Master 2 internship - Cell lineage analysis based on stochastic models of population dynamics : application to the germline

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Biomathematical background: Stochastic cell population models

The development and homeostasis of multicellular organisms are underlain by tightly controlled and coordinated cell dynamics, ensuring the production of the right number of cells of the right type at the right time, and involving key cell decision making events such as proliferation, differentiation and cell death.

Dividing cell populations are well represented by stochastic branching processes, where individual cells divide independently from each other and the division rate may depend on the cell type and/or age (*e.g.* multi-type age-dependent "Bellman-Harris" branching process [3, 7, 4, 10]). Such a framework is especially useful to represent low cell numbers and cell-cell variability, and has been applied in different cell kinetics contexts [1, 9, 6, 5, 2]. The longtime asymptotic behavior (*e.g.* sub or supercritical) of such cell population models can be deduced from cell transition rates that typically involve unknown or difficult-to-measure parameters (*e.g.* division, differentiation, cell death rates). In turn, biological measurements can give insight into the cell population states at different time (*e.g.* developmental stages) and the cell cycle-phase distribution. Thanks to mathematical modeling, one can then infer, from the experimental data, the key parameters of cell transition events, as well as the most likely cell population history. Additionally, such a theoretical framework may be used to guide experimentalists to optimize cell labeling protocols in order to obtain the most informative data as possible.

This internship will focus on revisiting cell branching models to adapt them to the germline population, quantifying cell population outputs that can be directly compared to experimental data, and suggesting relevant cell biology experiments based on the modeling framework, model outputs and inferred transition rates.

Work program

The main objective of the internship is to design and start analyzing a quantitative model of a whole lineage process, with a focus on the female germline (reproductive lineage involved in oogenesis). The first step will be to design a population dynamics model from the earliest precursor stages (germ stem cells) up to the most differentiated cells (oocytes) (see Figure 1). The model will account both for the different cell types and the progression along the cell cycle within a given cell type. The model outputs will consist in the cell numbers (total number and number of each cell type) and the cell distribution within the different cell cycle phases. The role of the division mode (typically: symmetric or asymmetric division), a crucial cell decision making at the precursor stage, will be investigated in details to assess its impact on the size of the oocyte pool. In a second step, the transition rates will be inferred from data on cell numbers and cell-kinetics information identifying cells within specific phases of the cell cycle (such as the DNA replication phase and mitotic indexes).

The results of this modeling approach will give insight into the cell dynamics underlying the formation and possible maintenance of the oocyte pool, which is of critical importance for the reproductive fitness of females, and will allow to compare different evolutionary strategies involving either renewed (as in fish) or exhausted (as in mammals) oogenesis.

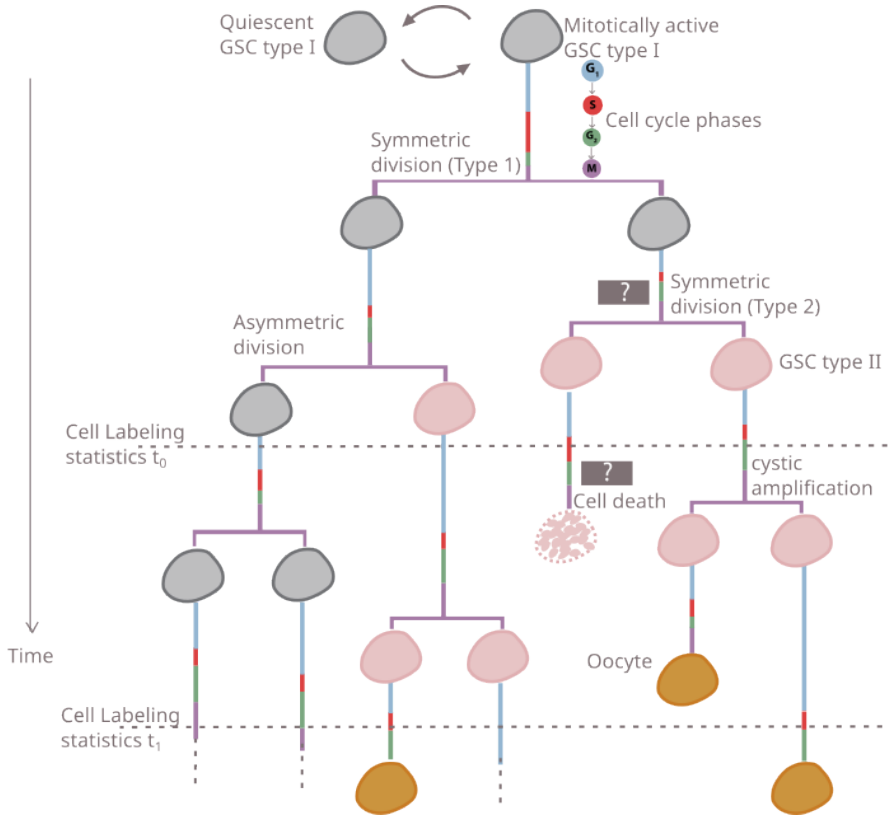

Figure 1: Nearly twenty years ago, a groundbreaking discovery revealed the presence of germline stem cells (GSCs) in the ovaries of adult female fish [8]. GSCs are the very first cell types committed to the germline, which involves several progenitor cell and culminates into the release of mature gametes, namely oocytes in females. GSCs undergo two types of proliferation, self-renewal (type I, isolated cells), and cystic amplification (type II, clustered cells), before entering meiosis and oocyte growth. While the existence of these cells is now well established, the control of the different steps of – and whether they actually support the formation of new immature oocytes in adult female ovaries in physiological conditions – remains largely unknown.

Environment and perspectives

The M2 subject is part of the interdisciplanary and collaborative ANR project *PROBA* involving MUSCA and the *Laboratoire de Génomique et Physiologie des Poissons* (INRAE Rennes). The M2 work can give rise to a funded PhD thesis. The perspectives will consist for instance in studying a spatially structured cell population model and the associated mean-field formalism, in close collaboration with experimentalists performing 3D spatial imaging of the whole-ovary at the single cell level.

Expected skills Solid background in Applied Mathematics, including expert knowledge on stochastic processes and stochastic simulations. Strong interest for interdisciplinary work is required, and experience in statistical analysis, ideally applied to biological issues, would be a plus.

References

[1] T. Antal and P.L. Krapivsky. Exact solution of a two-type branching process: clone size distribution in cell division kinetics. *J. Stat. Mech. Theory Exp.*, 2010(07):P07028, 2010.

[2] F. Clément and J. Olayé. A stochastic model for neural progenitor dynamics in the mouse cerebral cortex. *Math. Biosci.*, 372:109185, 2024.

[3] K.S. Crump and C.J. Mode. A general age-dependent branching process. I. *J. Math. Anal. and Appl.*, 24(3):494–508, 1968.

[4] G. Jones. Calculations for multi-type age-dependent binary branching processes. *J. Math. Biol.*, 63:33–56, 2011.

[5] B. Li, A. Sierra, J.J. Deudero, F. Semerci, A. Laitman, M. Kimmel, and M. Maletic-Savatic. Multi-type bellman-harris branching model provides biological predictors of early stages of adult hippocampal neurogenesis. *BMC Syst. Biol.*, 11(5):90, 2017.

[6] H.R. Macmillan and M.J. Mcconnell. Seeing beyond the average cell: branching process models of cell proliferation, differentiation, and death during mouse brain development. *Theory Biosci.*, 130:31–43, 2011.

[7] A. Marguet. *Branching processes for structured populations and estimators for cell division.* These de doctorat, Université Paris-Saclay (ComUE), November 2017.

[8] S. Nakamura, K. Kobayashi, T. Nishimura, S. Higashijima, and M. Tanaka. Identification of germline stem cells in the ovary of the teleost medaka. *Science*, 328(5985):1561–1563, 2010.

[9] R.E. Nordon, K.-H Ko, R. Odell, and T. Schroeder. Multi-type branching models to describe cell differentiation programs. *J. Theor. Biol.*, 277(1):7–18, 2011.

[10] N.M. Yanev. Stochastic models of cell proliferation kinetics based on branching processes. In A. Almudevar, D. Oakes, and J. Hall, editors, *Statistical modeling for biological systems: In memory of Andrei Yakovlev*, pages 3–20. Springer International Publishing, Cham, 2020.