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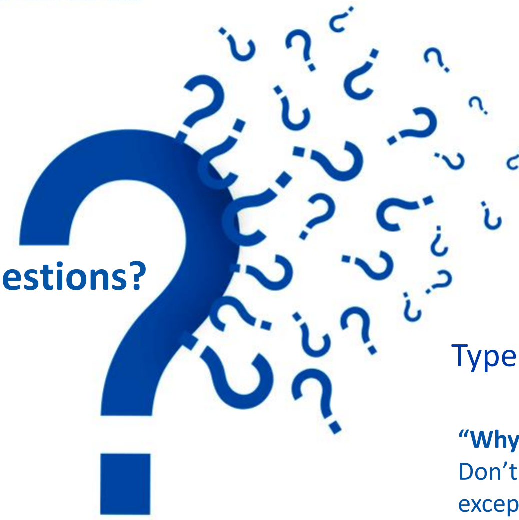

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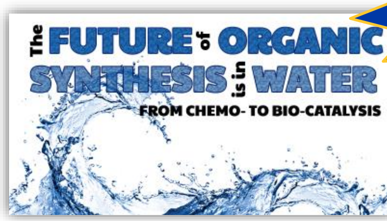

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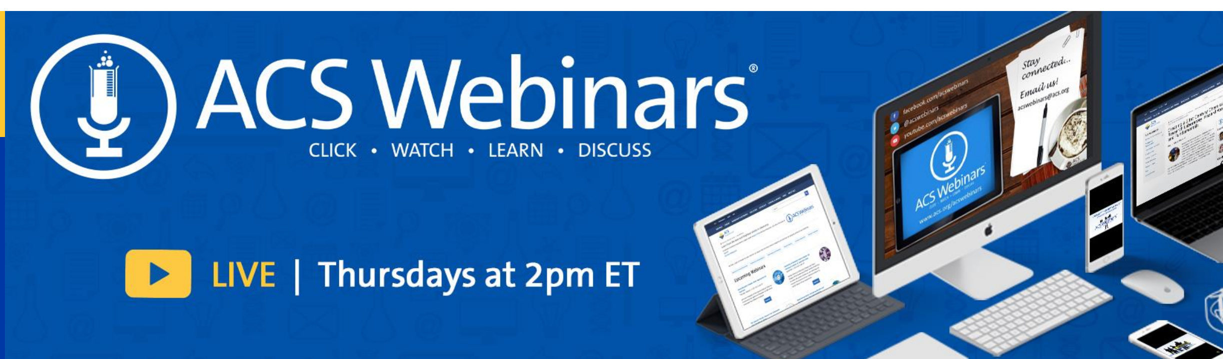

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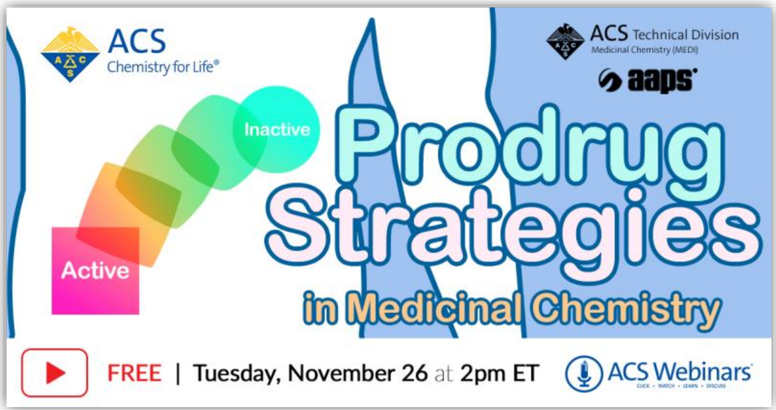

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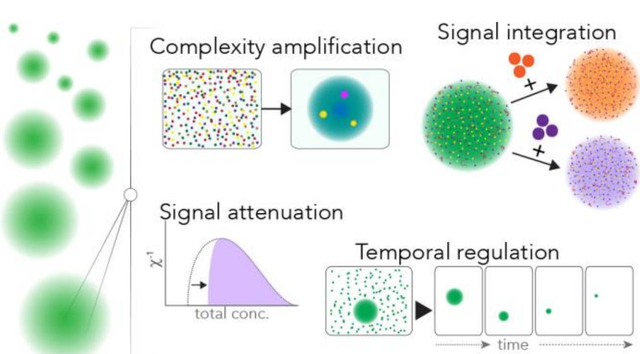
Functional Implications of Intracellular Phase Transitions

Alex S. Holehouse* and Rohit V. Pappu*

Cite this: *Biochemistry* 2018, 57, 17, 2415-2423
Publication Date: January 11, 2018
https://doi.org/10.1021/acs.biochem.7b01136



Abstract

Intracellular environments are heterogeneous milieus comprised of macromolecules, osmolytes, and a range of assemblies that include membrane-bound organelles and membraneless biomolecular condensates. The latter are nonstoichiometric assemblies of protein and RNA molecules. They represent distinct phases and form via intracellular phase transitions. Here, we present insights from recent studies and provide a perspective on how phase transitions that lead to biomolecular condensates might contribute to cellular functions.

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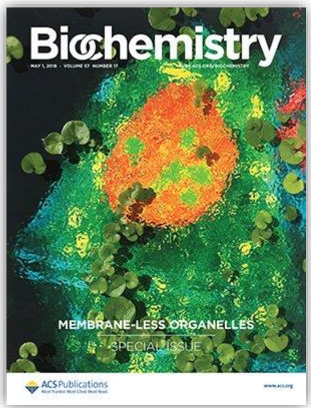

May 1, 2018, Volume 57, Issue 17, Pages 2403-2564

In this **Special Issue**, *Biochemistry* explores the exciting interdisciplinary field of **Membraneless Organelles**.

All biological systems use location as a determinant of function at different scales, ranging from whole organisms to atoms within biomolecules. How to get key actors to the right locations at the right time and how to keep them there until they are no longer needed are key logistical challenges cells must perfect in order to thrive. Cells use different strategies to regulate localization; the best known is compartmentalization into traditional membrane-bound organelles such as the nucleus, endoplasmic reticulum, or Golgi complex. In the past few years, it has been proposed that membraneless organelles exist and complement larger classical organelles.

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13

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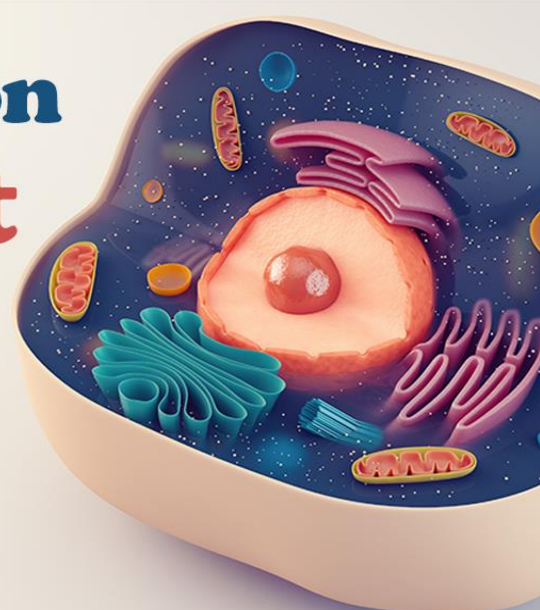
Phase Separation of Multivalent Proteins

Recent Findings and New Frontiers



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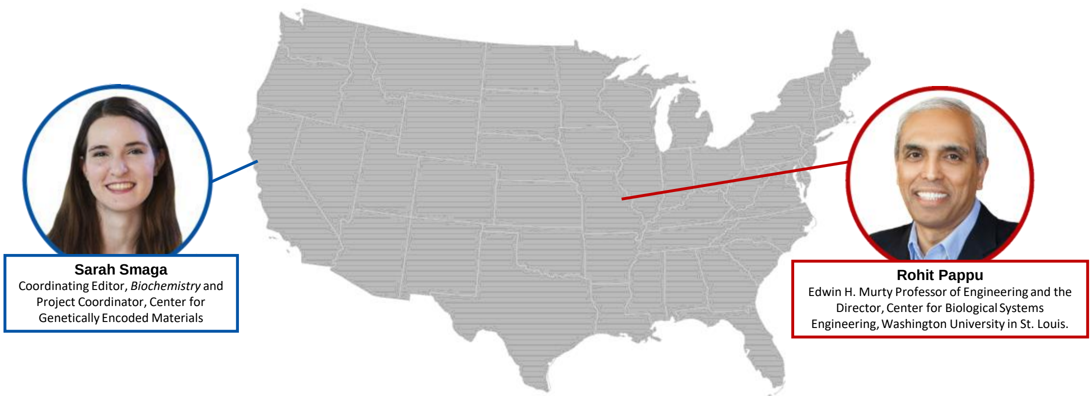

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Phase Separation of Multivalent Proteins

Rohit Pappu

Washington University in St. Louis
James McKelvey School of Engineering

Pappu Lab

Washington University in St. Louis
CSELS
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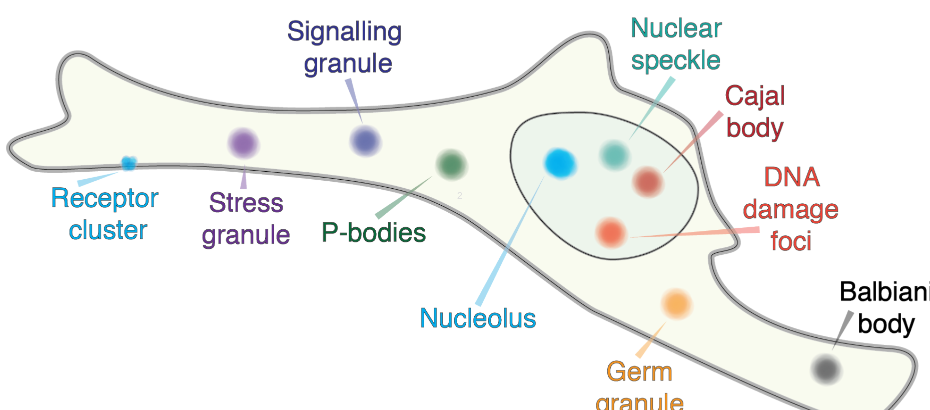
Membraneless organelles enable spatial and temporal organization of cellular matter



Banani,…,Hyman, Rosen, 2017, Nature Rev. Mol. Cell Biol.
Shin, Brangwynne, 2017, Science

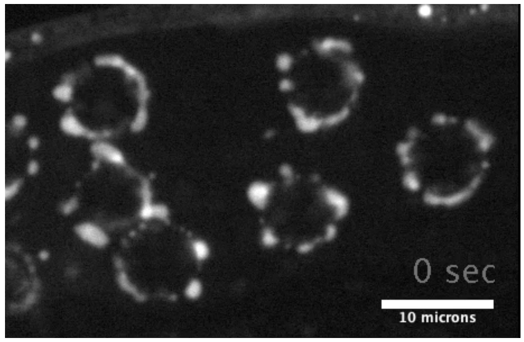
Membraneless organelles are also known as *biomolecular condensates* because they concentrate biomolecules via processes that resemble the condensation of liquids

Banani,…,Hyman, Rosen, 2017, Nature Rev. Mol. Cell Biol.
Shin, Brangwynne, 2017, Science

***Nucleoli* - where ribosomal subunits are assembled - are examples of biomolecular condensates**

Feric et al., Cell (2016)

Membraneless organelles have the characteristics of dense liquids



Example of P-granules

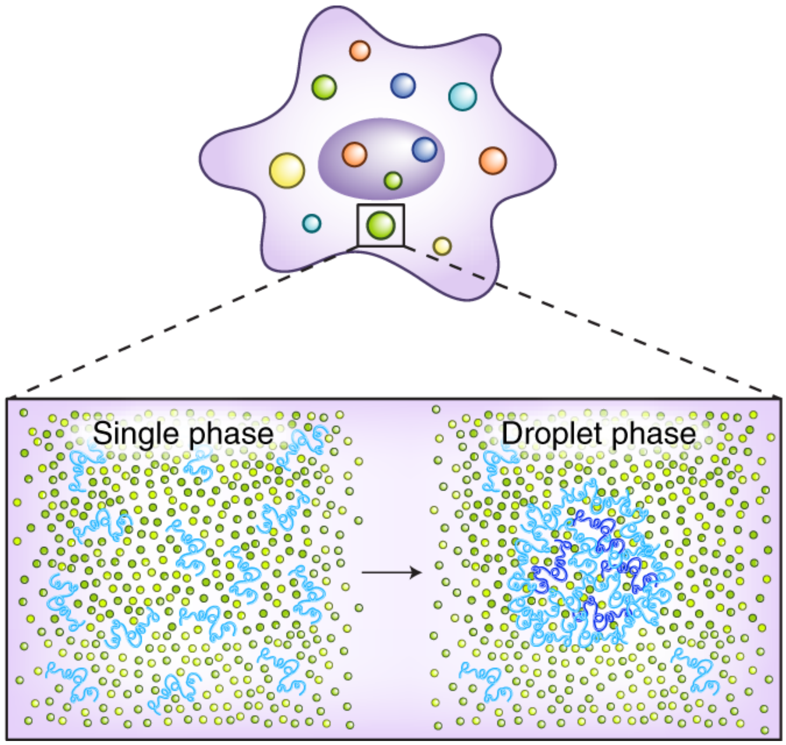
Brangwynne *et al. Science* (2009)

5

Biomolecular condensates are proposed to form via:

Phase separation of multivalent protein and RNA molecules

Jülicher and Hyman, 2014, *Annu. Rev. Cell Biol*.
Banani,…,Hyman, Rosen, 2017, *Nature Rev. Mol. Cell Biol*.
Shin, Brangwynne, 2017, *Science*



Tang, Nature Methods (2018)

We seek an appropriate theoretical framework for describing phase transitions of multivalent protein & RNA molecules?

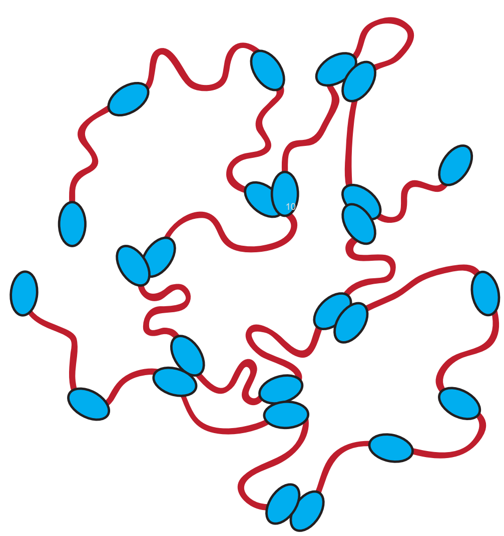
Fuxreiter, Wu, 2016, *Cell*
Lin, Forman-Kay, Chain, 2018, *Biochemistry*
Choi, Holehouse, Pappu, 2020, *Annu. Rev. Biophys.*

Multivalent protein and RNA molecules are biological instantiations of ***associative polymers***

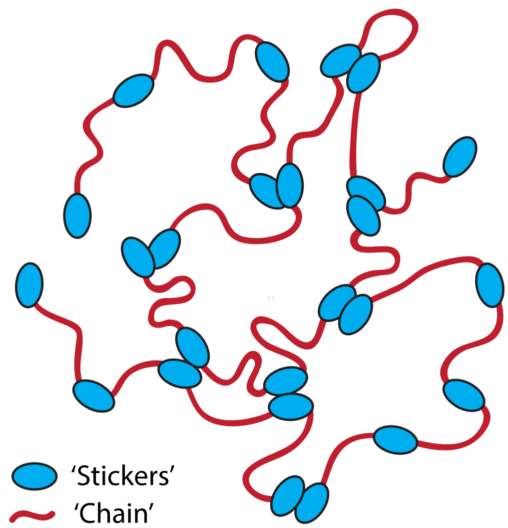
Semenov & Rubinstein, *Macromolecules* (1998)

Associative Polymers

Stickers *interspersed by* Spacers



Stickers *vs.* Spacers



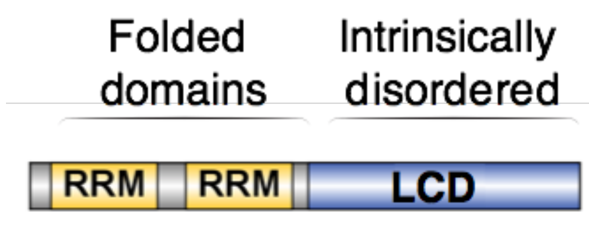
Stickers interact preferentially with one another **to form physical crosslinks**

How do we tell *stickers* from *spacers*?

We shall first consider disordered low-complexity domains

GSMASASSSQRGRSGSGNFGGGRGGGFGGNDNFGRGGNFSGRGGFG
GSRGGGGYGGSGDGYNGFGNDGSNFGGGGSYNDFGNYNNQSSNFGP
MKGGNFGGRSSGPYGGGGQYFAKPRNQGGYGGSSSSSSYGSGRRF

hnRNP-A1



RRM: RNA Recognition Motif
LCD: Low Complexity Domain

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We leverage *thermodynamic principles* of phase separation

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Phase Separation is a *density transition* described by a coexistence curve

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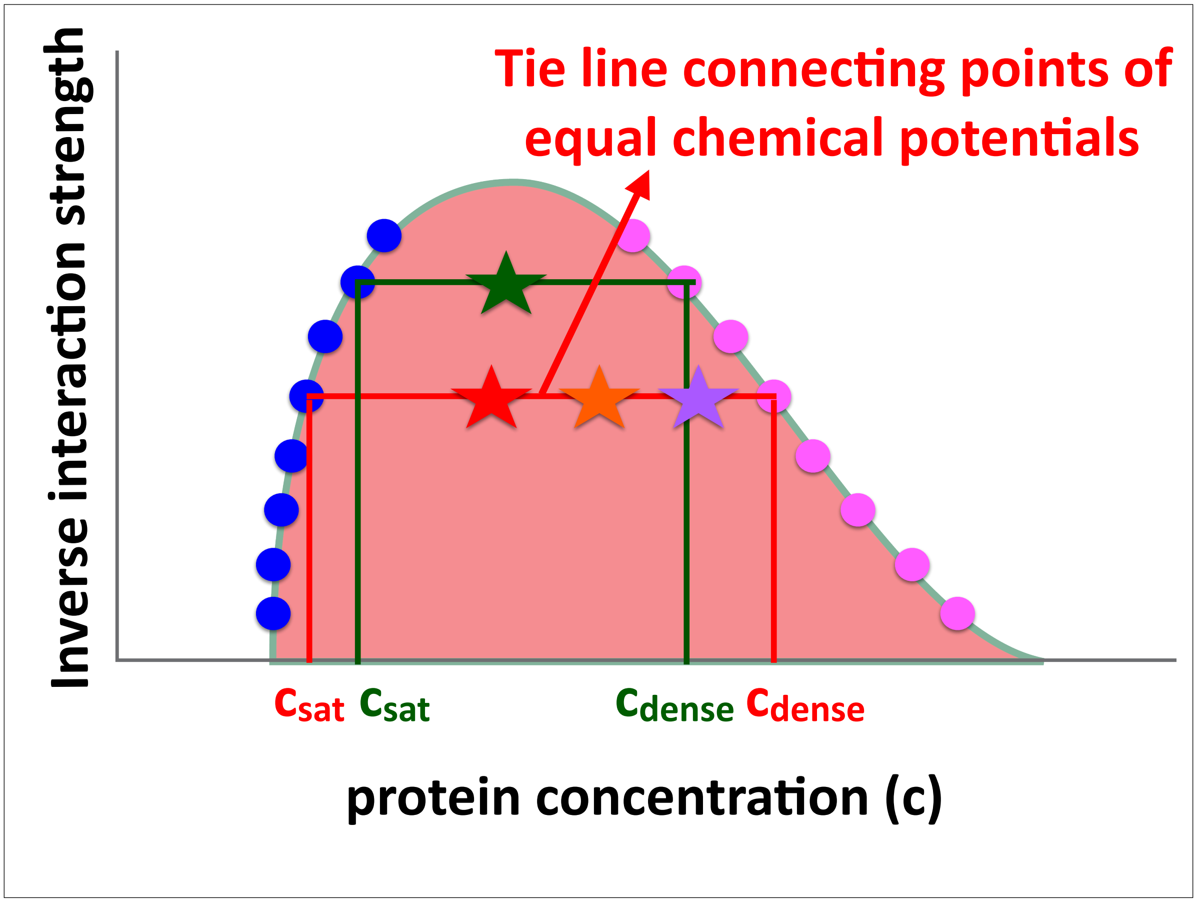
We shall first orient ourselves using a pseudo-binary (protein + "solvent") mixture as an example

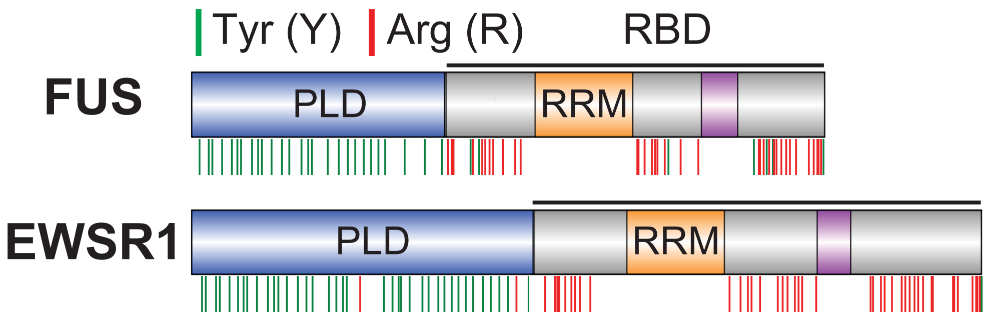
16

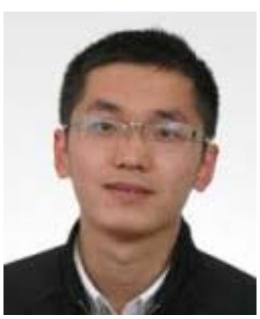


Zeroth-order criteria for delineating *stickers* vs. *spacers*

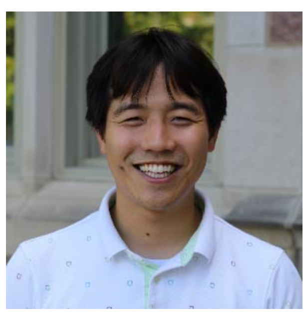
Changes to *stickers* will change c_{sat} whereas changes to spacers will change material properties and the cooperativity of phase separation

Demonstration using proteins with disordered prion-like domains (PLDs) and RNA binding domains (RBDs)





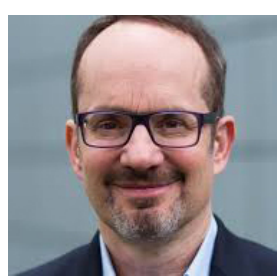
Jie Wang



Jeong-Mo Choi

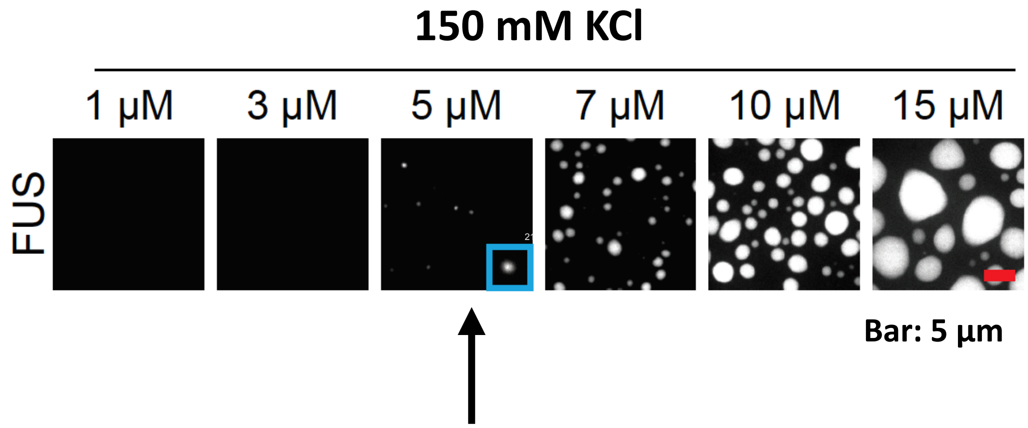
Alex Holehouse

Simon Alberti



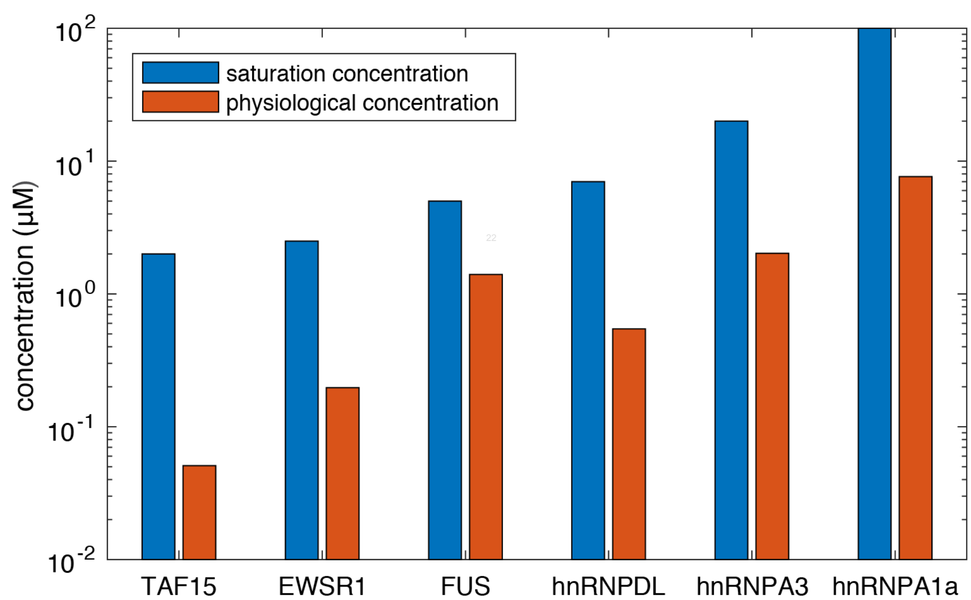
Tony Hyman

In vitro Phase separation of FUS



Saturation concentration c_{sat}

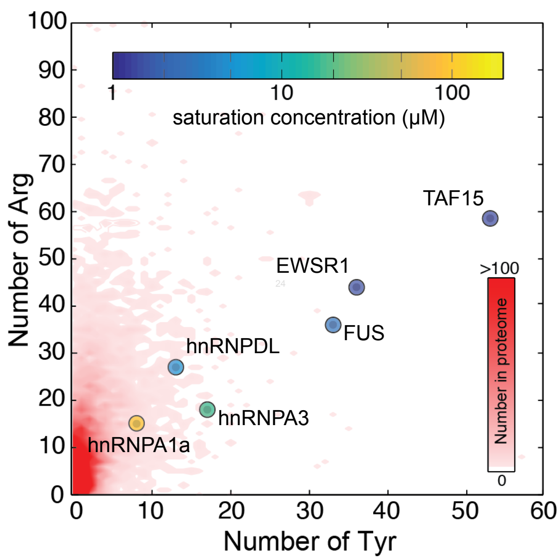
c_{sat} values of disordered FUS family proteins are sequence-specific



Determinants of sequence-specific c_{sat} values?

23

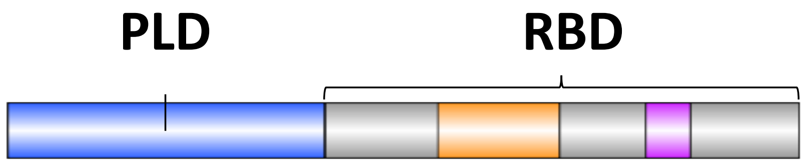
Large numbers of Tyr in PLD *and* Arg in RBD

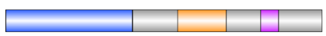


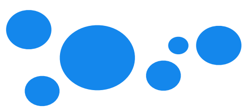
High frequencies of Tyr *and* Arg are uncommon

24

Phase separation requires Tyr (Y) *and* Arg (R)

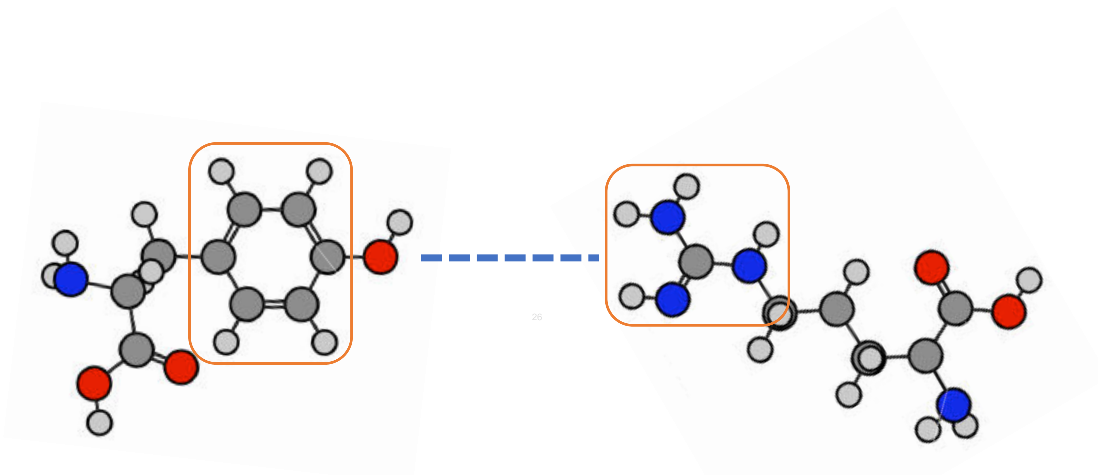




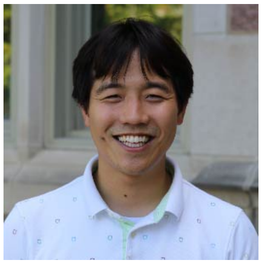


c_{sat} = 2 μM
(75 mM KCl)

Amino Acid Stickers

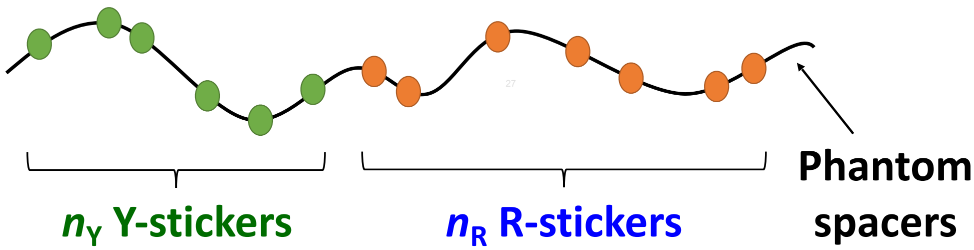


Tyrosine **Arginine**



Jeong-Mo Choi

Mean-field stickers and spacers model

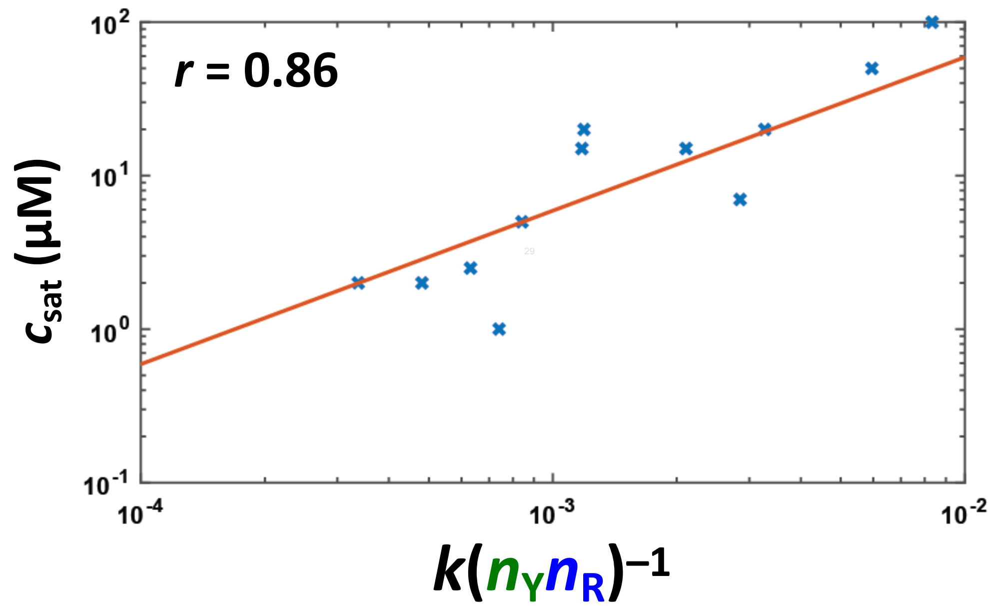


Wang, Choi, Holehouse,…,Pappu, Alberti, Hyman, *Cell* (2018)
Choi, Holehouse, Pappu *Annu. Rev. Biophys.* (2020)

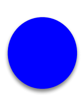
Theory predicts c_{sat} based on joint valence of TYR *and* ARG

$$c_{sat} = k\left(n_Y n_R\right)^{-1} \ \mu\text{M}$$

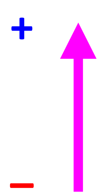
Mean field theory for associative polymers is a good predictor of experimentally derived c_{sat}



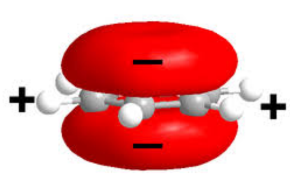
Working hypothesis: Stickers are distinguished by intrinsic multipole moments



Monopole moment (charge): q (e)

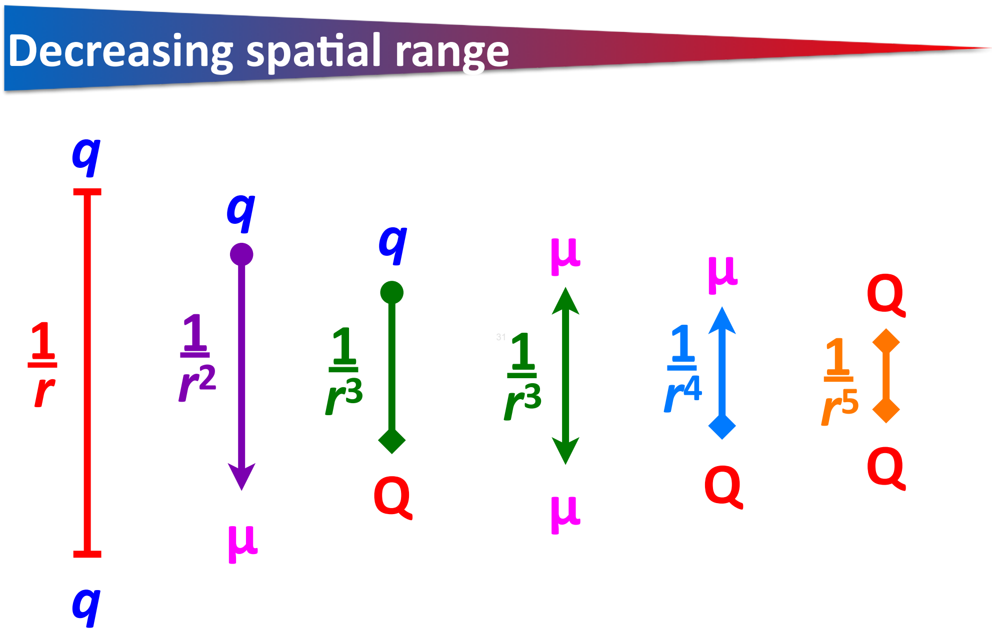


Dipole moment: μ (D)



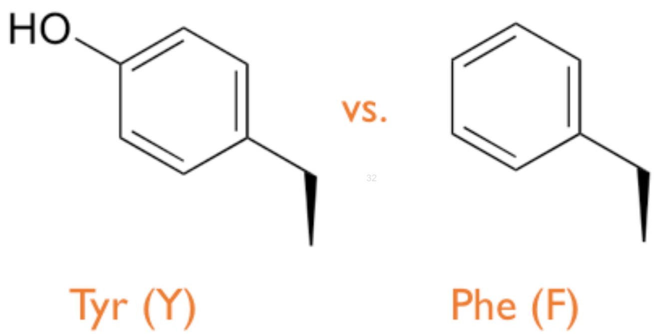
Quadrupole moment: Q_{zz} (De)

q: Monopole; μ: Dipole; Q: Quadrupole



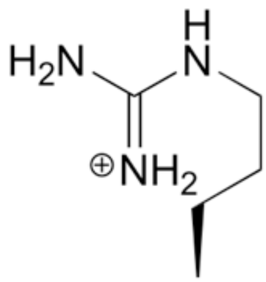
Burley & Petsko, Adv. Protein Chem. (1988)
Pappu et al., J. Comput. Chem. (1996)

Intrinsic valence can be defined by multipole moments

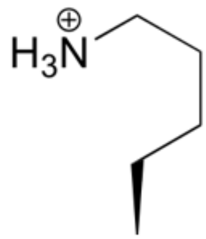


Tyr (Y)	Phe (F)
μ = 1.48 D	μ = 0 D
Q_{zz} ≈ –5 DÅ	Q_{zz} ≈ –5 DÅ

Intrinsic valence can be defined by multipole moments



vs.



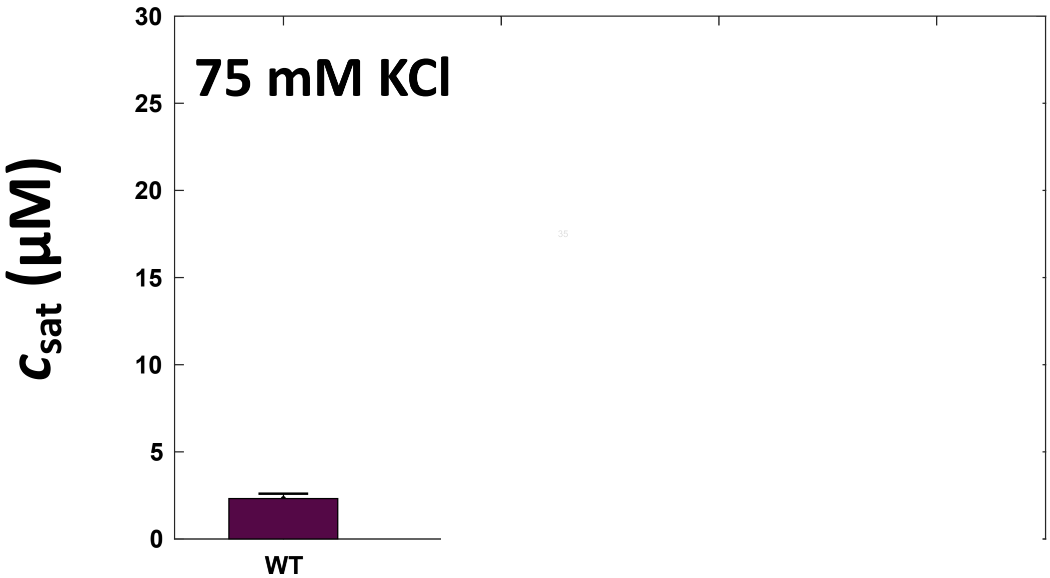
Arg (R)	Lys (K)
$q = 1\ e$ $\mu = 0$ D $Q_{zz} \approx -25$ DÅ	$q = 1\ e$ $\mu = 0$ D $Q_{zz} \approx 0$ DÅ

33

Prediction is that Arg-Tyr make for stronger stickers than Arg-Phe, Lys-Tyr, and Lys-Phe

34

Tyr *and* Arg: stronger stickers than Phe and Lys



Cationic and aromatic *stickers* encode a *hierarchy* of *interaction ranges* and *interaction strengths*

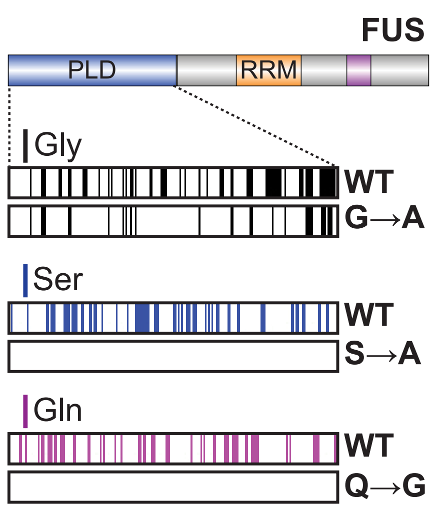
See: Nott et al., (2015) *Mol Cell*; Brady et al,, (2017) *PNAS*, Vernon et al., (2018) *eLife*

FUS family proteins ≠ (YYY…YY)$_n$-(RR…RR)$_m$

Sequence features of *spacers* are important determinants of material properties and the cooperativity of phase transitions

37

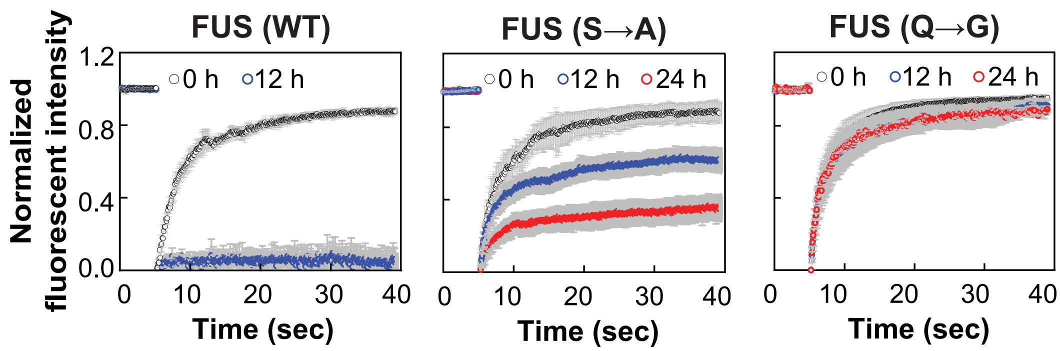
Spacers are sequence regions that have negligible impact on c_{sat}



$c_{sat} \approx 3 – 5\ \mu M$

…while impacting material properties

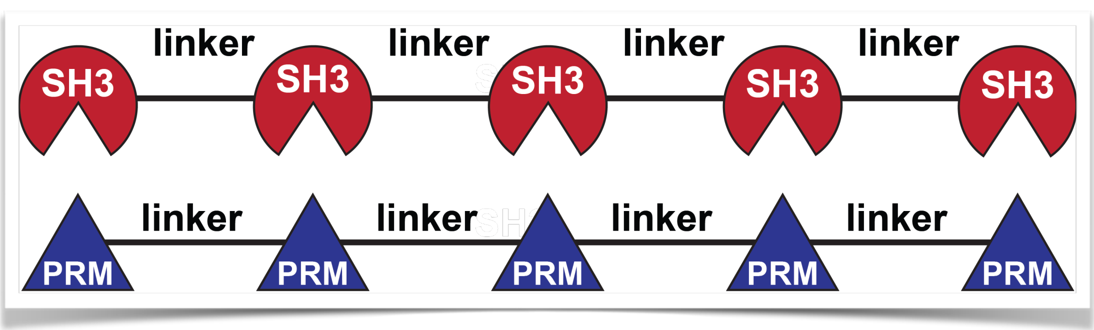
FRAP data show that Gly-rich spacers enhance rates of molecular exchange across phase boundaries



Rates of molecular exchange are tied to rates of breaking and making physical crosslinks and this is governed by intrinsic valence of spacer residues

Other examples of *stickers*-and-*spacers*

Folded domains connected by *intrinsically disordered* linkers



Li et al., *Nature* (2012)
Harmon et al., *eLife* (2017)

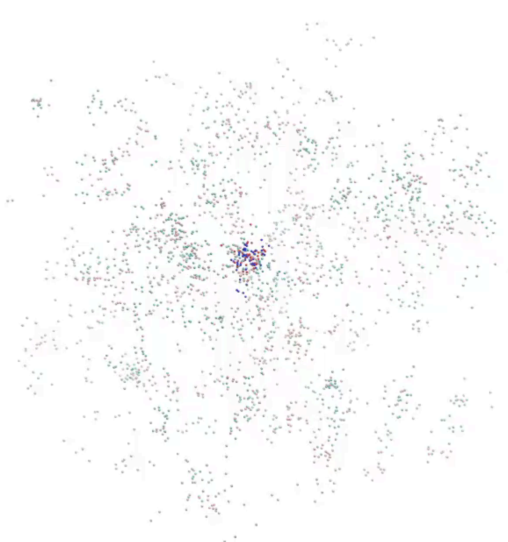
Sequence-encoded effective solvation volumes (v_{es}) of disordered linkers determine whether percolation (the formation of system-spanning networks) is driven by phase separation or if it occurs without phase separation

Harmon, Holehouse, Rosen, Pappu *eLife* (2017)

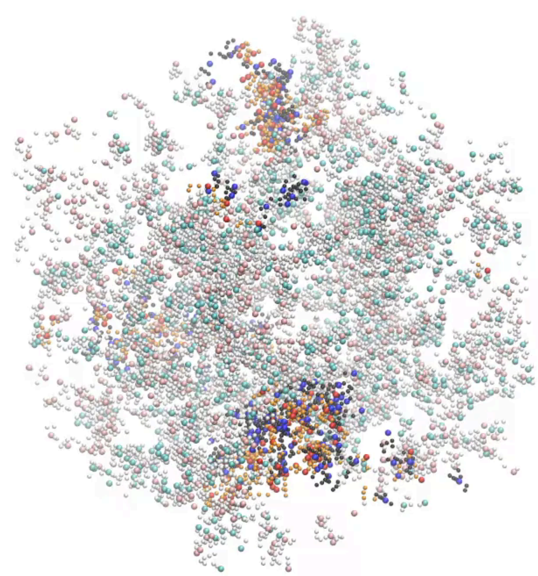
41

Phase behavior of poly-SH3 + poly-PRM

Linkers with $v_{es} = 0$



Linkers with $v_{es} >> 0$



42

Stickers and spacers come in different flavors

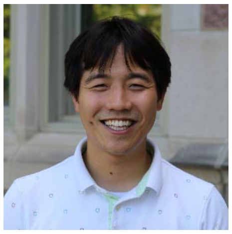
There is an evolved synergy between structure and disorder and identities of stickers and spacers will be context dependent

Harmon, Holehouse, Rosen, Pappu, *eLife* (2017)
Wang, Choi, Holehouse,…,Pappu, Alberti, Hyman, *Cell* (2018)
Choi, Holehouse, Pappu *Annu. Rev. Biophys.* (2020)

43

Biomolecular condensates have hundreds of distinct protein and RNA components

We have developed a lattice-based engine to simulate phase transitions of coarse-grained descriptions of multivalent protein and RNA molecules in multicomponent systems



Jeong-Mo Choi

Furqan Dar

LaSSI

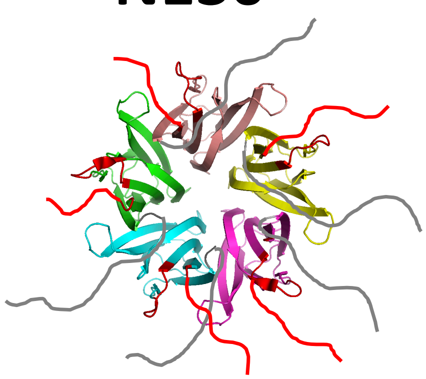
Lattice Simulation Engine For Sticker And Spacer Interactions

https://github.com/Pappulab/LASSI

Choi, Dar, Pappu *PLoS Comput. Biol.* (2019)

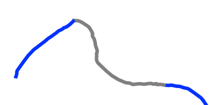
Example of a multicomponent system
NPM1 + rpL5

N130



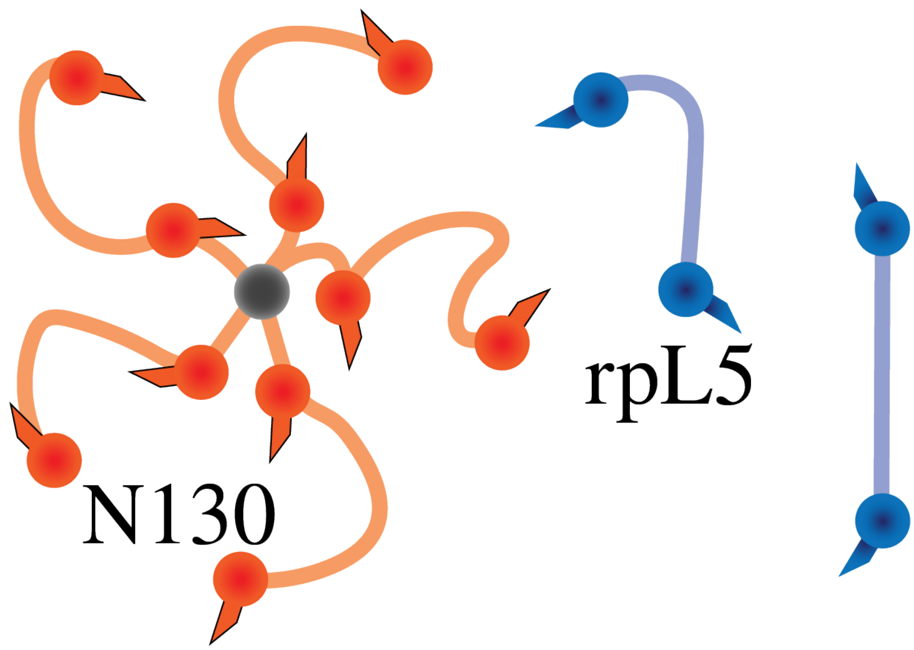
+

rpL5

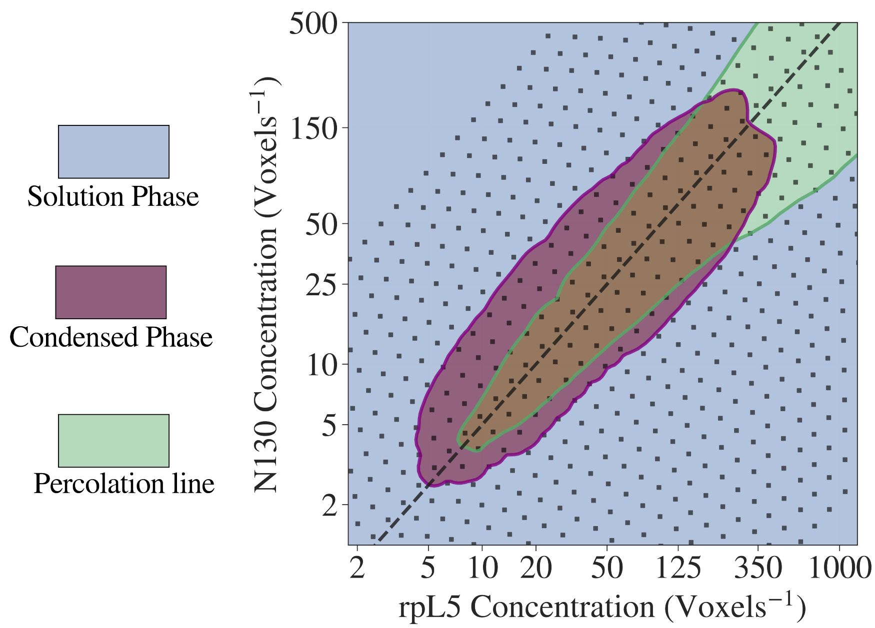


Mitrea et al., *eLife.* (2018)
Mitrea et al., *Nature Commun*. (2018)

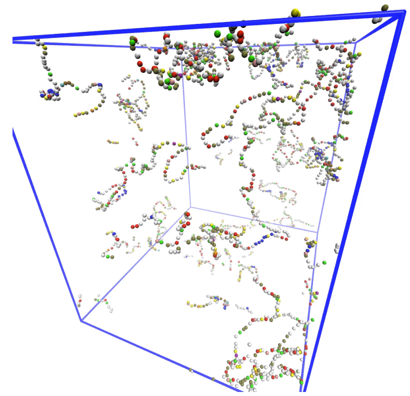
N130 + rpL5



Phase boundaries for multicomponent systems are closed loops

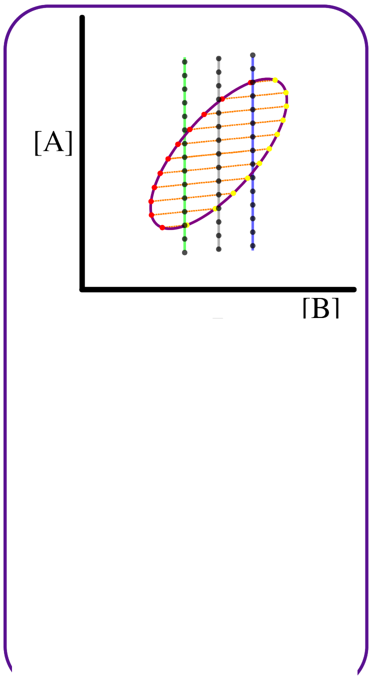


Condensates
are really *network fluids*
defined by physical
crosslinks among stickers



Dias, Araujo, Telo da Gama, *Adv. Colloid. Int. Sci.* (2017)
Harmon, Holehouse, Rosen, Pappu *eLife* (2017)
Choi, Dar, Pappu *PLoS Comput. Biol*. (2019)

When heterotypic interactions dominate, the concept of a saturation concentration ceases to apply



Demonstrates how phase behavior is controlled by the combination of stoichiometry, affinities, valence, and extent of crosslinking

Stickers and *spacers* framework applied to LCD-RNA phase behavior

Steven Boeynaems

Alex Holehouse

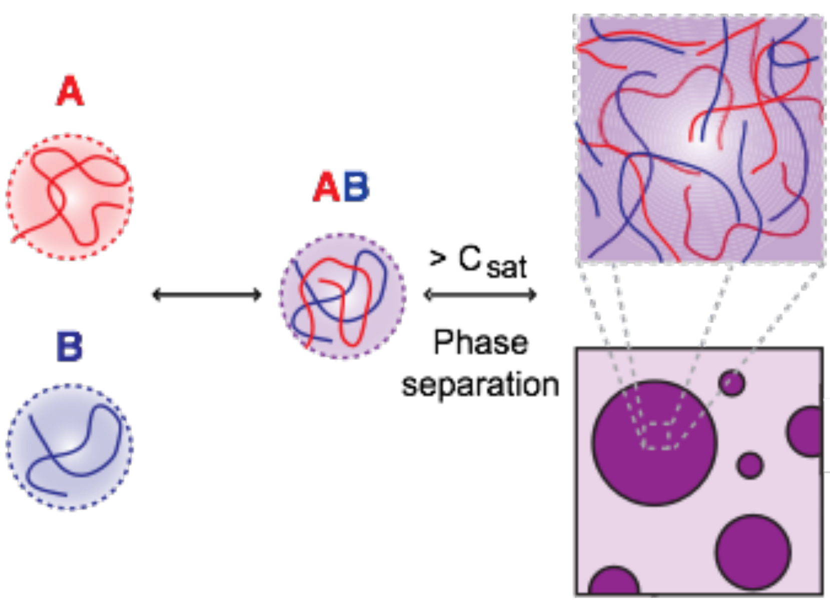
Venera Weinhardt

Aaron Gitler

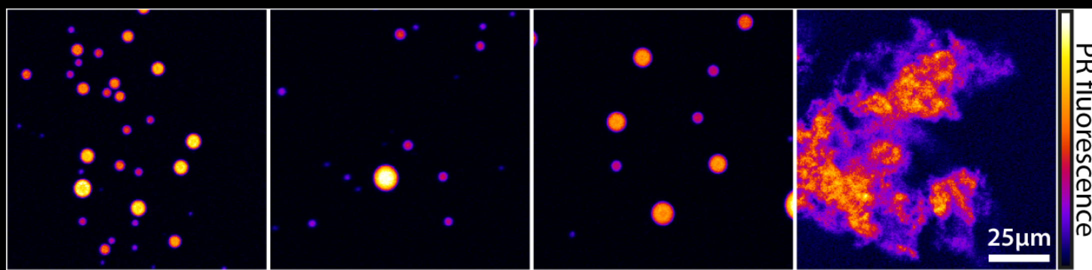
$(PR)_{30}$ + hompolymeric RNA

Boeynaems, Holehouse, Weinhardt et al.
PNAS (2019) **116**: 7889

Polyelectrolytes undergo phase separation via complex coacervation



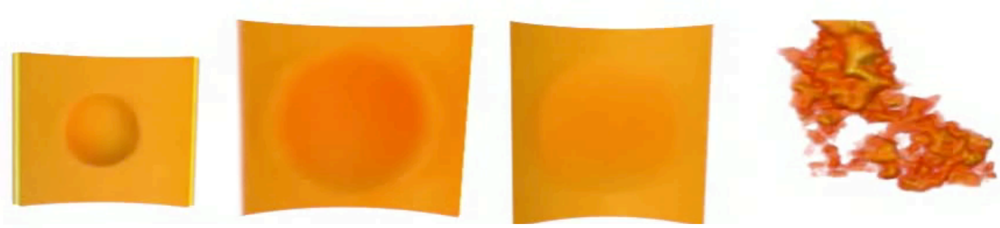
$(PR)_{30}$ condensates have irregular morphologies with poly rG



poly-rA poly-rU poly-rC poly-rG

$100\ mM\ K_2HPO_4/KH_2PO_4$, pH 7.0

$(PR)_{30}$ coacervation with homopolymeric RNAs - Soft x-ray tomography (SXT)



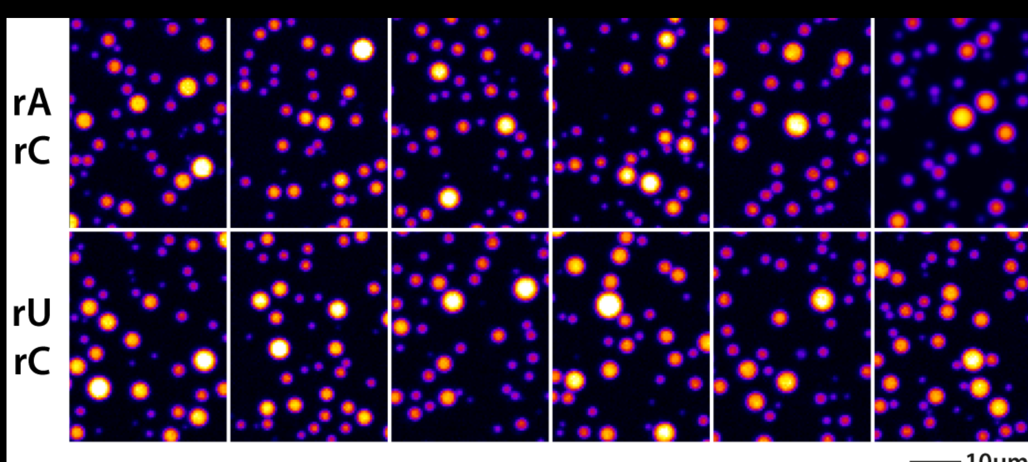
poly-rA poly-rU poly-rC poly-rG 1 µm

Hypothesis: RNA structure impacts condensate morphology

59

$(PR)_{30}$ coacervation with mixture of *non-base pairing* RNAs yields spherical condensates

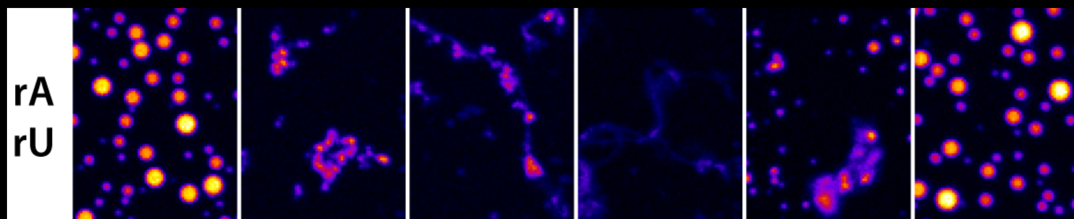
rA:100%	rA:80%	rA:60%	rA:40%	rA:20%	rA:0%
rC: 0%	rC: 20%	rC: 40%	rC: 60%	rC: 80%	rC: 100%



rU:100%	rU:80%	rU:60%	rU:40%	rU:20%	rU:0%
rC: 0%	rC: 20%	rC: 40%	rC: 60%	rC: 80%	rC: 100%

60

(PR)$_{30}$ coacervation with mixture of *base-pairing* RNAs alters condensate morphologies



rU:100%	rU:80%	rU:60%	rU:40%	rU:20%	rU:0%
rC: 0%	rC: 20%	rC: 40%	rC: 60%	rC: 80%	rC: 100%

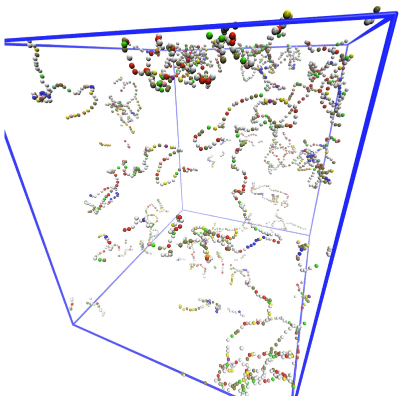
100 mM K_2HPO_4/KH_2PO_4, pH 7.0

Is the impact of RNA structure on condensate morphology stable or metastable?

PIMMS Simulation Engine

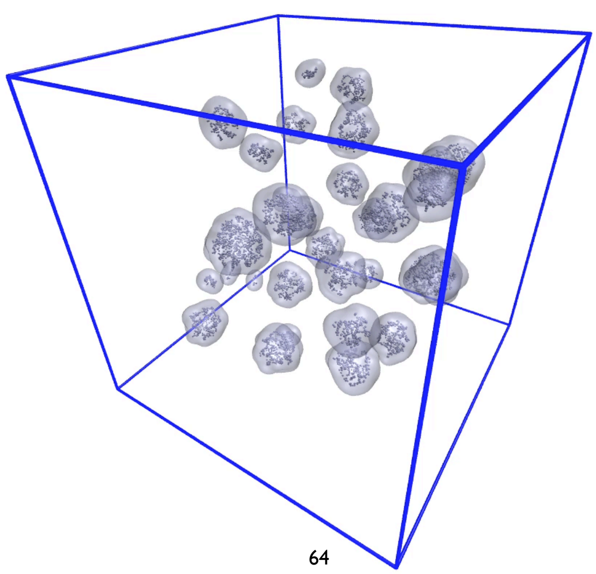
Polymer **I**nteractions in **M**ulticomponent **M**ixture**S**

- Monte Carlo Simulation Engine
- Single-bead per residue on lattice
- Ultra coarse-grained RNA
- Learned forcefield captures chemical heterogeneity



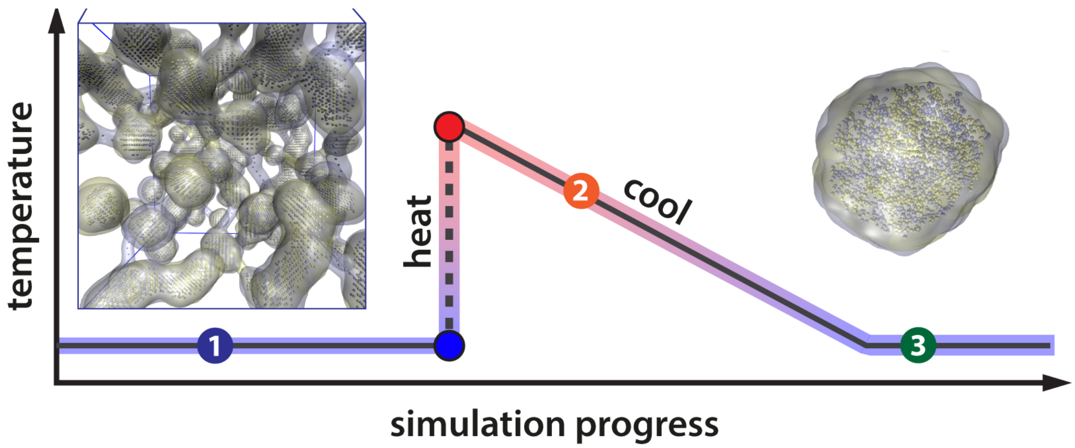
Alex Holehouse

Coarse-grained simulations of $(PR)_{30}$ + poly-rA shows the formation of spherical droplets



64

Arrested networks are disrupted by heating followed by annealing to spherical assemblies



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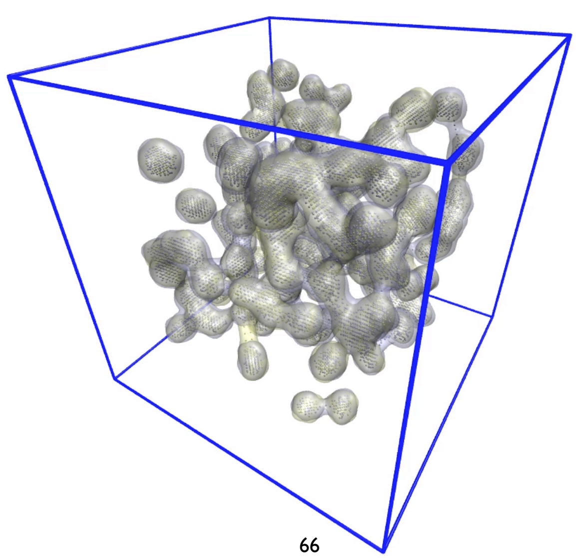
Coarse-grained simulations of $(PR)_{30}$ + poly-rA + poly-rU



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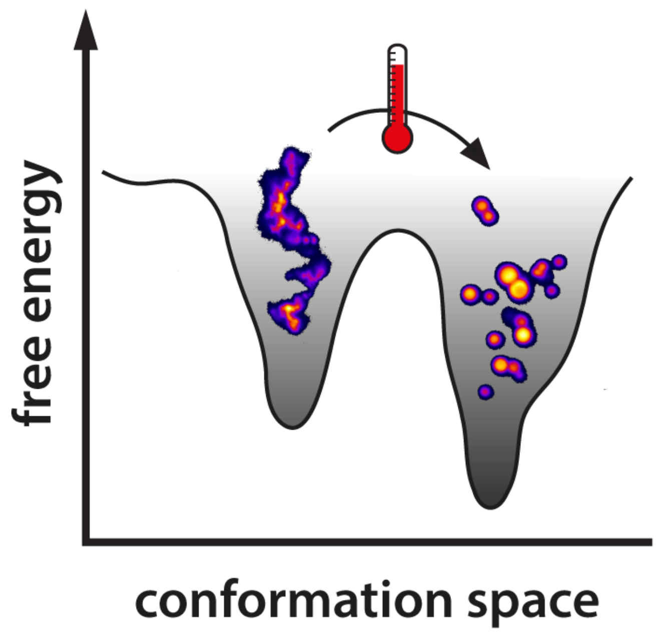
Networks are examples of dynamically arrested phase separation



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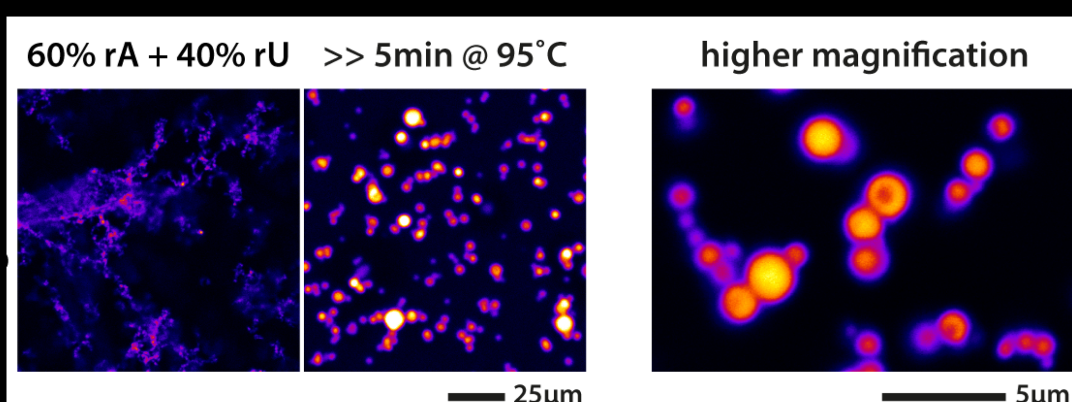
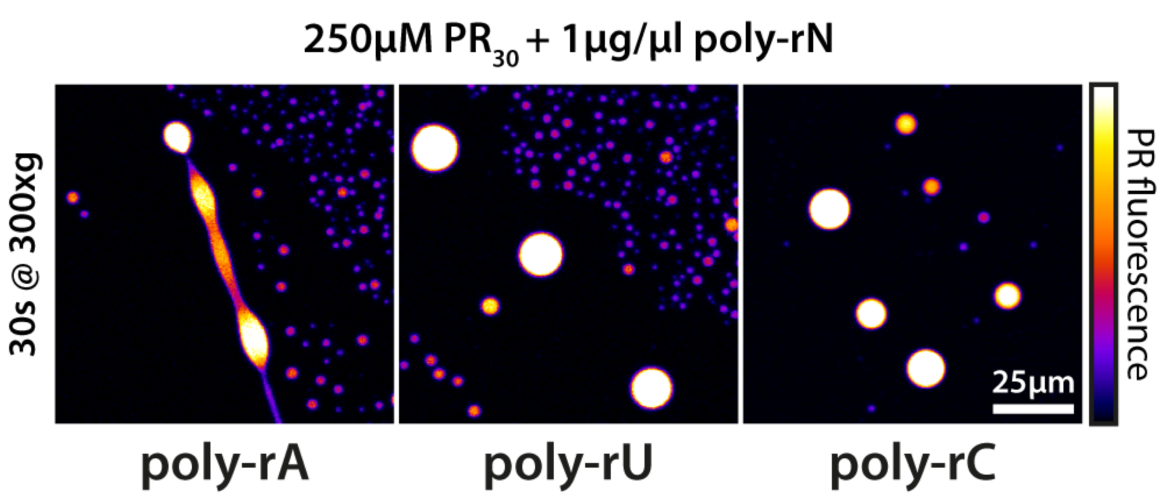
Heating followed by annealing leads to disruption of filamentous networks and equilibration to spherical condensates



Impact of nucleobase (anion) vs. amino acid (cation)?

69

Nucleobase impacts dynamics of fusion



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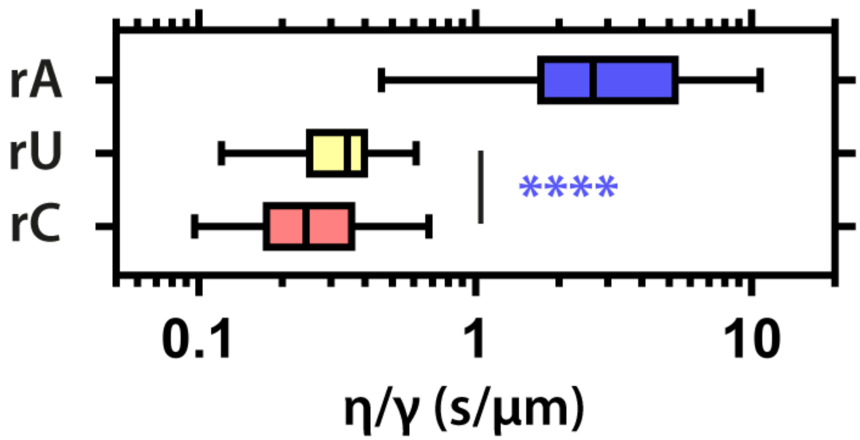
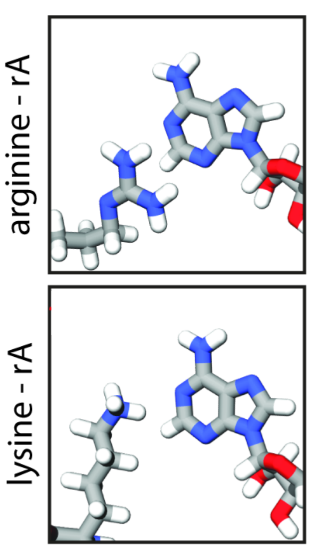
Inverse capillary velocity reveals differences between purines vs. pyrimidines

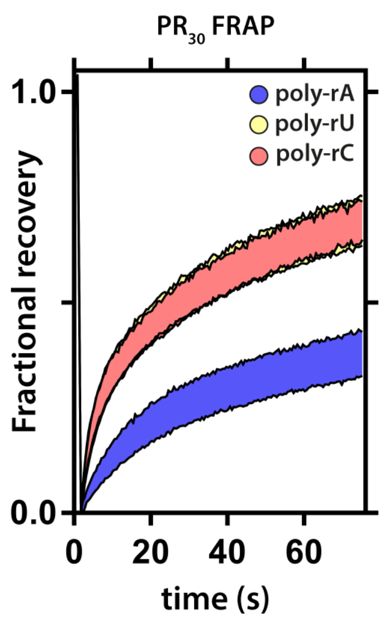


Condensates formed by coacervation with poly-purines slow fusion

Nature of the amino acid cation also impacts dynamics of fusion



Dependence of internal protein dynamics on nucleobase is also governed by type of cation

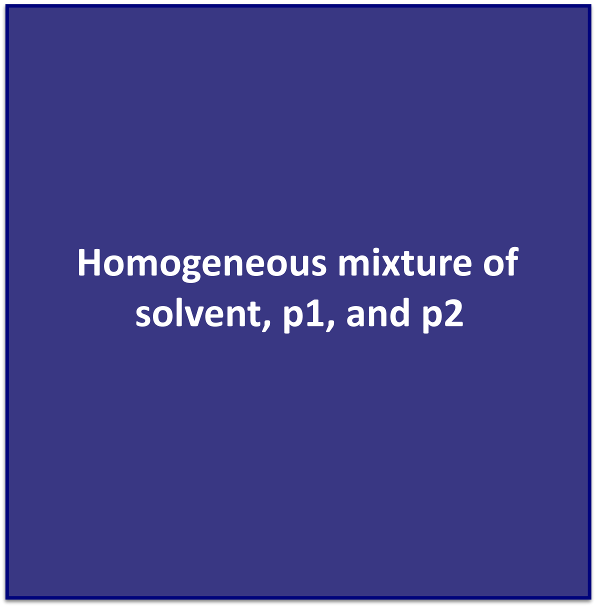


73

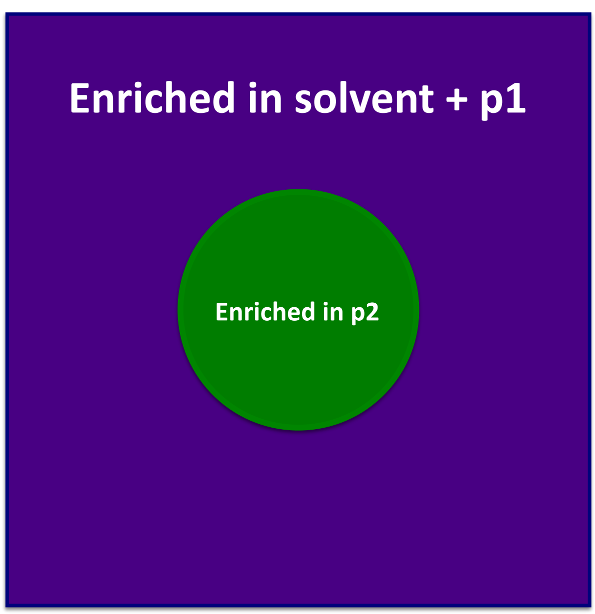
Phase behavior of multicomponent systems

74

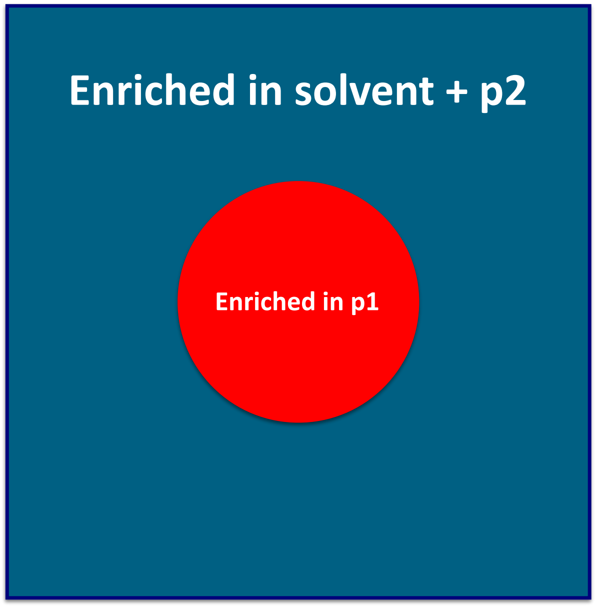
_n_ polymers plus solvent can have _n_+1 coexisting phases


Homogeneous mixture of solvent, p1, and p2

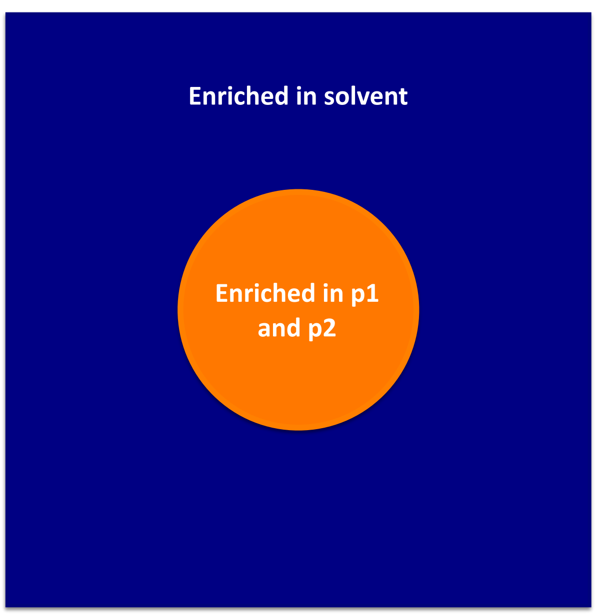
75


Enriched in solvent + p1
Enriched in p2

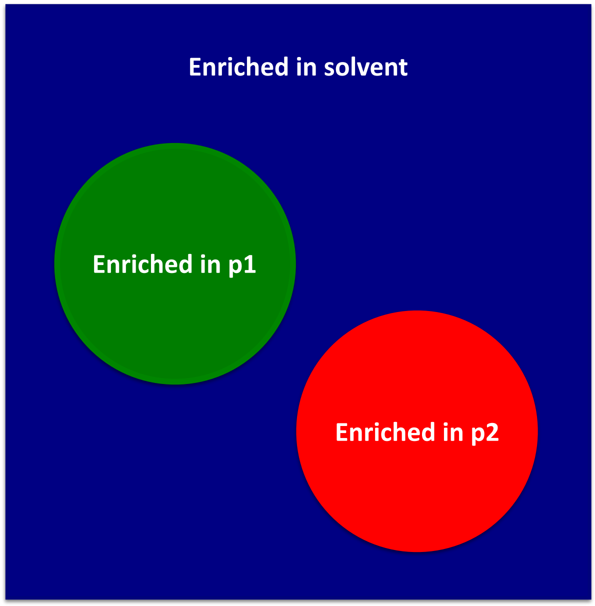
76


Enriched in solvent + p2
Enriched in p1

77

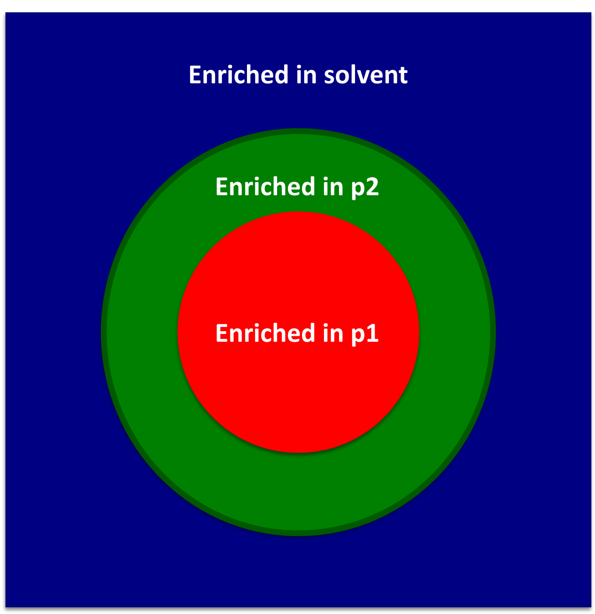

Enriched in solvent
Enriched in p1
and p2

78

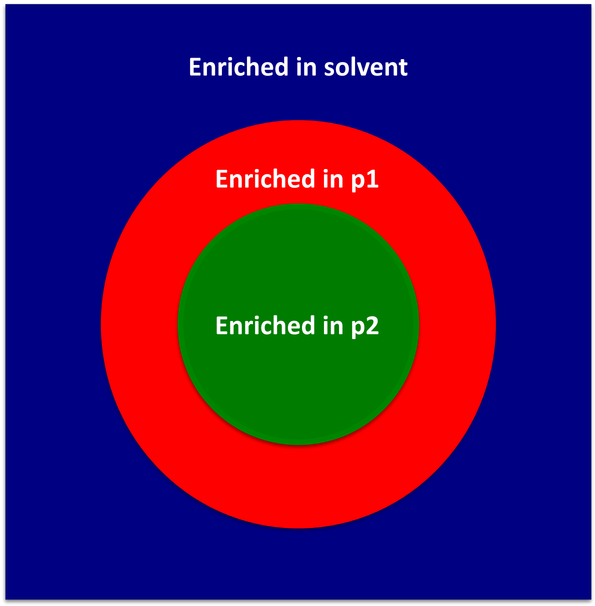

Enriched in solvent
Enriched in p1
Enriched in p2

79

79


Enriched in solvent
Enriched in p2
Enriched in p1

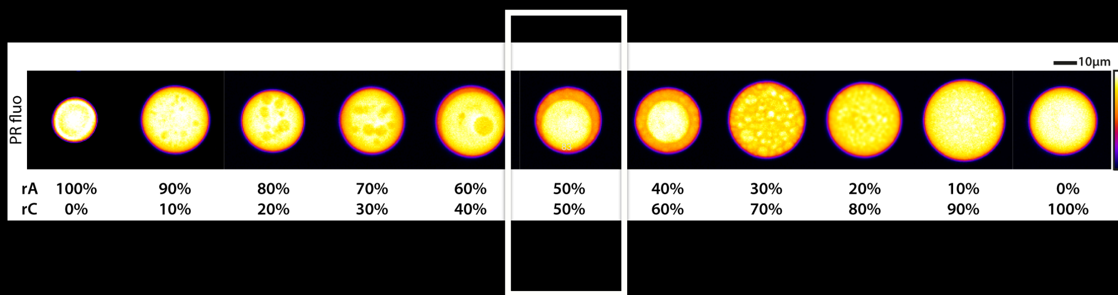
80



81

Mixtures of $(PR)_{30}$ + poly-rA + poly-rU?

Mixtures of $(PR)_{30}$ + poly-rA + poly-rU



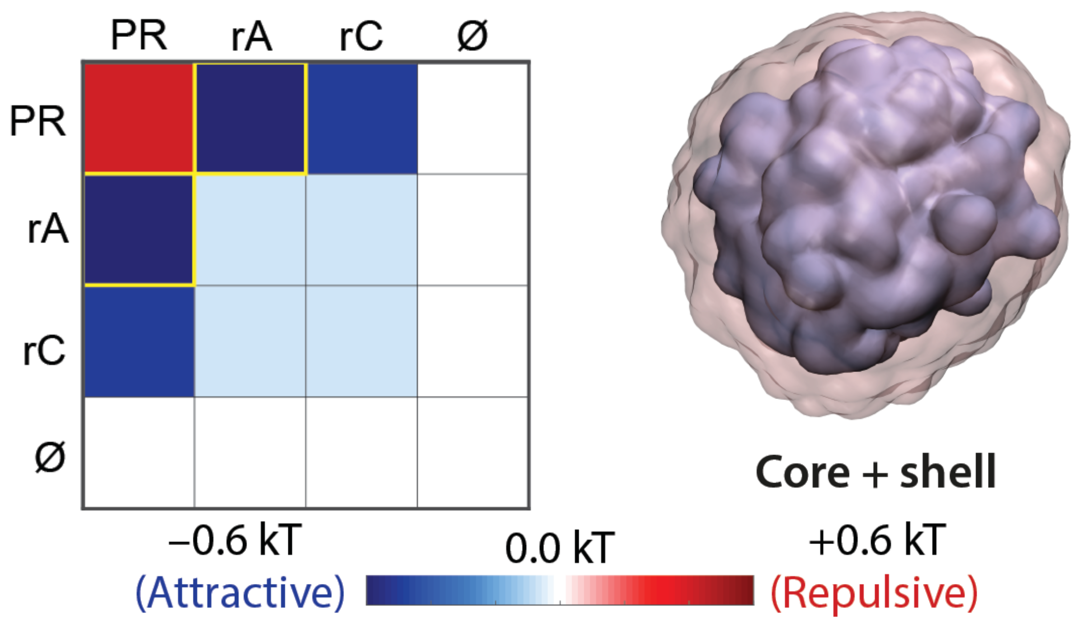
100 mM K_2HPO_4/KH_2PO_4, pH 7.0

83

$(PR)_{30}$ + 50% poly-rA + 50% poly-rU

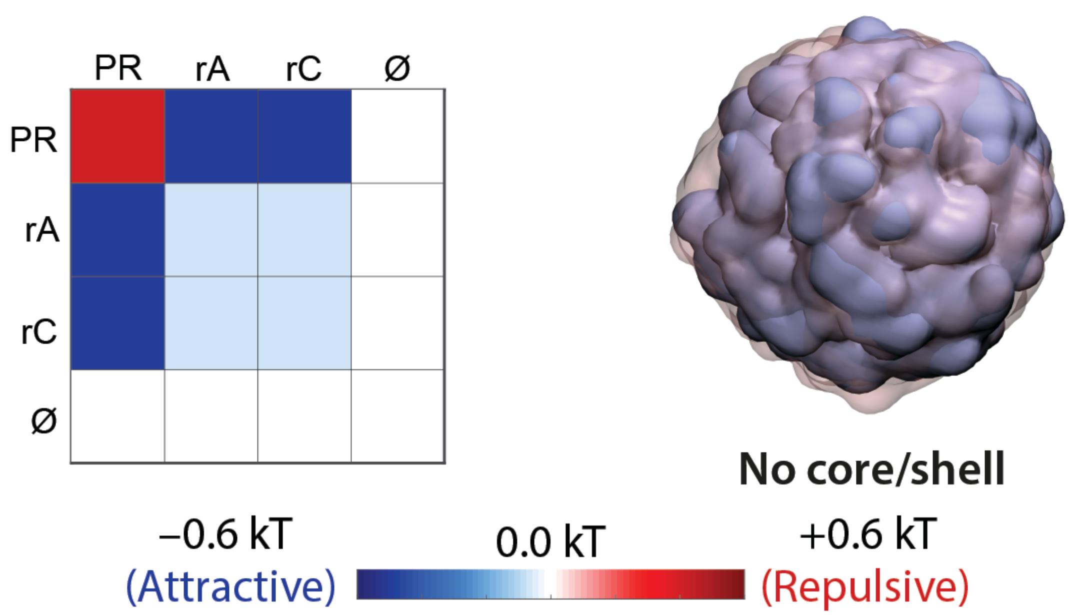
84

Stronger $(PR)_{30}$ - poly-rA interactions yields poly-rA core and poly-rC shell



85

Equivalence of interactions abrogates core-shell structure



86

Overall Summary

RNA structure and composition **as well as *Arg / Lys valence vs. composition* will contribute to driving forces, morphologies, dynamics, and spatial organization of LCD:RNA condensates**

Decipherable rules governing the driving forces of condensate formation can be extracted using quantitative deployment of the stickers-and-spacers formalism

Acknowledgments

90

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Functional Implications of Intracellular Phase Transitions

Alex S. Holehouse* and Rohit V. Pappu*

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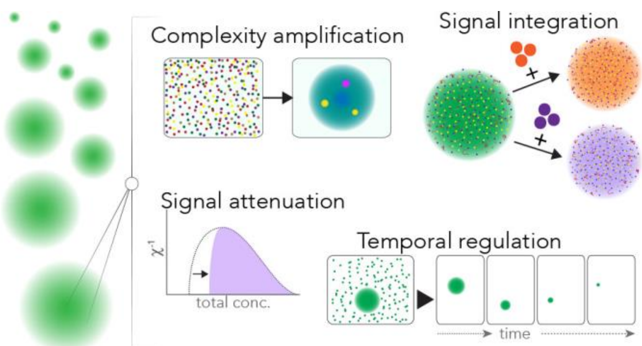
Publication Date: January 11, 2018
https://doi.org/10.1021/acs.biochem.7b01136



Abstract

Intracellular environments are heterogeneous milieus comprised of macromolecules, osmolytes, and a range of assemblies that include membrane-bound organelles and membraneless biomolecular condensates. The latter are nonstoichiometric assemblies of protein and RNA molecules. They represent distinct phases and form via intracellular phase transitions. Here, we present insights from recent studies and provide a perspective on how phase transitions that lead to biomolecular condensates might contribute to cellular functions.

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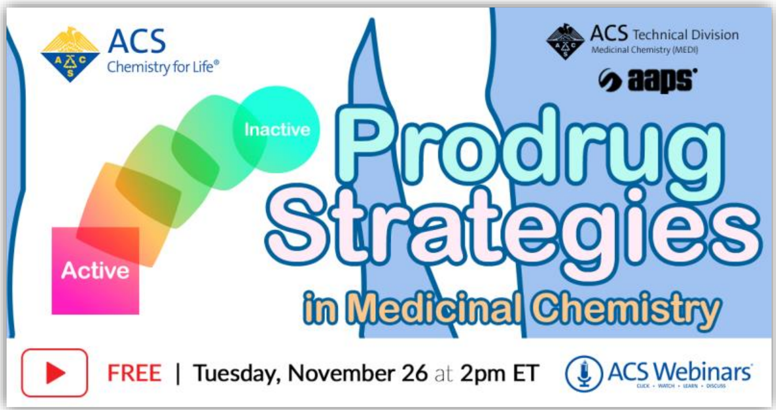

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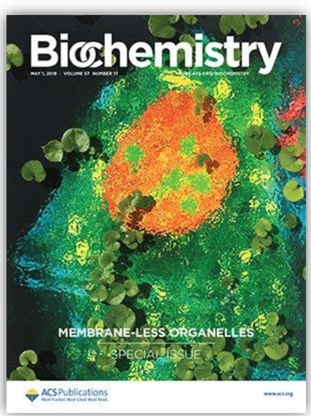

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All biological systems use location as a determinant of function at different scales, ranging from whole organisms to atoms within biomolecules. How to get key actors to the right locations at the right time and how to keep them there until they are no longer needed are key logistical challenges cells must perfect in order to thrive. Cells use different strategies to regulate localization; the best known is compartmentalization into traditional membrane-bound organelles such as the nucleus, endoplasmic reticulum, or Golgi complex. In the past few years, it has been proposed that membraneless organelles exist and complement larger classical organelles.

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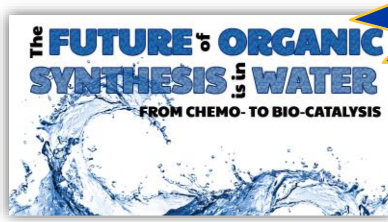

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