Molecular Dynamics of the FUS Protein Fibril: Phosphorilation Effect

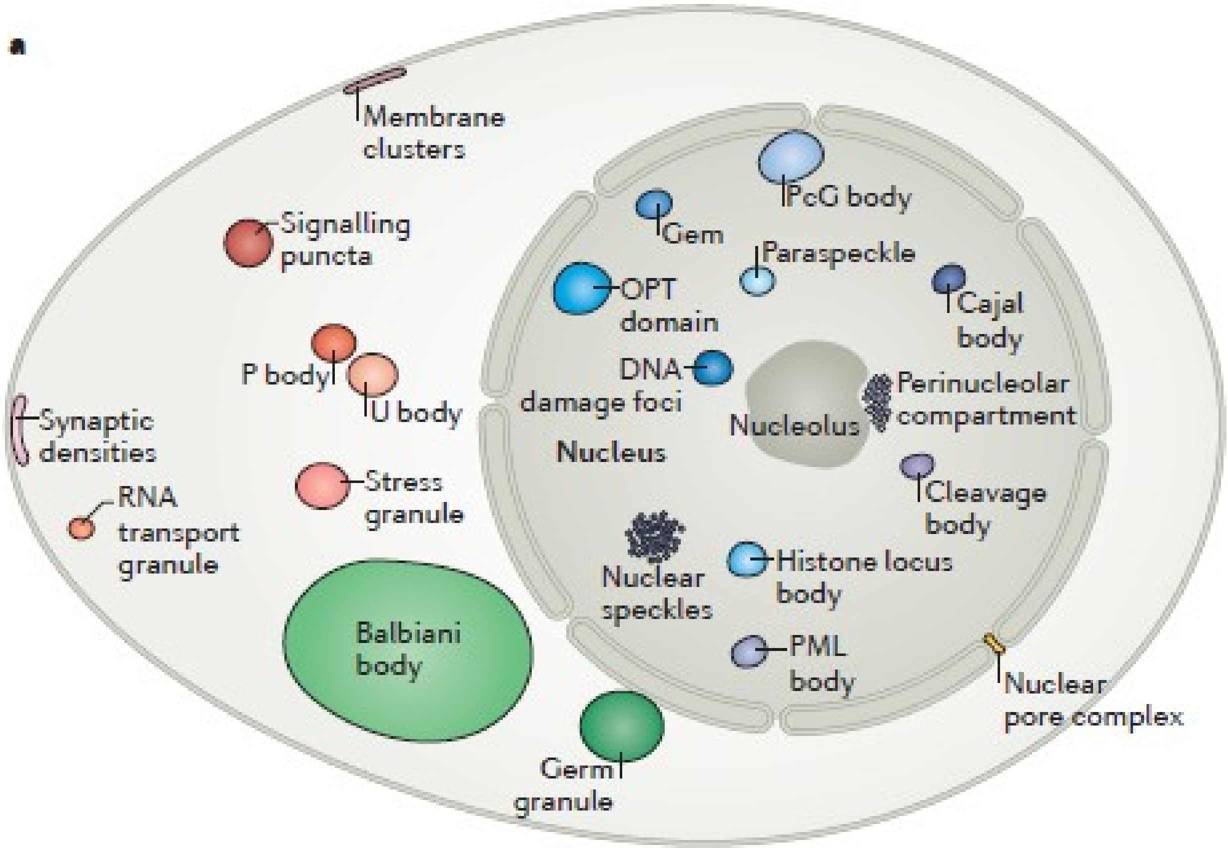
Y. Mamasakhlisov (Yerevan State University; Institute of Applied problems of Physics, Yerevan)

A. Poghosyan (Institute for Informatics and Automation problems, Yerevan)

Outline

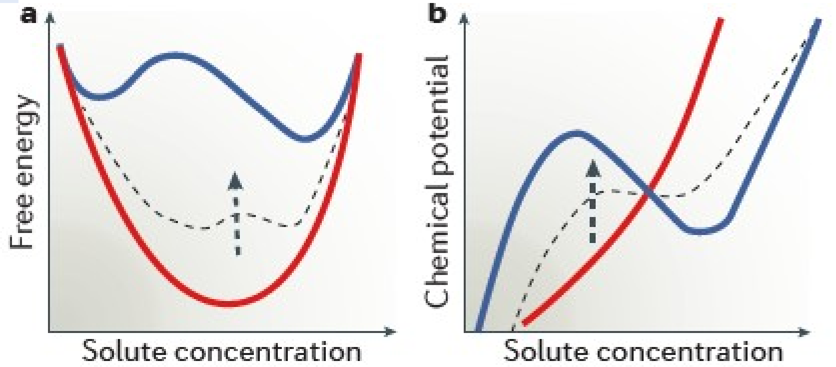
- Membraneless organels
- Double-strand breaks and biomolecular condensate
- Biomoleculat condensate and fibril stability
- FUS fibril stability and phosphorilation

Membraneless organels, Banani, S., Lee, H., Hyman, A. et al. Nat. Rev. Mol. Cell. Biol. **18**, 285 (2017).



Liquid-liquid phase separation, Brangwynne, C., Tompa, P. & Pappu, R. Nature Phys. **11**, 899 (2015)

$$\frac{F}{k_B T} = \frac{\phi}{N} \ln \frac{\phi}{2} + (1-\phi)\ln(1-\phi) - \alpha(\sigma\phi)^{3/2}$$



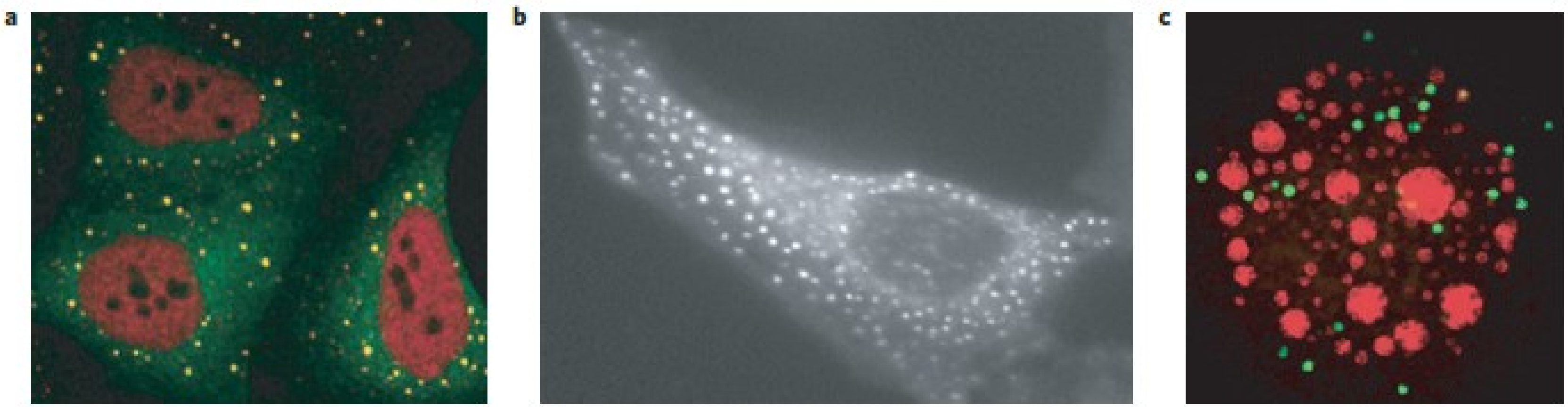
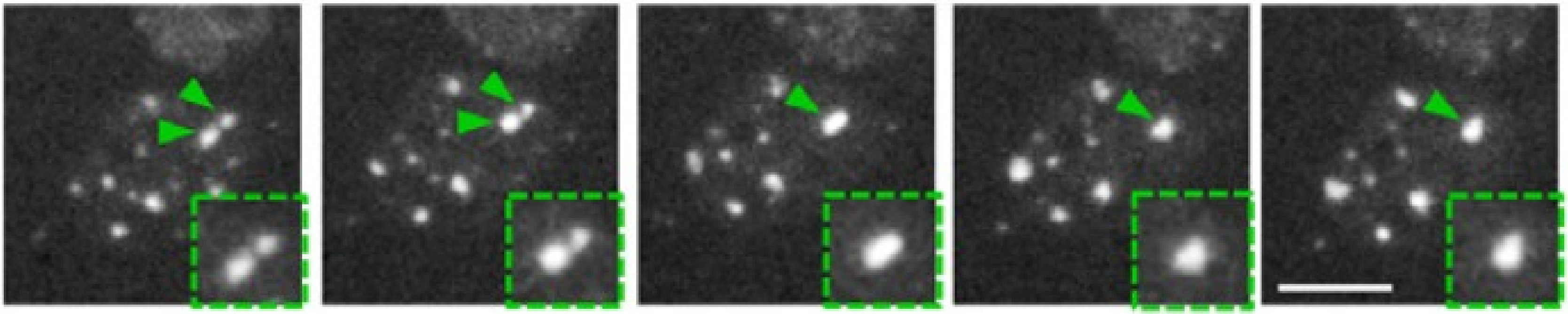
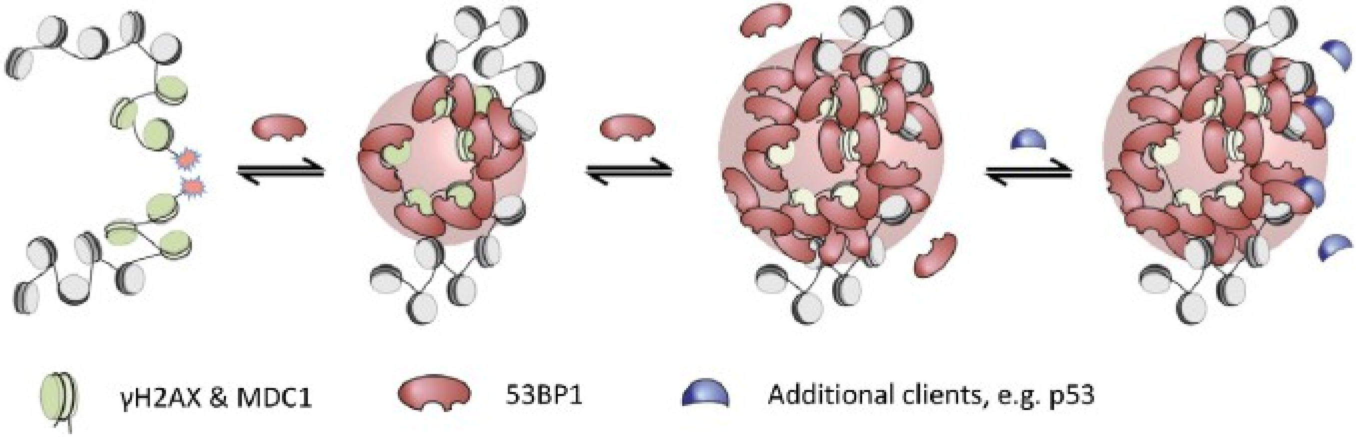


Figure 1 | Examples of membrane-less bodies in cells. a, P bodies (yellow) in tissue culture cells (adapted from ref. 63, NPG). **b**, Purinosomes (adapted from ref. 3, AAAS). **c**, Nucleoli (red) and histone locus bodies (green) in the nucleus of a large *X. laevis* oocyte (adapted from ref. 14, NPG).

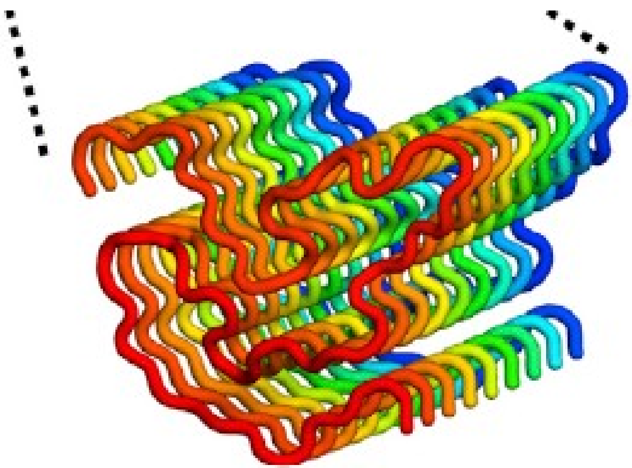
Phase separation of 53BP1 determines liquid-like behavior of DNA repair compartments, Kilic S., et al. EMBO J. **38**, e101379(2019)

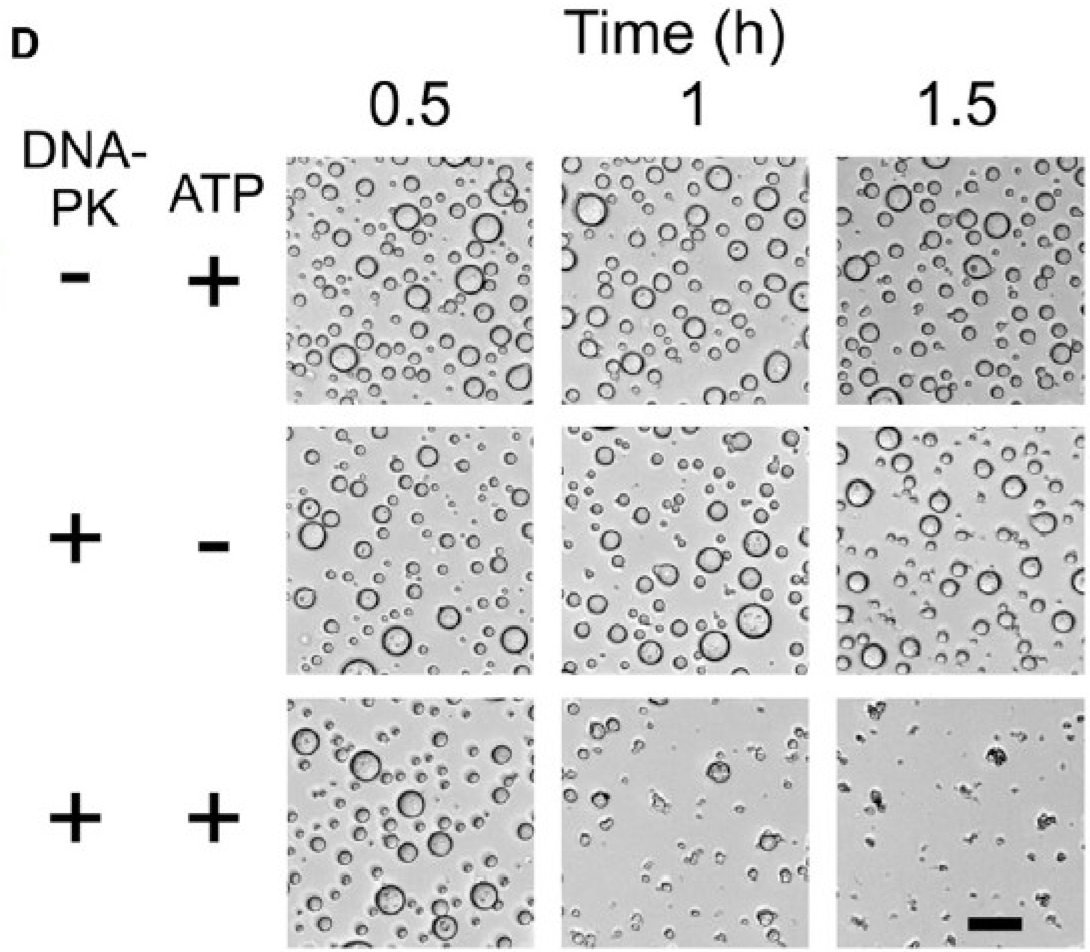
- The 53BP1 protein clusters exhibit the droplet-like behavior





FUS fibril and stability of biomolecular condensate, Murray D. T., et al. Cell. 2017 Oct 19;171(3):615-627





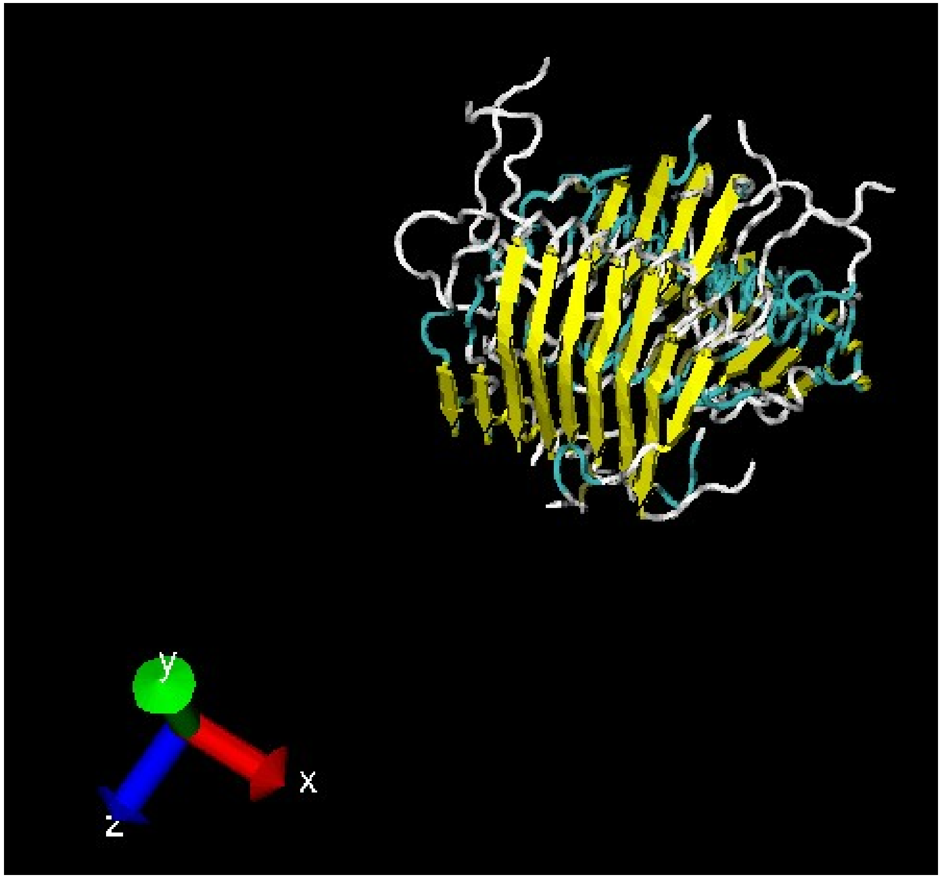
Molecular dynamics (MD)

$$m_i \frac{\mathrm{d}^2 \mathbf{r}_i}{\mathrm{d}t^2} = -m_i \gamma_i \frac{\mathrm{d}\mathbf{r}_i}{\mathrm{d}t} + \mathbf{F}_i(\mathbf{r}) + \mathring{\mathbf{r}}_i$$

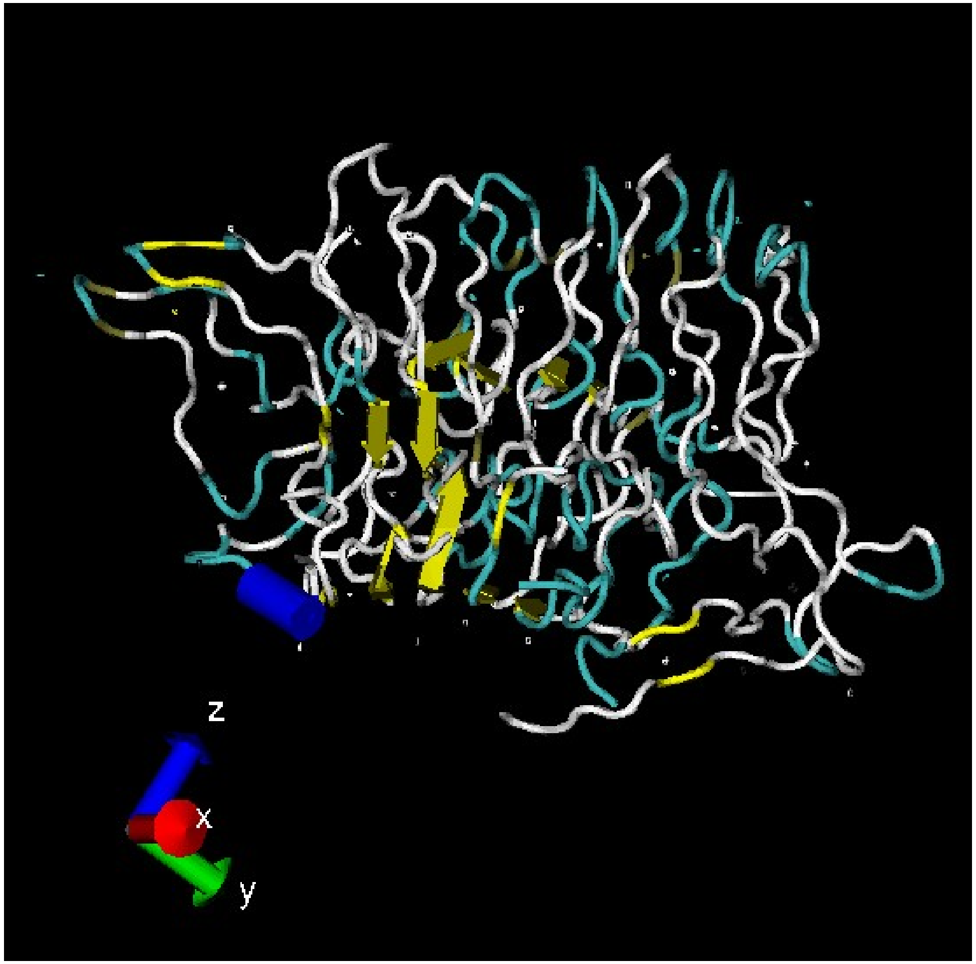
$$\begin{aligned}
\mathbf{v}' &= \mathbf{v}(t - \frac{1}{2}\Delta t) + \frac{1}{m}\mathbf{F}(t)\Delta t \\
\Delta \mathbf{v} &= -\alpha\, \mathbf{v}'(t + \frac{1}{2}\Delta t) + \sqrt{\frac{k_B T}{m}\alpha(2-\alpha)}\, \mathbf{r}^G{}_i \\
\mathbf{r}(t + \Delta t) &= \mathbf{r}(t) + \left(\mathbf{v}' + \frac{1}{2}\Delta \mathbf{v}\right)\Delta t
\end{aligned}$$

$$\begin{aligned}
\mathbf{v}(t + \frac{1}{2}\Delta t) &= \mathbf{v}' + \Delta \mathbf{v} \\
\alpha &= 1 - e^{-\gamma \Delta t}
\end{aligned}$$

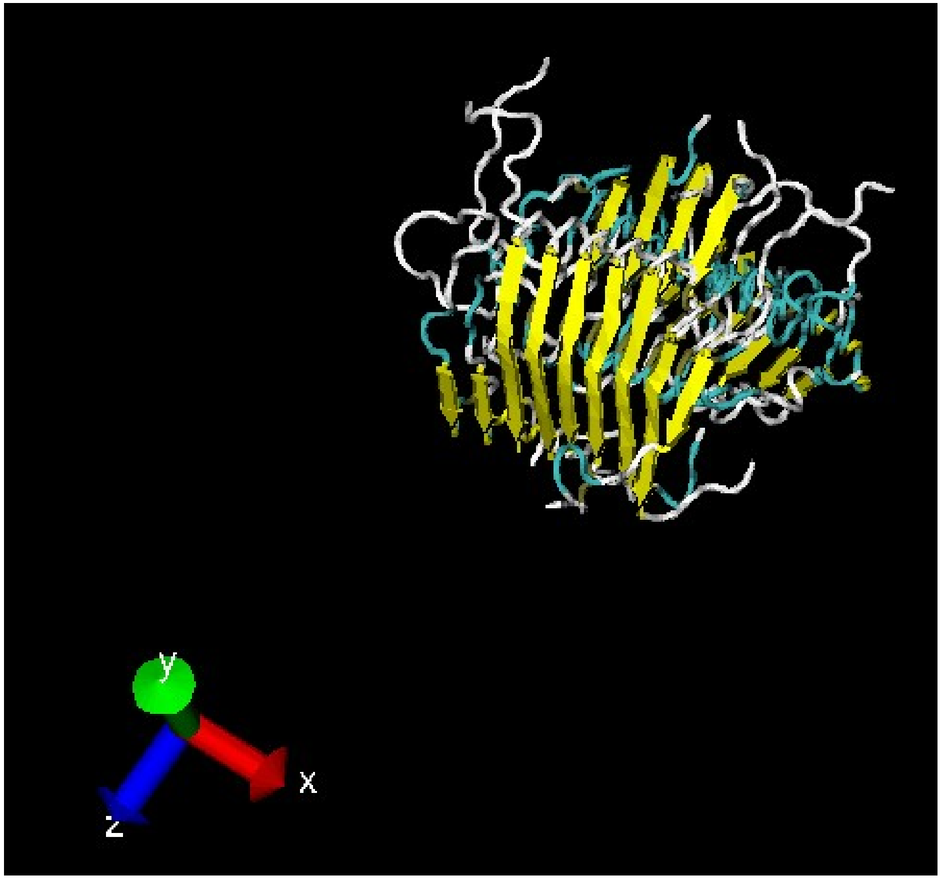
MD simulation, 150 ns, CHARMM ff, 0.5M NaCl, without phosphorilation (WT)

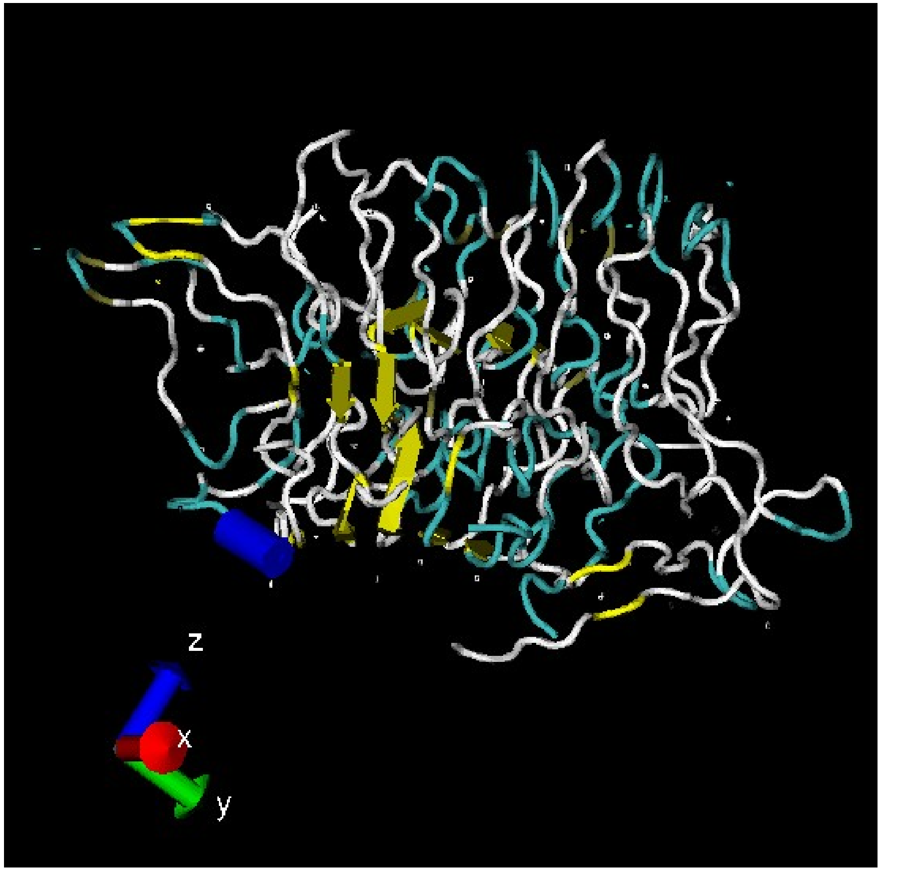


MD simulation, 150 ns, CHARMM ff, 0.5M NaCl, phosphorilated

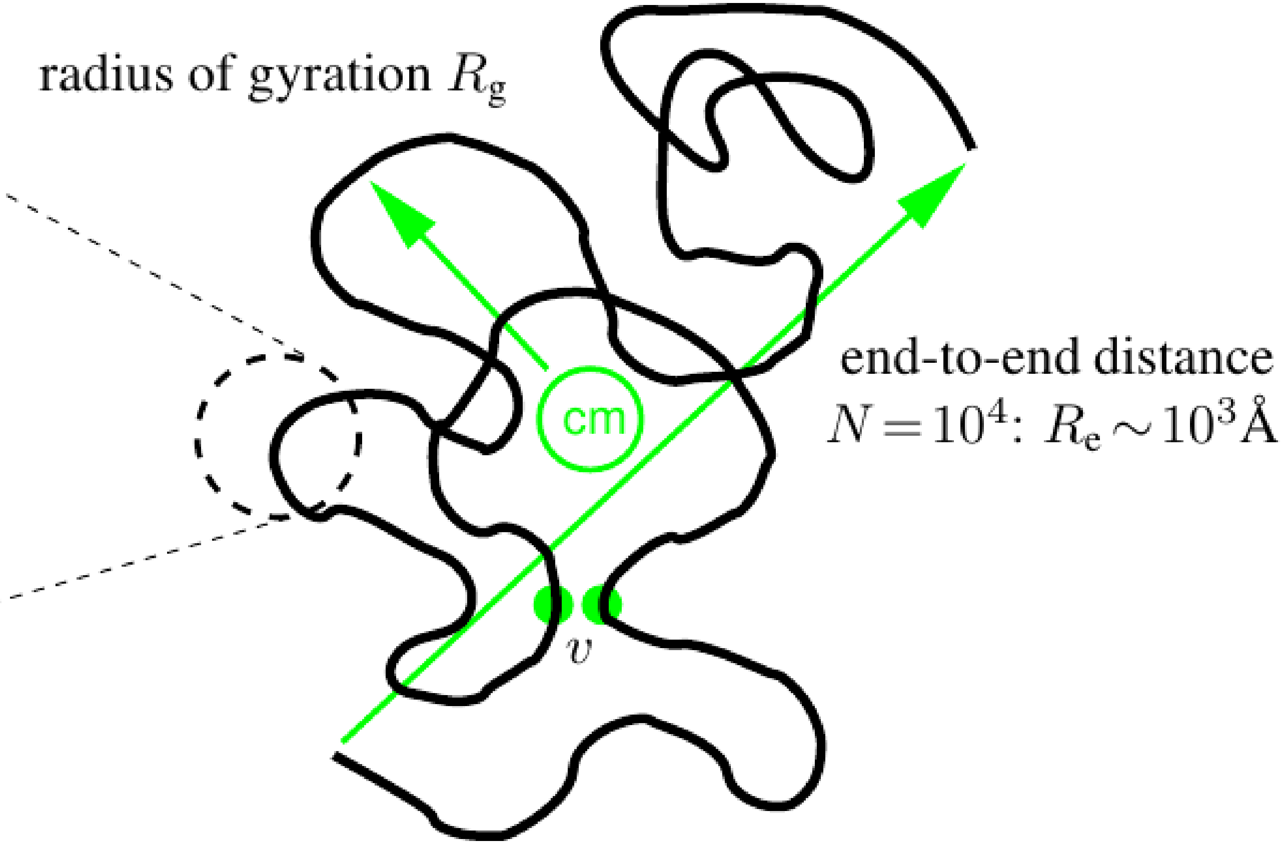


Let’s compare …

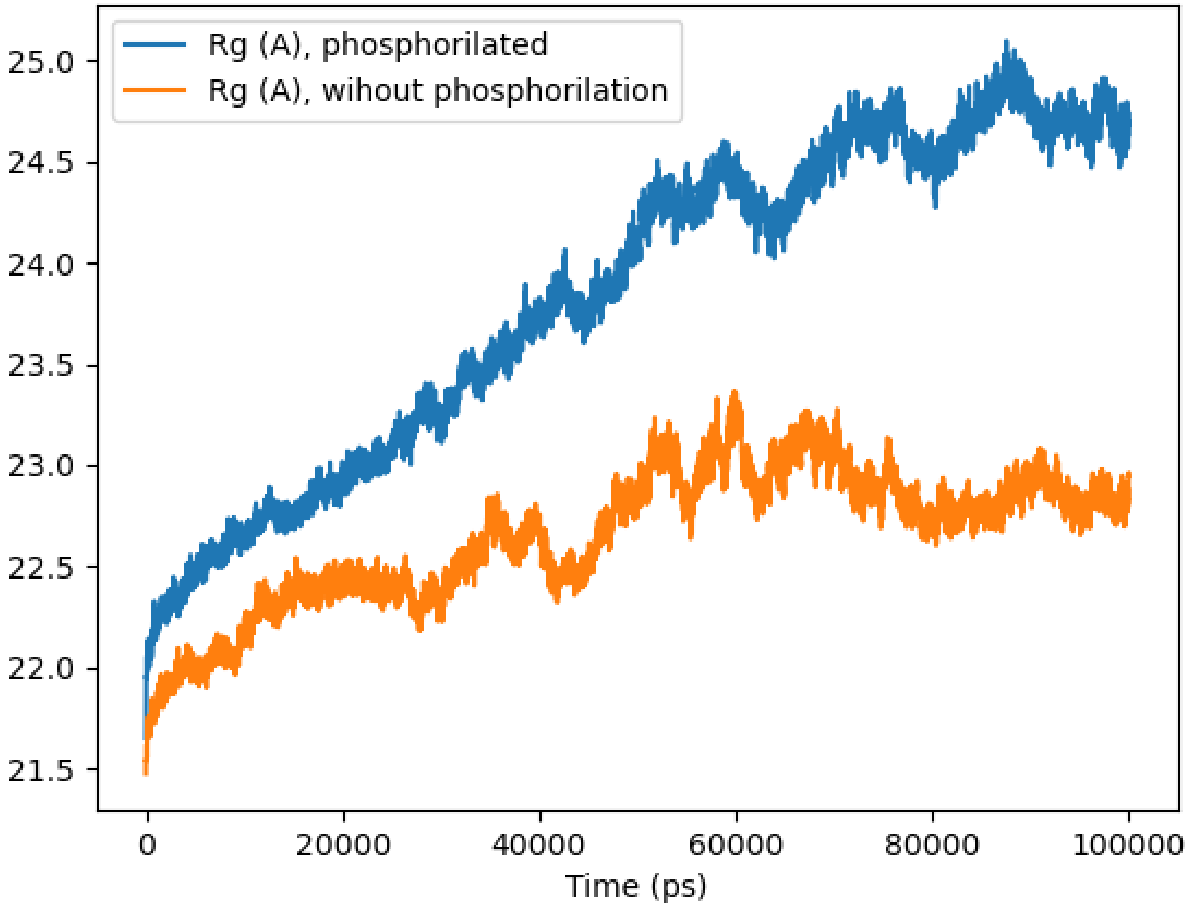




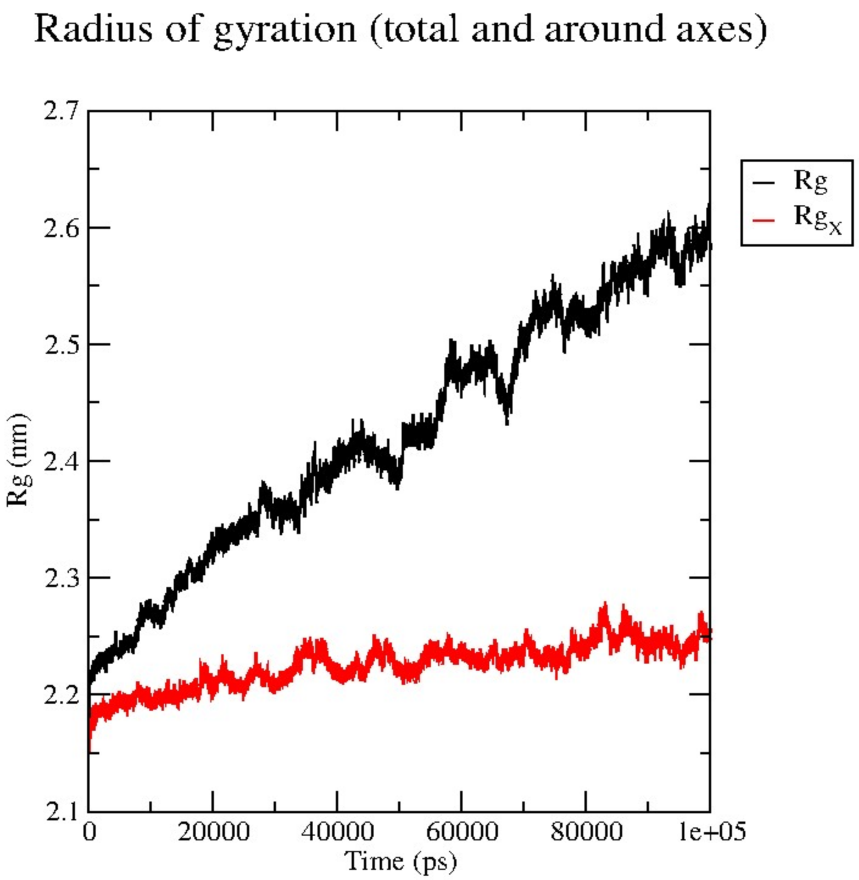
Radius of gyration as a measure of space occupied by a polymer

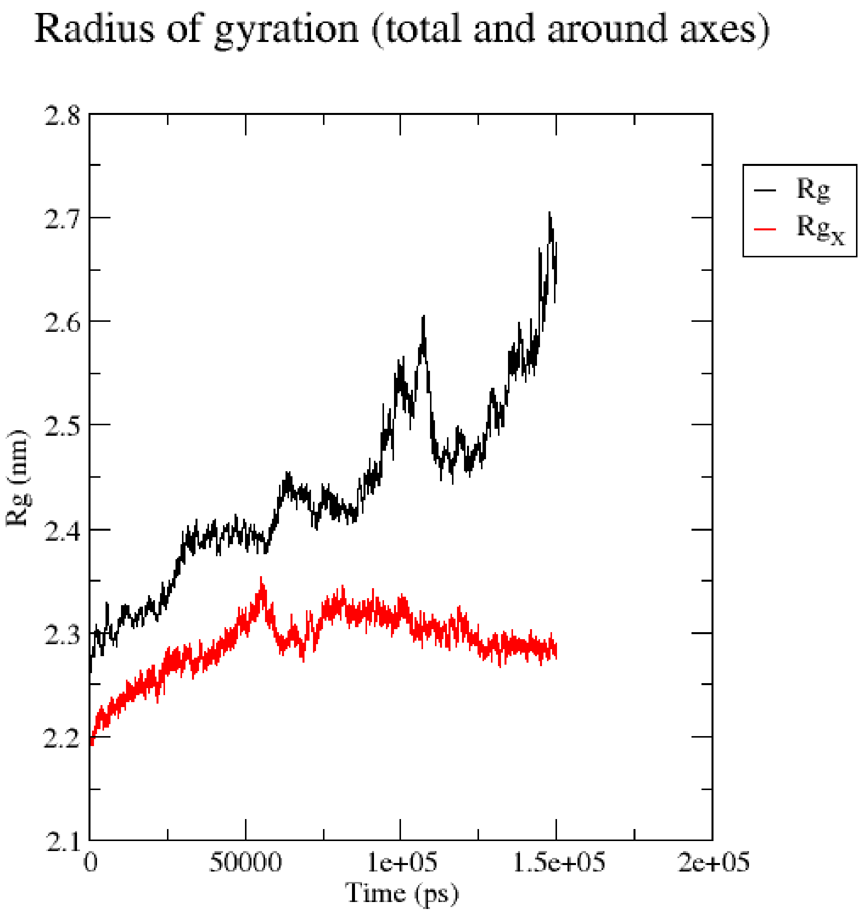


Radius of gyration vs time (0.5 M NaCl)

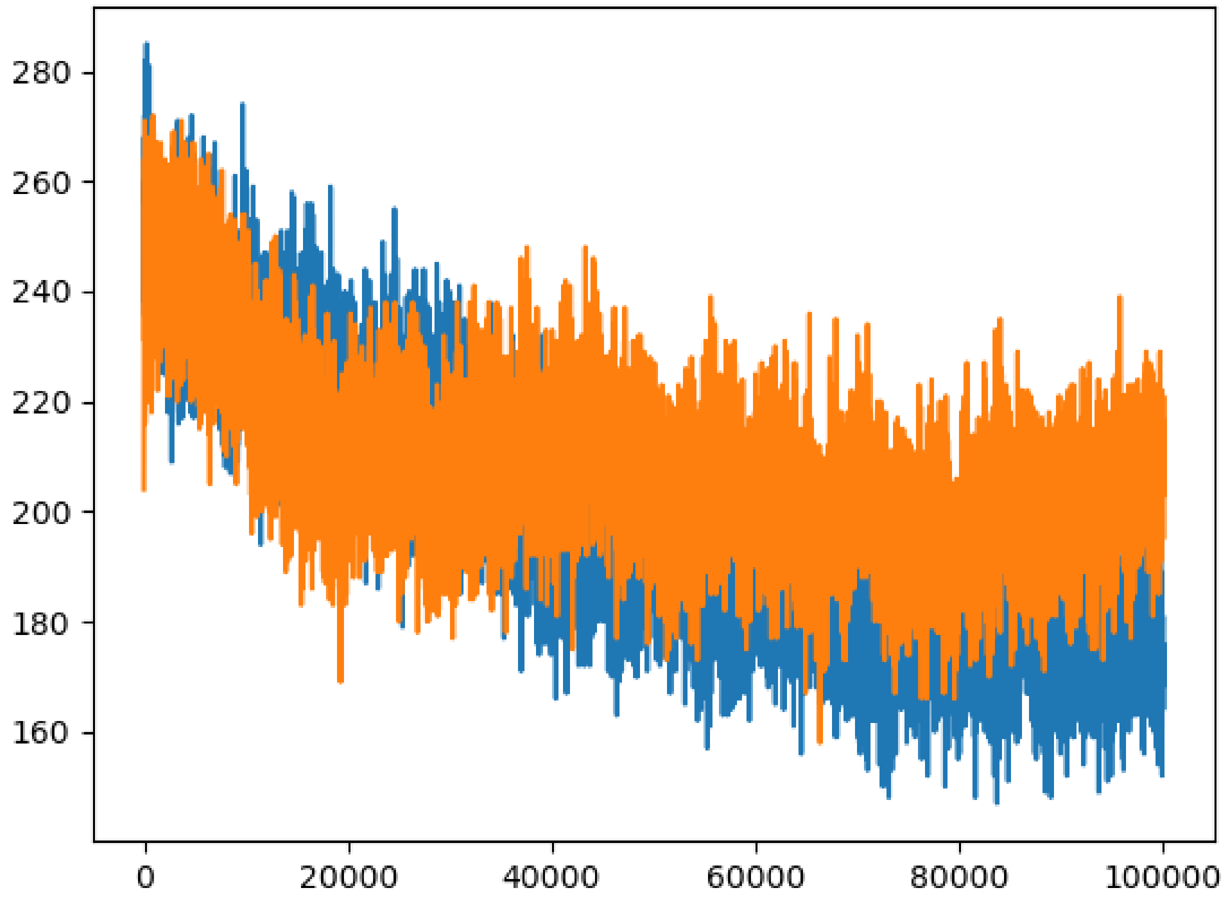


Radius of gyration vs time (no salt vs 0.15 M NaCl)

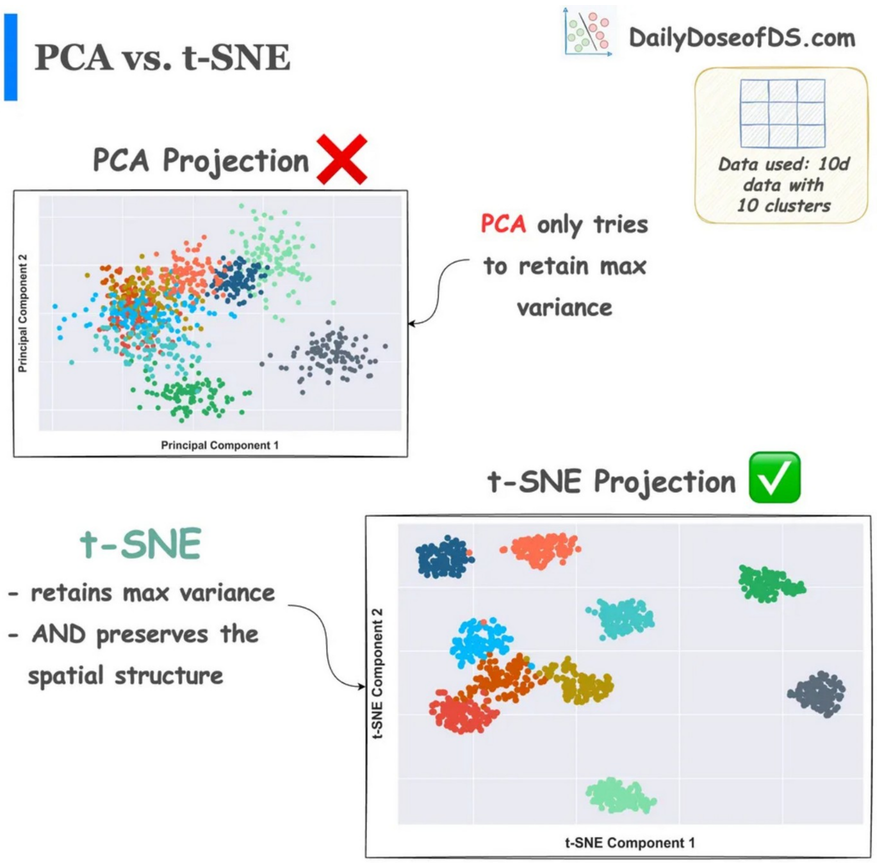




The number of intra-molecular hydrogen bonds vs time



Dimensionality reduction: t-SNE algorithm



x_i —Project→ y_i

High-dimensional data point → Low-dimensional data point

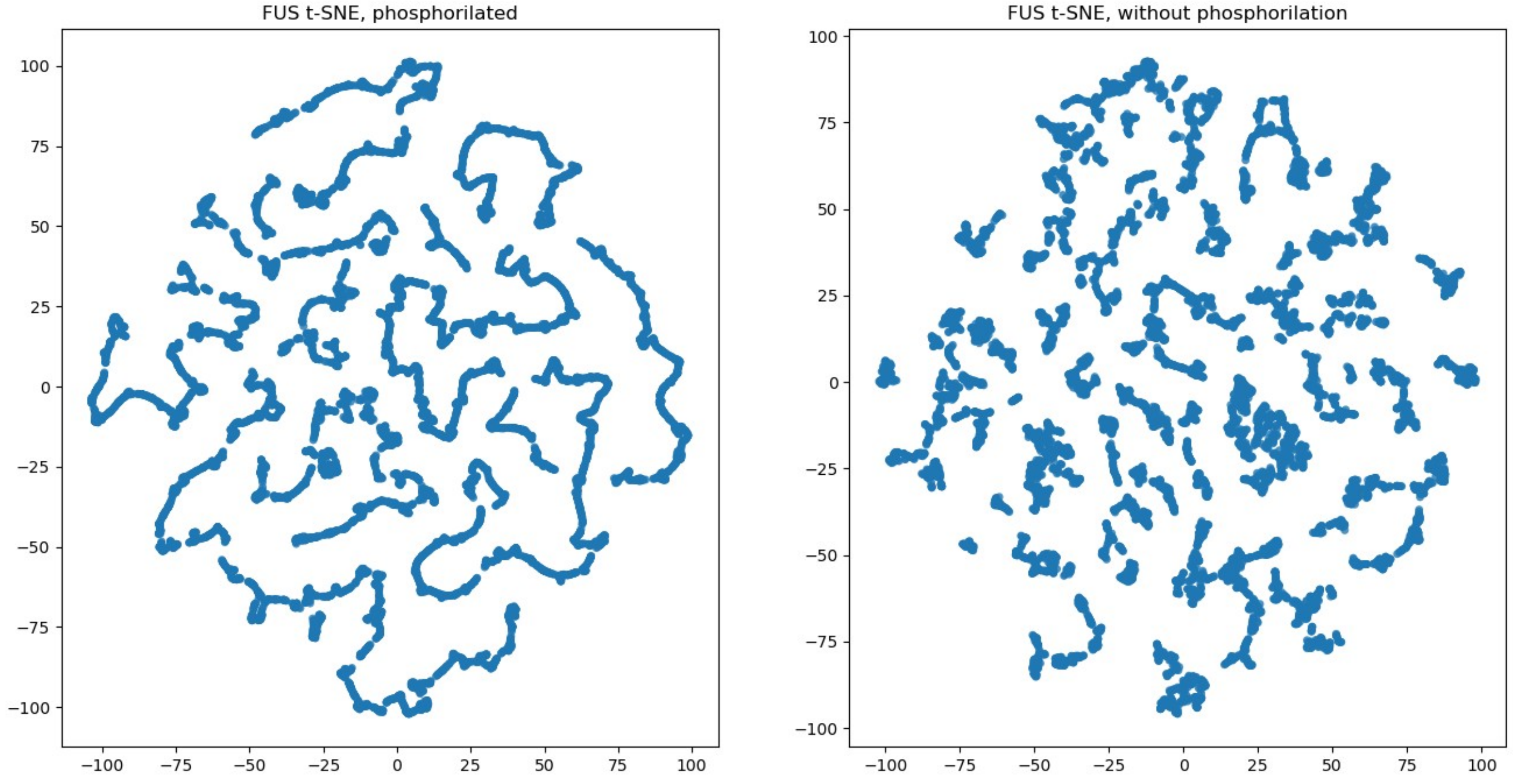
$$p_{j|i} = \frac{\exp\left(-\|\mathbf{x}_i - \mathbf{x}_j\|^2 / 2\sigma_i^2\right)}{\sum_{k \neq i} \exp\left(-\|\mathbf{x}_i - \mathbf{x}_k\|^2 / 2\sigma_i^2\right)}$$

$$\mathrm{KL}\left(P \,\|\, Q\right) = \sum_{i \neq j} p_{ij} \log \frac{p_{ij}}{q_{ij}}$$

$$q_{ij} = \frac{\left(1 + \|\mathbf{y}_i - \mathbf{y}_j\|^2\right)^{-1}}{\sum_k \sum_{l \neq k} \left(1 + \|\mathbf{y}_k - \mathbf{y}_l\|^2\right)^{-1}}$$

$$q_{j|i} = \frac{\exp\left(-\|y_i - y_j\|^2\right)}{\sum_{k \neq i} \exp\left(-\|y_i - y_k\|^2\right)}$$

t-SNE (t-distributed stochastic neighbor embedding) projection: the effect of phosphorilation



Conclusions:

- MD simulation confirmed the experimental results for the FUS fibril destabilization

- Dynamics of the the phosphorylated FUS fibril pass through a quasi-continuous manifolds of states separated by free energy barriers

- The manifolds of states that the WT FUS fibril passes through are more compact than the phosphorylated ones.

Conclusions:

- MD simulation confirmed the experimental results for the FUS fibril destabilization for different salt concentrations

- Dynamics of the the phosphorylated FUS fibril pass through many basins of attraction separated (probably) by free energy barriers

- The basins of attraction that the WT FUS fibril passes through are more compact than the phosphorylated ones.

Thank you for your attention