EndoEmbryo Understanding how endo/exocytic fluxes shape embryo morphogenesis through statistical inference

Keywords
Stochastic modeling, inverse problem, Bayesian filtering, deep-learning-based inference.
Tissue Morphogenesis, intracellular trafficking, multiscale modeling. actomyosin contractility.

Supervision
Philippe Roudot[1,3], Claudio Collinet[2,3] et Thomas Lecuit[2,3]
[1]Inst. De Mathématiques de Marseille, [2]Inst. De Biologie du développement de Marseille, [3]Turing Center for Living System

Expected profile for the candidate
The candidate will have a formal training in applied mathematics or computer science with a keen interest in cell biology.
Deadline for application on February 16, 2023 at https://centuri-livingsystems.org/phd2023-17/

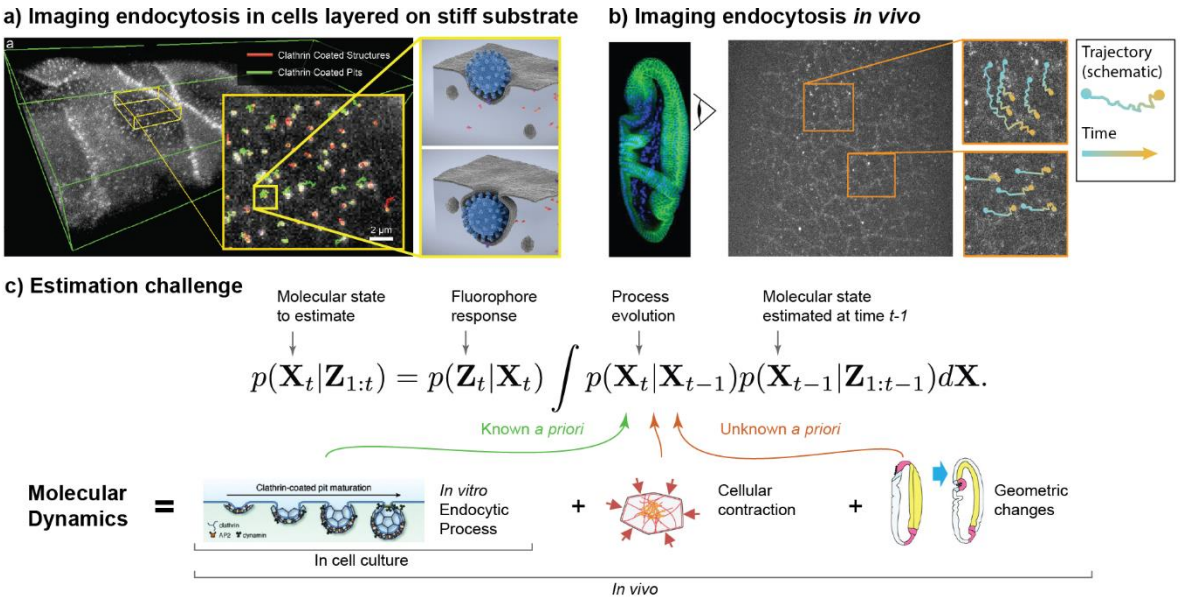

Figure 1: Multi-factorial dynamics occurring in living tissues challenge the quantification of intracellular process *in vivo.*

General challenges in measuring molecular processes *in vivo*
Building upon fluorescence microscopy that selectively images molecules of interest, innovations in image processing[1] and Bayesian inferences[2] and neural networks[3] have enabled the estimation of thousands parameters that describe molecular processes in single-cell experiments [4], [5] (Figure 1.a). The resolution of this inverse problem have however been limited to samples cultured on stiff coverslips that present a distorted view of the biological process occurring in-vivo [6], [7]. Measuring those processes in a more physiologically relevant environment (embryo, collagen matrices etc…), remains challenging due to the geometry and dynamics of three-dimensional scenes[8] (Figure 1.b) and poorer signal quality in deep tissue[9]. One of the key numerical challenges in computer vision for physiological images comes from the lack of *a priori* modelling for the dynamics process to be recognized in the data (Figure 1.c). Accelerating the framerate solves this motion modelling challenge, but it is at the cost of the fluorophore response quality. To estimate the parameters of nanometric molecular processes in their native environment, the PhD candidate will develop Bayesian inference approaches that combines *a priori* knowledge on the spatial repartition of molecules and fluorophore response[10]. In order to scale toward the estimation to the higher number of parameters, we will investigate recent advances in the combination of stochastic model inference and deep neural network[11]. This project will focus on this long-term challenge through the study of the role of intracellular trafficking in tissue morphogenesis.

Biological background
Tissue morphogenesis relies on spatial patterns and polarity of cell surface molecules, such as adhesion molecules, signaling receptors and actomyosin contractility[12]. Trafficking by endo/exocytosis (E/E) endows the cell with a capacity to exchange molecules with the outside and to polarize cell surface protein distribution and signaling [9], [10]. How E/E is exploited to generate patterns of signaling and adhesion molecules at the cell surface and in turn regulates actomyosin contractility to drive morphogenesis is still unknown. This project aims at explaining how E/E fluxes of relevant adhesion molecules and signaling receptors are regulated to control cell mechanics during tissue morphogenesis in the fly embryo. We will probe this complex system by measuring the spatial distribution and the dynamic of E/E events as well as correlating them to patterns of actomyosin contractility and cell morphogenesis. In turn the resulting dynamic will be used to measure endo/exocytic fluxes and non-invasively interrogate the temporal hierarchy of endo/exocytic events in morphogenetic pathways.

The candidate will be trained in the following skills

- Understanding the image formation process in fluorescence microscopy.
- Modeling biodynamics under constrains of computational scalability.
- Bayesian filtering for biodynamics, using statistical and deep-learning-based inference.
- Interdisciplinary communication.
- Formulating biological hypothesis and quantitatively interrogate them.

References

[1] D. Sage *et al.*, “Super-resolution fight club: assessment of 2D and 3D single-molecule localization microscopy software,” *Nat. Methods*, vol. 16, no. 5, Art. no. 5, May 2019, doi: 10.1038/s41592-019-0364-4.
[2] P. Roudot, L. Ding, K. Jaqaman, C. Kervrann, and G. Danuser, “Piecewise-Stationary Motion Modeling and Iterative Smoothing to Track Heterogeneous Particle Motions in Dense Environments,” *IEEE Trans. Image Process.*, vol. 26, no. 11, pp. 5395–5410, Nov. 2017, doi: 10.1109/TIP.2017.2707803.
[3] R. Spilger *et al.*, “Deep probabilistic tracking of particles in fluorescence microscopy images,” *Med. Image Anal.*, vol. 72, p. 102128, Aug. 2021, doi: 10.1016/j.media.2021.102128.
[4] E. Meijering, I. Smal, and G. Danuser, “Tracking in molecular bioimaging,” *Signal Process. Mag. IEEE*, vol. 23, no. 3, pp. 46–53, 2006.
[5] C. Manzo and M. F. Garcia-Parajo, “A review of progress in single particle tracking: from methods to biophysical insights,” *Rep. Prog. Phys.*, vol. 78, no. 12, p. 124601, 2015, doi: 10.1088/0034-4885/78/12/124601.
[6] B. M. Baker and C. S. Chen, “Deconstructing the third dimension – how 3D culture microenvironments alter cellular cues,” *J. Cell Sci.*, vol. 125, no. 13, pp. 3015–3024, Jul. 2012, doi: 10.1242/jcs.079509.
[7] J. B. Kim, “Three-dimensional tissue culture models in cancer biology,” *Semin. Cancer Biol.*, vol. 15, no. 5, pp. 365–377, Oct. 2005, doi: 10.1016/j.semcancer.2005.05.002.
[8] M. K. Driscoll and G. Danuser, “Quantifying Modes of 3D Cell Migration,” *Trends Cell Biol.*, vol. 25, no. 12, pp. 749–759, Dec. 2015, doi: 10.1016/j.tcb.2015.09.010.
[9] P. Pantazis and W. Supatto, “Advances in whole-embryo imaging: a quantitative transition is underway,” *Nat. Rev. Mol. Cell Biol.*, vol. 15, no. 5, Art. no. 5, May 2014, doi: 10.1038/nrm3786.
[10] Á. F. García-Fernández, J. L. Williams, K. Granström, and L. Svensson, “Poisson Multi-Bernoulli Mixture Filter: Direct Derivation and Implementation,” *IEEE Trans. Aerosp. Electron. Syst.*, vol. 54, no. 4, pp. 1883–1901, Aug. 2018, doi: 10.1109/TAES.2018.2805153.
[11] J. Pinto, G. Hess, W. Ljungbergh, Y. Xia, H. Wymeersch, and L. Svensson, “Can Deep Learning be Applied to Model-Based Multi-Object Tracking?” arXiv, Feb. 16, 2022. Accessed: Sep. 16, 2022. [Online]. Available: http://arxiv.org/abs/2202.07909
[12] C. Collinet and T. Lecuit, “Programmed and self-organized flow of information during morphogenesis,” *Nat. Rev. Mol. Cell Biol.*, vol. 22, no. 4, Art. no. 4, Apr. 2021, doi: 10.1038/s41580-020-00318-6.