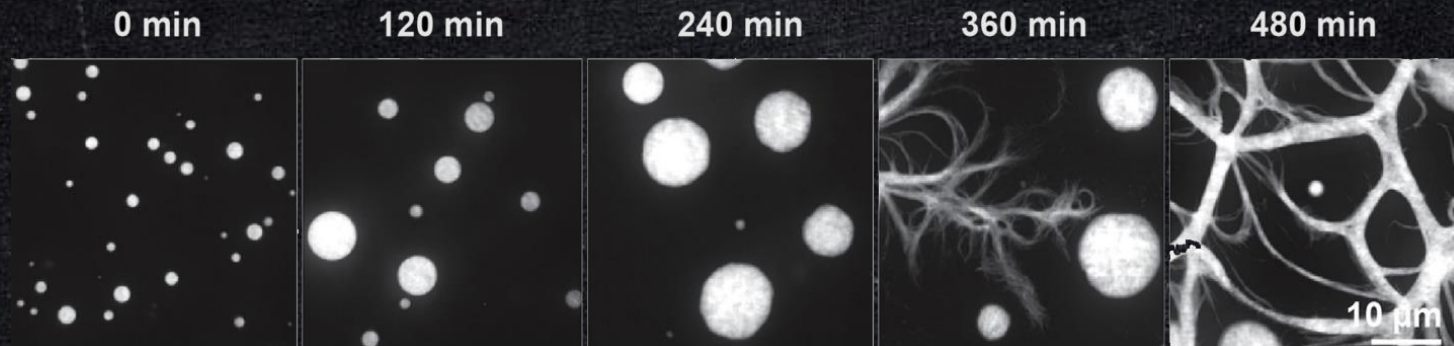
quick
recovery



fusion

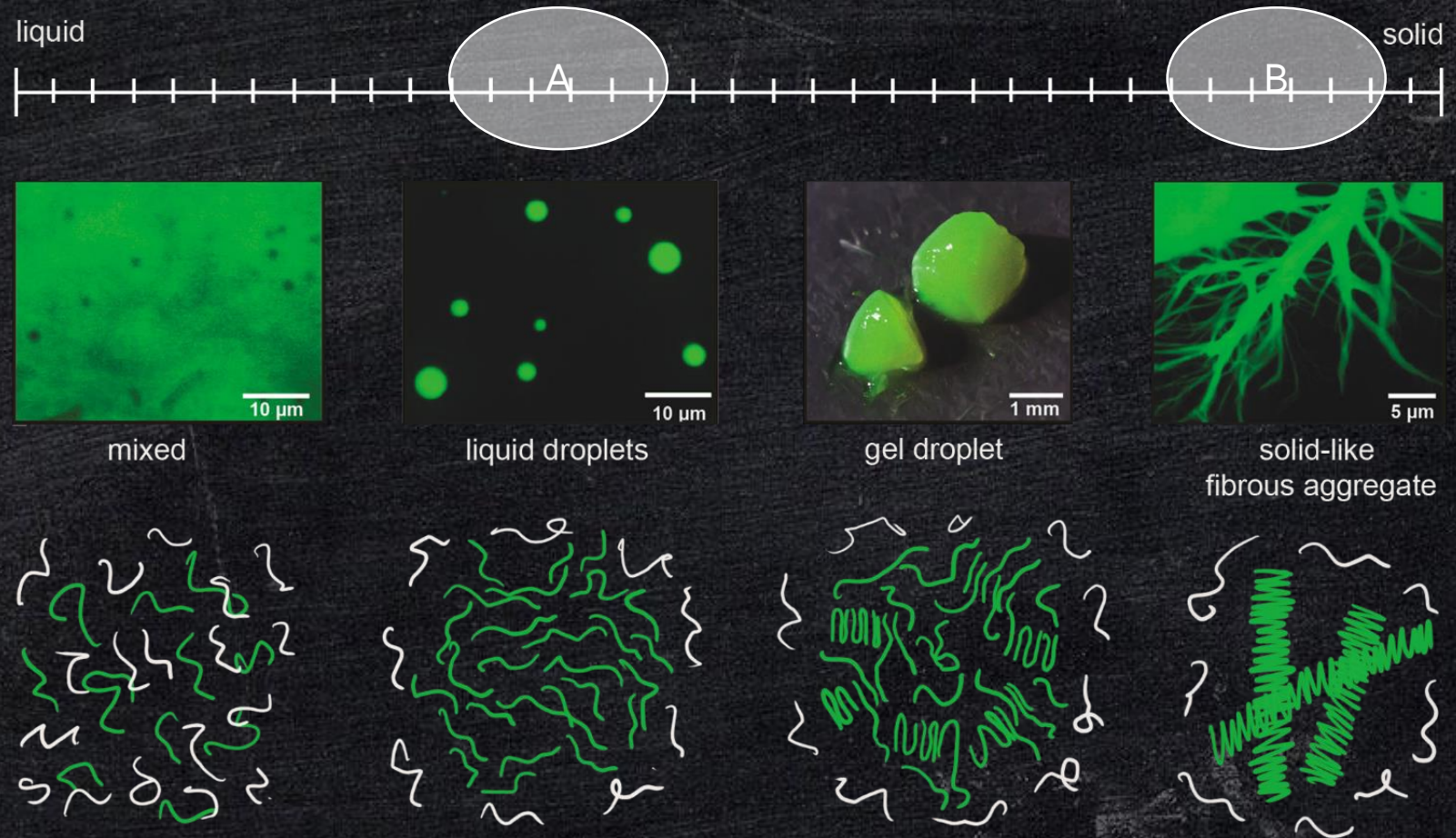


aging

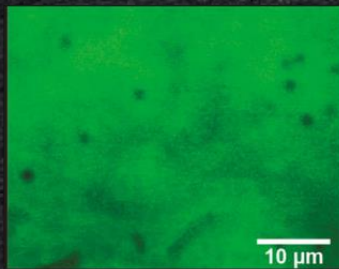


these droplets can age

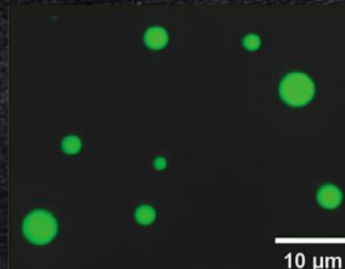
IDPs can access different phase-separated material states



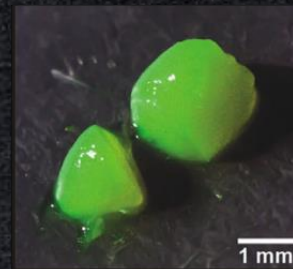
Pathological protein aggregation are caused by aberrant phase transitions



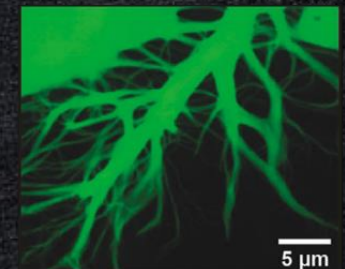
mixed



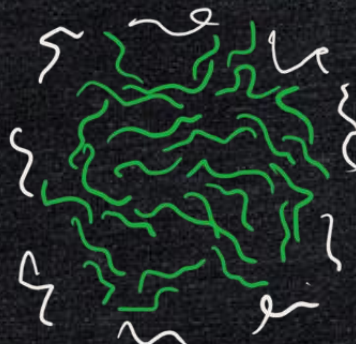
liquid droplets



gel droplet



solid-like
fibrous aggregate

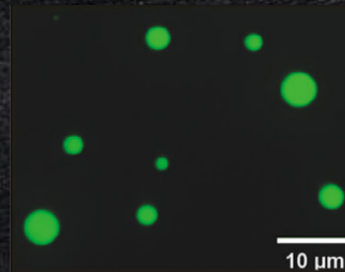


Each protein has a preferred location on the phase continuum

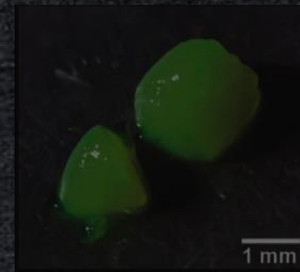
concentrate unnecessary biochemical reactions, when for example mRNA has to be collected, such that other rescuing mRNA can be transcribed and save the cell (during a stress response) - they are stored in P bodies



mixed



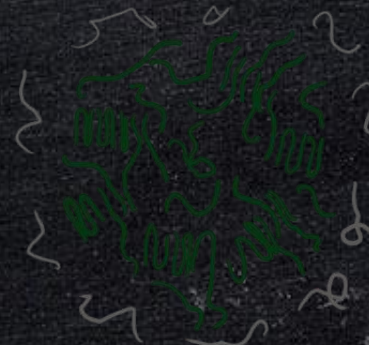
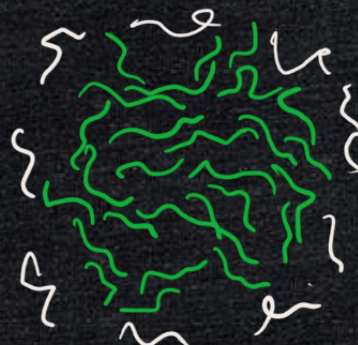
liquid droplets



gel droplet



solid-like
fibrous aggregate



Each protein has a preferred location on the phase continuum

storage + inactivation of proteins (like hormones e.g.) when protein needed again then simply released instead of newly transcribed and translated



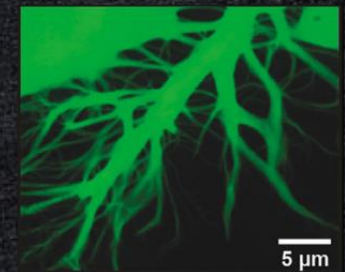
mixed



liquid droplets



gel droplet



solid-like
fibrous aggregate

