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Comparative dynamics of female germ cell populations : insight from imaging and multiscale modeling

Frédérique Clément, Romain Yvinec

Journées INRAE-INRIA, 04-05 Juillet 2023

Collaborative background

Biological background

Available and future data

Modeling questions and approaches

Collaborative background

- ⊙ EPC CNRS-INRAE-INRIA MUSCA

*MU*ltiSCAle population dynamics for physiological systems

CRI Saclay – MaiAGE – PRC

- ⊙ Projet GinFiz ANSES 2020

Gonadal aromatase inhibition and other toxicity pathways leading to Fecundity Inhibition in Zebrafish: from initiating events to population impacts

collaboration INERIS (Rémy Beaudouin) + Laboratoire de Physiologie et Génomique des Poissons (LPGP, Violette Thermes)

- ⊙ Projet IMMO Digit-Bio INRAE 2021

Imagerie et modélisation multi-échelles pour la compréhension de la dynamique ovarienne chez le poisson

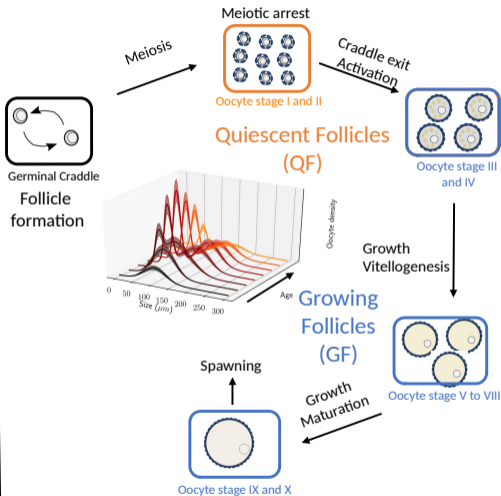
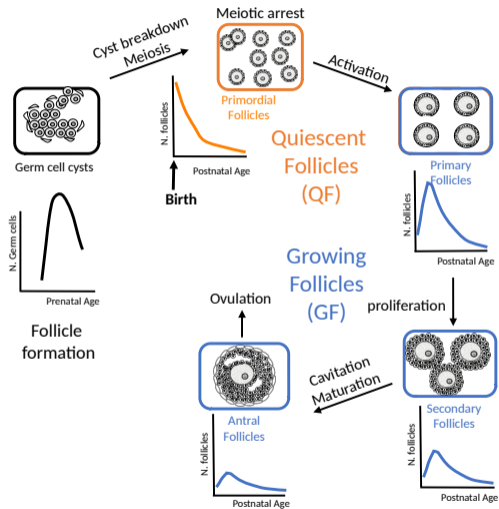
collaboration LPGP

- ⊙ AAPG ANR CES 45 OVOPAUSE 2022

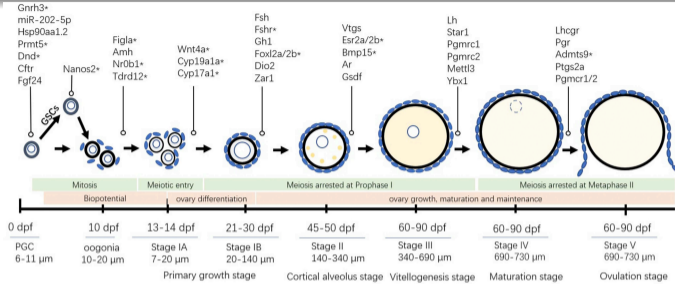
Dynamics and regulation of female germ cell populations: understanding aging through population dynamics models

collaboration LPGP + INSERM

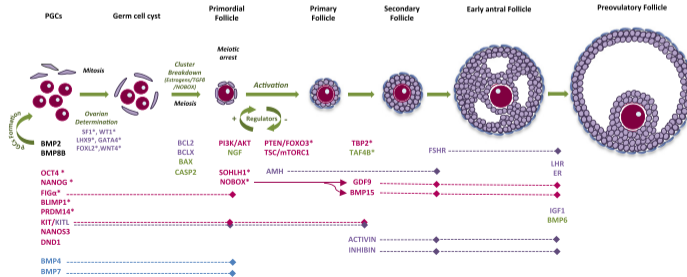
Comparative vertebrate oogenesis (1)



Comparative vertebrate oogenesis (2)



Li & Ge Mol. Cell. Endocrinol. 2020



Sánchez & Smith Acta Bioch. Biophys. 2012

Main questions and related outcomes

Population scale

- ⊙ Kinetics of oocyte pool exhaustion / intensity of oocyte pool renewal
- ⊙ Shaping of the oocyte (size/maturation) distribution
- ⊙ Contribution of direct and indirect interactions within the oocyte population
Management of oocyte resources / Driving of ovarian cyclicity

Oocyte/follicle scale

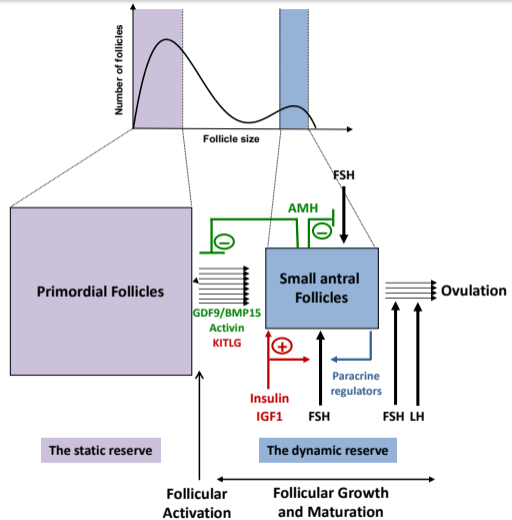
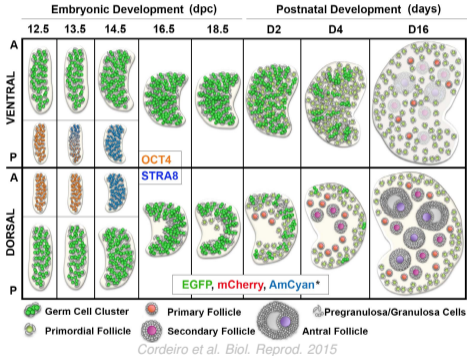
- ⊙ Coupled dynamics between germ cells and somatic cells
- ⊙ Mechanisms underlying the proper sequence of morphogenetic events

Preserving the ovarian resources

- ⊙ Ovarian aging
- ⊙ Reproductive fitness

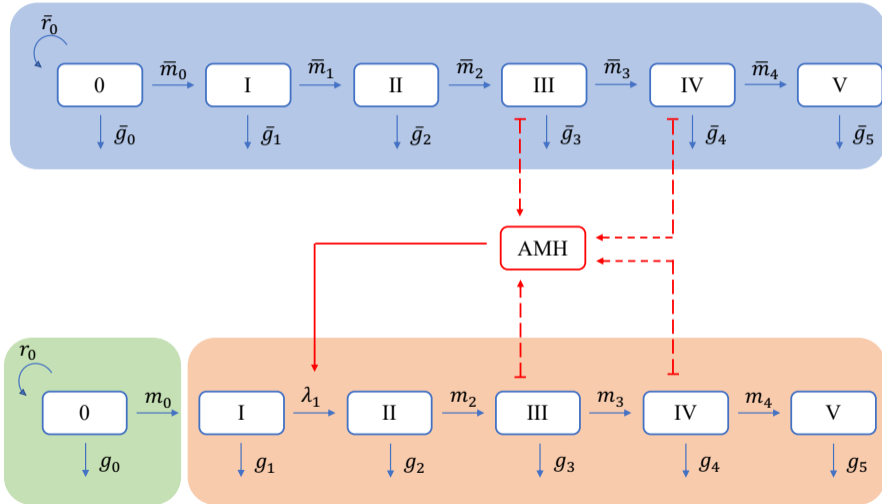
Knowledge driven modeling approaches (Mammals)

Embedding cell biology/developmental biology/endocrine information



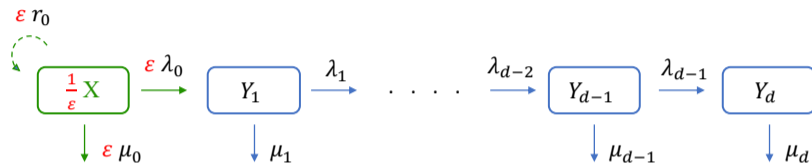
Knowledge driven modeling approaches (Mammals)

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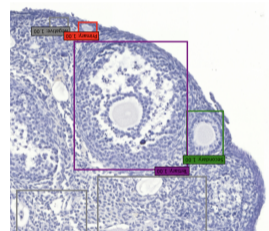
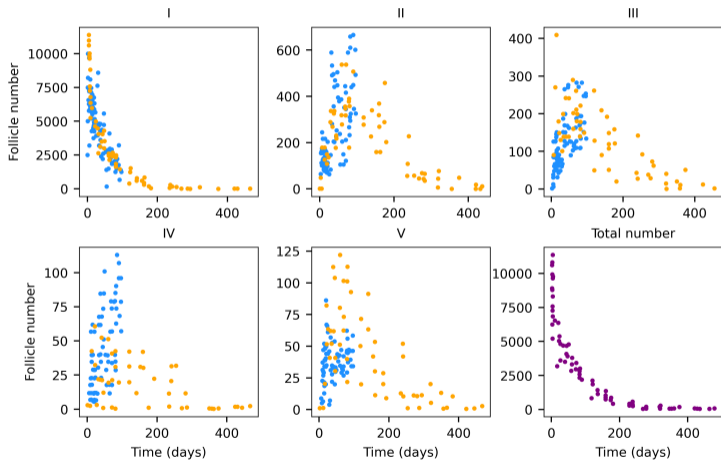
Stochastic compartmental population dynamics

Multiple timescales and order of magnitudes \Rightarrow Model reduction



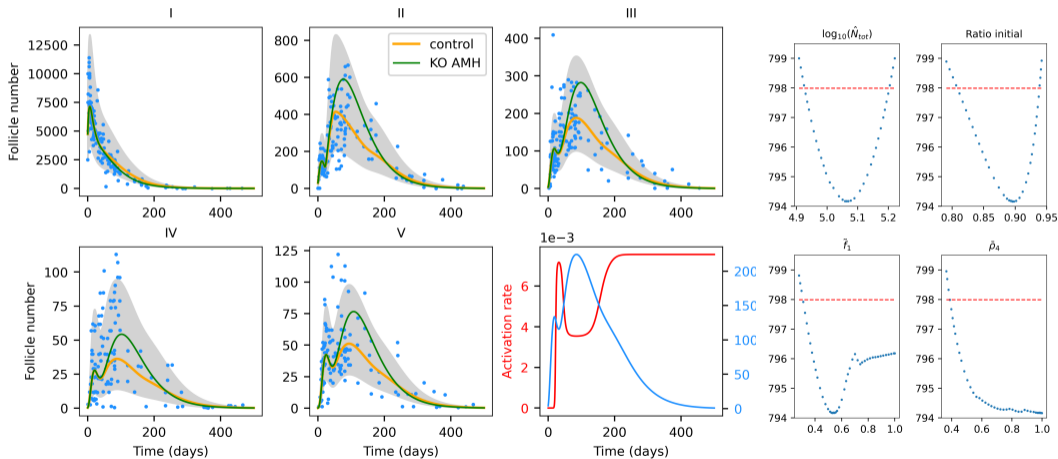
	Transition	Rate
Birth (reserve)	$(X^\varepsilon, Y^\varepsilon) \rightarrow (X^\varepsilon + \varepsilon, Y^\varepsilon)$	$\frac{r_0(Y^\varepsilon)}{\varepsilon} X^\varepsilon$
Maturation (reserve)	$(X^\varepsilon, Y^\varepsilon) \rightarrow (X^\varepsilon - \varepsilon, Y^\varepsilon + e_1)$	$\frac{\lambda_0(Y^\varepsilon)}{\varepsilon} X^\varepsilon$
Death (reserve)	$(X^\varepsilon, Y^\varepsilon) \rightarrow (X^\varepsilon - \varepsilon, Y^\varepsilon)$	$\frac{\mu_0(Y^\varepsilon)}{\varepsilon} X^\varepsilon$
Maturation, $i \in \llbracket 1, d-1 \rrbracket$	$(X^\varepsilon, Y^\varepsilon) \rightarrow (X^\varepsilon, Y^\varepsilon - e_i + e_{i+1})$	$\frac{\lambda_i(Y^\varepsilon)}{\varepsilon} Y_i^\varepsilon$
Death, $i \in \llbracket 1, d \rrbracket$	$(X^\varepsilon, Y^\varepsilon) \rightarrow (X^\varepsilon, Y^\varepsilon - e_i)$	$\frac{\mu_i(Y^\varepsilon)}{\varepsilon} Y_i^\varepsilon$

Data-driven parameter estimation : low-throughput data



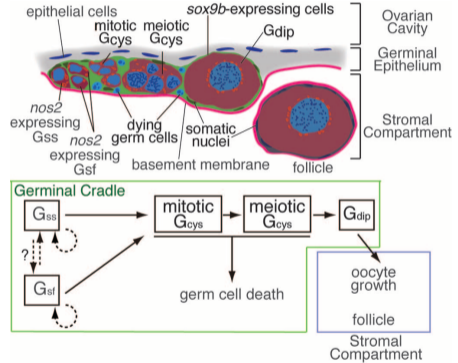
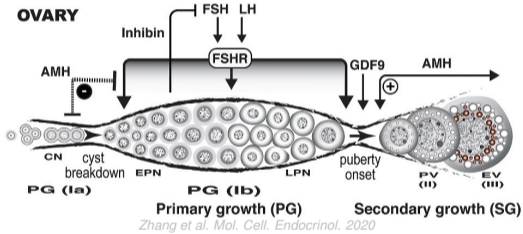
Data-driven parameter estimation : low-throughput data

Model selection, parameter identifiability, perturbation prediction



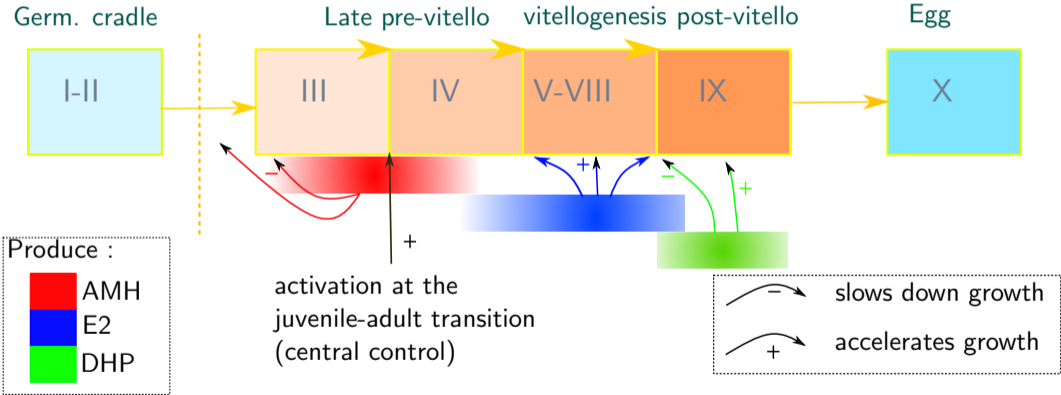
Knowledge driven modeling approaches (Fish)

Embedding cell biology/developmental biology/endocrine information



Knowledge driven modeling approaches (Fish)

Embedding cell biology/developmental biology/endocrine information



Deterministic size-structured population dynamics

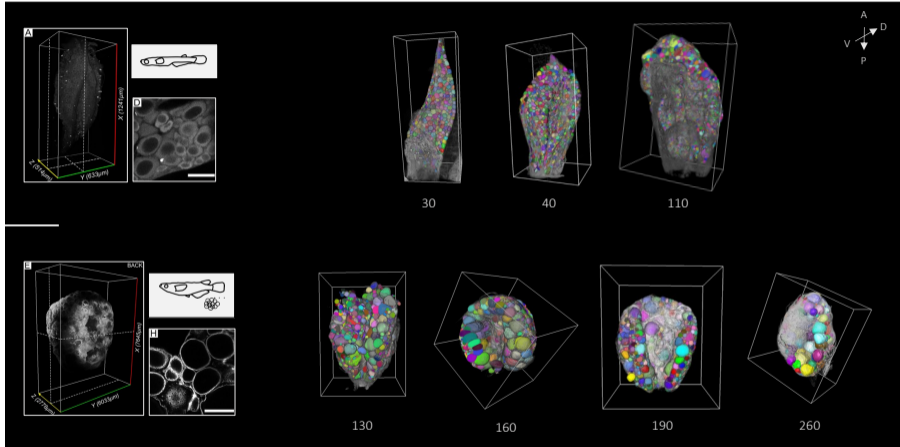
Nonlinear conservation laws: numerical scheme and asymptotic behavior

Parameters	Interpretation	Output	Interpretation
λ_0	Cradle exit rate	ρ_0	number of cells in the cradle
r_0	Cradle renewal rate	ρ	size density from stage III to IX
λ	growth speed from stage III to IX	ρ_1	number of stage X oocytes
W_i	"quantity" of hormone i secreted		

$$\left\{ \begin{array}{l} \frac{d}{dt}\rho_0(t) = r_0(\rho_0)\rho_0(t) - \lambda_0(W_{AMH}(t))\rho_0(t), \quad t > 0 \\ \lim_{x \rightarrow 0}(\lambda\rho) = \lambda_0\rho_0(t), \quad \text{sur } [0, +\infty) \\ \partial_t\rho + \partial_x(\lambda(x, W_{AMH}, W_{E2}, W_{DHP})\rho) = 0, \quad x \in [0, 1], \quad t > 0 \\ \frac{d}{dt}\rho_1(t) = \lim_{x \rightarrow 1}(\lambda\rho) - \text{spawn}(t), \quad t > 0 \\ W_i(t) = \int_0^1 \omega_i(x)\rho(t, x)dx, \quad i \in \{AMH, E2, DHP\} \end{array} \right.$$

Data-driven parameter estimation : DL-based data extraction

Work of Violette Thermes and collaborators

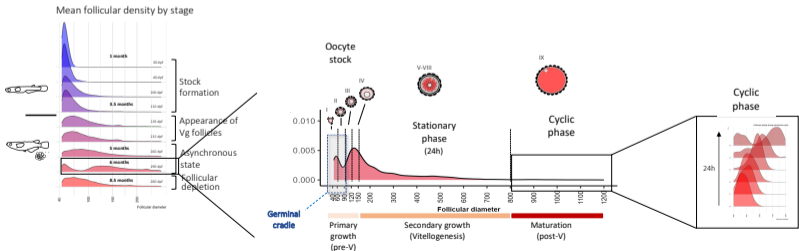
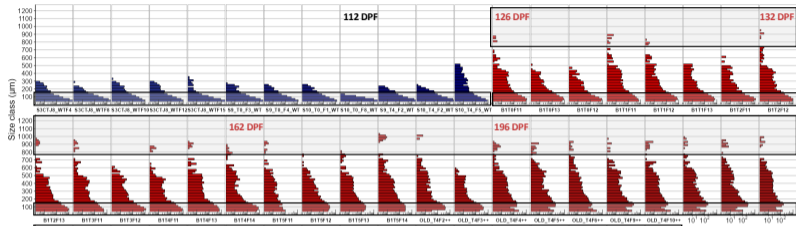


Inputs : 3D ovarian imaging / Automatic follicle segmentation and classification

Outputs : age/space-varying distribution in size/class of the total population of ovarian follicles

Data-driven parameter estimation : DL-based data extraction

Work of Violette Thermes and collaborators

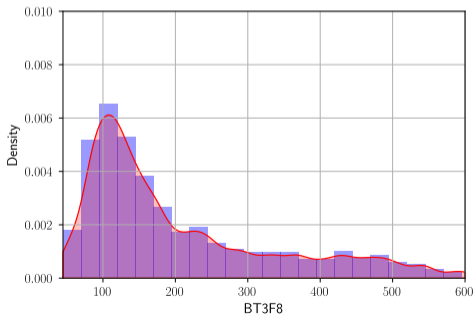
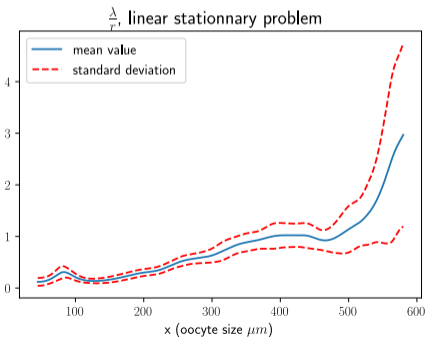


Data-driven parameter estimation

Nonparametric inverse problem on stationary state

$$\begin{cases} \bar{\rho}(0) = r \\ \partial_x (\lambda(x)\bar{\rho}) = 0, \quad x \in [0, 1] \end{cases}$$

Hormonal interactions cannot be deduced from purely stationary data, yet we can infer the size-dependent oocyte growth speed.



Ongoing/ future directions

Stochastic and deterministic models of structured populations with nonlinear and nonlocal terms

- Wellposedness / stationary solutions
- Inverse problems
- Structuring variable(s)
Coupling with cell dynamics models on the single-follicle level
Spatial distribution
- Physics-based modeling (morphogenesis)

