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Modeling Ovarian Folliculogenesis: Morphogenesis and Population Dynamics

Celine Bonnet, Keltoum Chahour, Frederique Clement, Marie Postel,
Frédérique Robin, Romain Yvinec

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INTRODUCTION

We present stochastic population dynamic models applied to several situations to understand ovarian folliculogenesis

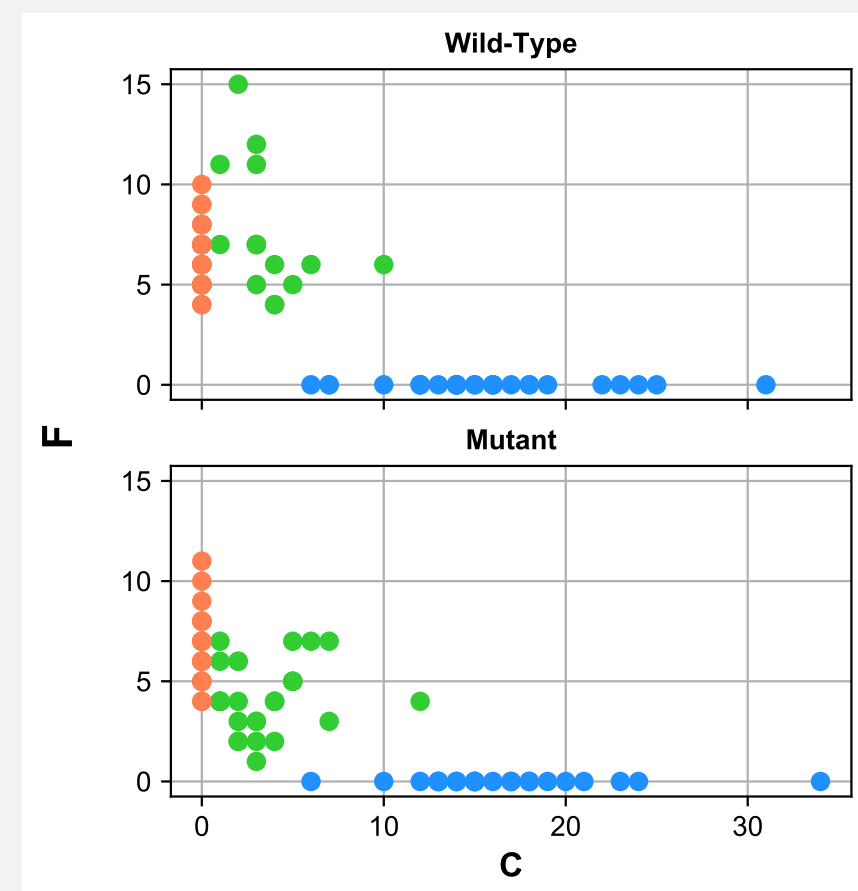
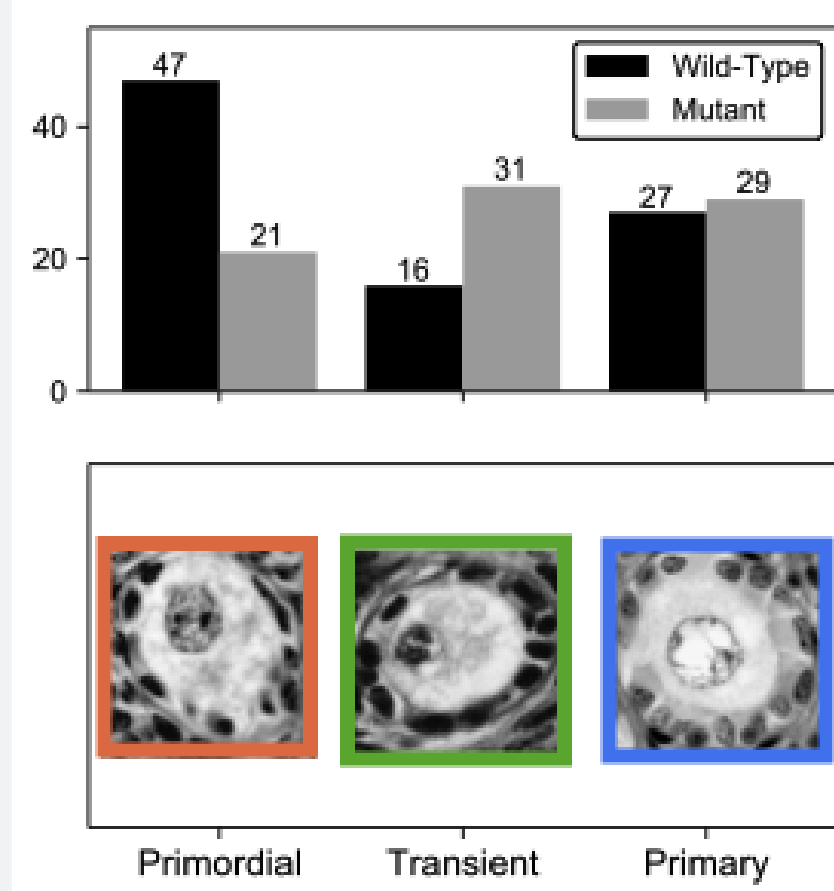
- ◇ Somatic cell population dynamics in a single follicle (either in the activating or basal growing phase)
- ◇ Whole follicle population dynamics during the reproductive lifespan

CELL DYNAMICS IN AN ACTIVATING FOLLICLE

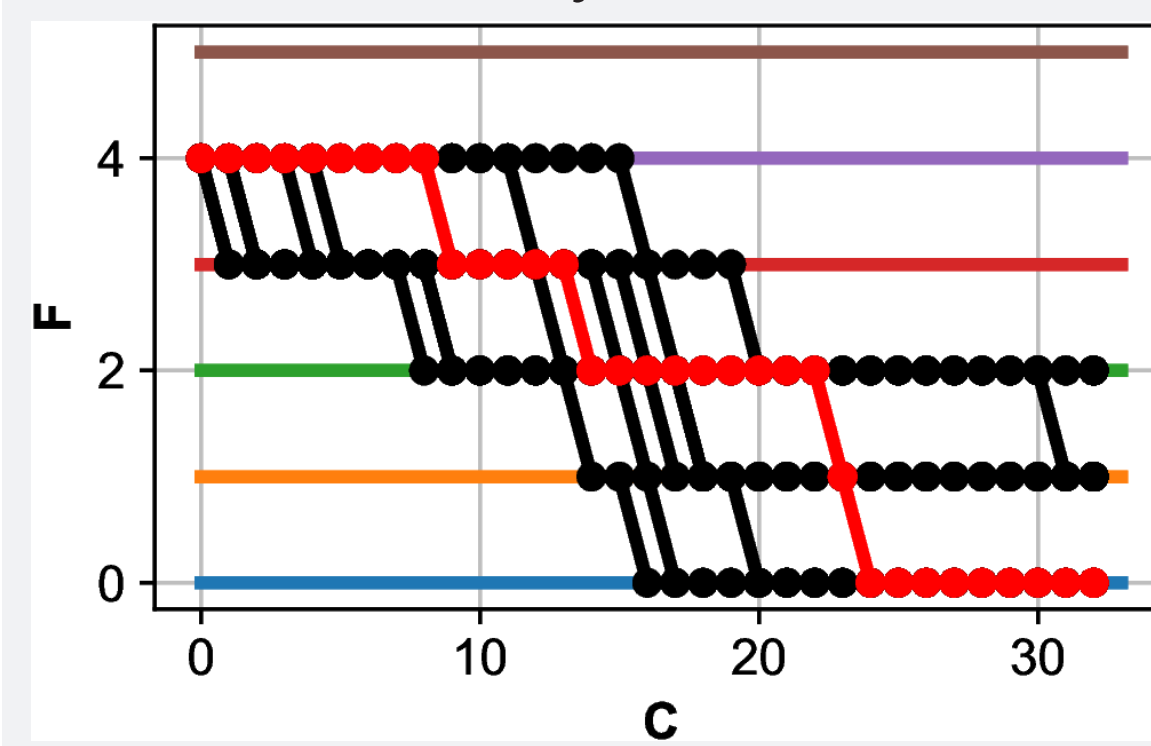
Somatic cell transition and proliferation during follicle activation

Key questions: What are the kinetics of follicle activation?
Are transition and proliferation concomitant?

Data: Cell counts (Lundy et al., J. Reprod. Fertil., 115 (1999); Wilson et al. Biol Reprod 64 (2011))



Model: Flattened (F) and Cuboidal (C) cell dynamics



Stochastic Nonlinear Model

- Spontaneous transition
- Auto-amplified transition
- Cuboidal Proliferation
- Self-renewing asymmetric divisions

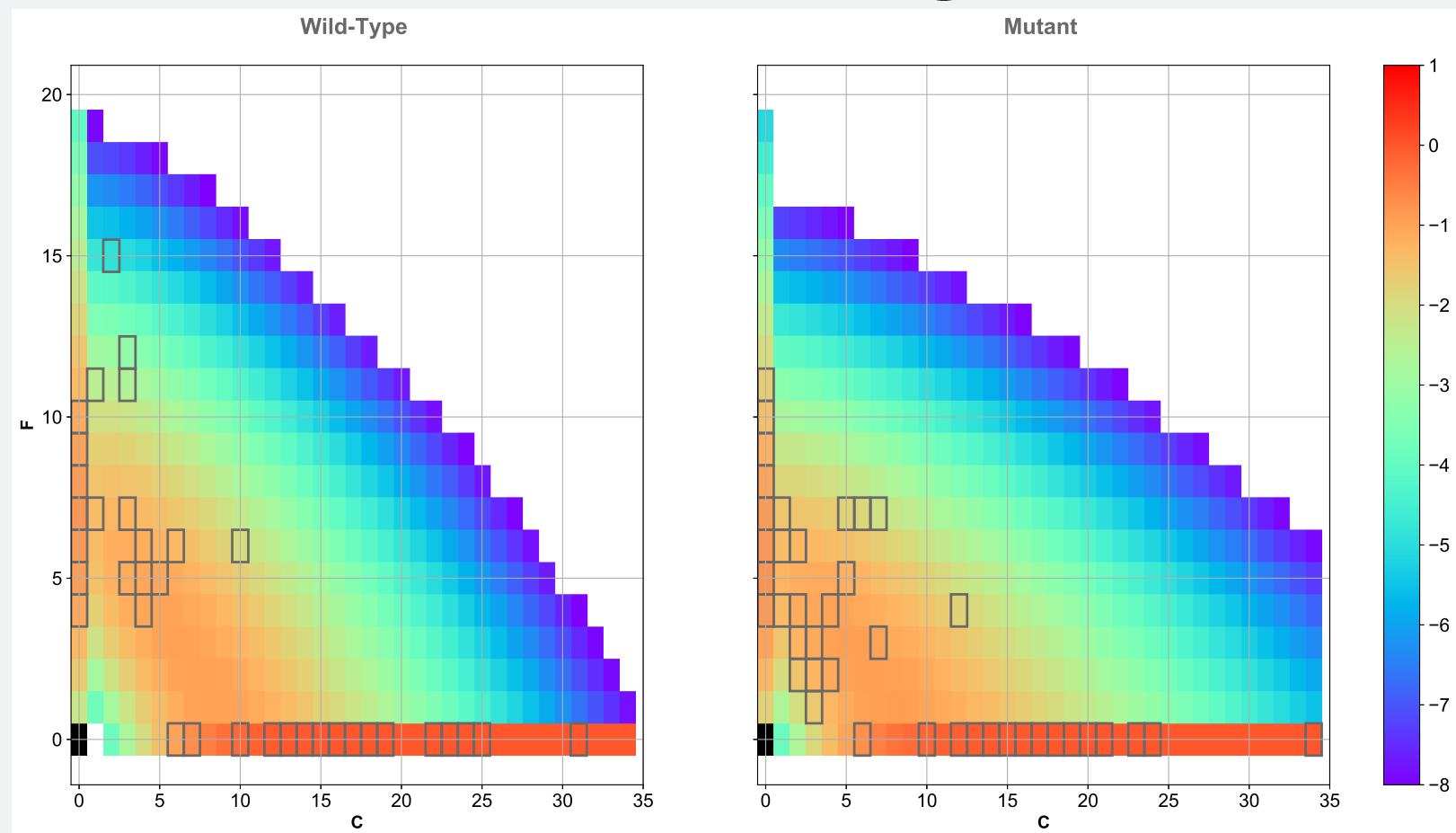
Cell events

- $(F, C) \rightarrow (F - 1, C + 1)$
- $(F, C) \rightarrow (F - 1, C + 1)$
- $(F, C) \rightarrow (F, C + 1)$
- $(F, C) \rightarrow (F, C + 1)$

Rate

- αF
- $\beta \frac{FC}{F+C}$
- γC
- δF

Data Fitting



Results: see [3]

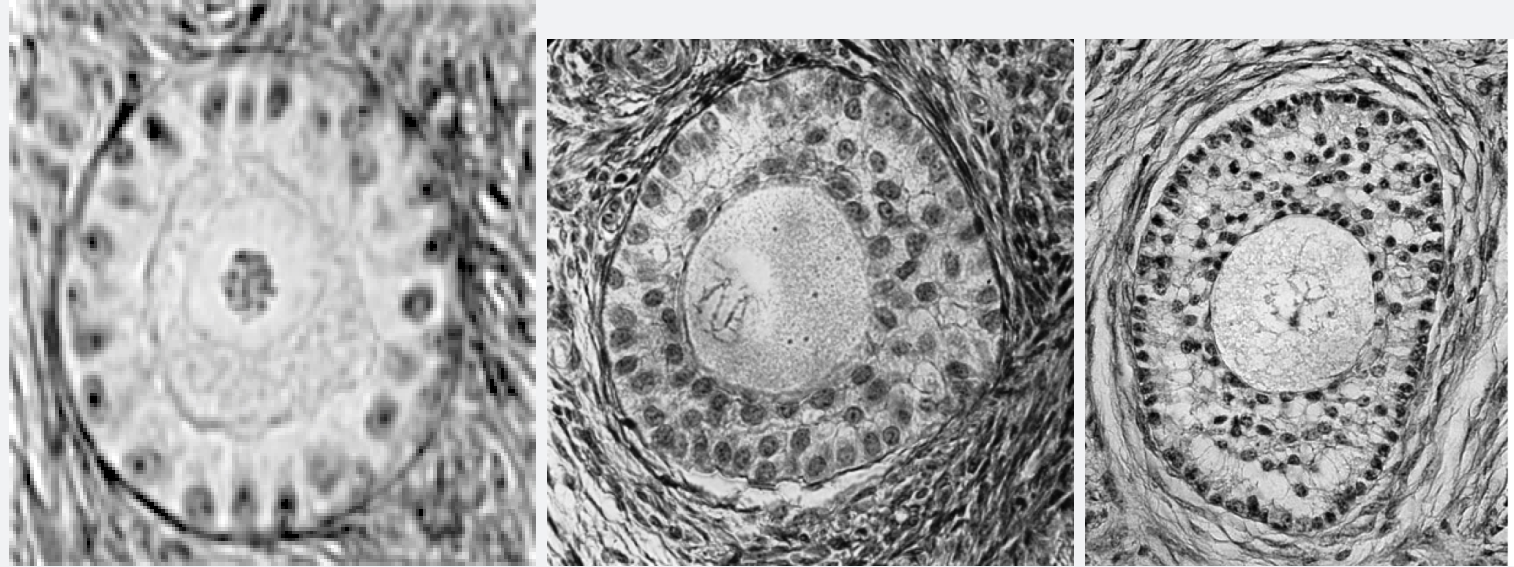
- Clear separation between transition and proliferation in Wild-type.
- Auto-amplification is not mandatory, especially for the Mutant dataset

CELL DYNAMICS IN A GROWING FOLLICLE

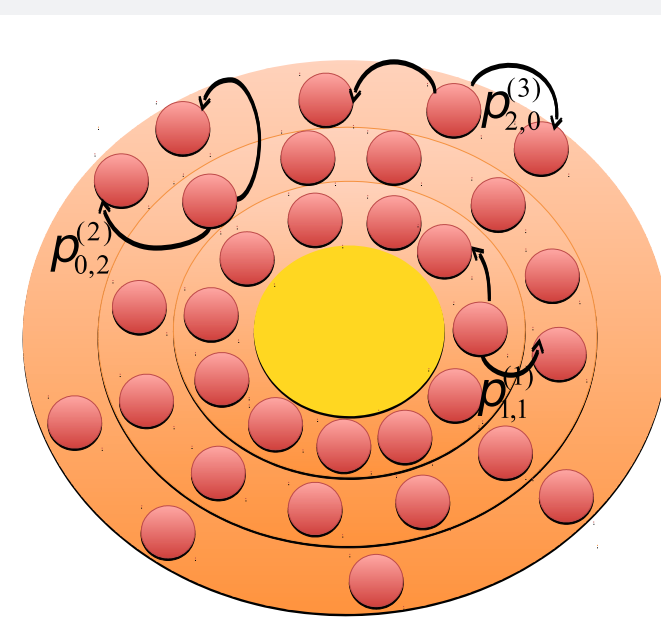
Somatic cell proliferation during basal follicle growth

Key questions: What is the rate of growth?
Is proliferation oocyte-dependent?

Data: Total cell numbers, Oocyte and Follicle diameters at three time points (Lundy et al., J. Reprod. Fertil., 115 (1999); Smith et al. J. Reprod. Fertil., 100 (1994))



Model: Cell proliferation and repartition in successive layers



Stochastic Linear Model

- Both daughter cells stay on mother's layer
- One daughter cell into next mother's layer
- Both daughter cells into next mother's layer

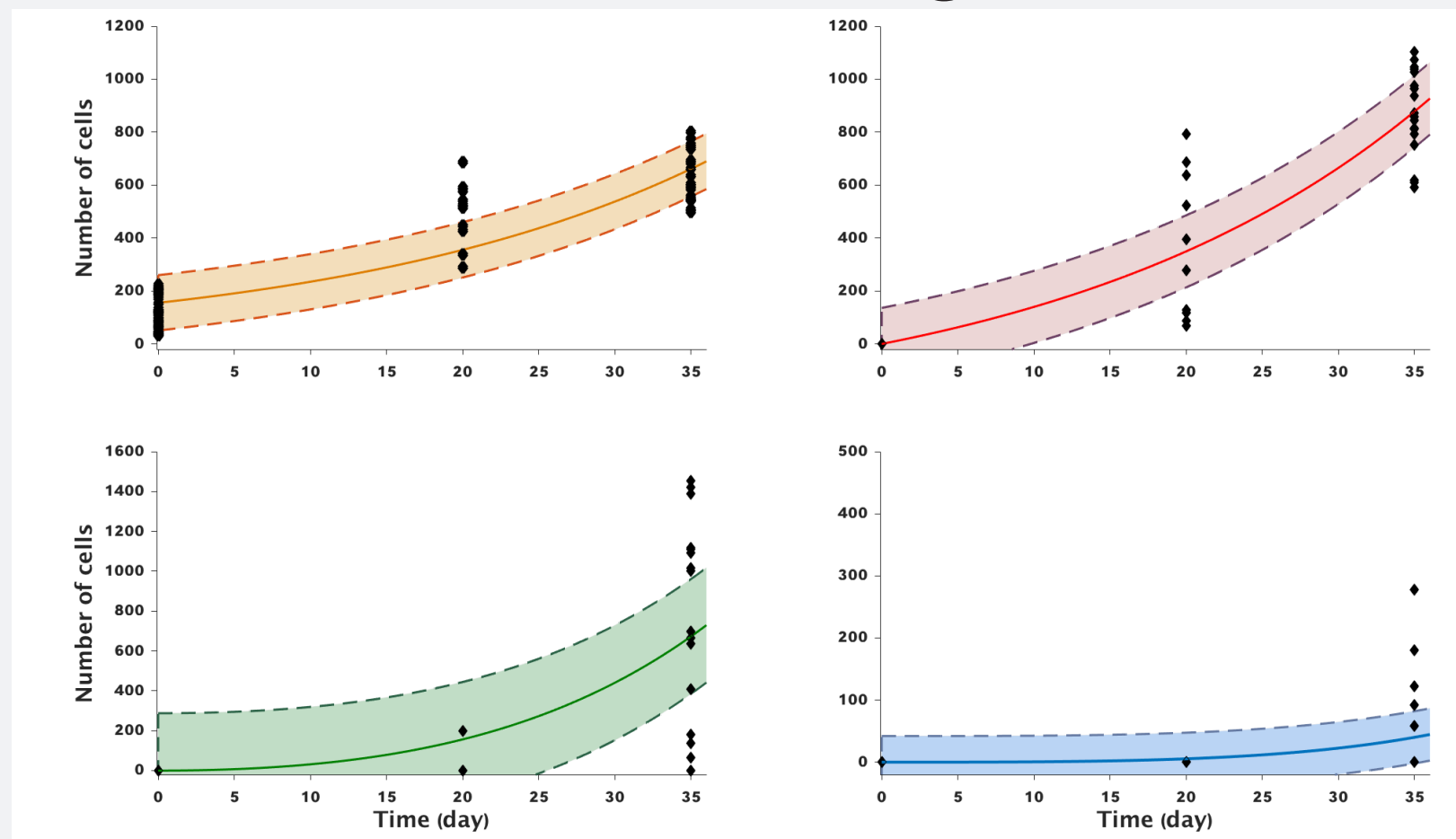
Cell events

- $N^j \rightarrow 2N^j$
- $N^j \rightarrow N^j + N^{j+1}$
- $N^j \rightarrow 2N^{j+1}$

Rate

- $p_{2,0}^j b_j N^j$
- $p_{1,1}^j b_j N^j$
- $p_{0,2}^j b_j N^j$

Data Fitting



Results: see [2]

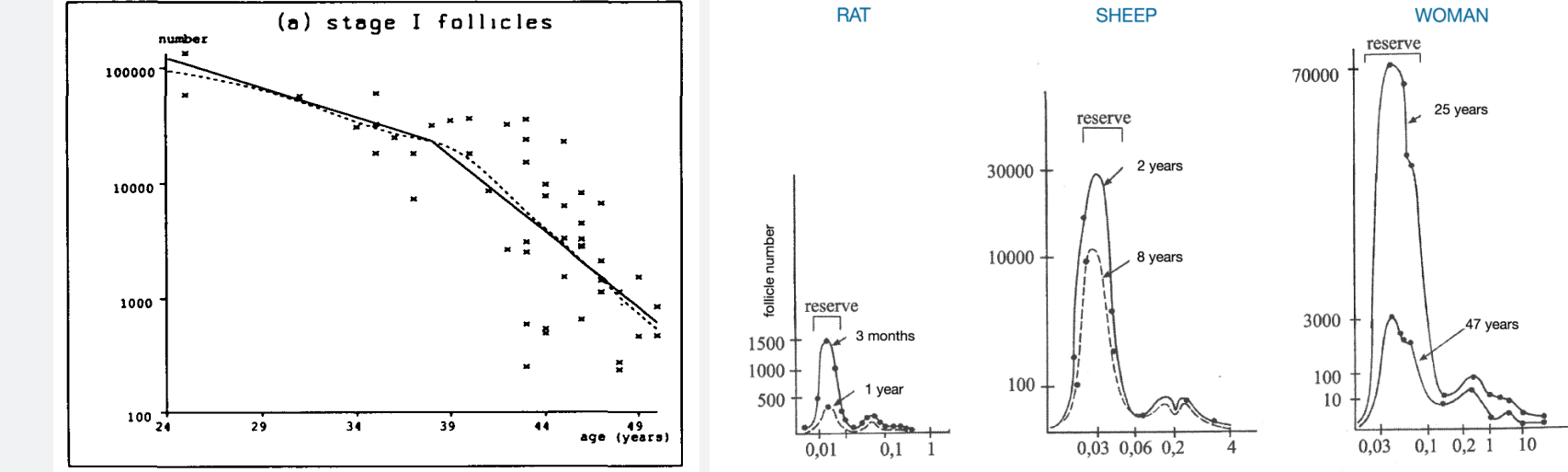
- Data are compatible with
- an exponential growth phase.
 - a layer-dependent growth rate is decreasing with oocyte distance

WHOLE FOLLICLE POPULATION DYNAMICS

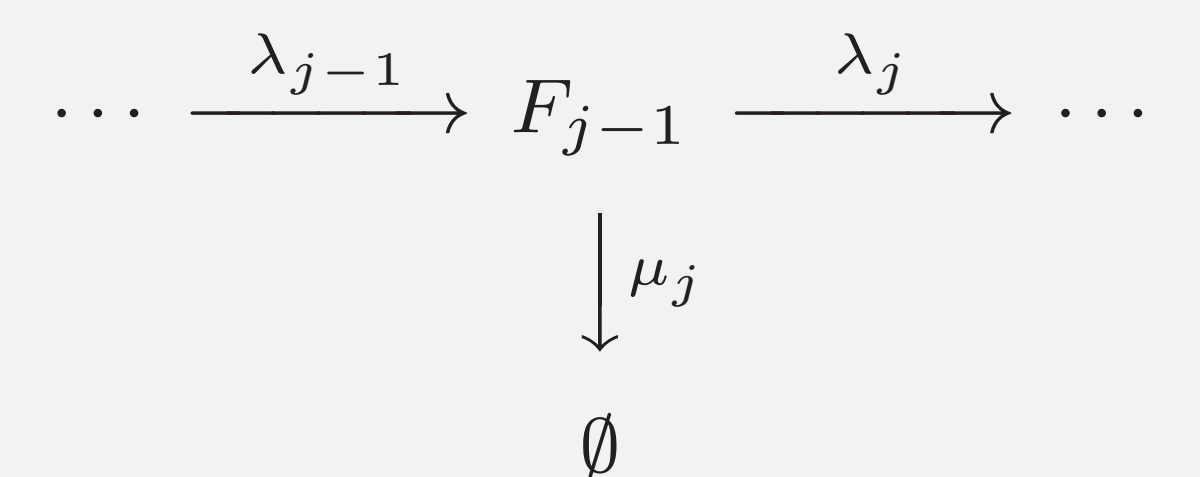
Nonlinear interactions between follicular populations

Key questions: How a quasi-stable maturity repartition is achieved?
What is the role of nonlinear interactions?

Data: Follicle counts according to maturity class (Faddy and Gosden, Human Reproduction, 10 (1995); Thibault and Levasseur 2001)



Model: Population-dependent follicle maturity and atresia



Stochastic Nonlinear Model

- Follicle activation
- Follicle maturation
- Follicle atresia

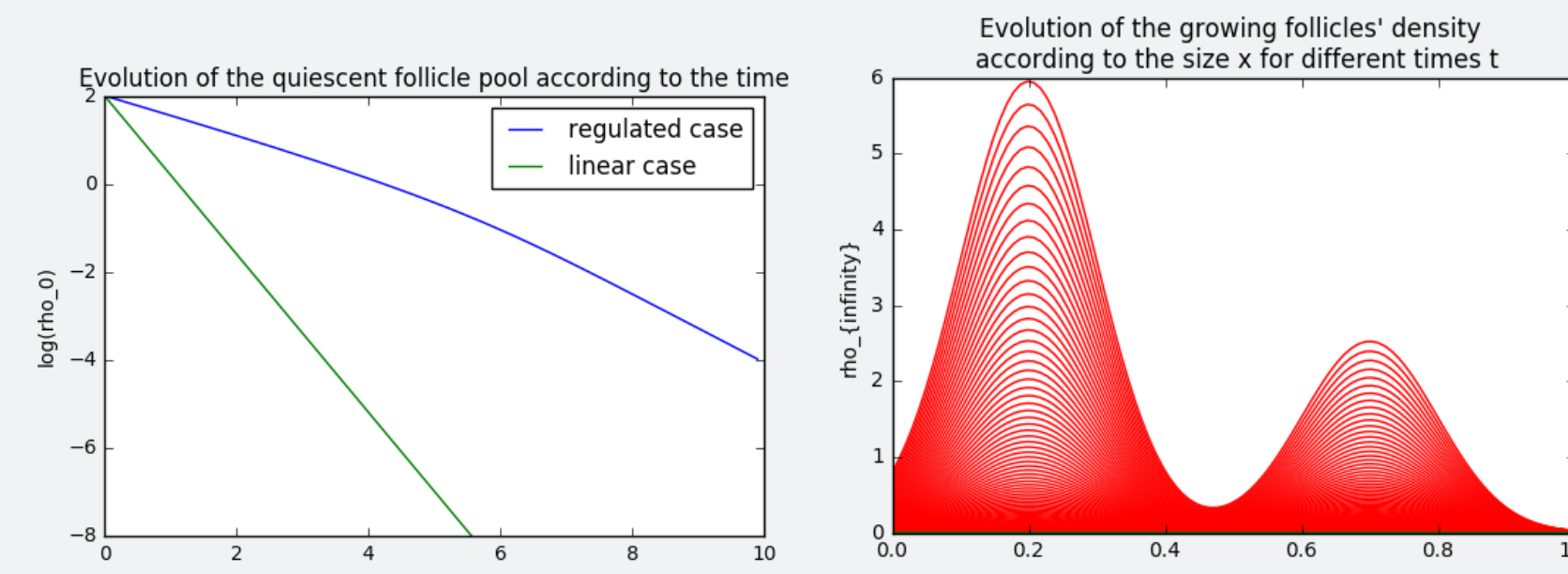
Follicle events

- $F_0 \rightarrow F_1$
- $F_j \rightarrow F_{j+1}$
- $F^j \rightarrow \emptyset$

Rate

- $\varepsilon \frac{\lambda_0}{1 + K \sum_{j=1}^d a_j F_j} F_0$
- $\lambda_j F_j$
- $\mu_j F_j$

Qualitative agreement



Results: see [1]

- Time-scale separation explains quasi-stable maturity repartition.
- Removal of activation inhibition explains acceleration of reserve exhaustion

MATHEMATICAL TOOLBOX

- (Structured) Population dynamics model: deterministic and stochastic models.
- Long-time and asymptotic analysis, time-scale separation.
- Transient analysis: analytical and numerical solutions, first passage time.
- Statistical methods: parameter estimation and identifiability analysis.

CONCLUSION AND PERSPECTIVE

Mathematical modeling helps:

- ◇ to test different follicle growth scenario and make prediction
- ◇ to challenge biological knowledge on follicle dynamics.

Current study and future projects will focus on different scales:

- ★ **Intra-cellular scale:** FSHR signaling network and its role in follicle selection (for a review of gonadotropin signaling models, see [5]).
- ★ **Follicle scale:** coupling cell dynamics with biomechanics model to model antrum formation (extending and revisiting previous model [4]).
- ★ **Ovarian scale:** Complement follicle population dynamics with (i) ovarian reserve formation and (ii) ovarian cycle dynamics. Comparative physiology approaches will also be taken into account.

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- [5] R. Yvynec, P. Crépieux, E. Reiter, A. Poupon, and F. Clément. Advances in computational modeling approaches of pituitary gonadotropin signaling. *Expert Opinion on Drug Discovery*, 13(9):799–813, Sept. 2018.

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