# M2+PhD: Memory-driven active instabilities & Gastruloids modelling

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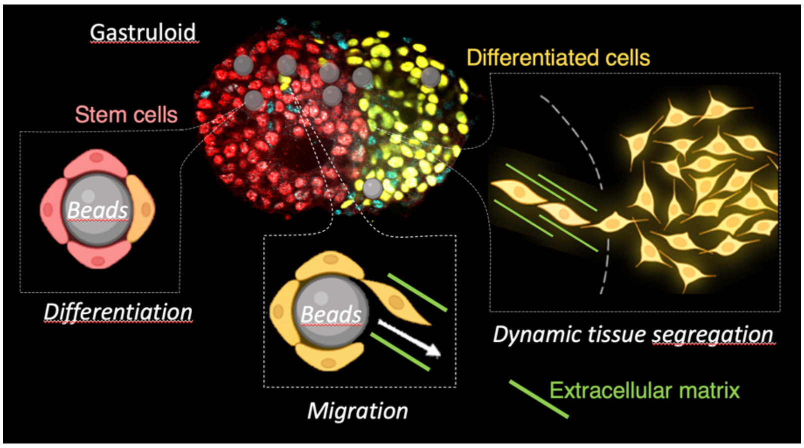


**Context** Gastrulation is an early process in embryonic development during which epiblasts differentiate and organize into 3 fundamental germ layers (endoderm, mesoderm, and ectoderm). This highly conserved process involves the coupling of localized cell differentiation and active cell migration.

The team of Virgile Viasnoff recently developed a novel class of scaffolded human Gastruloids [1] (organoids mimicking the process of gastrulation) that enables the spatial control of cellular differentiation.

This work uncovers a feedback loop between differentiation and migration. Indeed, the differentiating cells deposit a chemical trail – called *extracellular matrix* - that then serves as a guiding track for the subsequent differentiating cells. Such cumulative deposition of an extracellular matrix in the Gastruloids acts as a patterned memory of the development history. With such mature experimental data, we are ready to develop a novel class of theoretical models.

**Objective** We aim to understand how the crosstalk between cell motility and environmental memory triggers memory-driven active instabilities that support an active phase separation in cell types.

**Methods** We propose to adapt recently proposed frameworks [2-3] to the context of a phase separation process. More specifically, we will couple several fields – fraction in stem versus differentiated cells and associated fluxes, and the local nematic order in guiding filaments – in terms of the times needed for cells to

(1) differentiate,
(2) migrate over the system size,
(3) deposit and remodel the guiding matrix.

We expect that the phase separation between stem and differentiated cells (mimicking tissue separation) is maintained by the difference in motilities between the two cell types. Self-propelled objects exhibit a tendency to accumulate in areas where their motility is lower. Such decreased motility could be caused by a higher particle density, thus resulting in the celebrated motility-induced phase separation [4]. In our model, the matrix deposition could compete with density, resulting in counter-intuitive results. We will then explore how such a system behaves and affects the spatial organization of a model Gastruloid based on the spatial distribution of cell differentiation. We will explore the structure of attraction basins leading to similar final tissue organization and compare them to the experimental data.

**Perspectives** This PhD is an opportunity to gain joint expertise in active matter modeling and/or advanced image analysis methods. The modeling will guide new experiments in which the applicant might be involved according to his/her taste. We do not require any previous experience in biology.

**The team** **Jean-François Rupprecht** is a theoretician at the Centre de Physique Théorique, Aix-Marseille Luminy campus, leading research on active matter models. **Virgile Viasnoff** is a biophysicist at the CINAM Aix-Marseille Luminy campus, leading physical model, image analysis & experiments on living systems. We have a long-standing experience of working together [7] and in interdisciplinary studies.

**PhD funding**: PhD funding is available.
*This PhD subject is related to the "Inference of cell rearrangements & theory of active phase separation in cell assemblies" M2 internship advertised elsewhere.*

**Location**: Marseille Luminy, within the highly stimulating environment of the CENTURI (Turing Center for living matter) in the middle of the Calanques National Parc.

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**References**:

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[2] Adar, Joanny *Environment-stored memory in active nematics and extra-cellular matrix remodeling*, PRL (2024).
[3] d'Alessandro J, Barbier-Chebbah A, Cellerin V, et al. *Cell migration is guided by long-lived spatial memory*. Nat Commun (2021)
[4] Cates, Tailleur, Annual Review of Condensed Matter Physics (2015).
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[6] Prasad,…, Fattacioli, Rupprecht, Utada, Science (2023).
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