Post-doctoral position in mathematical biology
Bifurcation and robustness analysis in structured population models: Application to female reproductive cycles

EPC MUSCA, Centre INRIA de Saclay

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Biological and biomathematical background

There are major societal challenges associated with maintaining the reproductive fitness of female individuals, whether in a clinical, breeding, or ecological context. Understanding female reproductive (germ) cell population dynamics is instrumental for maintaining women health and fertility, managing ovarian aging, developing sustainable breeding practices, and monitoring the effects of micro-pollutants in humans, livestock and wild species.
The supply of mature female germ cells at each ovarian cycle ensues from a combination of developmental and (neuro-)endocrine processes spanning multiple timescales. On the one hand, the production and maturation of germ cells (oogenesis) is a longlasting process, initiated by the asynchronous activation of quiescent cells from a pool constituted early in life, and covering several weeks or months depending on the species. On the other hand, the typical period of an ovarian cycle extends from a few days to a few weeks, during which terminally maturating germ cells in the ovaries participate in and are controlled by both positive and negative hormonal feedback loops involving the different levels of the reproductive axis (especially the hypothalamus and pituitary gland) and culminating in ovulation. As a result, several waves of terminal maturation can be observed within a single ovarian cycle, and the recruitment into each wave is in turn deeply connected with the background oogenesis dynamics.
Mathematical modeling is a powerful mean to "tease apart complexity in the reproductive system, and to test and provide new hypotheses regarding pathological situations" [3]. Structured population models describe population dynamics in terms of individual characteristics such as age or size, and have been the matter of extensive studies. They have found concrete applications in cell and developmental biology (*e.g.* hematopoiesis, neurogenesis) and can help to understand basic physiology as well as pathological disorders. Up to now, most available mathematical models dedicated to reproductive biology have been designed either to represent the whole oogenesis, without accounting for cyclicity [6], or to mimic the oscillatory hormonal patterns along the ovarian cycle, without accounting for oogenesis [10]. The objective of the postdoc is to extend previous models developed in the MUSCA team to couple, in a mechanistic manner, oogenesis with ovarian cyclicity, to get insight into their reciprocal interactions on both the short and long term.

Work program

The work will be based on population dynamics models of the whole oogenesis (see Figure 1), formulated either as discrete compartmental models [1, 2] or as continuous structured population models [5]. In particular, one of the PDE model exhibits oscillatory solutions arising from a Hopf bifurcation, which qualitatively reproduces the periodic(cyclic) terminal maturation of a cohort of germ cells subject to an endocrine-mediated negative feedback. For the moment, the recruitment of the cohort is yet not explicitly connected with the dynamics of the less mature germ cells.

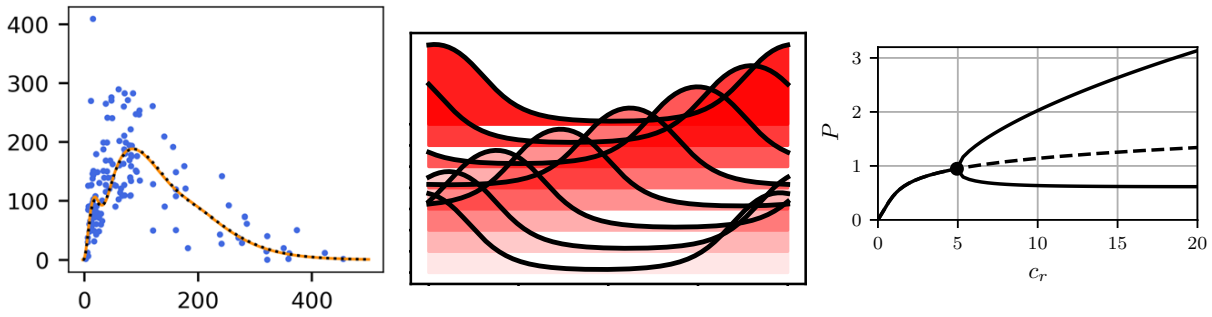

Figure 1: (Left panel) Instance of compartmental model fitting to germ cell numbers in different individuals according to aging (from [2]). (Middle panel) Occurrence of oscillatory solutions in the size-distribution of terminally maturating germ cells. (Right panel) Bifurcation diagram in the number of cells P according to the recruitment rate c_r (from [5])

The first objective will be to extend the existing size-structured PDE model [5] to account for the hormonally-controlled and population-dependent recruitment of the cyclic cohort, and for the (neuro-)endocrine conditions needed to trigger ovulation [4]. A detailed bifurcation analysis will then be performed to understand how the coupling between oogenesis and hormonal feedback shapes the properties of the ovarian cycle (*e.g.* one or several germ cell waves, number of germ cells per wave, ovarian cycle length and regularity).
The second objective will be to analyze the robustness of these properties with respect to the number and distribution of germ cells (*e.g.* stochastic fluctuations, inter-individual variability), as well as the effect of aging (*e.g.* diminishing quiescent pool, altered neuro-endocrine control), in the light of recent computational studies devoted to the ovarian cycle [7, 8, 9].
From these studies, theoretical results on the longtime analysis of coupled PDE/ODE systems are expected, as well as outcomes in comparative physiology highlighting the shared mechanisms and species-specific differences in germ cell dynamics among vertebrate species (*e.g.* in mammals compared to fish).

References

[1] G. Ballif, F. Clément, and R. Yvinec. Averaging of a stochastic slow-fast model for population dynamics: application to the development of ovarian follicles. *SIAM J. Appl. Math.*, 82(1):359–380, 2022.

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[7] S. Fischer-Holzhausen and S. Röblitz. Hormonal regulation of ovarian follicle growth in humans: Model-based exploration of cycle variability and parameter sensitivities. *J. Theor. Biol.*, 547:111150, 2022.

[8] E.J. Graham, N. Elhadad, and D. Albers. Reduced model for female endocrine dynamics: Validation and functional variations. *Math. Biosci.*, 358:108979, 2023.

[9] Sean D. Lawley, Mary D. Sammel, Nanette Santoro, and Joshua Johnson. Mathematical recapitulation of the end stages of human ovarian aging. *Sci. Adv.*, 10(2):eadj4490, 2024.

[10] R. Yvinec, P. Crépieux, E. Reiter, A. Poupon, and F. Clément. Advances in computational modeling approaches of pituitary gonadotropin signaling. *Expert Opin. Drug Discov.*, 13(9):799–813, 2018.

Expected skills A solid background in Applied Mathematics, including expert knowledge on ODE and PDE is required. Strong interest for interdisciplinary work is needed, and experience in analysis of parameter identifiability/sensitivity and parameter estimation, ideally applied to biological issues, would be a plus.