RÉPUBLIQUE FRANÇAISE
Liberté Égalité Fraternité

INRAE

IMMO

EXPLORATORY PROJECT

2021-2023

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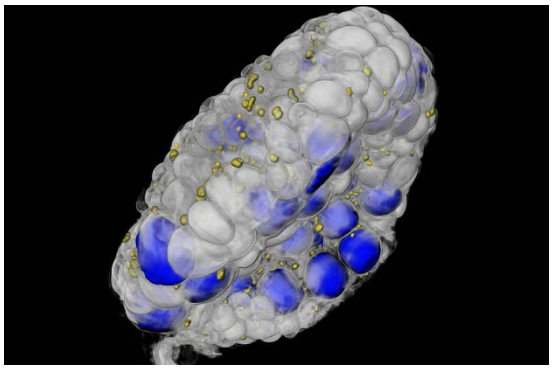
Keywords
Fertility
Oogenesis
3D imaging
Deep Learning
Dynamics of structured populations

Participating INRAE units
LPGP
PRC

External Partners
Inria (EPC INRIA-CNRS-INRAE MUSCA)

Visual representations of fish oocytes using AI and 3D imaging



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Context, key challenges and goals

In both natural habitats and fisheries, the formation and development of female gametes (oogenesis) is key to reproductive success in fish and is still little understood. The IMMO project seeks to study and model these mechanisms.

In multiple-spawning fish, oogenesis involves the permanent turnover of the anatomical structures, ovarian follicles, that support the development and growth of gametes until spawning occurs. Although many regulatory actors have already been identified, there are still gaps in our knowledge of the dynamics of this process. Important questions remain unanswered: whether there is detectable aging of the ovarian function; what the key regulators for the ovarian follicles at different stages of maturation might be; and the extent to which the follicle population self-regulates.

The goal of the IMMO project was to make use of new 3D-imaging and artificial intelligence (AI) techniques to generate visual images and to enumerate all oocytes in fish ovaries at different ages, in order to provide a comprehensive and quantitative description of the entire oocyte and ovarian-follicle populations. These data would then be used to validate a mathematical model describing follicle dynamics and their regulation over a fish's life span, making available information that could not be obtained from the data alone. The IMMO project used the female ovaries of the medaka, or zebra fish (*Oryzias latipes*), a model species from southeast Asia commonly found in exotic fishkeeping.

Outcomes

Distribution and size of oocytes in fish ovaries

The project enabled the precise quantification and measurement of the oocytes present in the ovaries at different life stages, from the larval stage to adulthood. The results show that follicle distribution evolves from a synchronic state in juveniles, where all follicles are in an early stage of vitellogenesis, to an asynchronic state in adults, where follicles at all stages of oogenesis are present. In females nearing end of life, the follicles are more synchronized at early stages of oogenesis. These data have made it possible for the stages of follicular growth in medaka to be re-

defined, and an association to be established between follicular size and biological functions (hormonal secretion, growth).

Multi-scale modelling of the dynamics of oogenesis

A mathematical model organized in size order was developed to describe the dynamics of the oocyte population. A first calibration was carried out using data on mice already available from the literature, while awaiting the integration into the model of the data on medaka obtained through the IMMO project.

The expert skills of the project partners, knowledge from the literature, and the data obtained in the first part of the project allowed oocyte sizes and the biological functions (hormonal secretion, growth) to be ascertained and linked. The resultant characterization enabled the construction of a multi-scale model, expressed through equations with partial derivatives, and integrating the entry, growth and exit of oocytes. This model was used to study the transitions between the different life phases observed in the first part of the project.

Future directions: two ANR projects and two theses

The analysis of the distribution by size of oocytes throughout the medaka's life span revealed major transitions at key stages of development, and possible signs of ovarian ageing in some individuals. These transitions were accompanied by a change in batch size, correlated with changes in the distribution and total number of oocytes. These outputs are very encouraging and have demonstrated the benefits of an interdisciplinary approach (combining applied mathematics, AI, cellular biology, microscopy, etc.) in improving understanding of ovarian dynamics across all different life stages of the medaka.

The partnerships established through the project are set to continue thanks to the funding obtained for a five-year **ANR project ANR (OVOPAUSE)**, which began in 2022 (project lead: INRIA MUSCA, partners: INRAE LPGP, Université Paris-Cité). The project builds on the work of the IMMO exploratory project, through **Marlène Davilma's thesis** (2023-2026), in particular. The thesis seeks to evaluate germline stem cell proliferation in germinal cradles, in order to understand the dynamics of the entire oocyte reserve. A second project made possible by IMMO is the five-year ANR project (PROBA), which began in October 2025 (project lead: LPGP; partner: INRIA). This project will allow better understanding and modelling of germ-cell lineage throughout a fish's life, with particular attention to the balance between proliferation and growth in germ cells.

The study and calibration of the model created through the IMMO project also formed the backbone of **Louis Fostier's thesis** (Multiscale mathematical modelling of oogenesis in fish 2022-2025), co-funded by DIGIT-BIO and successfully defended in October 2025. This thesis has provided the substance of two articles directly connected to the IMMO project (one already published and the other submitted for publication).

A further follow-up to IMMO was awarded GIS FC3R funding in 2024. The OVOTOX project, in partnership with the INERIS, seeks to develop an integrative approach for the evaluation of reproductive toxicity of endocrine disruptors in fish.

Last, a mobility grant awarded by the DIGIT-BIO Metaprogramme has allowed Romain Yvinec to travel to Duke University (North Carolina, USA) as a visiting researcher, strengthening collaborative ties on the modelling of the physiology of female reproduction. This grant resulted, in particular, in methodological advances in the application of physics-informed neural networks (PINNs), the topic of Louis Fostier's second paper.

Publications

- Guillaume Ballif, Frédérique Clément, and Romain Yvinec, Nonlinear compartmental modeling to monitor ovarian follicle population dynamics on the whole lifespan, Journal of Mathematical Biology 89:9, 2024. Doi 10.1007/s00285-024-02108-6 , https://hal.archives-ouvertes.fr/hal-03739205
- Guillaume Ballif, Frédérique Clément, and Romain Yvinec, Averaging of a Stochastic Slow-Fast Model for Population Dynamics: Application to the Development of Ovarian Follicles, SIAM Journal on Applied Mathematics, 82(1) :359-380 2022. doi : 10.1137/21M1409615 ; https://hal.science/hal-03405177

- Manon Lesage, Manon Thomas, Thierry Pécot, Tu-Ky Ly, Nathalie Hinfray, et al. An end-to-end pipeline based on open source deep learning tools for reliable analysis of complex 3D images of ovaries. Development (Cambridge, England), 2023, 150 (7), pp.dev201185. doi : 10.1242/dev.201185. https://hal.science/hal-04062159
- Frédérique Clément, Louis Fostier, Romain Yvinec. Well-posedness and bifurcation analysis of a size-structured population model: Application to female gametes dynamics. SIAM Journal on Applied Dynamical Systems 24(3): 2427–2472, 2025; doi: 10.1137/24M1705147 hal-04699357v1 https://hal.science/hal-04699357
- Louis Fostier, Manon Lesage, Violette Thermes, Frédérique Clément, Romain Yvinec. Data-driven PINN inference of oocyte dynamics in fish ovaries. 2026. _x005F_xffff_hal-05536280_x005F_xffff_ https://inria.hal.science/hal-05536280
- Marlène Davilma, Stéphanie Gay, Manon Thomas, Sully Mak, Fabrice Mahé, Laurence Dubreil, Jérôme Montfort, Aurélien Brionne, Julien Bobe, Violette Thermes. Identification of miR-187 as a modulator of early oogenesis and female fecundity in medaka. bioRxiv preprint doi: https://doi.org/10.64898/2026.01.09.698593.
- Codes for the analysis of 3D images are available on the LPGP GitHub, along with a guide and test results: https://github.com/INRAE-LPGP/ImageAnalysis_CombineLabels
- Codes for the mathematical model and parameter inferencing are available on the GitHub: https://github.com/lfostier/pinn_ovo

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