PhD PROJECT PROPOSAL

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Inferring the physical mechanisms that drive embryonic development

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Abstract

Multicellular organisms develop from simple fertilized eggs to their complex adult forms via a series of dynamic rearrangements, requiring embryonic tissues to generate stress, deform, and reorganize. These rearrangements depend on the interplay between active, energy consuming fluctuating forces and cellular attributes such as cell-cell adhesion, cortical tension, and viscoelastic response. While many theoretical models have been proposed to describe how such cell-scale attributes impact the tissue-scale dynamics of development, to our knowledge no physical model has been obtained directly from data using modern inference techniques. The goal of this PhD will be to obtain such a model.

To this aim, the student will perform live imaging of *Drosophila* embryo development under different controlled conditions, and in particular controlling development speed by varying temperature. Using recently developed analytical tools to quantify active fluctuations and infer stochastic dynamical models, they will then aim to quantitatively capture the experimentally observed tissue dynamics from data, from cell-scale rearrangements to embryo-scale flows of tissue.

Keywords

Embryo development, tissue dynamics, inference, non-equilibrium processes

Scientific Question and Objectives

The key objective is to obtain data-driven models describing the dynamics of the fly embryo at the cellular scale, and with predictive power at the embryo scale. To this aim, it is essential to articulate experimental work, data acquisition and treatment, and data-driven modeling.

Our objectives are to: (1) map cell-scale fluctuations and correlate them to tissue flow speed, in particular at different temperatures (and thus different developmental speeds); (2) infer a physical model of tissue dynamics from the experimental data collected ; and (3) use predictions of the model and experimental perturbations to shed light on the role of non-equilibrium processes during development.

*: Mandatory

Proposed approach

The project will intertwine experimental, data analysis and theoretical work. In the first semester (S1), the student will get to grips with the experimental model and the confocal microscopy techniques, benefitting from the existing expertise in the group of EG. Starting in S2, the student will aim to analyze the resulting movies, tracking cell nuclei and cell-cell junctions using image analysis software such as FIJI. At this stage, the student will also be encouraged to mobilize the broad expertise existing in the Centuri community on this subject (Rupprecht, Lenne, Roudot groups for instance) as well as expertise in PR's group. Through elementary estimators (corrected mean-squared displacements), this will allow the student to start quantitatively mapping nonequilibrium activity in the embryo.

In S3, the pipeline will be enriched by performing experiments at different temperatures and, independently, under exposure to drugs that affect metabolism, enabling us to change the rate of energy consumption. This will allow us to decouple the effects of passive, thermal and actively regulated, non-equilibrium processes. In parallel, the student will familiarize with Stochastic Force Inference techniques (Frishman and PR 2020) to reconstruct models from the obtained tracking data. These models will consist either in effective interactions between tracked nuclei or, if segmentation is successful, cell-shape dynamics *à la* vertex models. The student will integrate in PR's team, where the inference methods are developed and broadly used, to perform these tasks.

S4 and S5 will consist in the exploitation and consolidation of the pipeline, systematic exploration of parameters, and interpretation of the results. We note that while the goal of going all the way from imaging to analysis of inferred models is very ambitious, an alternate, more descriptive approach consisting in mapping the nonequilibrium fluctuations using activity estimators such as the recently developed Mean Back Relaxation would be a feasible fallback plan retaining the interdisciplinary nature of the project.

Interdisciplinarity and implication of the two labs

This ambitious yet feasible PhD project bridges between EG's expertise on *Drosophila* embryo manipulation and imaging, and PR's expertise on non-equilibrium stochastic processes and data analysis. It is set at the interface between experimental developmental biology, bioenergetics and statistical mechanics, and will combine advanced microscopy with cutting-edge data analysis methods. This project is thus highly interdisciplinary both in its methods and in its goals.

As described in the previous section, after a first semester of familiarization with the experimental setup, the student will integrate in both groups. We expect to have monthly joint group meetings with the two groups, as well as regular meetings with both advisors, to ensure that the student is exposed to the necessary expertise on both sides to achieve this project. Finally, we note that some goals (cell segmentation and tracking, vertex models, full embryo development) strongly resonate with the Centuri community, and the student will be encouraged to interact and, if the opportunity arises, collaborate with other local groups.

Specify with whom the person recruited will collaborate and on what aspects *

The student will work with EG on the experimental aspects of the project, will work jointly with EG and PR on the data analysis aspects, and will work with PR on the inference aspects of the project.

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PhD student's expected profile

We expect the student to have a physics background, with both theoretical and experimental experience in biological physics, soft matter and/or statistical physics. The student should have lab experience, preferably including some experience with microscopy, as well as strong proficiency with theoretical statistical physics tools (fluctuation-dissipation relation, Langevin Dynamics…). Experience in programming (Python) is necessary. Prior experience in image analysis (FIJI, Trackmate or alternatives), and/or in data-driven approaches / machine learning would be a plus.

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Is this project the continuation of an existing project or an entirely new one? In the case of an existing project, please explain the links between the two projects

This is an entirely new project and collaboration. EG has an ANR project that will begin in 2025, which also involves the physical mechanisms that drive development. The work associated with that project will develop experimental capabilities that can be utilized for this PhD project, but the two projects will have significantly different scientific questions and technical approaches.

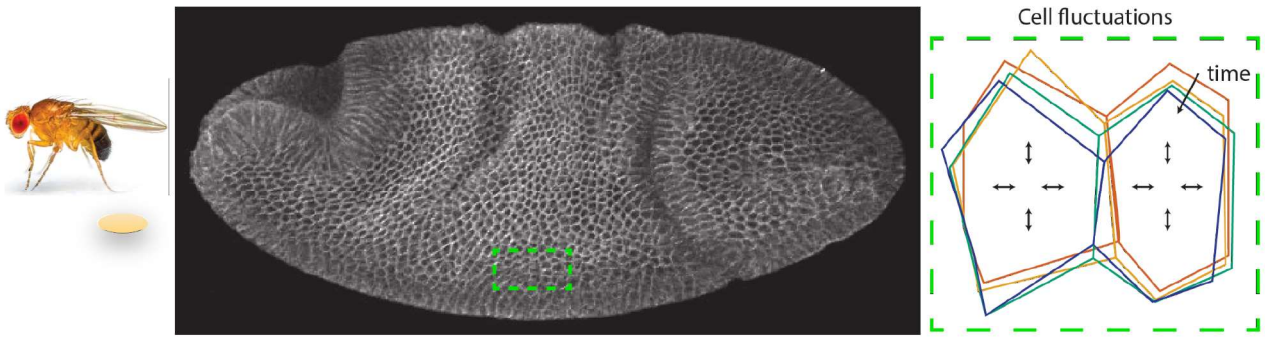
Two to five references related to the project

1) Kim, Pochitaloff, Stooke-Vaughan, Campas. Embryonic tissues as active foams. *Nat Phys* **17**, 859-866 (2021).
2) Clément, Dehapiot, Collinet, Lecuit, Lenne. Viscoelastic Dissipation Stabilizes Cell Shape Changes during Tissue Morphogenesis. Curr Biol **27** 3132-3142 (2017).
3) Crapse, *et al.* Evaluating the Arrhenius equation for developmental processes. *Mol Syst Biol* **17**, e9895 (2021).
4) Muenker, Knotz, Krüger, Betz. Onsager regression characterizes living systems in passive measurements. *bioRxiv* doi: 10.1101/2022.05.15.491928 (2023).

Two main publications from each PI over the last 5 years

1) Gehrels, E.W.*, Chakrabortty, B.*, Perrin, M.-E., Merkel, M., Lecuit, T. Curvature gradient drives polarized flow in the *Drosophila* embryo. *PNAS* **120** (6), e2214205120 (2023).
2) Bailles, A.*, Gehrels, E.W.*, Lecuit, T. Mechanochemical principles of spatial and temporal patterns in cells and tissues. *Annu Rev Cell Dev Biol* **38**, 321-347 (2022).
1) Frishman, A.*, Ronceray, P*. Learning force fields from stochastic trajectories. *Physical Review X* **10** (2), 021009 (2020).
2) Ronceray, P. Two steps forward – and one step back? Measuring fluctuation-dissipation breakdown from fluctuations only. *Journal Club for Condensed Matter Physics* **2** (July 2023).

Project's illustrating image



*: Mandatory