



# 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

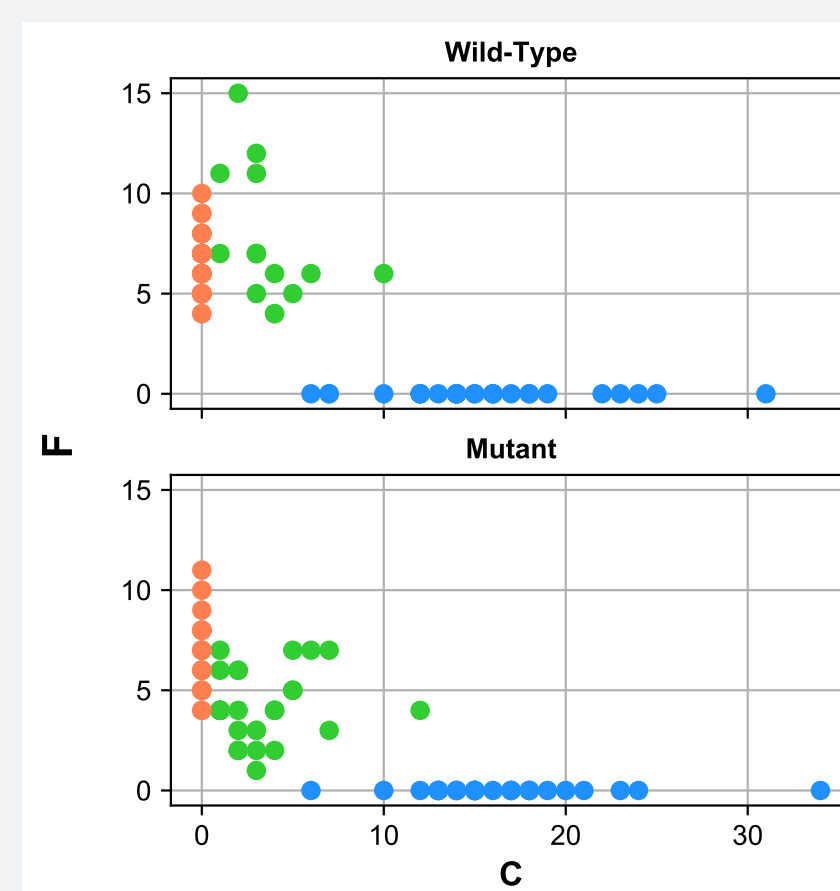
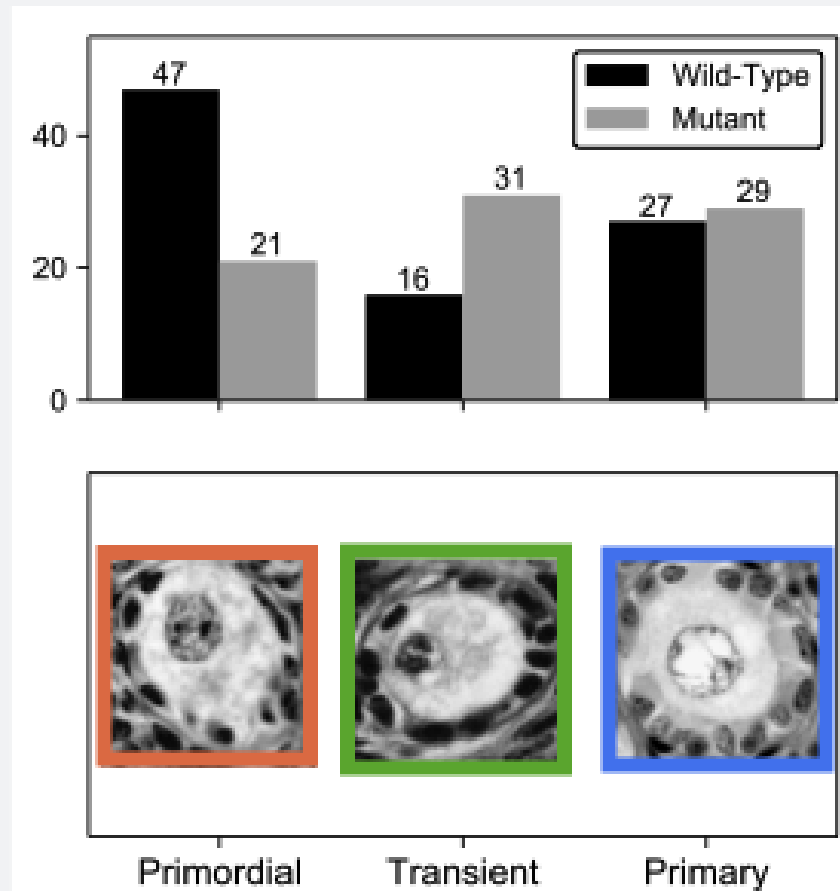
- ◇ Somatic cell population dynamics in a single follicle (either in the activating or basal growing phase)
- ◇ Whole follicle population dynamics during the reproductive lifespan

## CELL DYNAMICS IN AN ACTIVATING FOLLICLE

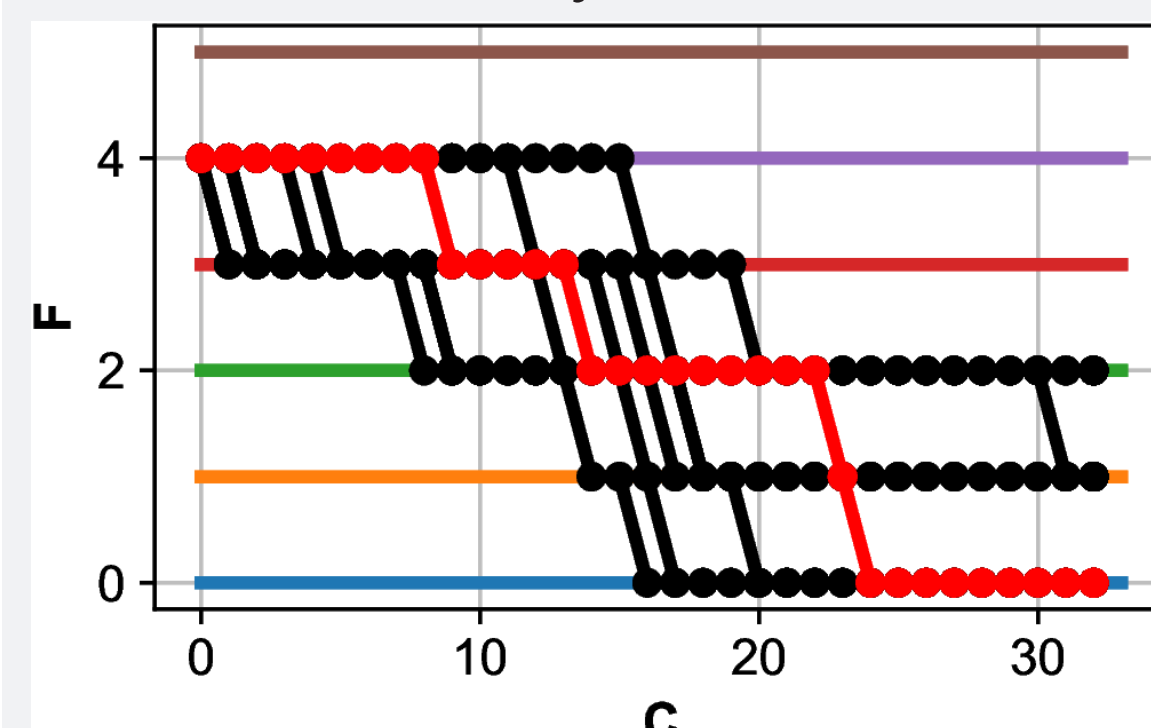
### Somatic cell transition and proliferation during follicle activation

**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

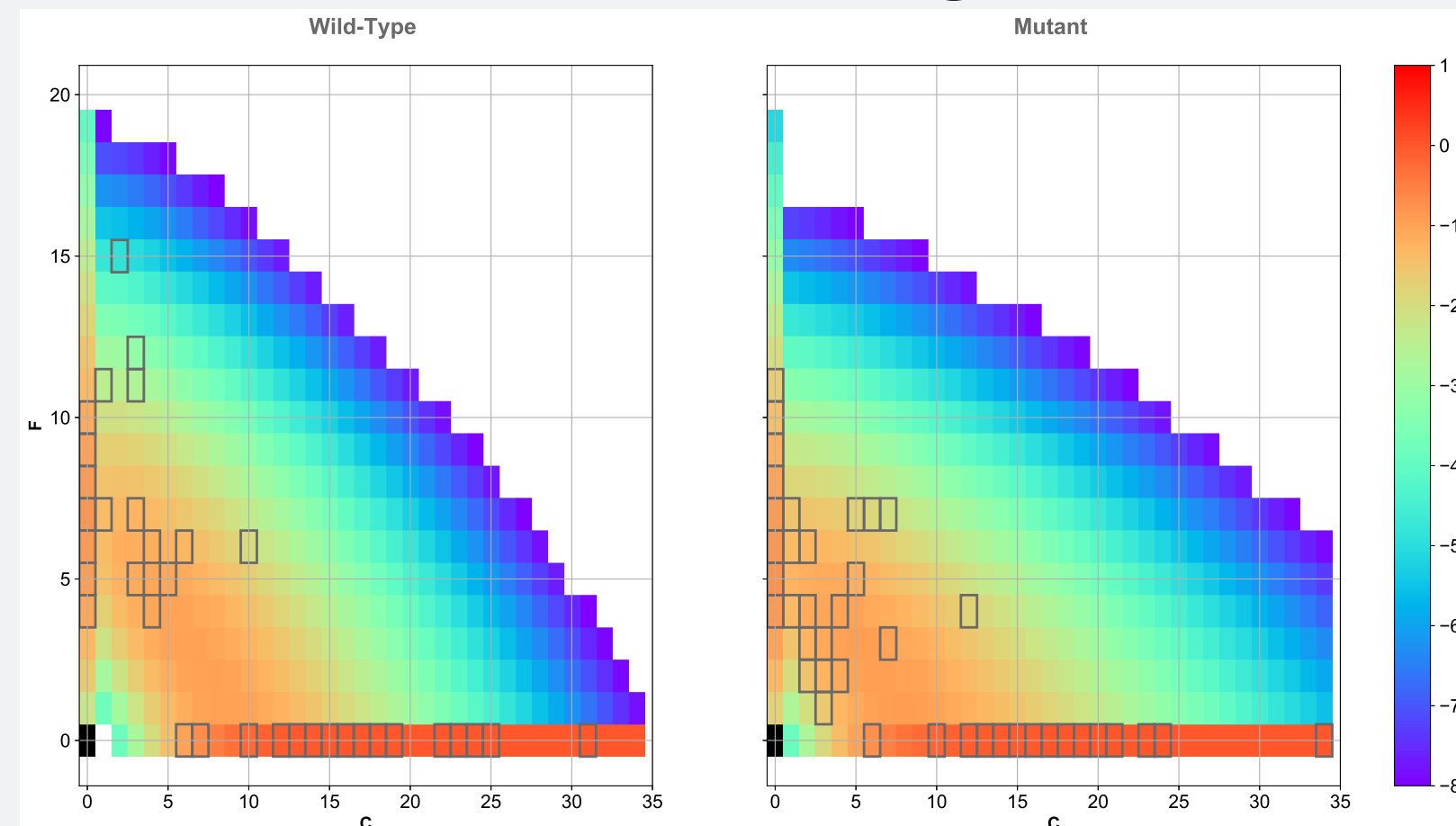
### Cell events

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

### Rate

$\alpha F$   
 $\beta \frac{FC}{F+C}$   
 $\gamma C$   
 $\delta F$

### Data Fitting



**Results:** see [3]

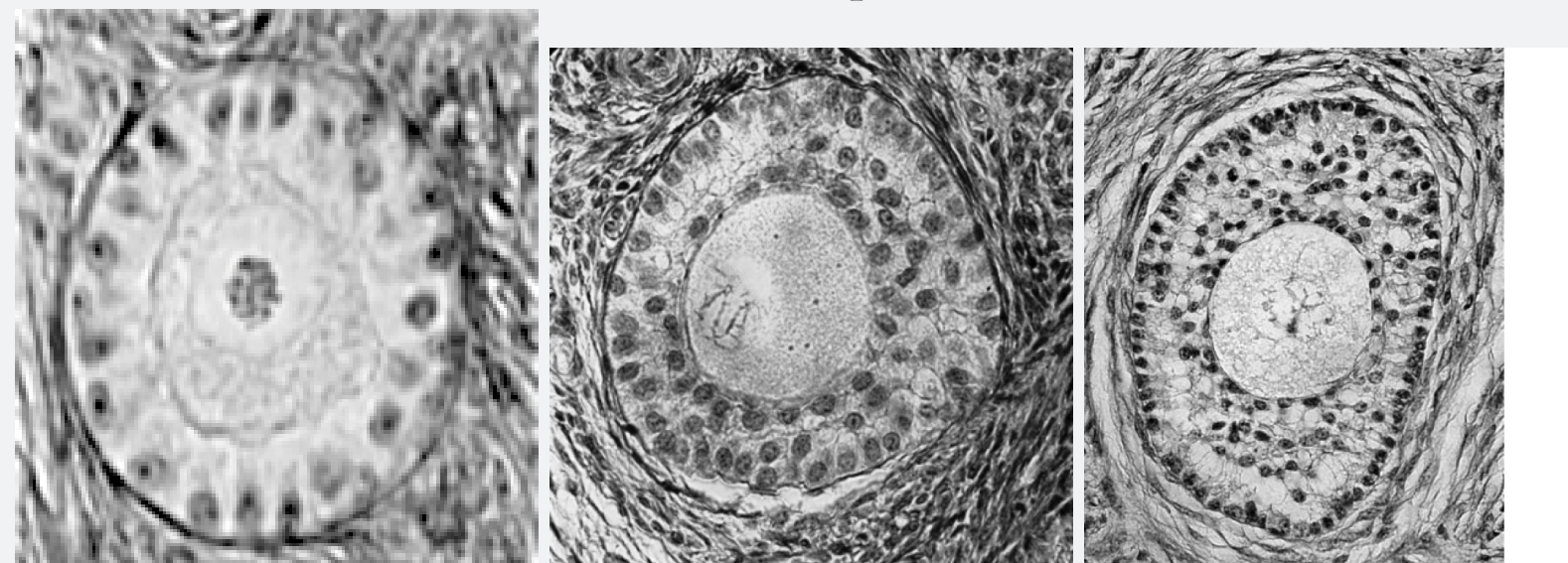
- Clear separation between transition and proliferation in Wild-type.
- Auto-amplification is not mandatory, especially for the Mutant dataset

## CELL DYNAMICS IN A GROWING FOLLICLE

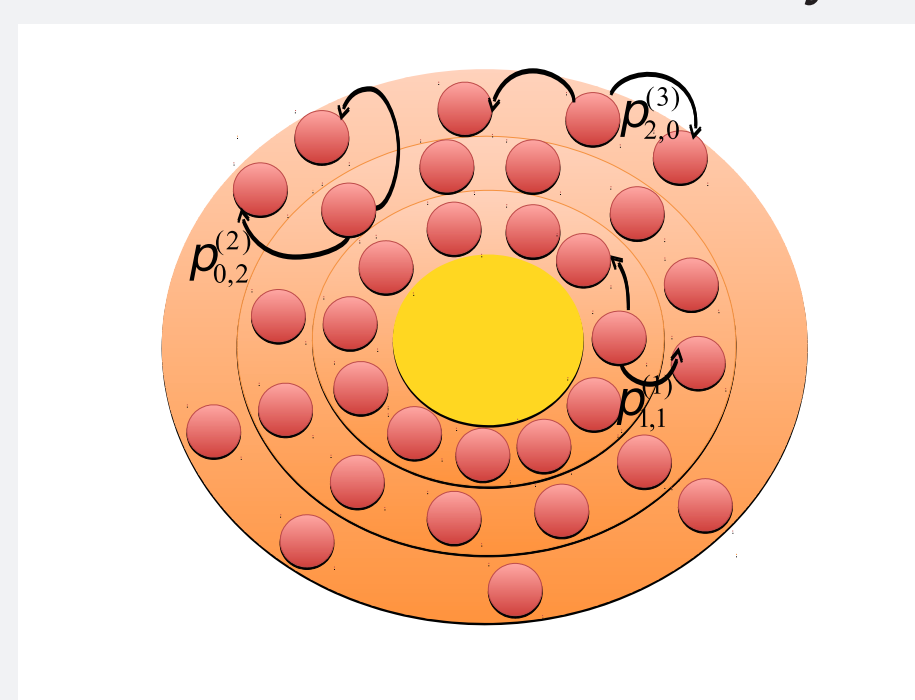
### Somatic cell proliferation during basal follicle growth

**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

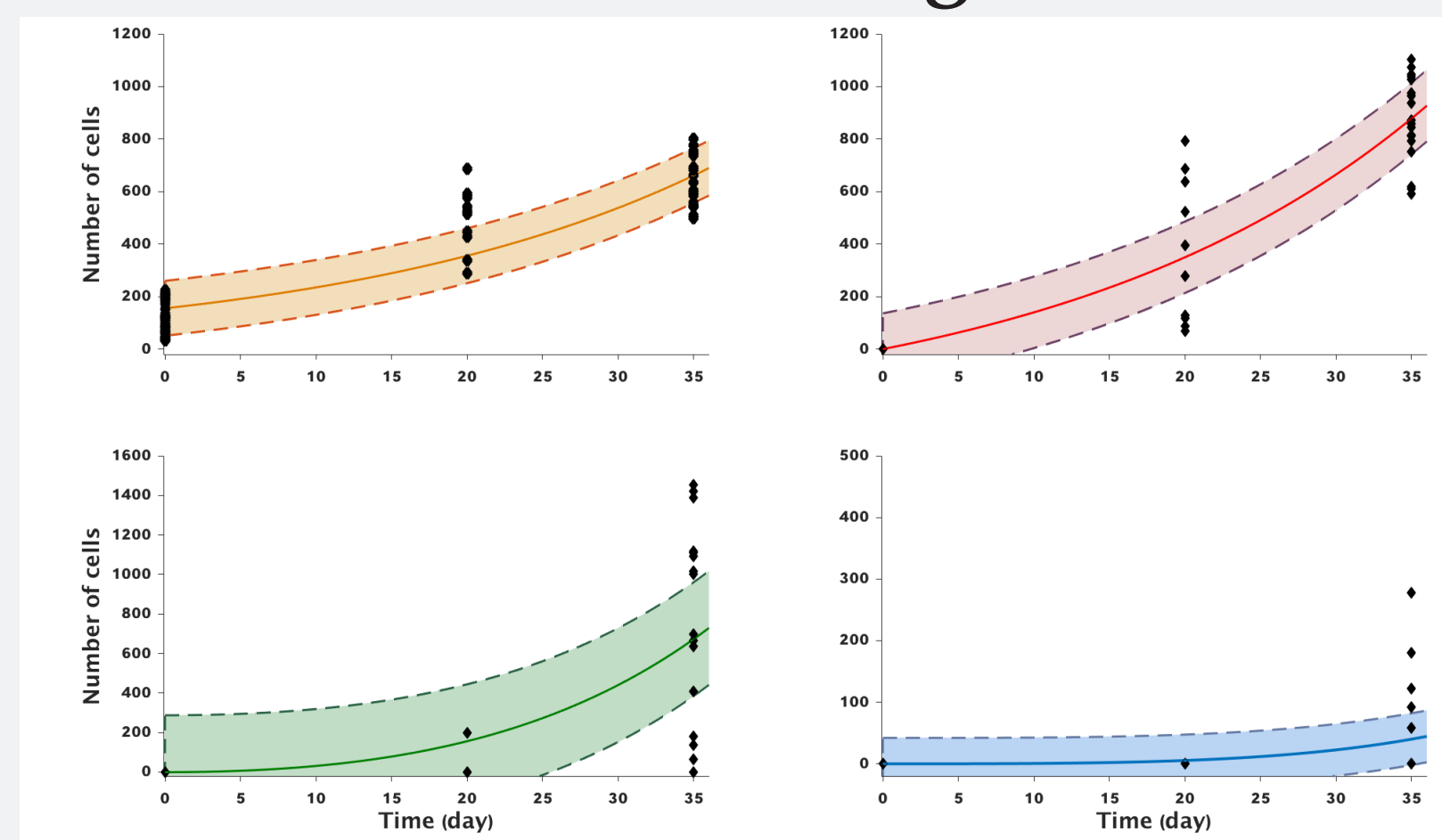
### Cell events

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

### 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]

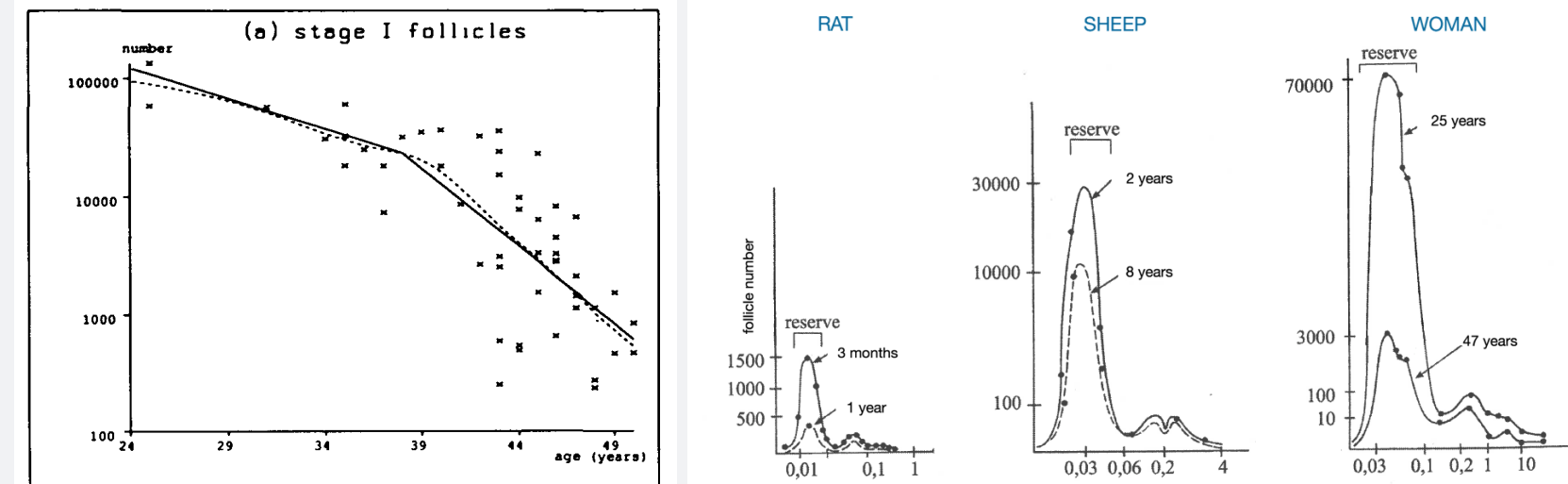
- Data are compatible with
- an exponential growth phase.
  - a layer-dependent growth rate is decreasing with oocyte distance

## 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

$$\dots \xrightarrow{\lambda_{j-1}} F_{j-1} \xrightarrow{\lambda_j} \dots$$

$$\downarrow \mu_j$$

$$\emptyset$$

### Stochastic Nonlinear Model

Follicle activation  
Follicle maturation  
Follicle atresia

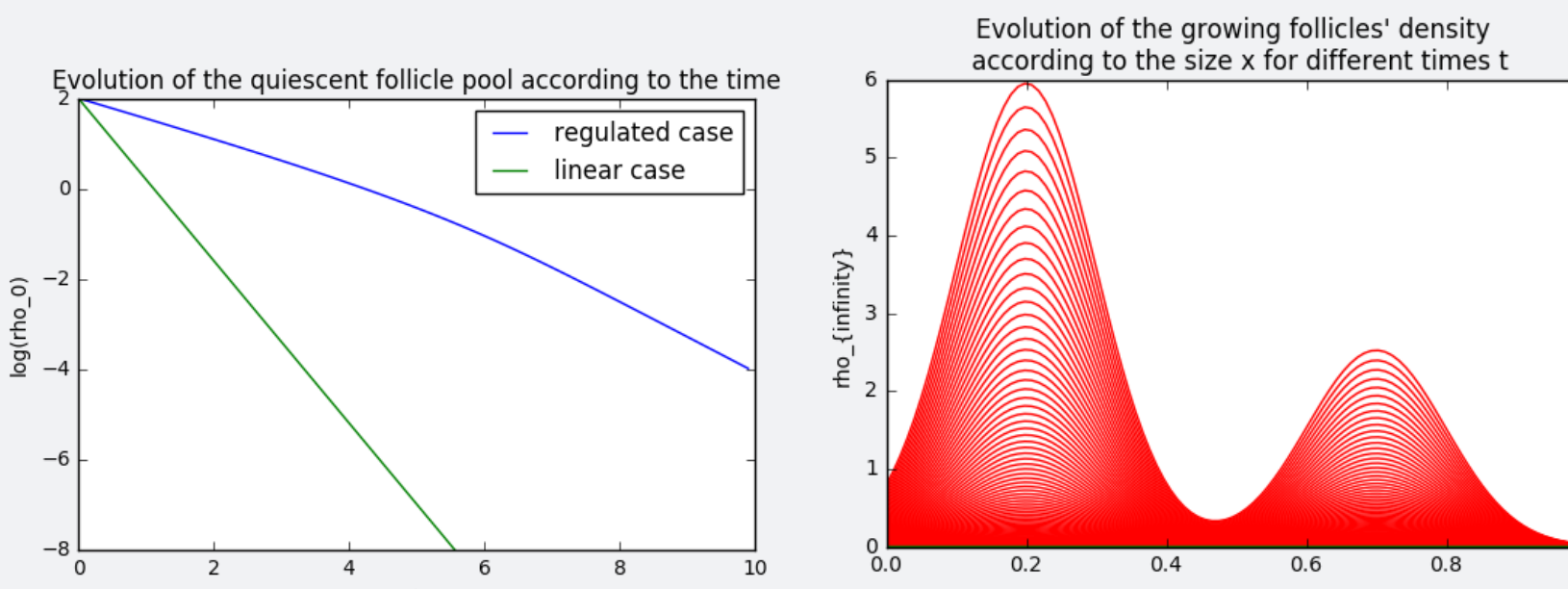
### Follicle events

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

### 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.

## REFERENCES

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- [5] R. Yvinec, P. Crépeux, 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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