Sriram Fest

Happy Anniversary!

Examples of Fluctuations and microphase separation in Nuclei

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The characteristics of nuclear membrane fluctuations in stem cells

Sedigheh Ghanbarzadeh Nodehi[a], G. V. Shivashankar[b,c], Jacques Prost[d,e,1], and Farshid Mohammad-Rafiee[a,f,1]

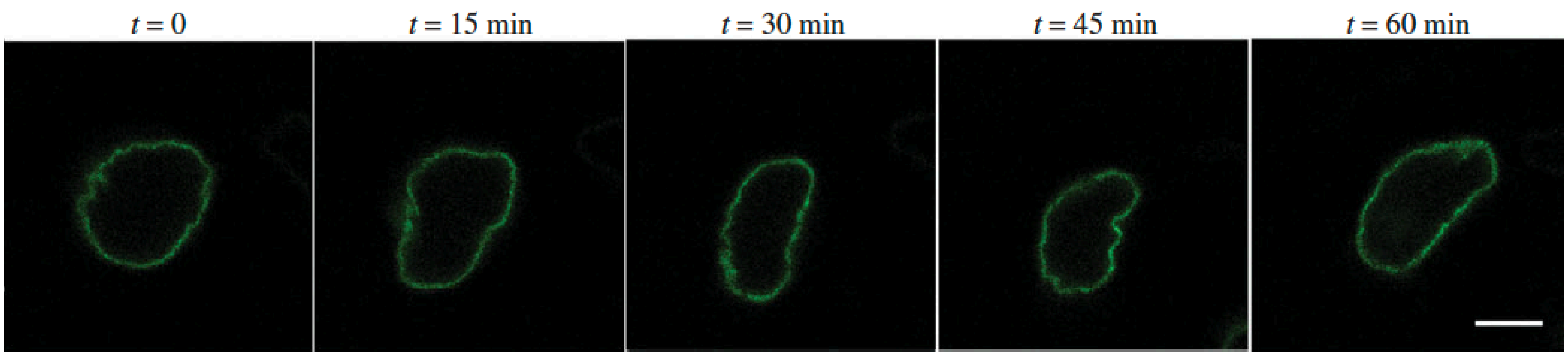
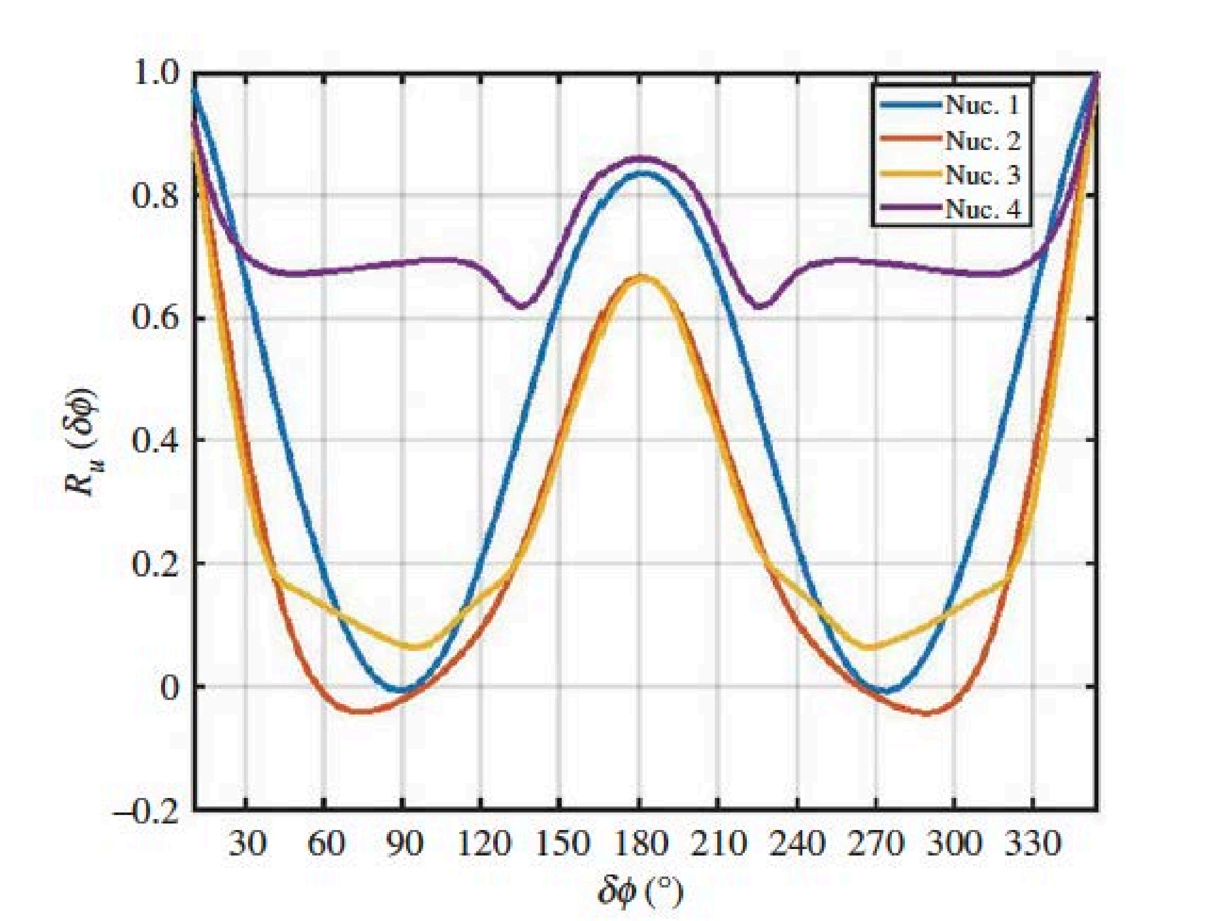
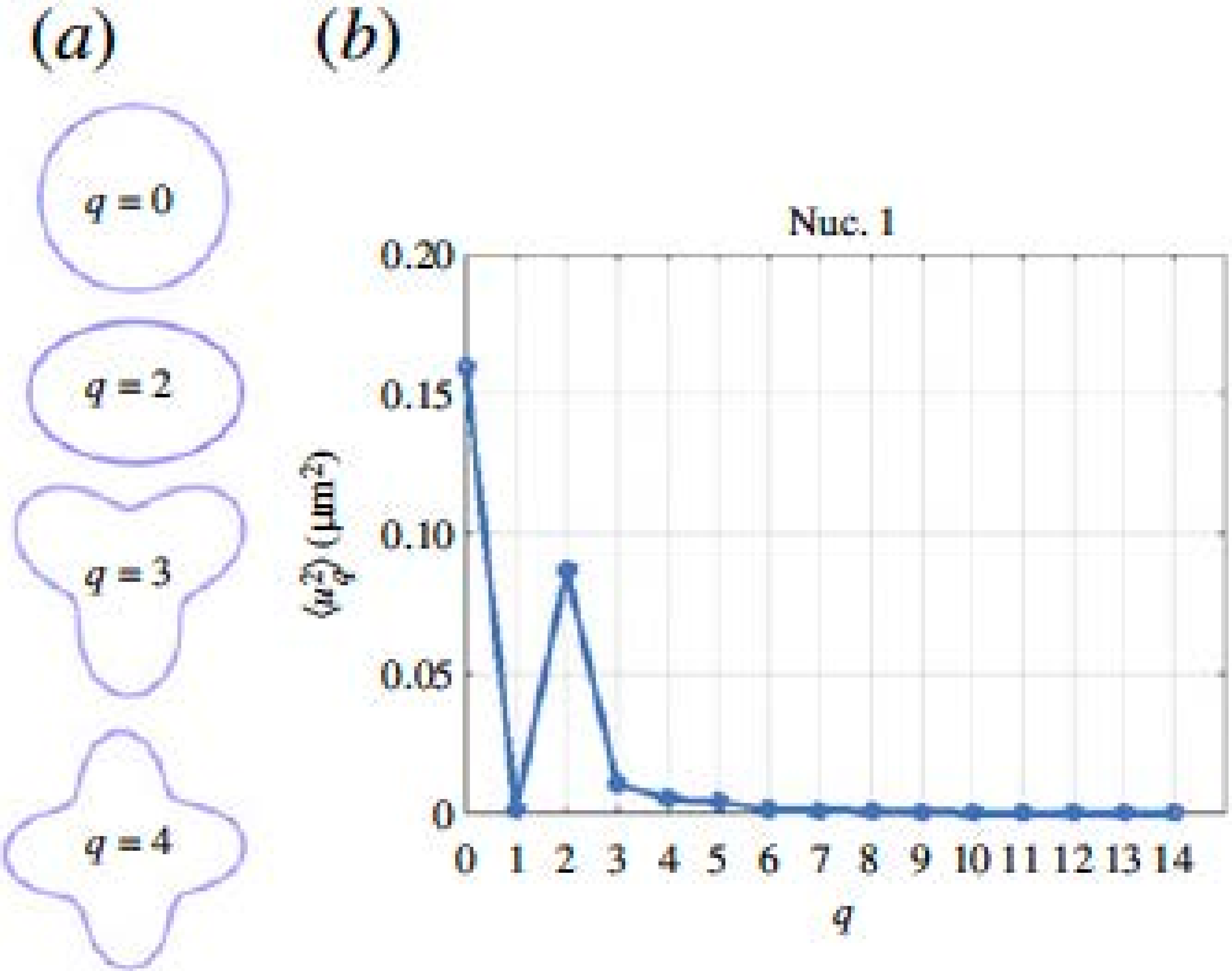


Figure 1. Stained membrane of the nucleus of an ES cell [16] over time with 15 min time intervals is shown. The scale bar is 5 μm. The total image sequences are in 10 s time resolution and reveal the highly dynamic nature of the ES cell nucleus.



$$R_u(\delta\phi) = \frac{\langle u(\phi,\, t)\, u(\phi + \delta\phi,\, t)\rangle_{\phi,t}}{\left\langle u(\phi,\, t)^2 \right\rangle_{\phi,t}},$$

$$u(\phi, t) = r(\phi, t) - \langle r(\phi)\rangle$$


(a)
(b)
q = 0
q = 2
q = 3
q = 4
Nuc. 1
0.20
0.15
0.10
0.05
0
⟨u_q^2⟩ (μm^2)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
q

Two-time correlations

$R_{00}(\tau) = \langle w_0(t)w_0(t+\tau)\rangle = \langle w_0(t')w_0(t'-\tau)\rangle = R_{00}(-\tau)$

$R_{20}(\tau) = \langle w_2(t)w_0(t+\tau)\rangle = \langle w_0(t')w_2(t'-\tau)\rangle = R_{02}(-\tau)$

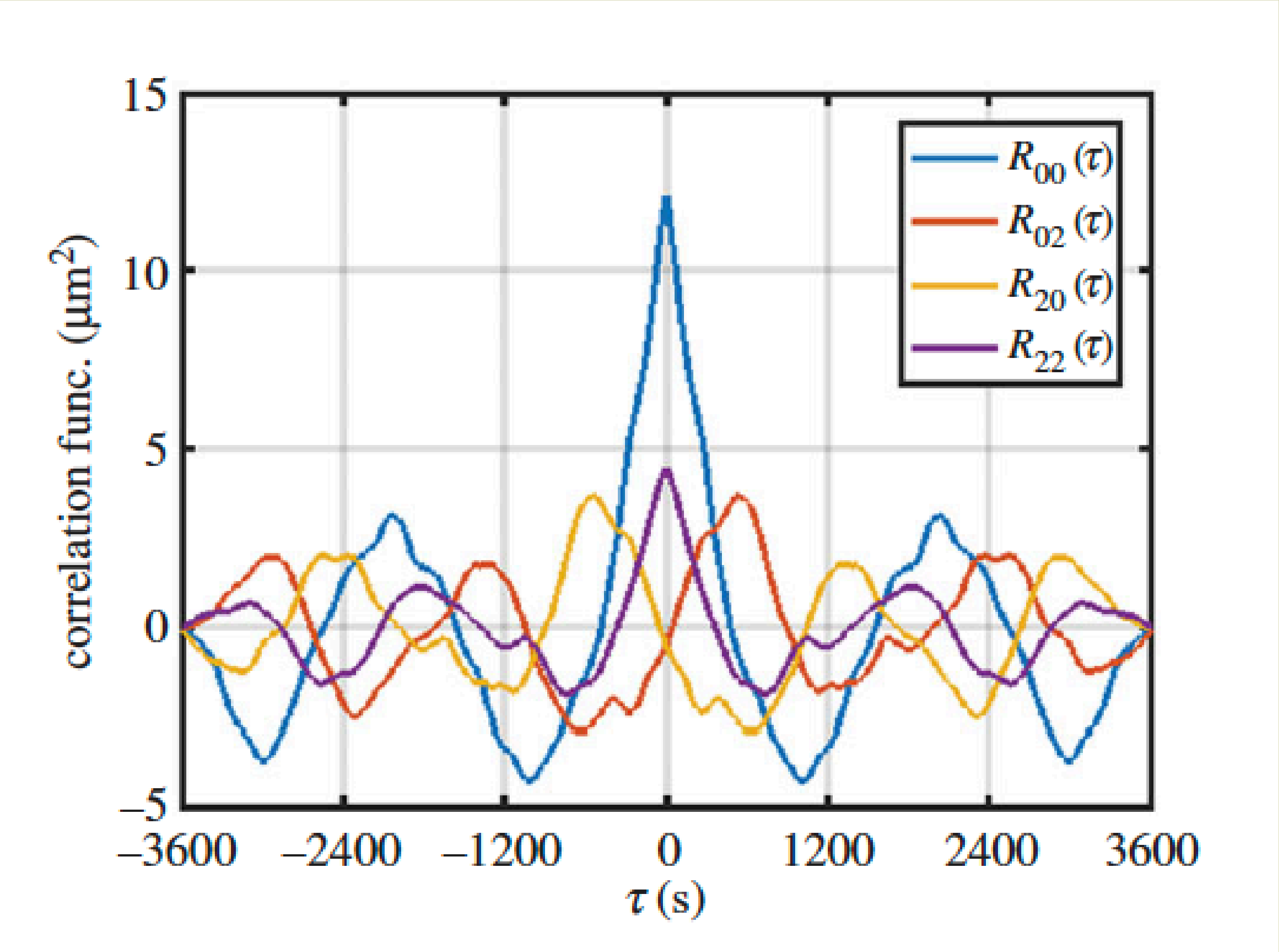
$R_{02}(\tau) = \langle w_0(t)w_2(t+\tau)\rangle = \langle w_2(t')w_0(t'-\tau)\rangle = R_{20}(-\tau)$

$R_{22}(\tau) = \langle w_2(t)w_2(t+\tau)\rangle = \langle w_2(t')w_2(t'-\tau)\rangle = R_{22}(-\tau)$

$t'=t+\tau$, time translational symmetry, product commute

If (t, -t) symmetry: $R_{20}(\tau) = R_{02}(\tau)$, equilibrium

A contrario, if $R_{20}(\tau) \neq R_{02}(\tau)$: Non equilibrium



$$R_{02}(\tau) \neq R_{20}(\tau)$$

OUT OF EQUILIBRIUM

$$\frac{dw_0}{dt}(t) = A\,w_0(t) + B\,w_2(t) + \zeta_0(t)$$

$$\frac{dw_2}{dt}(t) = C\,w_0(t) + D\,w_2(t) + \zeta_2(t),$$

$$\frac{dR_{00}}{d\tau}(\tau) = A\,R_{00}(\tau) + B\,R_{20}(\tau),$$

$$\frac{dR_{02}}{d\tau}(\tau) = A\,R_{02}(\tau) + B\,R_{22}(\tau),$$

$$\frac{dR_{20}}{d\tau}(\tau) = C\,R_{00}(\tau) + D\,R_{20}(\tau)$$

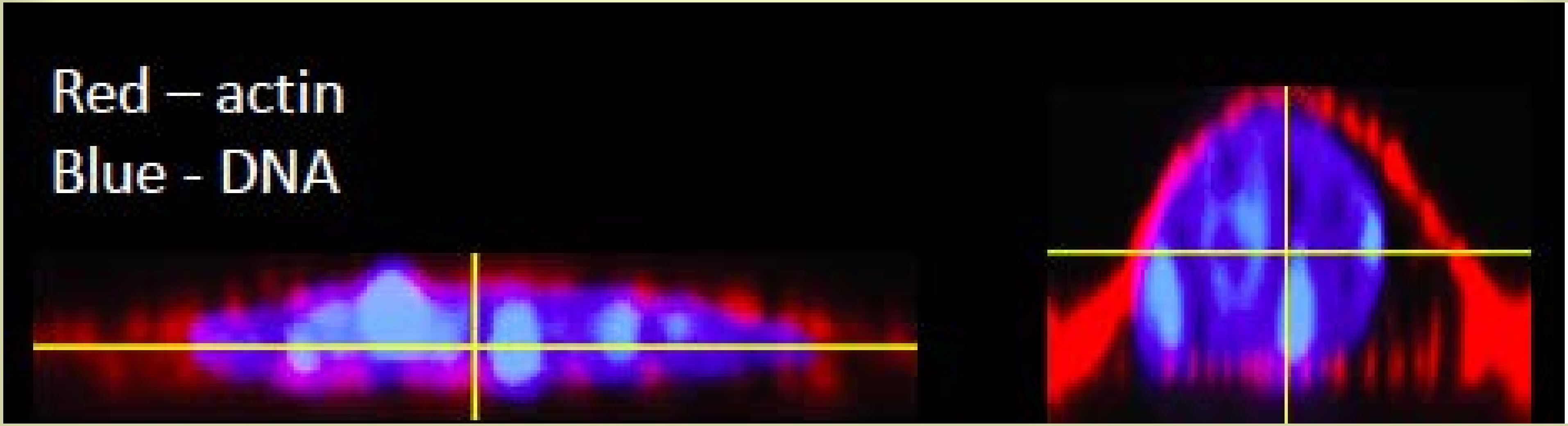
$$\frac{dR_{22}}{d\tau}(\tau) = C\,R_{02}(\tau) + D\,R_{22}(\tau).$$

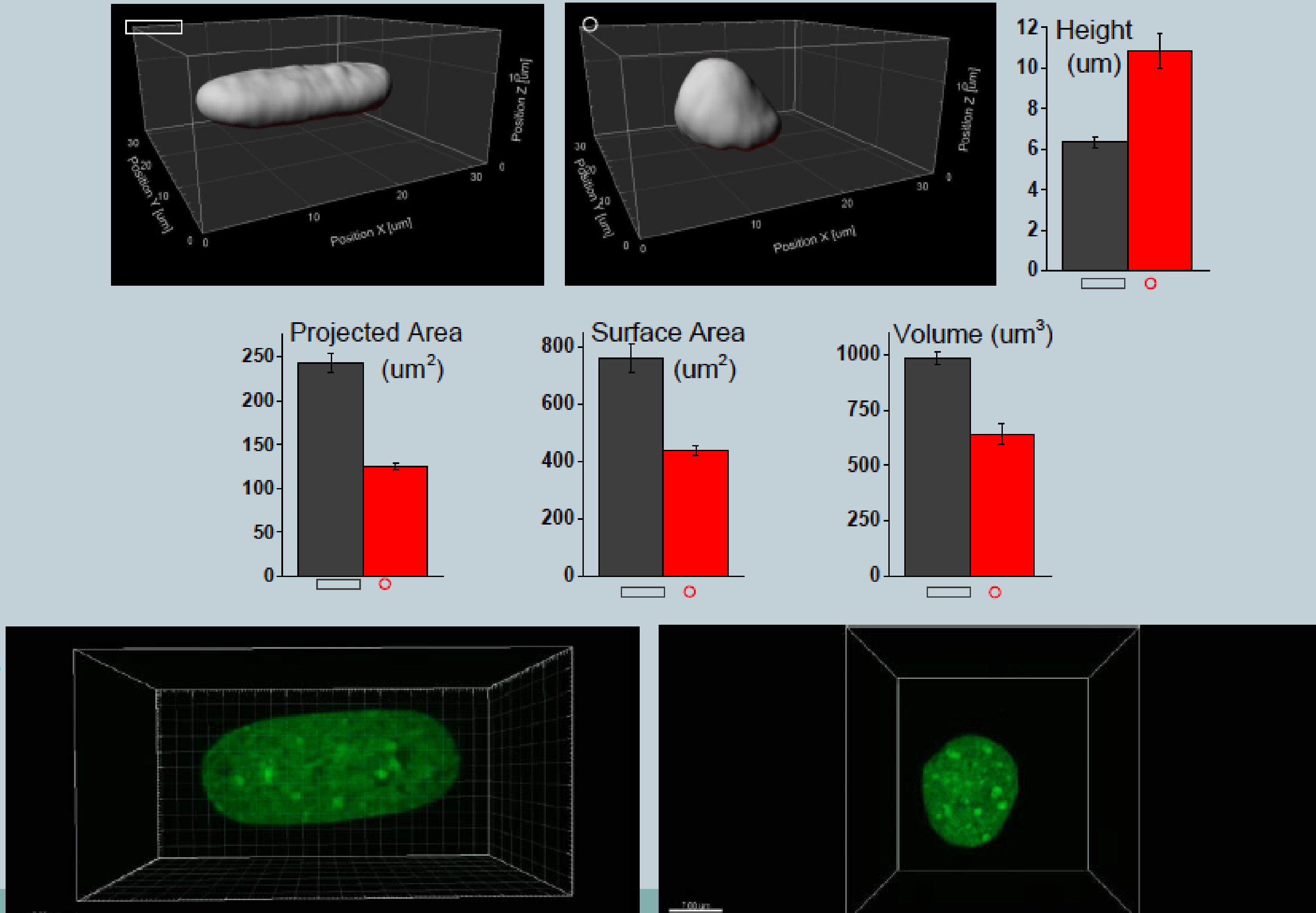
Onsager 👎 😀

Cell Nucleus Fluctuations

differentiated cell

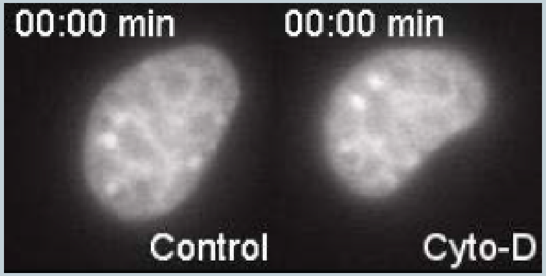
E. Makhija, D. S. Jokhun, and G. V. Shivashankar, Proc. Natl. Acad. Sci. U.S.A. , 113 , E32 (2016).

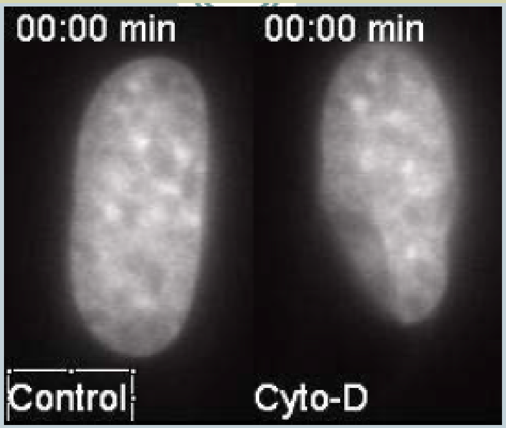


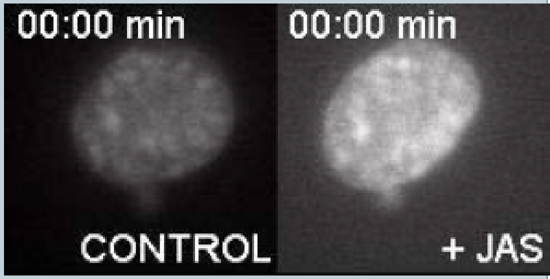


Position X [um]
Position Y [um]
Position Z [um]
Height
(um)
12
10
8
6
4
2
0
Projected Area
(um2)
250
200
150
100
50
0
Surface Area
(um2)
800
600
400
200
0
Volume (um3)
1000
750
500
250
0

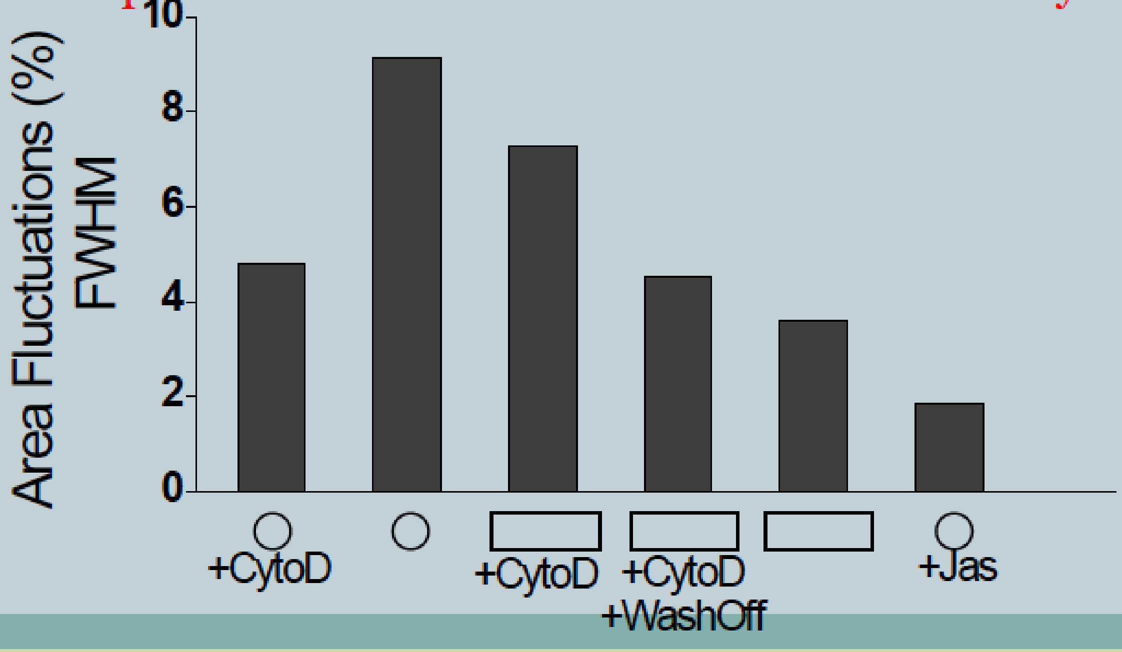
H2B

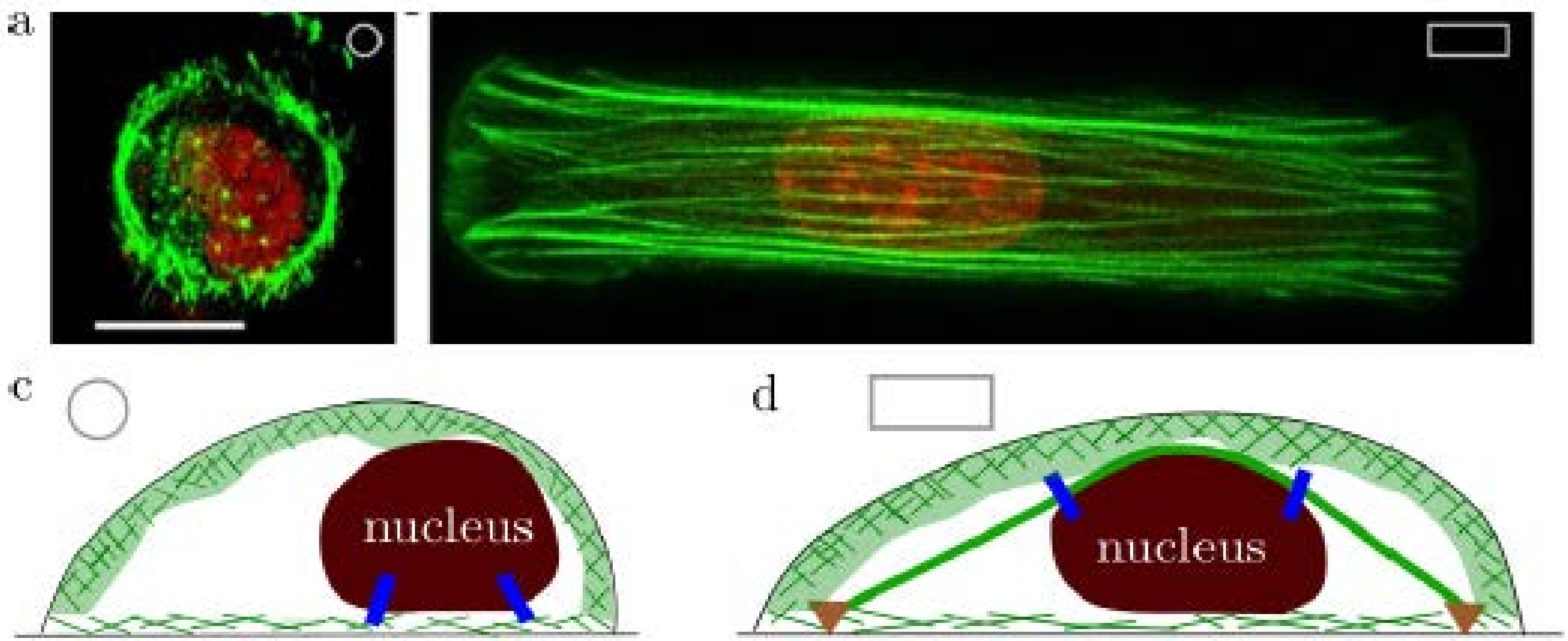




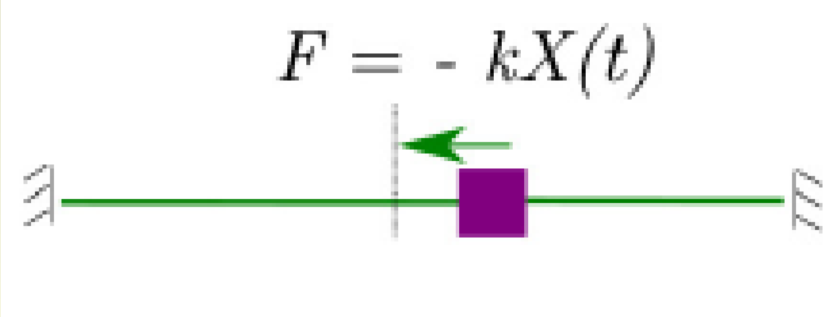


Non-monotonous dependence of PNA fluctuations on Actin Polymerization State!





J.-F. Rupprecht,[1] A. Singh Vishen,[2] G. V. Shivashankar,[1] M. Rao,[2] and J. Prost[1,



$$(\tau_v \partial_t + 1)\sigma(x,t) = \eta \partial_x v(x,t) + \zeta \Delta\mu + \theta_A + \phi_T,$$

$$\langle \phi_T(x,t)\phi_T(x',t')\rangle \;=\; 2\Lambda_T \delta_{x,x'}\delta_{t,t'}$$

$$\langle \theta_A(x,t)\theta_A(x',t')\rangle = \Lambda_A \delta_{x,x'} \exp(-|t-t'|/\tau_A)/\tau_A.$$

$$(\tau_v \partial_t + 1)\sigma^{(L)} = \zeta\Delta\mu + \frac{\eta \dot{x}_t}{L + x_t} + \frac{\int_{-L}^{x_t}(\theta_A + \phi_T)}{L + x_t},$$

$$\sigma^{(L)} \;-\; \sigma^{(R)} \;=\; f(x_t) \;-\; m\dot{v}_t$$

$$\tau_v \ddot{v}_t + \dot{v}_t + \frac{\lambda(x_t)}{m} v_t = \frac{f + \tau_v \dot{f} + \mu(x_t)\left[\Theta_A + \Phi_T\right]}{m},$$

$$(\langle \Theta_A(t)\Theta_A(s)\rangle \;=\; \Lambda_A \exp(-|t \;-\; s|/\tau_A)/\tau_A)$$

$$\mu^2(x) = \frac{2L}{L^2 - x^2} = \frac{\lambda(x)}{\eta}.$$

Multiplicative noise

$$\tau_v \;\ll\; \tau_A \;\ll\; t_u,$$

$$t_u \;=\; \eta^2 L/\max(\Lambda_A, \Lambda_T)$$

$$\dot{x}_t = \frac{f}{\lambda} - \frac{\Lambda_T \mu \mu'}{2\lambda^2} + \frac{\mu\left[\Theta_A + \Theta_T\right]}{\lambda},$$

$$\partial_t P = \partial_x \left\{ \left[-\frac{f}{\lambda} + \frac{\Lambda_T \mu \mu'}{2\lambda^2} \right] P + \frac{\Lambda \mu}{2\lambda} \partial_x \frac{\mu}{\lambda} P \right\},$$

$$\Lambda = (\Lambda_T^2 + \Lambda_A^2)^{1/2}.$$

$$\partial_t P = \partial_x \left\{ -\frac{f}{\lambda} P + \Lambda_A \frac{\mu}{2\lambda} \partial_x \frac{\mu}{\lambda} P \right\}$$

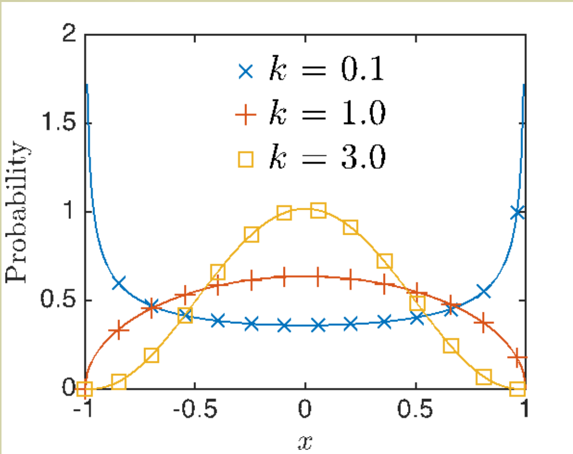
$$P(x) = \frac{\sqrt{\pi}\,\Gamma\left(k + \frac{1}{2}\right)}{L\Gamma(k+1)} (1 - (x/L)^2)^{-1/2+k},$$

$$k = (KL^2\eta)/(2\Lambda_A)$$

Maximal fluctuations when noise-induced destabilization and focusing force are balanced

$$P(x) = \frac{\sqrt{\pi}\Gamma\left(k+\frac{1}{2}\right)}{\Gamma(k+1)}(1-x^2)^{-1/2+k}, \longrightarrow \mathrm{Var}[X] \propto \mathbf{1/(k+1/2)^{3/2}}$$

no optimal restoring force/activity?

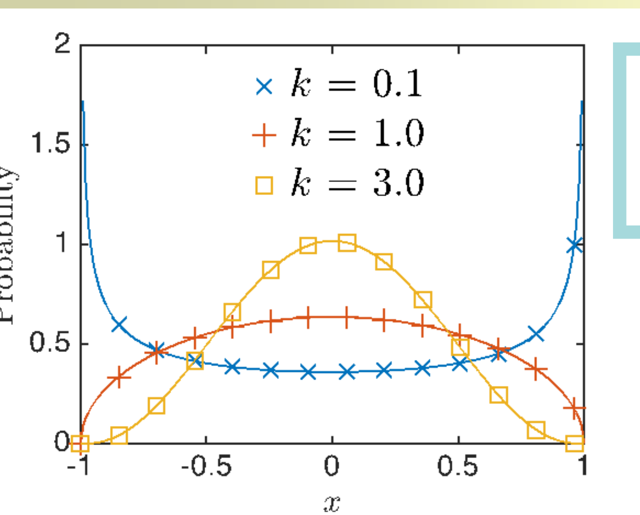


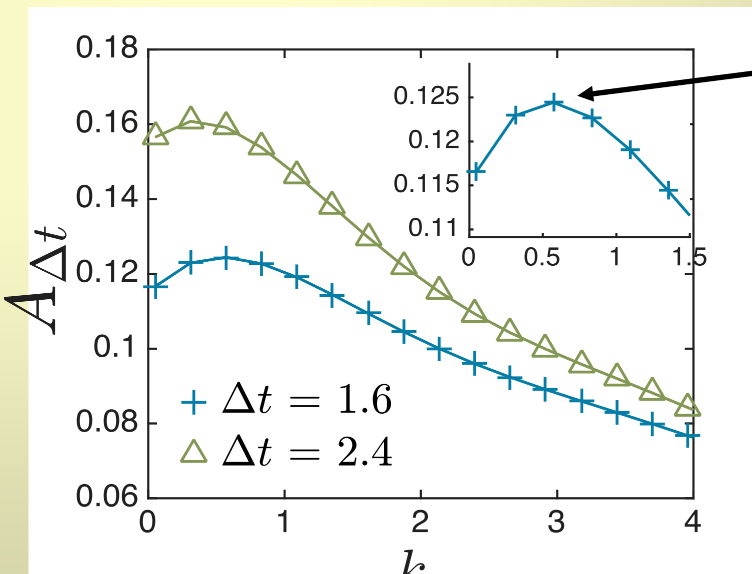
> what is measured in experiments is $A_{\Delta t} = \left\langle (X - \bar{X}_{\Delta t})^2 \right\rangle_s$

$\langle . \rangle_s$: average over large number of cells (random realisation)
$\bar{X}_{\Delta t}$ is an average position over an observation window Δt

Mean time to explore the whole gel: $t_{\mathrm{MFPT}} \approx 10 \times \eta/\gamma$

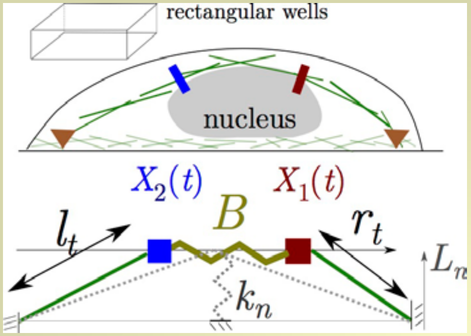
short-times $(\Delta t < t_{\mathrm{MFPT}})$: exploration limited to maximal *P(x)* regions





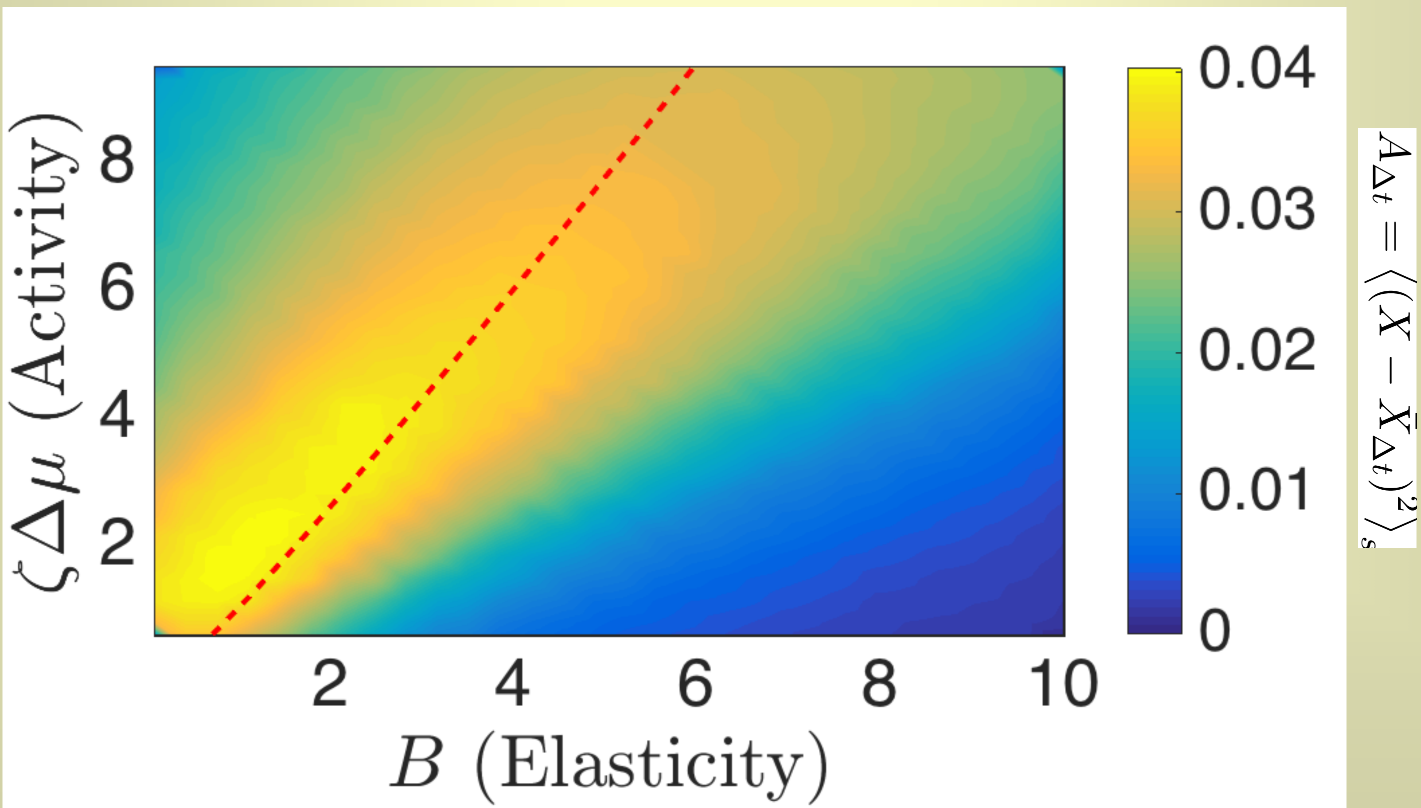
$k_{\mathrm{opt}} \to 1/2$

long-times $(\Delta t > t_{\mathrm{MFPT}})$: $A_{\Delta t} \to Var[X] \propto 1/K \to k_{\mathrm{opt}} \to 0$



Limit case: $L_n = 0$ $\zeta\Delta\mu_{opt} \approx 2B - \sqrt{B}$

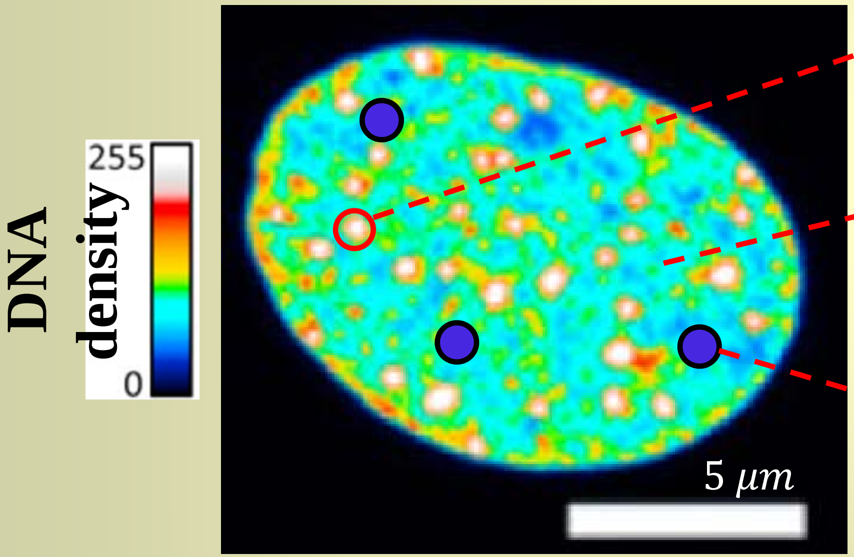
Optimum Activity exist again!



How enzymatic activity is involved in chromatin organization

Rakesh Das , Takahiro Sakaue, GV Shivashankar, Jacques Prost, Tetsuya Hiraiwa

➢ <u>Phase separated organization of chromatin</u>



Heterochromatin –
transcriptionally repressive

Euchromatin –
transcriptionally active

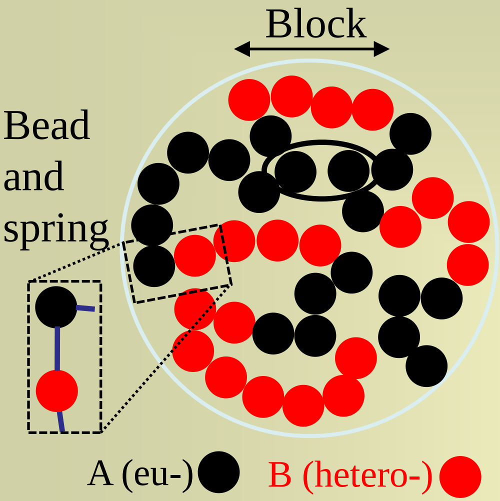
[Transcription – copying DNA into RNA]

Subnuclear condensates (SNCs) –
droplets of biochemical agents
(schematic)

S. Talwar et al., Biophys. J. **104**, 553 (2013)

G. V. Shivashakar,
Nat. Rev. Mol. Cell Biol. **18**, 717 (2017)

Copolymer model with Transient-Linking Activity (TLA)



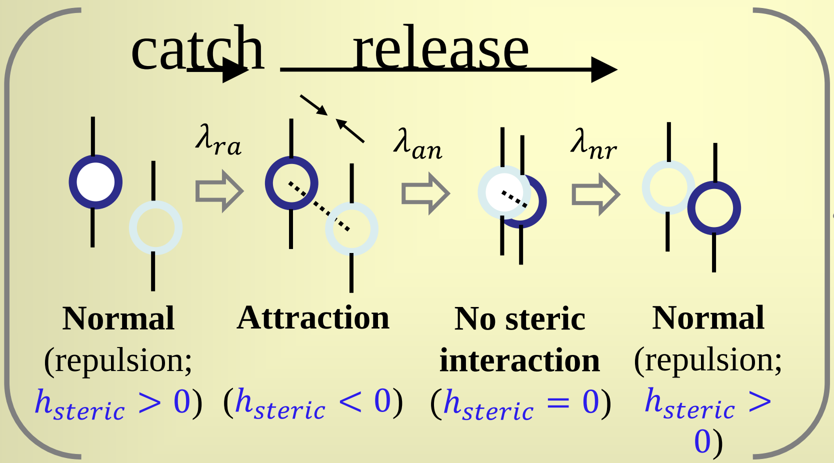
$$\frac{\partial \boldsymbol{x}_b}{\partial t} = -\Gamma \frac{\partial H(\boldsymbol{x}_b)}{\partial \boldsymbol{x}_b} + \sqrt{2\,\Gamma}\,\boldsymbol{\zeta}_b$$

$$H = \sum_{\text{n. n.}} h_{chain} + \sum_{\text{short range}} h_{steric} - \sum_{\text{short range}} h_{HC\ affinity} + H_{confine.}$$

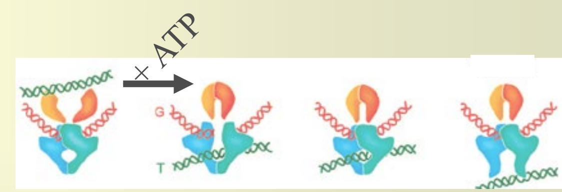
(short range)

$\zeta_b \equiv$ Univariate white Gaussian noise with zero mean

Mechanical perturbation



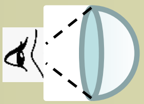
Reminiscent to Topoisomerase-II enzyme's action – resolves topological constraints of chromatin

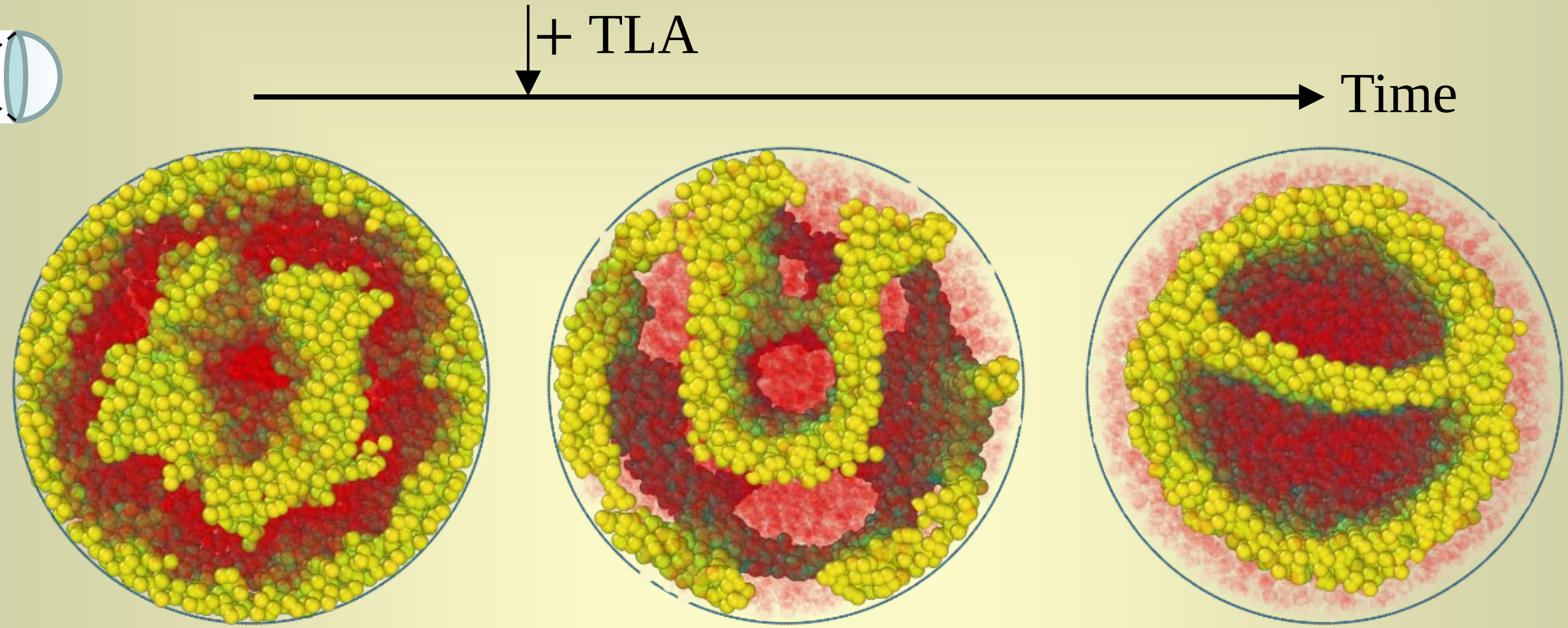


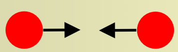
J. Roca, Nucleic Acids Res. **37**, 721 (2009)

- Transient-linking activity (TLA) $= {}^{\text{rate of catching}}/_{\text{rate of releasing}} = \lambda_{ra}\left(\frac{1}{\lambda_{an}} + \frac{1}{\lambda_{nr}}\right)$
- Only AA (i.e., eu-eu) pairs are subjected to TLA [A. S. Sperling et al., PNAS **108**, 12693 (2011)]

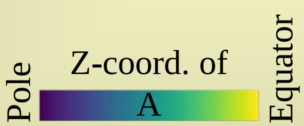
Transient-linking activity (TLA) alters chromatin organization



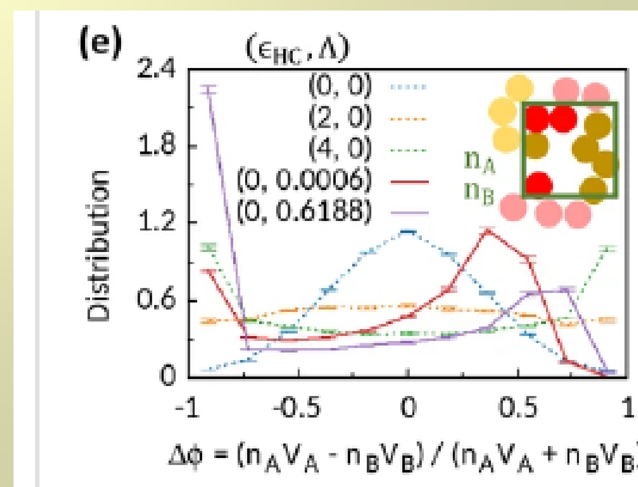




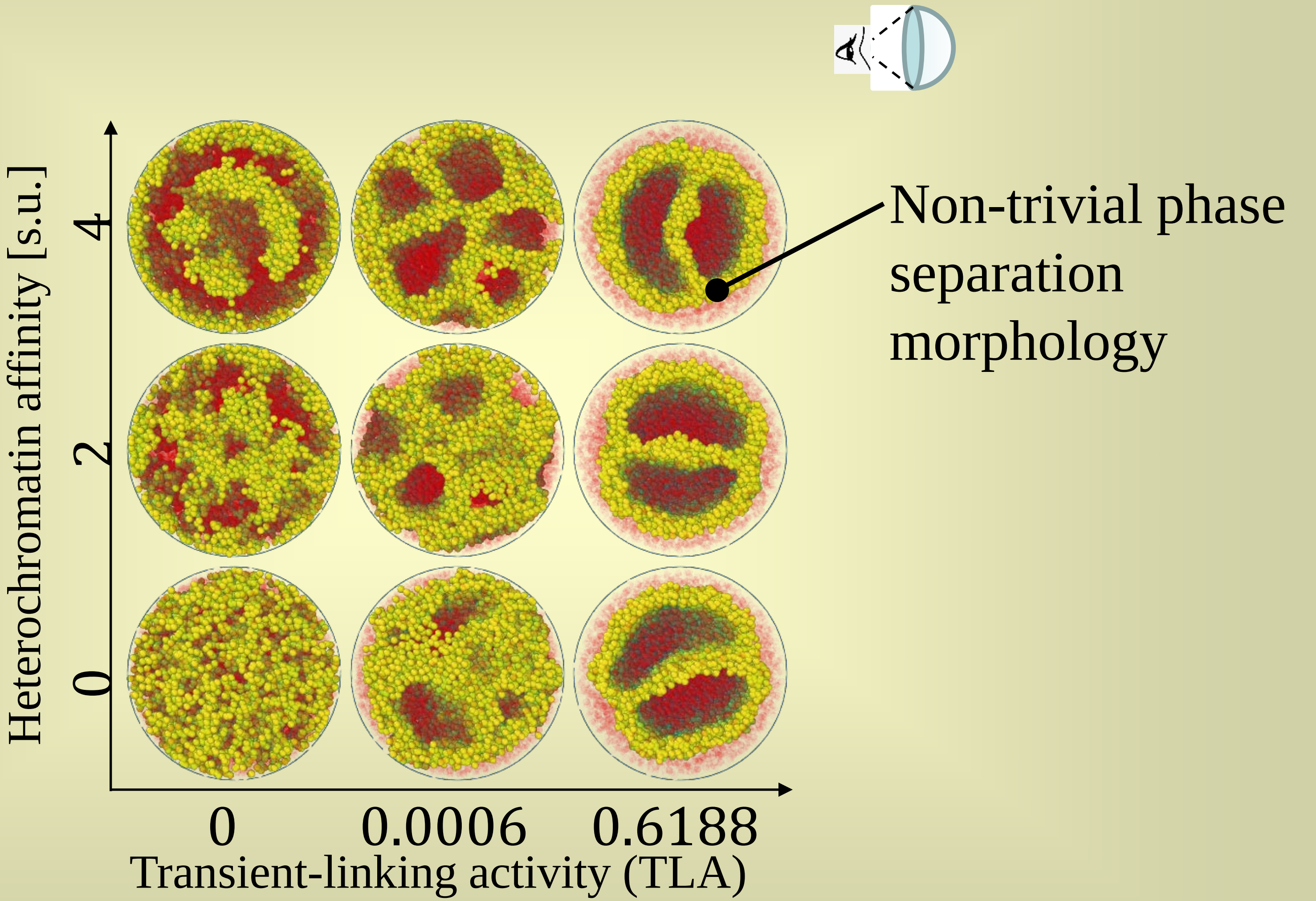
Euchromatin:



Heterochromatin: semi-transparent red



List of typical snapshots in transient-linking activity (TLA) vs. heterochromatin affinity phase space



Happy Birthday!