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Modeling Ovarian Folliculogenesis: Morphogenesis and Population Dynamics

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INTRODUCTION

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

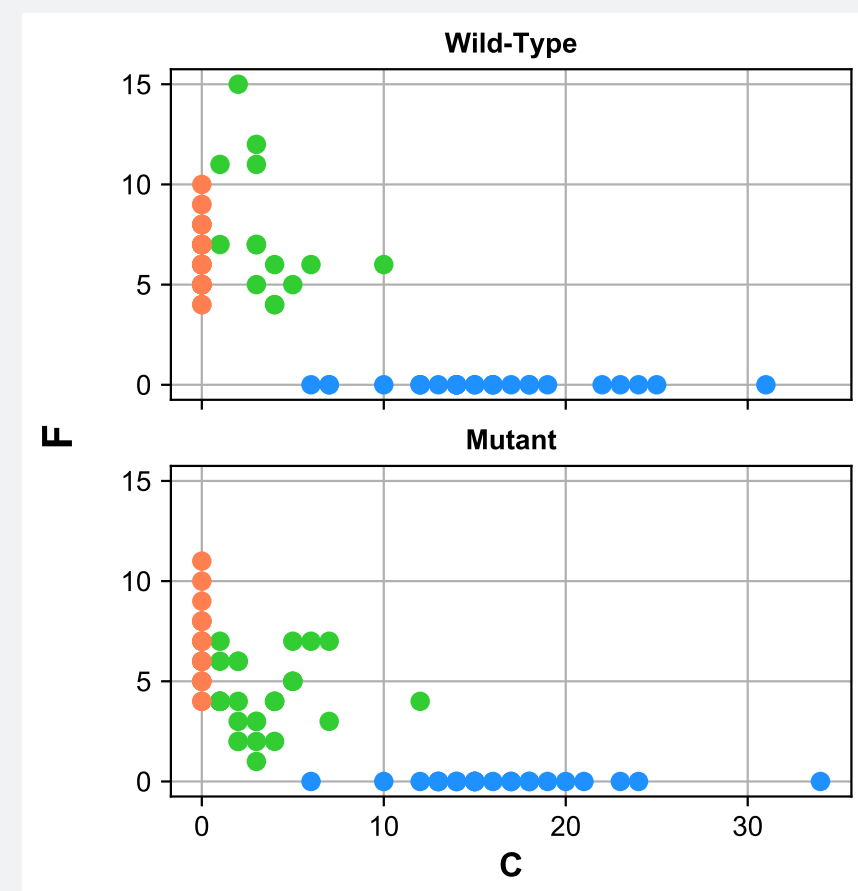
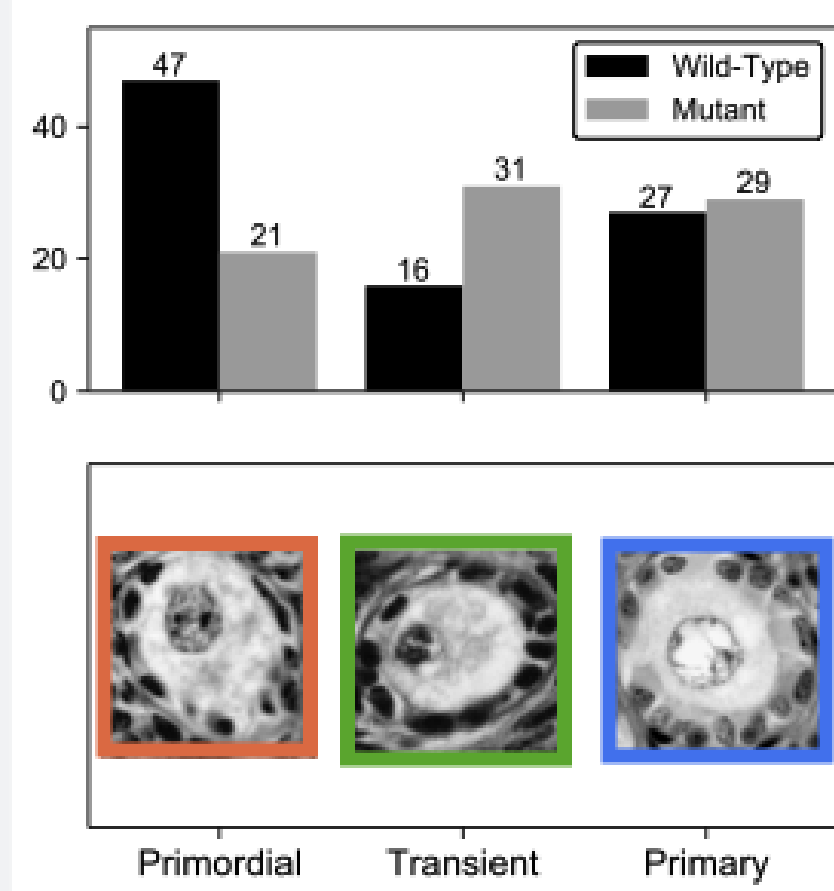
- ◇ Somatic cell population dynamics in a single follicle (either in the activating or basal growing phase)
- ◇ Whole follicle population dynamics during the reproductive lifespan

CELL DYNAMICS IN AN ACTIVATING FOLLICLE

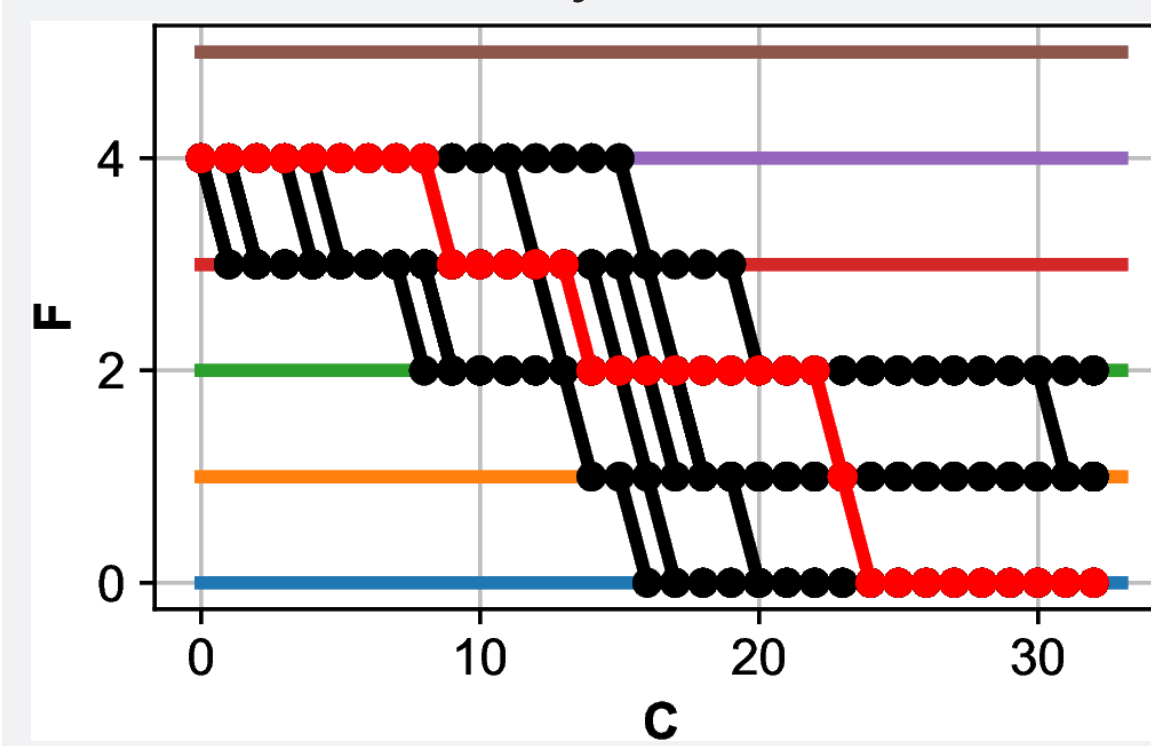
Somatic cell transition and proliferation during follicle activation

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

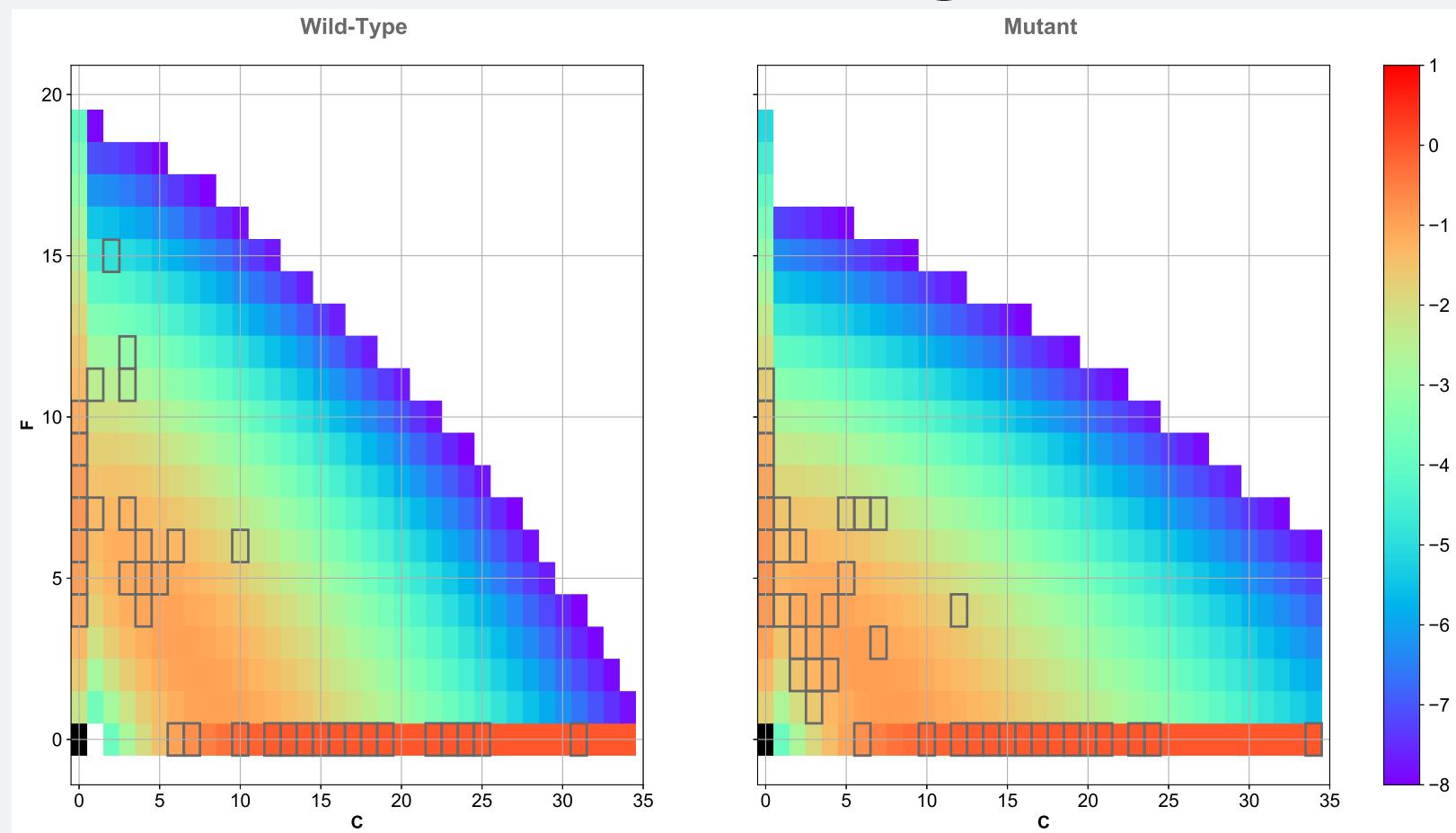
Cell events

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

Rate

αF
 $\beta \frac{FC}{F+C}$
 γC
 δF

Data Fitting



Results: see [3]

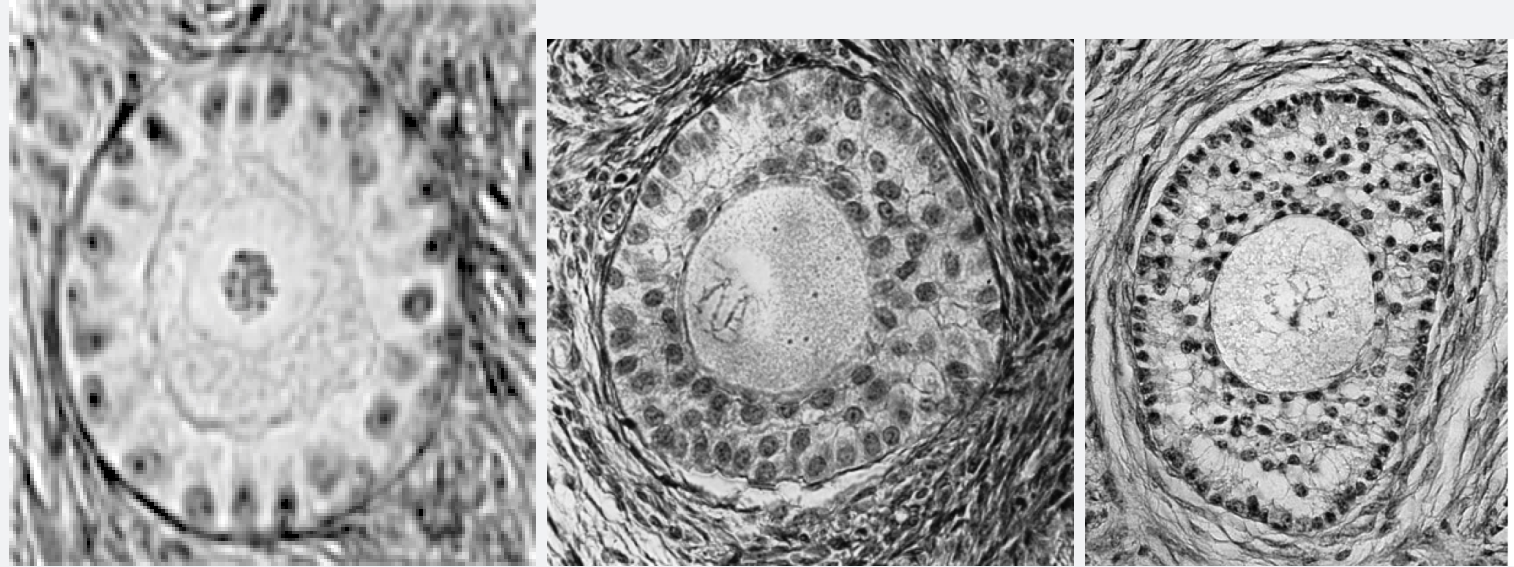
- Clear separation between transition and proliferation in Wild-type.
- Auto-amplification is not mandatory, especially for the Mutant dataset

CELL DYNAMICS IN A GROWING FOLLICLE

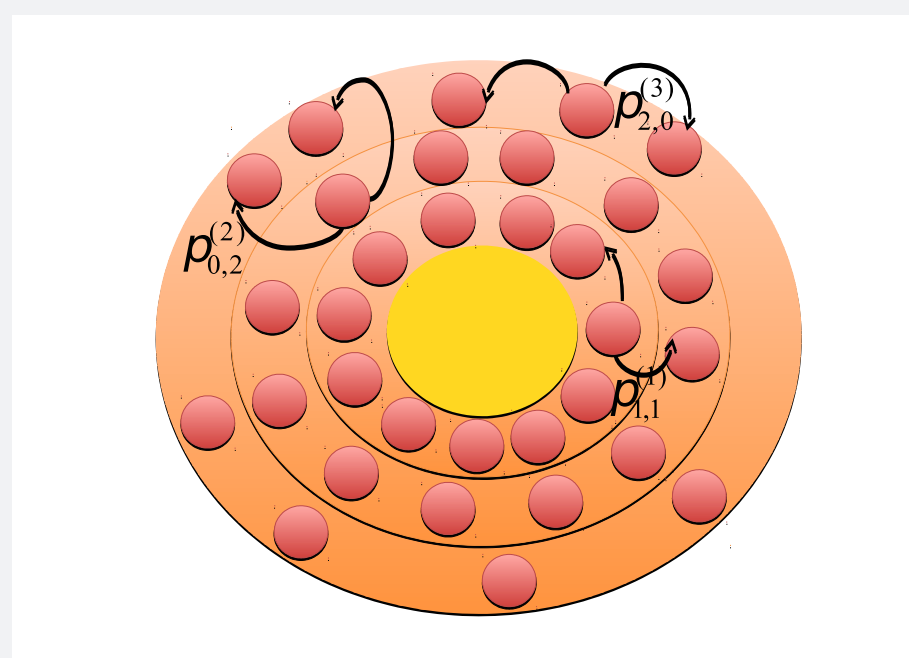
Somatic cell proliferation during basal follicle growth

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

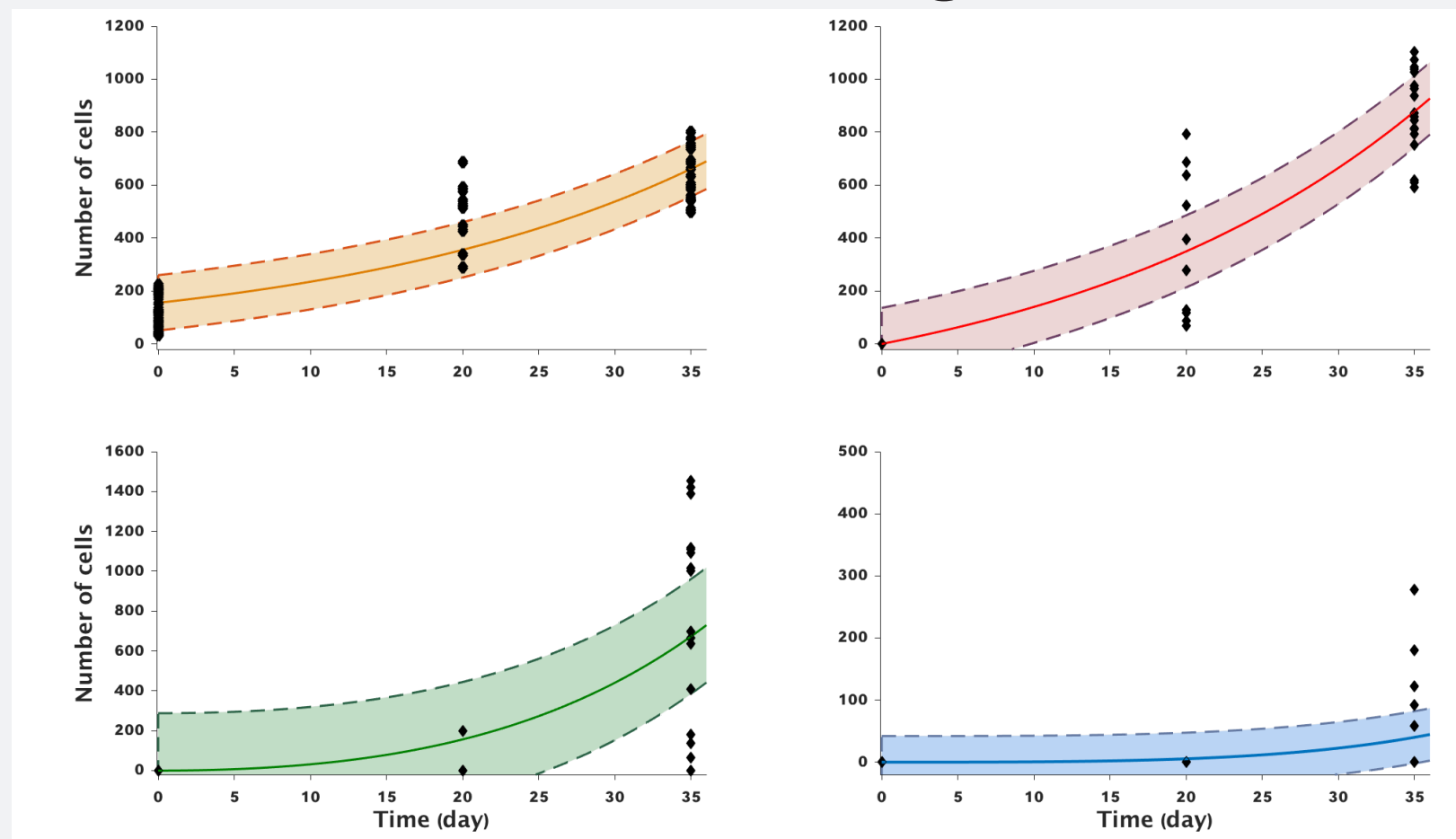
Cell events

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

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]

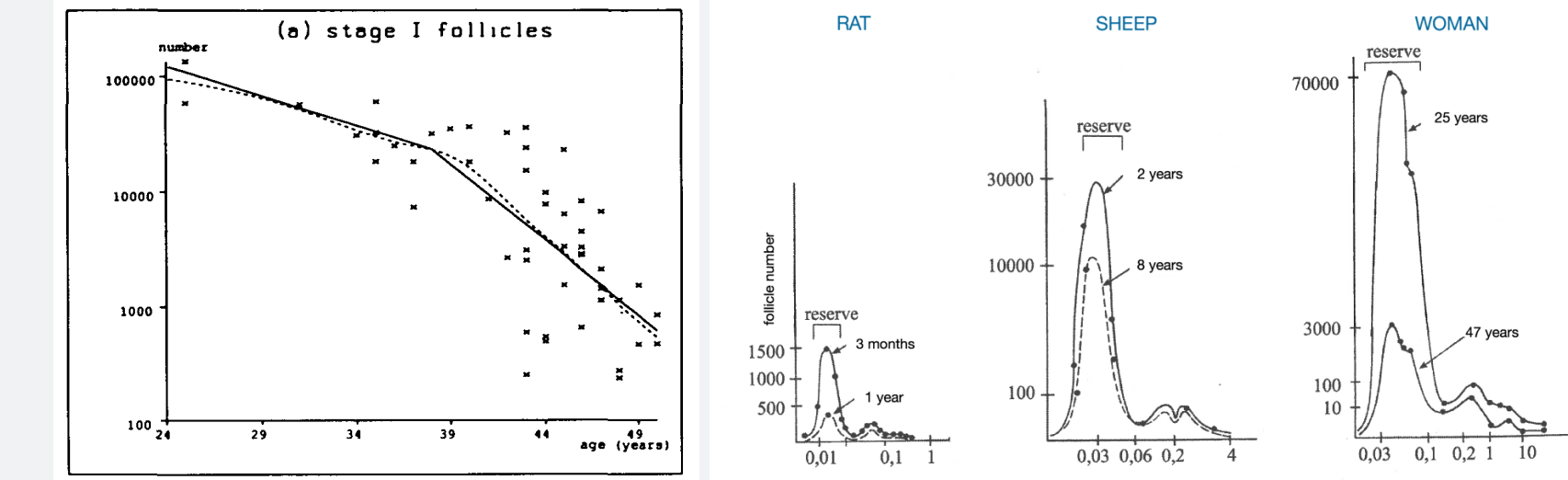
- Data are compatible with
- an exponential growth phase.
 - a layer-dependent growth rate is decreasing with oocyte distance

WHOLE FOLLICLE POPULATION DYNAMICS

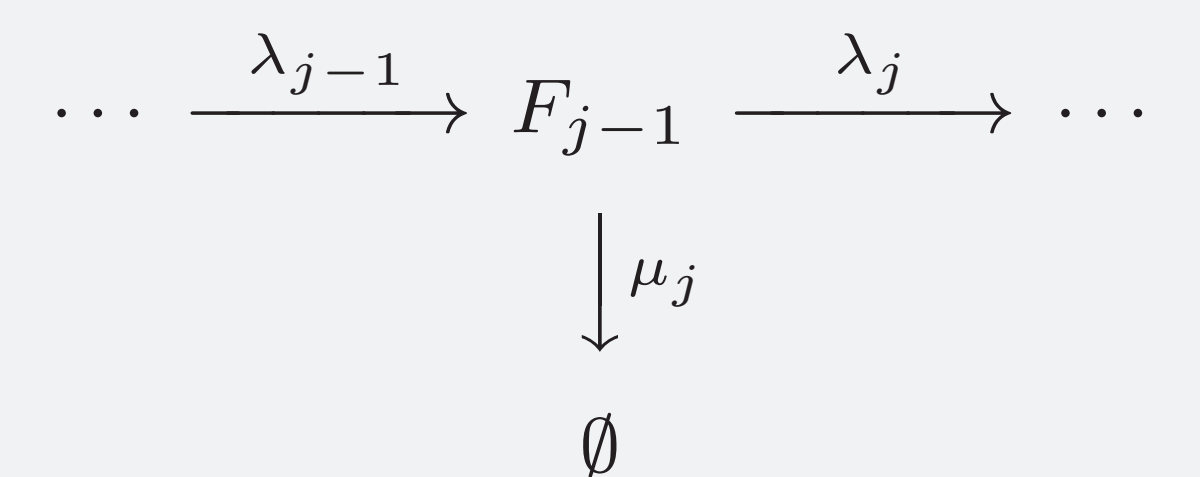
Nonlinear interactions between follicular populations

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

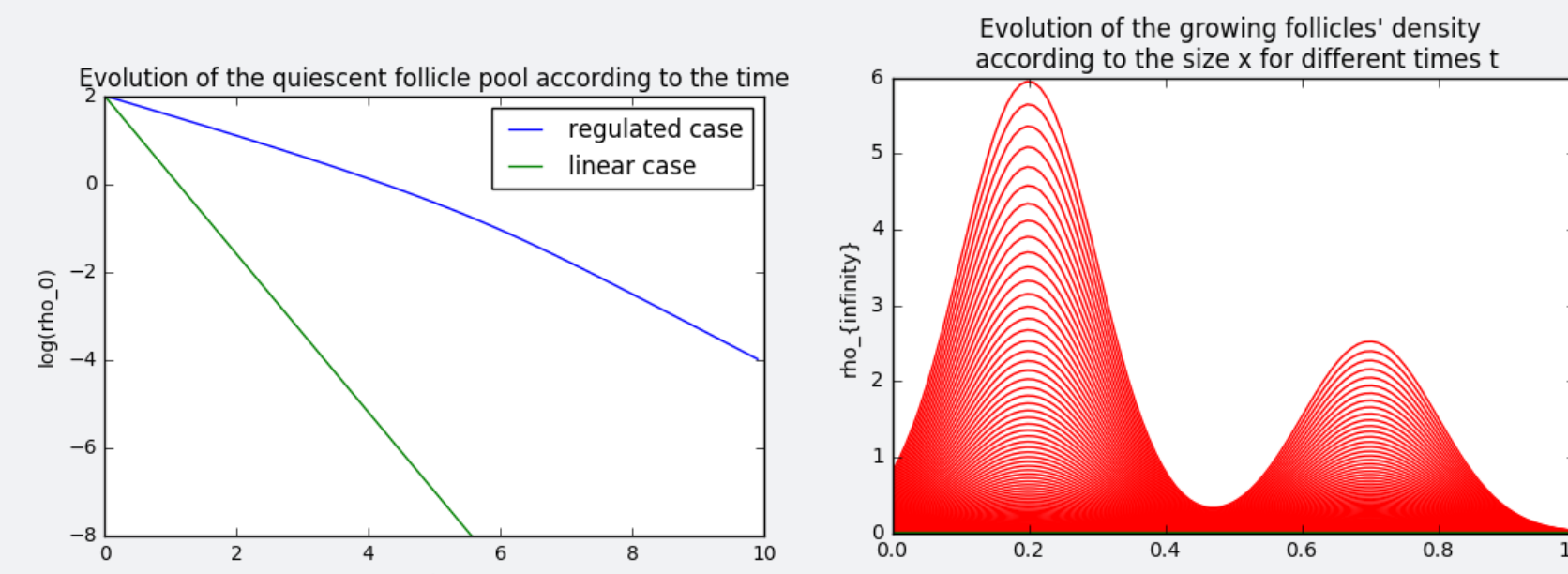
Follicle events

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

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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