

Diffusion based generative models for modern fluorescence microscopy

Clayton W. Seitz, Ph.D.

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Outline of the talk

Part I: The tradeoffs of live-cell microscopy

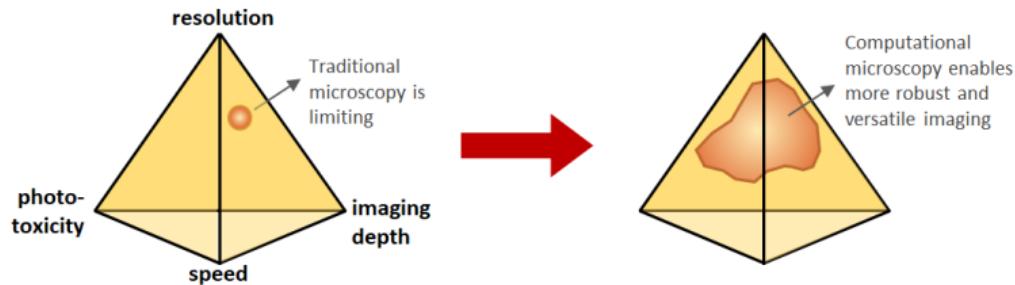
Part II: Deep learning models for modern microscopy

Part I: The tradeoffs of live-cell microscopy

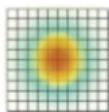
Fluorescence microscopy of living cells

Example videos for live cell microscopy in different contexts

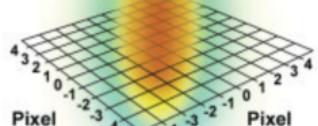
The tradeoffs of live-cell microscopy



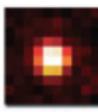
Single molecule localization microscopy



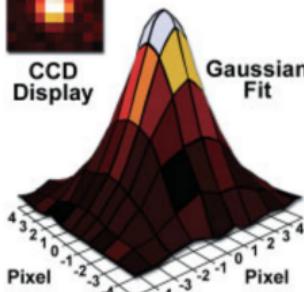
Point-Spread
Function



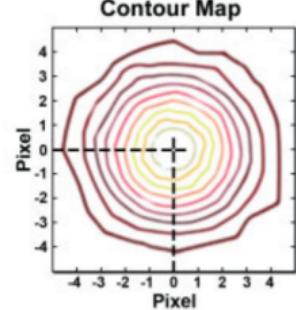
(a)



CCD
Display

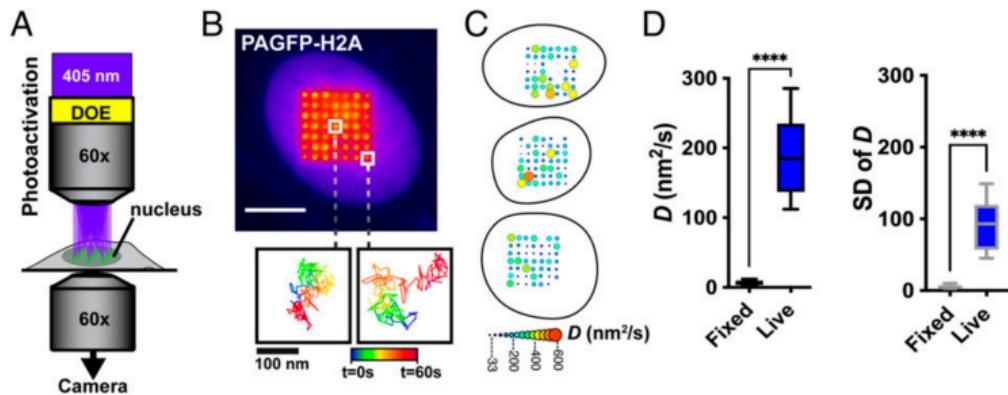


(b)

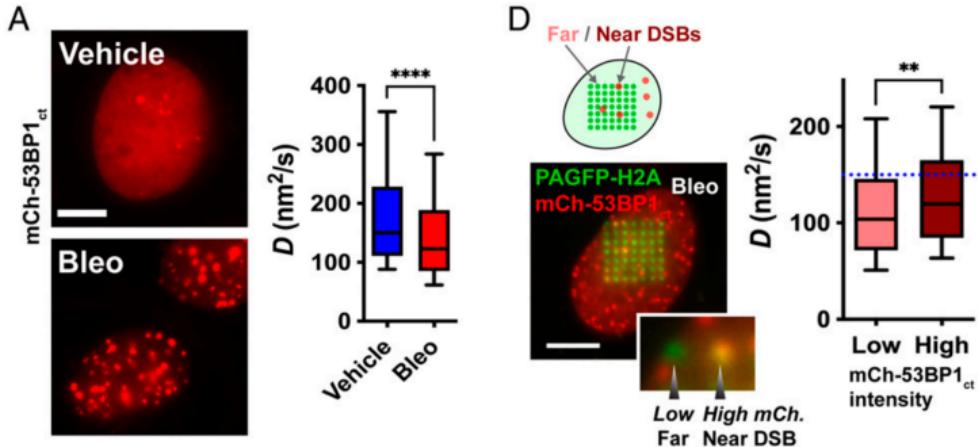


(c)

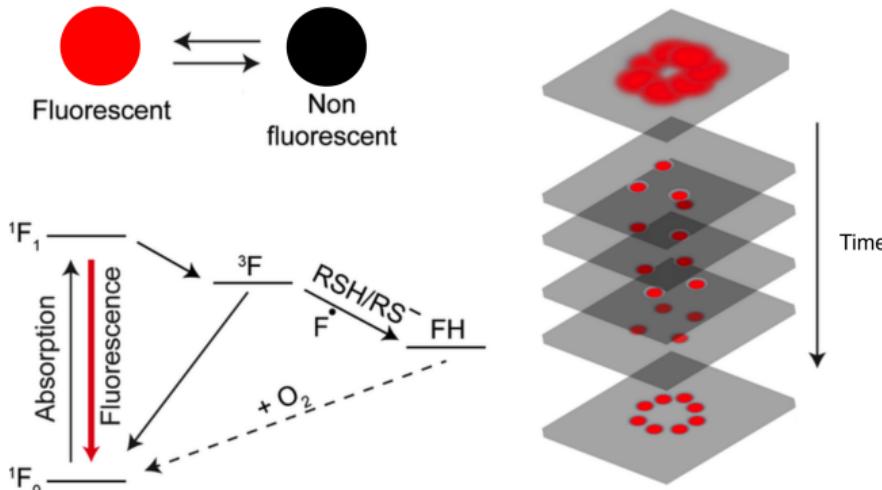
Single molecule localization microscopy



Single molecule localization microscopy

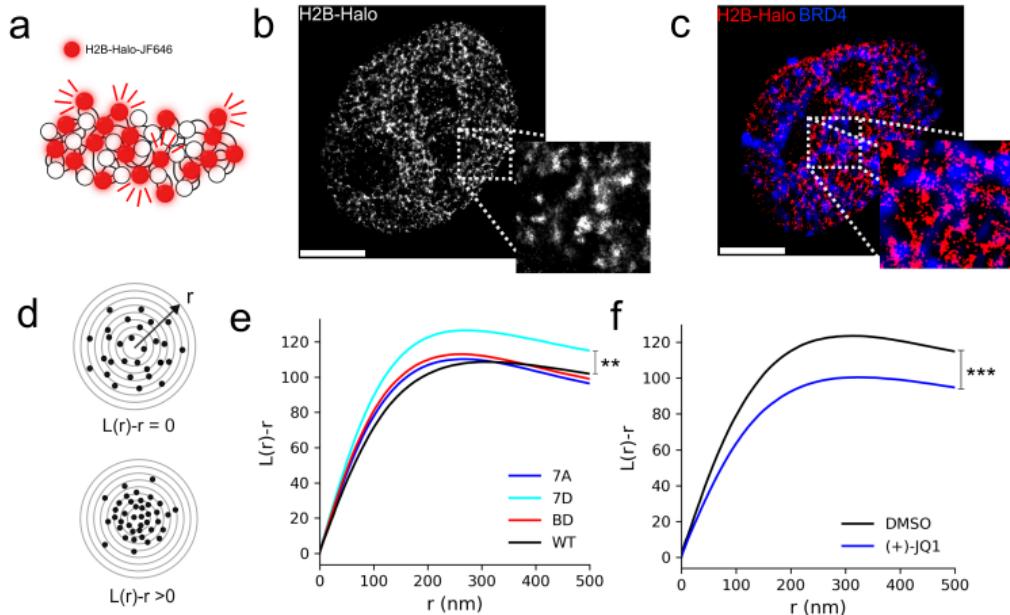


Single molecule localization microscopy



- ▶ STORM and similar nanoscopy techniques are limited by localization precision
- ▶ Higher lateral/axial resolution than other methods (e.g., SIM, STED, Confocal)
- ▶ Poor time resolution

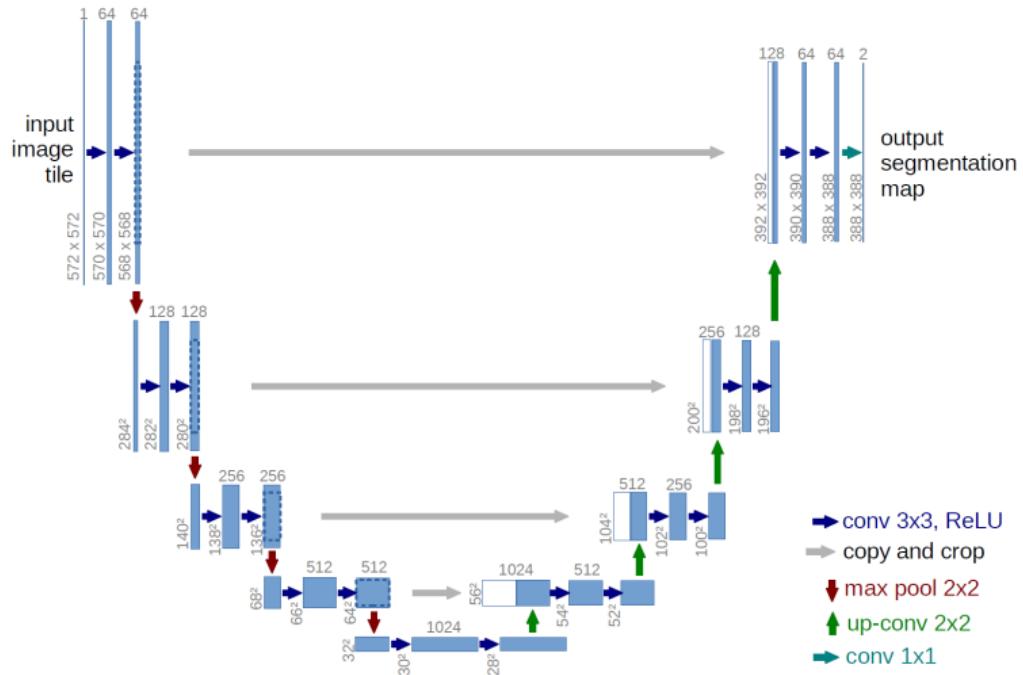
BRD4 binding is necessary for maintenance of nucleosome nanodomains



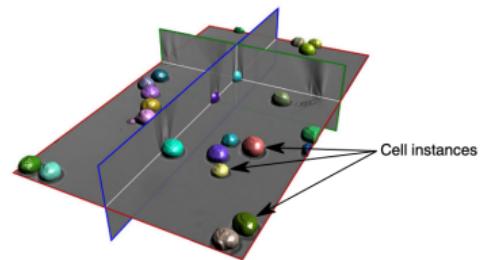
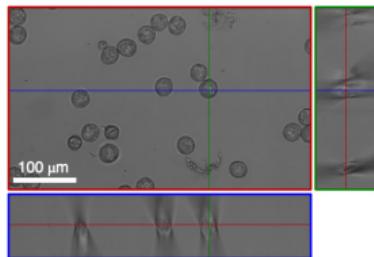
- ▶ H2B is densely labeled for super-resolution imaging
- ▶ BRD4 chromatin binding activity controls nanodomain density

Part II: Deep learning models for modern microscopy

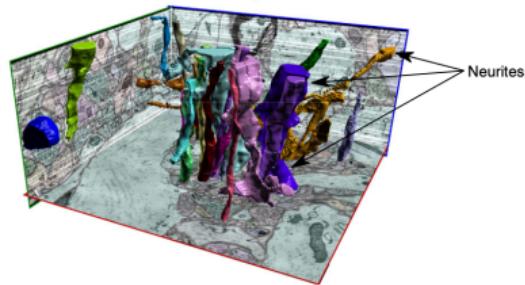
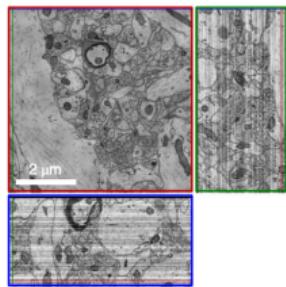
Deep learning based 3D reconstruction



Deep learning based 3D reconstruction



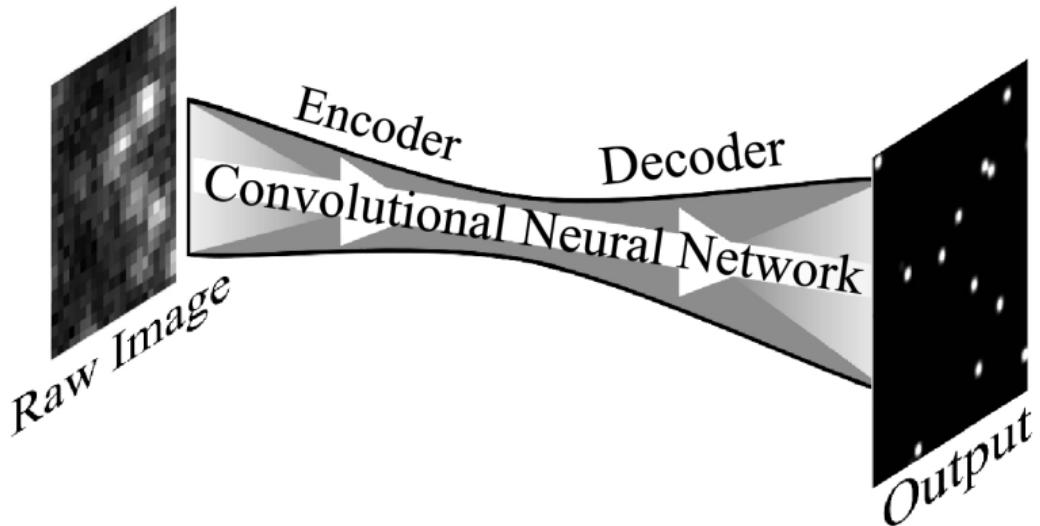
Deep learning based 3D reconstruction



Three-dimensional localization microscopy using deep learning

Deep learning based quantitative phase imaging

Resolution enhancement by deep learning



Nehme E. et al. Optica 5, 458-464 (2018)

- ▶ Prediction of high resolution images from low resolution ones
- ▶ Cannot report uncertainty, leading to overconfident results

Approach I: Resolution enhancement with a diffusion model

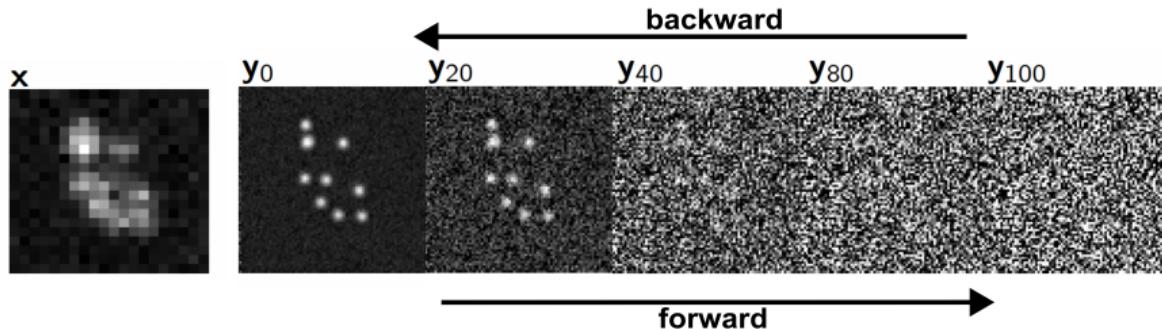
- ▶ Can sample from $p(\theta|x)$ using a stochastic process called Langevin dynamics

Drift and diffusion: $\theta_t = \overbrace{\theta_{t-1} - \frac{\beta}{2} \nabla f(\theta)}^{\mu} + \sqrt{\beta} \xi \quad \xi \sim \mathcal{N}(0, I)$

Approach I: Resolution enhancement with a diffusion model

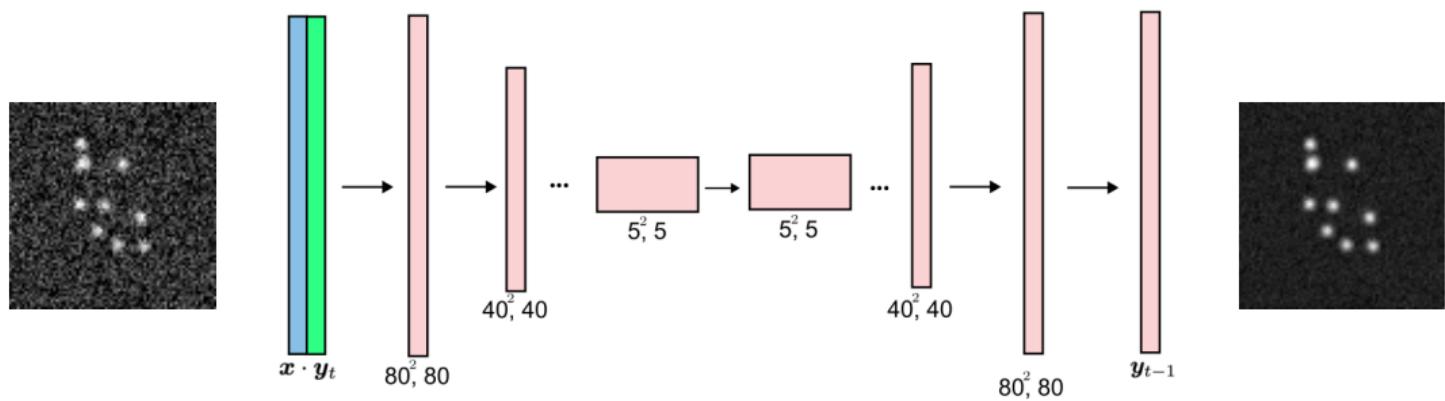
- ▶ Task: infer a high resolution image \mathbf{y}_0 from low resolution \mathbf{x}
- ▶ Drift is not available for image data, but can be learned from pairs $(\mathbf{x}, \mathbf{y}_0)$

$$p_{\psi}(\mathbf{y}_{t-1} | \mathbf{y}_t, \mathbf{x}) = \mathcal{N}(\mu_{\psi}, \beta_t I)$$



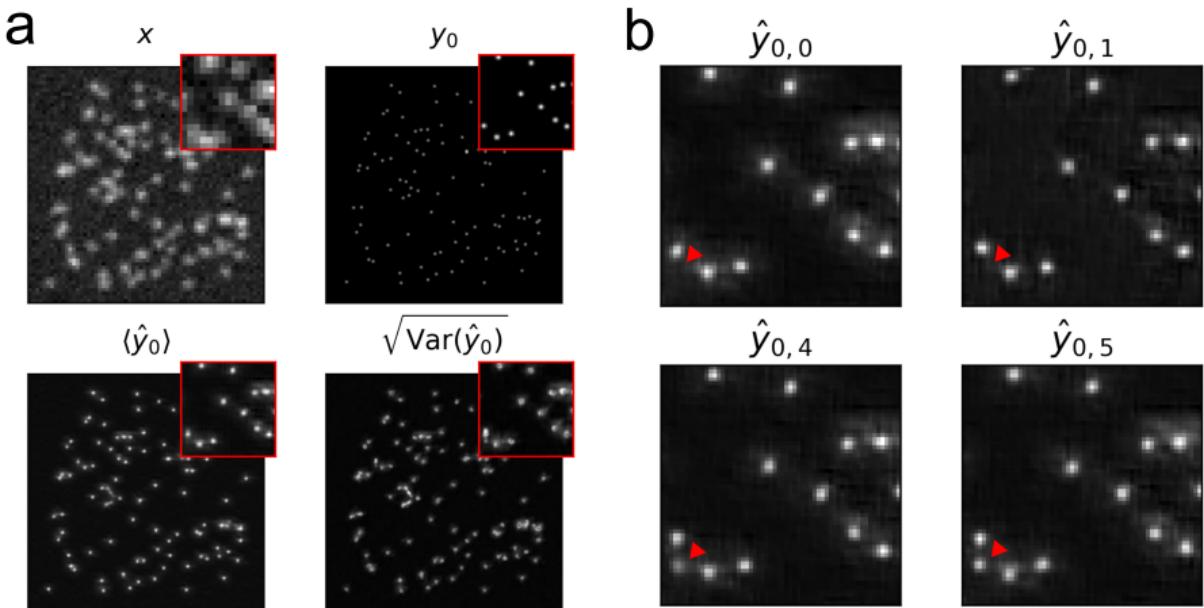
$$q(\mathbf{y}_t | \mathbf{y}_{t-1}) = \mathcal{N}\left(\sqrt{1 - \beta_t} \mathbf{y}_{t-1}, \beta_t I\right)$$

Approach I: Resolution enhancement with a diffusion model

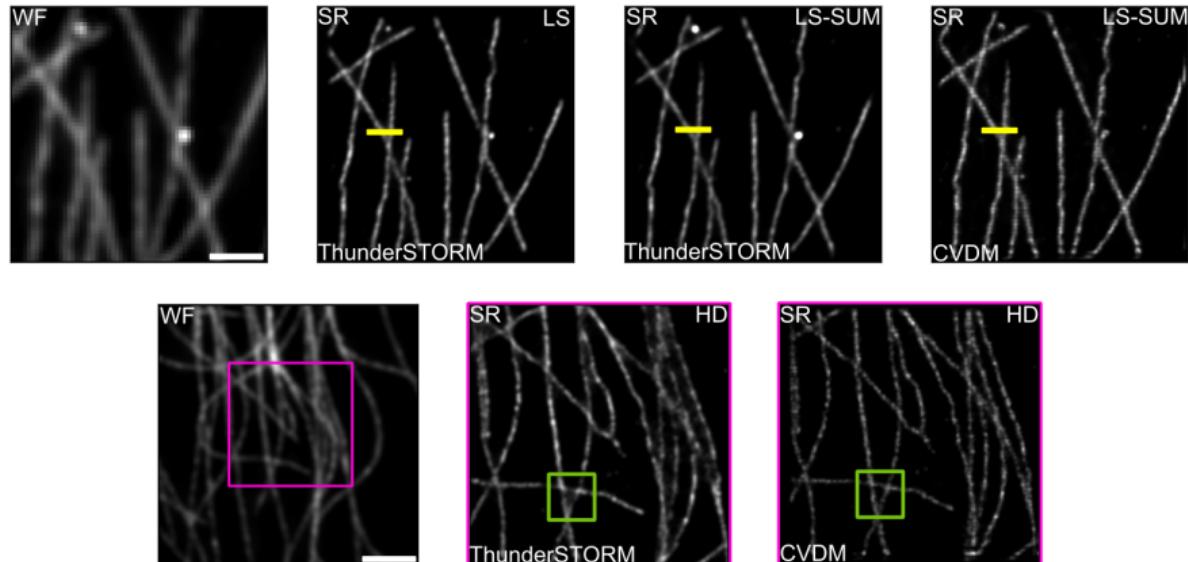


- ▶ A convolutional neural network ψ estimates the drift μ_ψ
- ▶ Denoising step: $\mathbf{y}_{t-1} \sim p_\psi(\mathbf{y}_{t-1} | \mathbf{y}_t, \mathbf{x}) = \mathcal{N}(\mu_\psi, \beta_t I)$

Super resolution with a diffusion model



Super resolution with a diffusion model



Selected Publications

- ▶ **C. Seitz**, D. Fu, M. Liu, H. Ma, and J. Liu. *BRD4 phosphorylation regulates the structure of chromatin nanodomains*. In Review. Phys Rev Lett. 2024
- ▶ **C. Seitz** and J. Liu. *Uncertainty-aware localization microscopy by variational diffusion*. In Progress. 2024
- ▶ **C. Seitz** and J. Liu. *Quantum enhanced localization microscopy with a single photon avalanche diode array*. In Progress. 2024
- ▶ M. Locatelli[†], J. Lawrimore[†], H. Lin[†], S. Sanaullah, **C. Seitz**, D. Segall, P. Kefer, S. Moreno Naike, B. Lietz, R. Anderson, J. Holmes, C. Yuan, G. Holzwarth, B. Kerry, J. Liu, K. Bonin, P. Vidi. *DNA damage reduces heterogeneity and coherence of chromatin motions*. PNAS 12 July 2022; 119 (29): 1-11
- ▶ M. Zhang, **C. Seitz**, G. Chang, F. Iqbal, H. Lin, and J. Liu *A guide for single-particle chromatin tracking in live cell nuclei*. Cell Biology International 15 January 2022; 46 (5): 683-700