
Random phase approximation, Gaussian chain renormalization, Phase behavior of intrinsically disordered proteins

Yi-Hsuan Lin

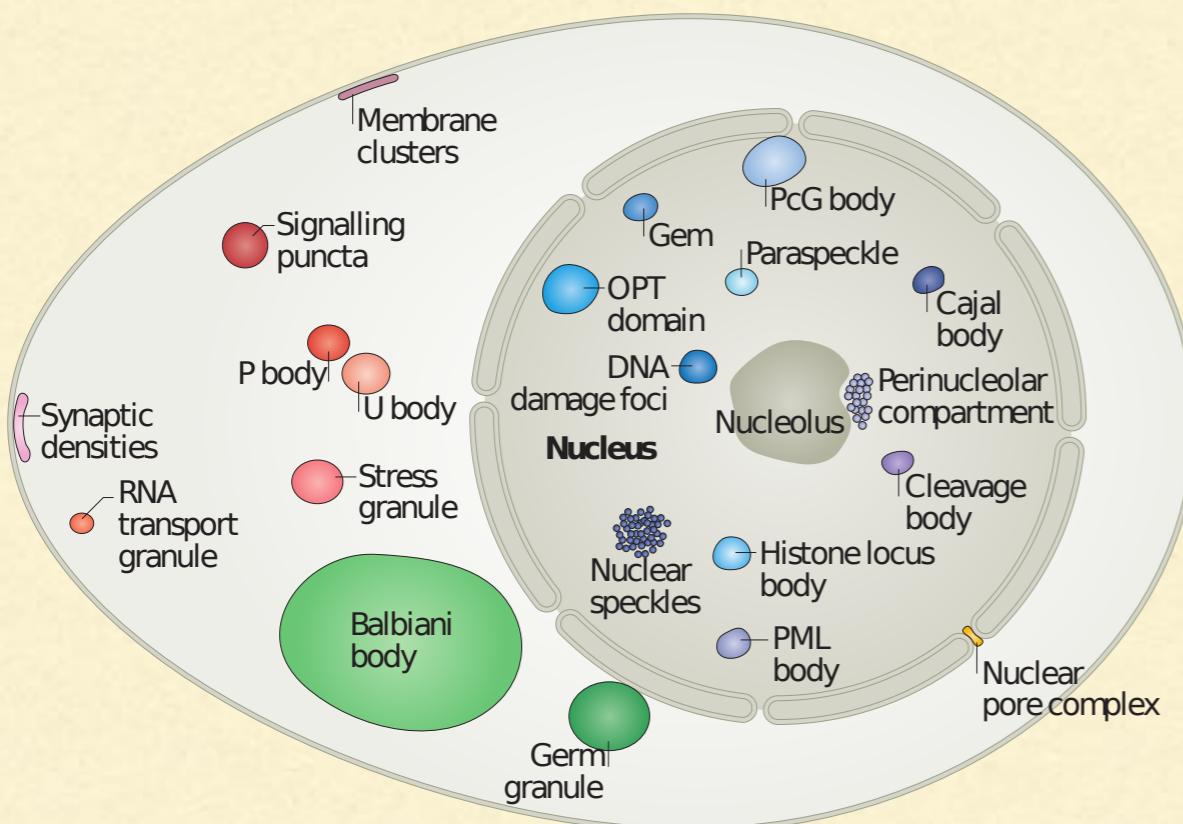
University of Toronto - Hospital for Sick Children

CAP Congress
June 4, 2019

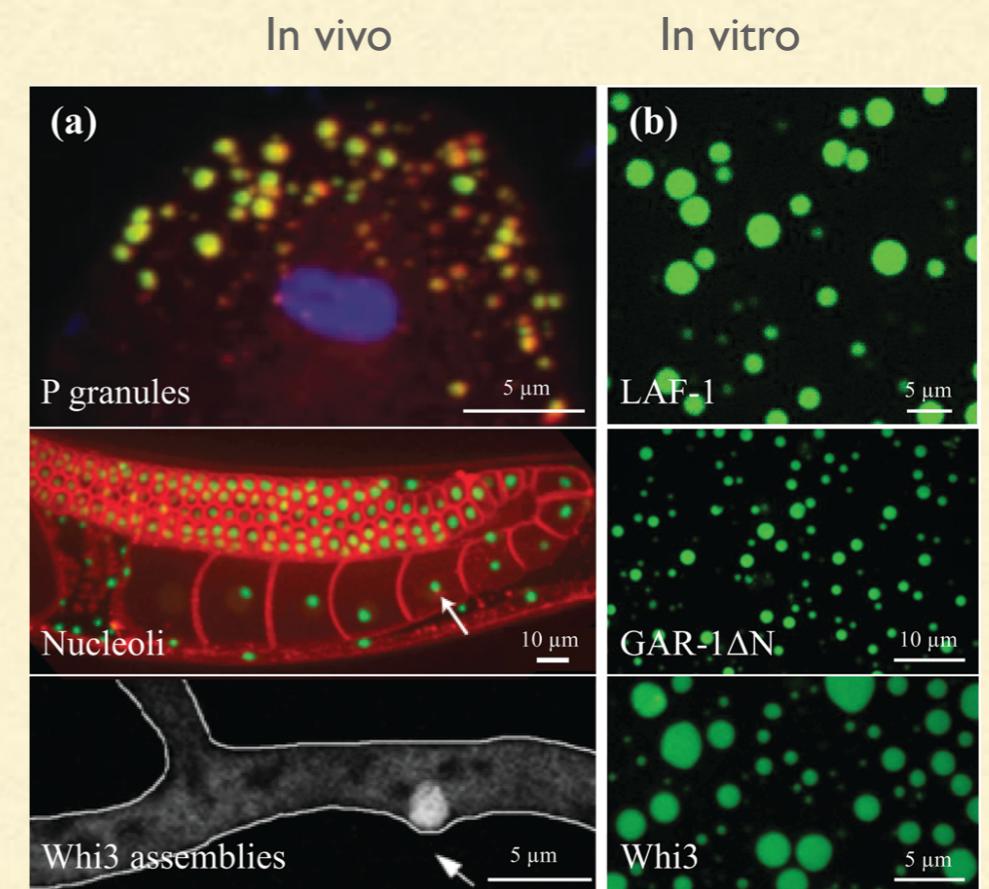


Liquid-liquid phase separation in biology

- Liquid-liquid phase separation (LLPS):
 - Formation of membraneless organelles, the “**biomolecular condensates**”
 - Critical in cellular integrity, homeostasis, gene regulation, and cell growth
 - **Intrinsically disordered proteins (IDPs)** are greatly involved
 - IDPs can also form droplets by themselves *in vitro* (in test tube)



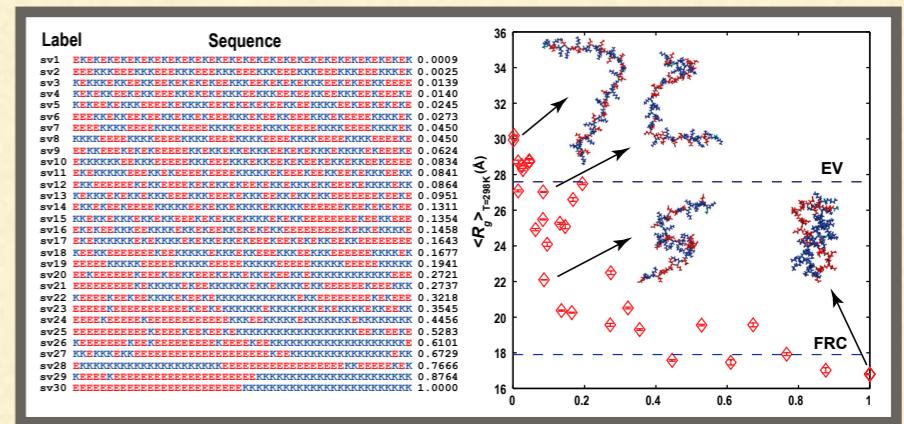
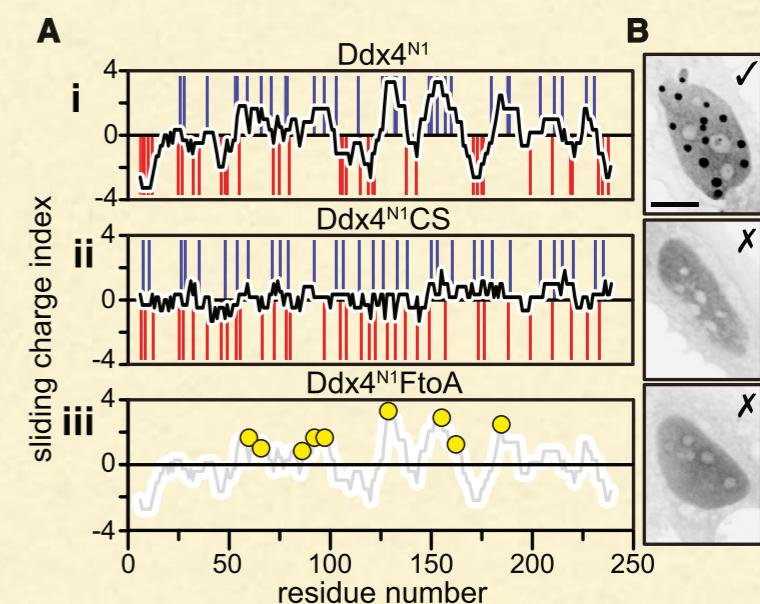
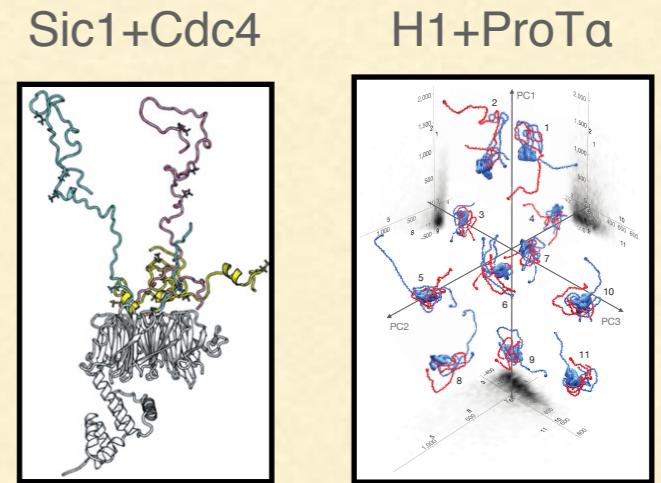
Banani et al (2017) *Nat Rev Mol Cell Biol* **18** 285



Taylor et al (2016) *Soft Matter* **12** 9142

Intrinsically disordered proteins (IDPs)

- Do not fold into a solid 3D structure when isolated
 - Few hydrophobic residues
 - Many charged, polar, π interactions
 - Charge sequences are rigorously synthesized by the cellular machinery
 - **Charged heteropolymers:**
 - Various net charges and fractions of charged residues
 - Various charge sequence patterns
 - Charge properties can be modulated
 - Phosphorylation/dephosphorylation:
$$\text{Ser}^0, \text{Thr}^0, \text{Tyr}^0 \rightleftharpoons \text{Ser}^{2-}, \text{Thr}^{2-}, \text{Tyr}^{2-}$$
 - pH dependency (pKa of charged amino acids):
$$\text{pH} > 6.04 \Rightarrow \text{His}^+ \rightarrow \text{His}^0$$
$$\text{pH} < 4.15 \Rightarrow \text{Glu}^- \rightarrow \text{Glu}^0$$
$$\text{pH} < 3.71 \Rightarrow \text{Asp}^- \rightarrow \text{Asp}^0$$
 - Sequence-specific behavior



Goal:
A general polymer theory for arbitrary charge
sequence pattern

Polymer partition function

- The complete partition function for an IDP solution plus salt and counter ions:
- Decomposition of free energy:
- Mixing Entropy:
- Ion free energy:
- Polymer partition function:

Polymer partition function

- The complete partition function for an IDP solution plus salt and counter ions:

$$Z = \frac{1}{n_p! n_s! n_c! n_w!} \int \prod_{\alpha=1}^{n_p} \prod_{\tau=1}^{N-1} d\mathbf{R}_{\alpha,\tau} \int \prod_i \prod_{a=1}^{n_s+n_c} d\mathbf{r}_a \exp \left\{ -\frac{3}{2l^2} \sum_{\alpha=1}^{n_p} \sum_{\tau=1}^N (\mathbf{R}_{\alpha,\tau+1} - \mathbf{R}_{\alpha,\tau})^2 - \mathcal{U}[\mathbf{R}, \mathbf{r}] \right\}$$

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- Decomposition of free energy:

$$f = -s + f_{\text{ion}} + f_{\text{p}}$$

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$$-s = \frac{\phi_p}{N} \ln \phi_p + \phi_s \ln \phi_s + \phi_c \ln \phi_c + (1 - \phi_p - \phi_s - \phi_c) \ln (1 - \phi_p - \phi_s - \phi_c)$$

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$$f_{\text{ion}} = -\frac{1}{4\pi} \left[\ln(1 + \kappa l) - \kappa l + \frac{1}{2}(\kappa l)^2 \right]$$

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$$\mathcal{U}_{pp}[\mathbf{R}] = \frac{1}{2} \sum_{\alpha, \alpha'=1}^{n_p} \sum_{\tau, \tau'=1}^{N-1} V^{\tau\tau'}(|\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}|)$$

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$$V^{\tau\tau'}(r) = \frac{e^2 \sigma_\tau \sigma_{\tau'} e^{-\kappa r}}{4\pi \epsilon k_B T r} + v_2 \delta^3(r)$$

$$\Rightarrow V_{\mathbf{k}}^{\tau\tau'} = \frac{\sigma_\tau \sigma_{\tau'}}{\nu_{\mathbf{k}}} + v_2 ; \nu_{\mathbf{k}} \equiv \frac{k^2}{4\pi l_B^2} + \sum_s z_s^2 \rho_s$$

Polymer field theory

- A field Hamiltonian derived from Hubbard-Stratonovich transformation

$$Z_p = \int \prod_{\alpha=1}^{n_p} \prod_{\tau=1}^{N-1} d\mathbf{R}_{\alpha,\tau} \exp \left\{ -\frac{3}{2l^2} \sum_{\alpha=1}^{n_p} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\alpha,\tau+1} - \mathbf{R}_{\alpha,\tau})^2 - \sum_{\alpha,\alpha'=1}^{n_p} \left[\sum_{\tau,\tau'=1}^{N-1} \frac{l_B \sigma_\tau \sigma_{\tau'} e^{\kappa |\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}|}}{|\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}|}) + v_2 \delta(\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}) \right] \right\}$$

- One-loop approximation for single-polymer partition function:

Polymer field theory

- A field Hamiltonian derived from Hubbard-Stratonovich transformation

$$\begin{aligned} Z_p &= \int \prod_{\alpha=1}^{n_p} \prod_{\tau=1}^{N-1} d\mathbf{R}_{\alpha,\tau} \exp \left\{ -\frac{3}{2l^2} \sum_{\alpha=1}^{n_p} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\alpha,\tau+1} - \mathbf{R}_{\alpha,\tau})^2 - \sum_{\alpha,\alpha'=1}^{n_p} \left[\sum_{\tau,\tau'=1}^{N-1} \frac{l_B \sigma_\tau \sigma_{\tau'} e^{\kappa |\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}|}}{|\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}|}) + v_2 \delta(\mathbf{R}_{\alpha,\tau} - \mathbf{R}_{\alpha',\tau'}) \right] \right\} \\ &\Rightarrow Z_p = \int \mathcal{D}\psi \mathcal{D}W \exp \left\{ -\frac{1}{2v_2} \int d\mathbf{r} W(\mathbf{r})^2 - \frac{1}{8\pi l_B} \int d\mathbf{r} |\nabla \psi|^2 - n_p \ln Q_p[\psi, W] \right\} \\ Q_p[\psi, W] &= \int \prod_{\tau=1}^{N-1} d\mathbf{R}_\tau \exp \left\{ -\frac{3}{2l^2} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 - i \sum_{\tau=1}^N (\sigma_\tau \psi(\mathbf{R}) + W(\mathbf{R})) \right\} \end{aligned}$$

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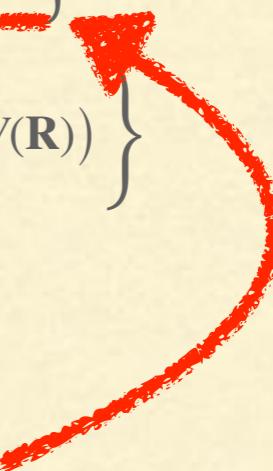
Correlation functions: charge-charge density-density density-charge

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$$\Rightarrow f_p = -\frac{\ln Z_p}{\Omega} = \frac{1}{2} \int \frac{d^3 k}{(2\pi)^3} \frac{v_2}{\nu_{\mathbf{k}}} \det \begin{pmatrix} \nu_{\mathbf{k}} + \rho G_{\mathbf{k}}^{ss} & \rho G_{\mathbf{k}}^{ds} \\ \rho G_{\mathbf{k}}^{ds} & \frac{1}{v_2} + \rho G_{\mathbf{k}}^{dd} \end{pmatrix}$$

Renormalized Gaussian correlation functions

$$Q_p[\psi, W] = \int \prod_{\tau=1}^{N-1} d\mathbf{R}_\tau \exp \left\{ -\frac{3}{2l^2} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 - i \sum_{\tau=1}^N (\sigma_\tau \psi(\mathbf{R}) + W(\mathbf{R})) \right\}$$

$$G_{\mathbf{k}}^{cc} = \frac{1}{N} \sum_{\tau, \tau'=1}^N \sigma_\tau \sigma_{\tau'} \langle e^{i\mathbf{k} \cdot (\mathbf{R}_\tau - \mathbf{R}_{\tau'})} \rangle_{Q_p} \quad , \quad G_{\mathbf{k}}^{dd} = \frac{1}{N} \sum_{\tau, \tau'=1}^N \langle e^{i\mathbf{k} \cdot (\mathbf{R}_\tau - \mathbf{R}_{\tau'})} \rangle_{Q_p} \quad , \quad G_{\mathbf{k}}^{dc} = \frac{1}{N} \sum_{\tau, \tau'=1}^N \sigma_\tau \langle e^{i\mathbf{k} \cdot (\mathbf{R}_\tau - \mathbf{R}_{\tau'})} \rangle_{Q_p}$$

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- Polymer is a bare Gaussian chain \Rightarrow Random phase approximation (RPA)

$$Q_p[\psi, W] \approx \int \prod_{\tau=1}^{N-1} d\mathbf{R}_\tau \exp \left\{ -\frac{3}{2l^2} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 \right\} \Rightarrow \langle e^{i\mathbf{k} \cdot (\mathbf{R}_\tau - \mathbf{R}_{\tau'})} \rangle_{Q_p} \approx \exp \left\{ -\frac{1}{6}(kl)^2 |\tau - \tau'| \right\}$$

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Inappropriate for polyelectrolytes

Renormalized Gaussian correlation functions

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- “Renormalized” Gaussian chain \Rightarrow rG-RPA

$$Q_p[\psi, W] \approx \int \prod_{\tau=1}^{N-1} d\mathbf{R}_\tau \exp \left\{ -\frac{3}{2ll_{eff}} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 \right\} \Rightarrow \langle e^{i\mathbf{k} \cdot (\mathbf{R}_\tau - \mathbf{R}_{\tau'})} \rangle_{Q_p} \approx \exp \left\{ -\frac{x}{6}(kl)^2 |\tau - \tau'| \right\}$$

$l_{eff} = l \cdot x[\psi, W]$

Renormalized Gaussian correlation functions

$$Q_p[\psi, W] = \int \prod_{\tau=1}^{N-1} d\mathbf{R}_\tau \exp \left\{ -\frac{3}{2l^2} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 - i \sum_{\tau=1}^N (\sigma_\tau \psi(\mathbf{R}) + W(\mathbf{R})) \right\}$$

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$$l_{eff} = l \cdot x[\psi, W]$$

- $x[\psi, W]$ solved by variational theorem:

$$H_x = \frac{3}{2xl^2} \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 , \quad \Delta H = \frac{3}{2l^2} \left(1 - \frac{1}{x} \right) \sum_{\tau=1}^{N-1} (\mathbf{R}_{\tau+1} - \mathbf{R}_\tau)^2 + \sum_{\tau, \tau'=1}^N [\sigma_\tau \sigma_{\tau'} \langle \psi \psi \rangle + \langle WW \rangle + (\sigma_\tau + \sigma_{\tau'}) \langle W \psi \rangle]$$

Renormalized Gaussian correlation functions

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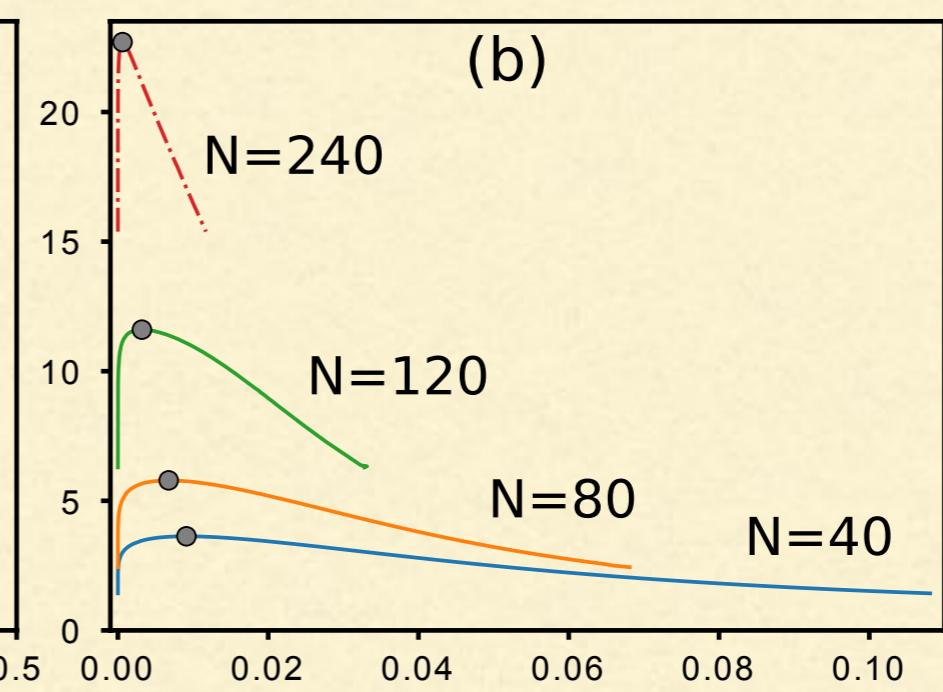
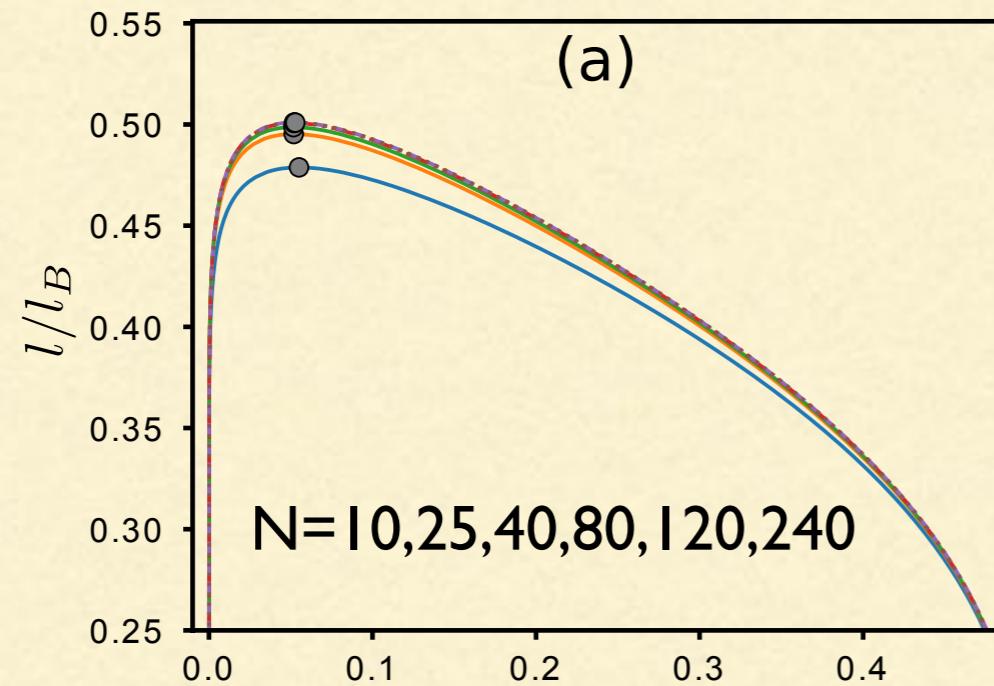
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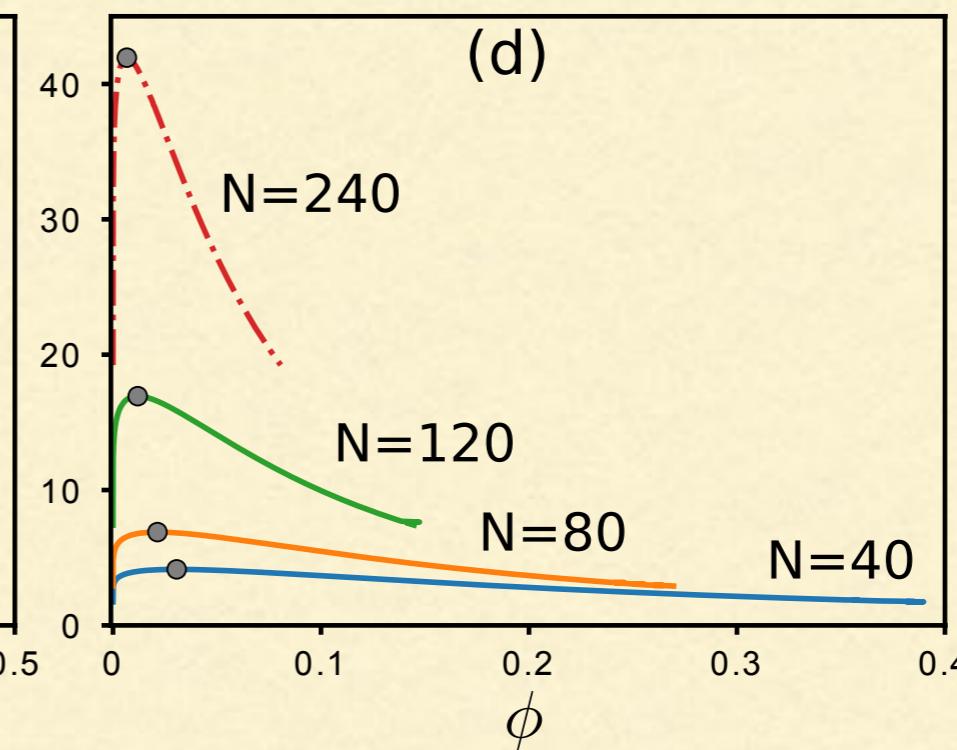
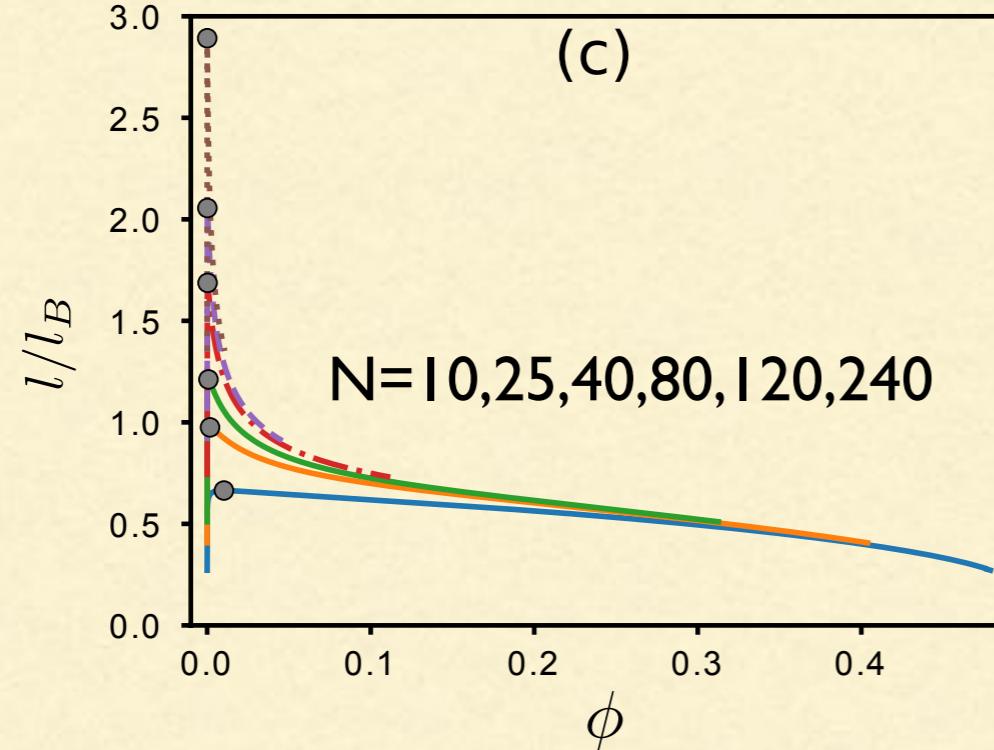
$$\boxed{\langle R_{\text{end-to-end}}^2 \rangle_x \langle \Delta H \rangle_x = \langle R_{\text{end-to-end}}^2 \Delta H \rangle_x}$$

Polyelectrolytes and 4-block polyampholytes

rG-RPA

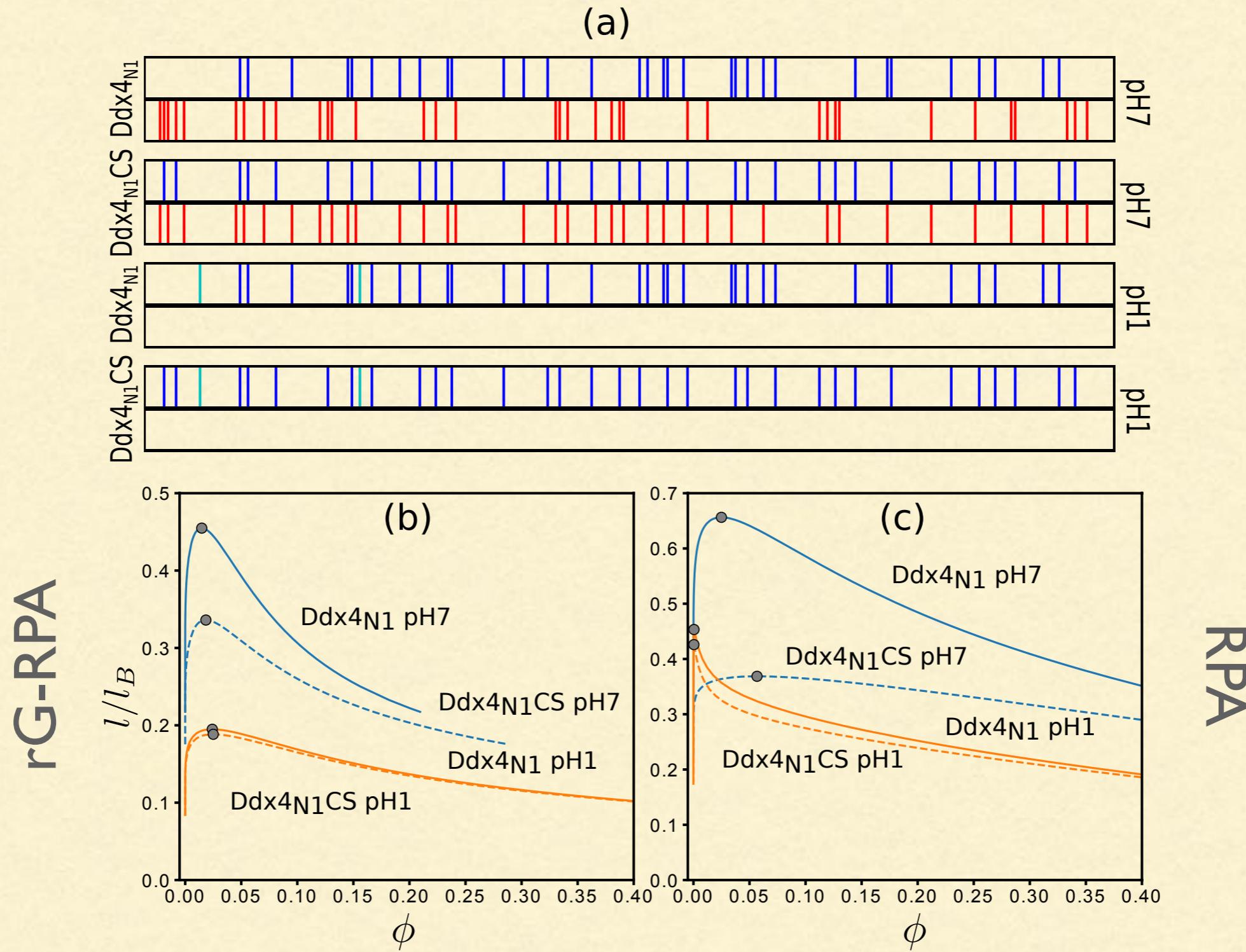


RPA



ϕ

Ddx4 at different pH values



Summary

- A free energy formula for polymers with arbitrary charge sequences is constructed by combining **random phase approximation** and **renormalized Gaussian chain**

Ongoing

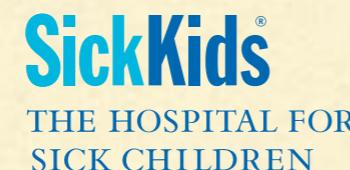
- To compare with phase separation experiments of intrinsically disordered proteins

Acknowledgement

Prof. Hue Sun Chan



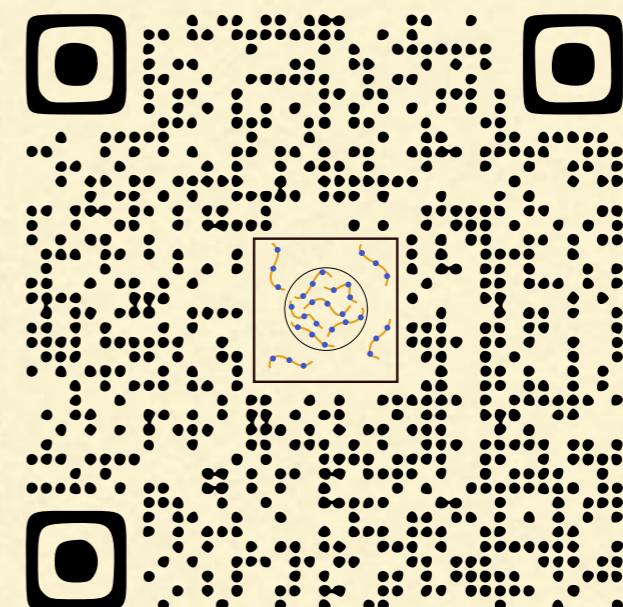
Prof. Julie Forman-Kay



Prof. Kingshuk Ghosh



Polymer physics for
phase separation in biology



<http://individual.utoronto.ca/yihuanlin/>

Thermodynamic theory for phase separation

- Define a free energy as a function of protein volume fraction:

$$\frac{F}{T} = f(\phi)$$

- Spinodal phase separation:

$$d^2f/d\phi^2 = 0$$

- Binodal phase separation: common tangent

$$(df/d\phi)_\alpha = (df/d\phi)_\beta = \frac{f_\alpha - f_\beta}{\phi_\alpha - \phi_\beta}$$

