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# Stochastic population dynamics applied to ovarian follicles development

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# Stochastic population dynamics applied to ovarian follicles development

Romain Yvinec

Physiologie de la Reproduction et des Comportements  
INRA Tours



# Acknowledgements

- ★ INRIA Saclay : Frédérique Clément, Frédérique Robin
- ★ INRA PRC : Team BIOS, BINGO (D. Monniaux, V. Cadoret, R. Dalbies-Tran)
- ★ INRA LPGP (J. Bobe, V. Thermes)
- ★ INERIS (R. Beaudouin)
- ★ Céline Bonnet (CMAP, X), Kerloum Chahour (U. Côte d'Azur)
- ★ INRA phase (Crédit incitatif)



*Inria*



maîtriser le risque  
pour un développement durable

# Population dynamics and ovarian follicles development

## Ovarian folliculogenesis : complex multiscale dynamics

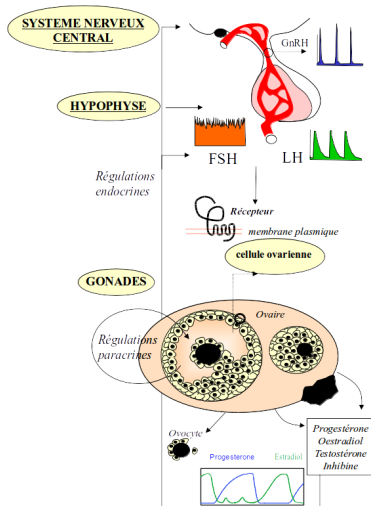
Encoding and decoding **neuro-hormonal signals**

Population dynamics : **gametogenesis**

Intra-cellular level : **signaling networks**



Yvinec et al., *Advances in computational modeling approaches of pituitary gonadotropin signaling*, Expert Opinion on Drug Discovery, 2018.





# Gametogenesis : Ovarian folliculogenesis

- Morphogenesis and maturation of ovarian follicles  
somatic and germ (egg) cells  
 ⇒ Somatic cell division and germ cell growth up to ovulation

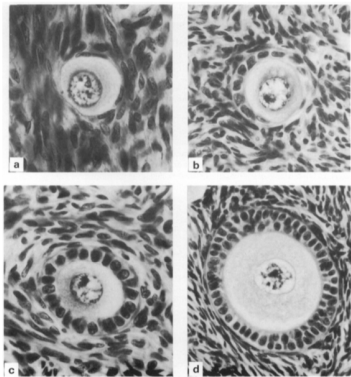
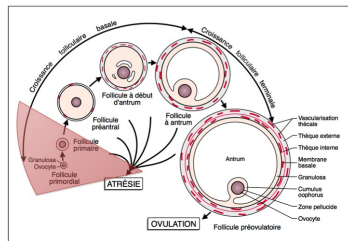


Fig. 1. Illustrations of follicle types: (a) Type B,  $\times 570$ ; (b) Type B/C,  $\times 570$ ; (c) Type C,  $\times 570$ ; (d) Type D,  $\times 410$ .

*Gougeon & Chainy, J. Reprod. Fert. 1987*

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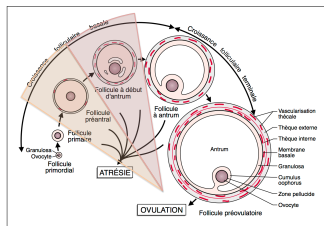
- Morphogenesis and maturation of ovarian follicles  
somatic and germ (egg) cells
- Pool of Quiescent follicles  
static reserve (perinatal in most mammals)  
 Slow activation



Monniaux, *Theriogenology* 2016

# Gametogenesis : Ovarian folliculogenesis

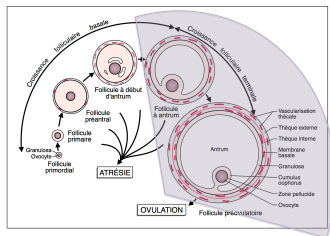
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 Dynamic reserve (starting at birth)  
 Spanning over several ovarian cycles



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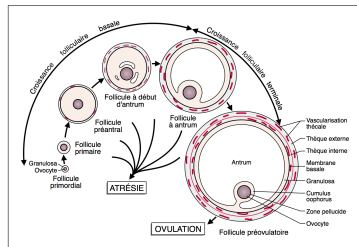
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 Slow activation
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Dynamic reserve (starting at birth)  
 Spanning over several ovarian cycles
- Terminal growth  
 After puberty : ovulation within an ovarian cycle



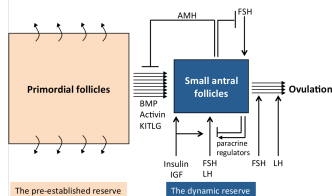
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Slow activation
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Dynamic reserve (starting at birth)  
Spanning over several ovarian cycles
- Terminal growth  
After puberty : ovulation within an ovarian cycle
- Interactions between all follicles via complex (neuro-) hormonal signals



Ovarian reserves of follicles and their regulations



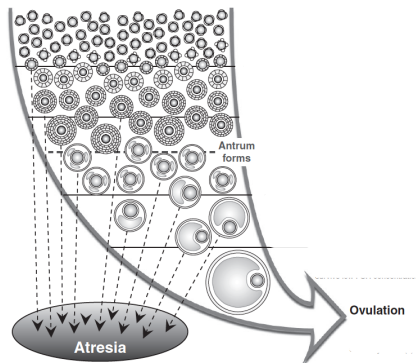
Monniaux, Theriogenology 2016

# Order of magnitude

## Follicle population in women

- Quiescent follicles
 

peri-natal	$\approx 5 \cdot 10^6$
At birth	$\approx 1 \cdot 10^6$
At puberty	$10^4 - 10^6$
At menopause	$< 10^3$
Activation rate	"A few per days"



Scaramuzzi et al., *Reprod.Fert. Dev.* 2011

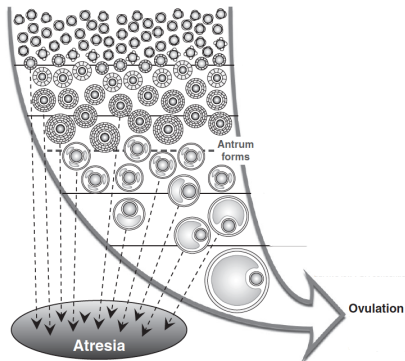
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Maturation time	120 – 180j
Basal follicles	$10^3 - 10^4$
Terminal follicles	$10^2$
Pre-Ovulatory follicles	a few
Atresia	Most of them !



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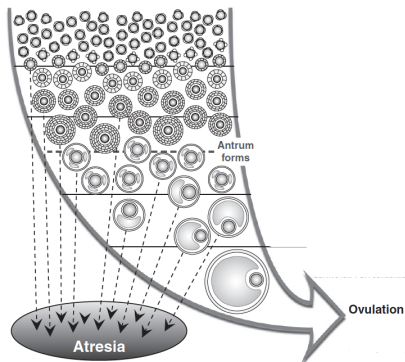
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- > **Only 400 follicles will ever reach the pre-ovulatory stage**



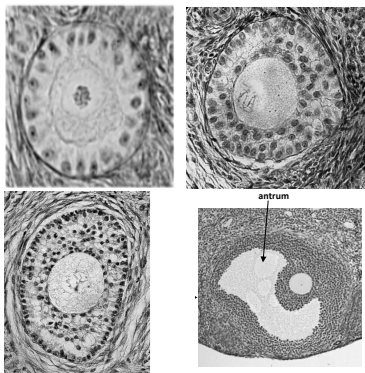
Scaramuzzi et al., *Reprod.Fert. Dev.* 2011



# Order of magnitude

- a single follicle (in women)  
 at different maturation stages
 

ovocyte (egg cell) diam. :	0.01 – 0.1mm
follicle diam.	0.03 – 20mm
somatic cells diam.	≈ 0.01mm
nb somatic cells	$10^2 - 10^7$



*Courtesy of Danielle Monniaux.*

# Scientific and societal issues

## Understanding of a complex process of developmental biology, occurring during the whole lifespan

- Numerous cell types involved, and various interactions
- Many different spatial and temporal scales
- Hormonal feedback (endocrine, paracrine, autocrine)
- Steric and biophysical constraint

## Preserve the reproductive ability

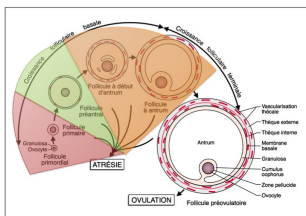
- Iatrogenic or physiological alterations
- Sensibility to environmental conditions
- Biodiversity preservation

## Control of the reproduction function (in humans and animals)

- Biotechnology of reproduction (*in vivo*, *ex vivo*, *in vitro*)
- Clinical, economical and environmental issues

# Modeling ovarian folliculogenesis

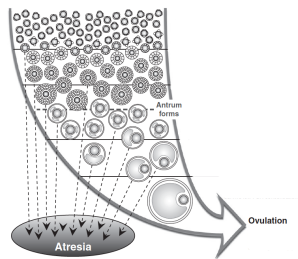
## Growth of a single follicle



Monniaux et al., M/S. 1999

- Thesis of F. Robin, (co-supervised. F. Clément)

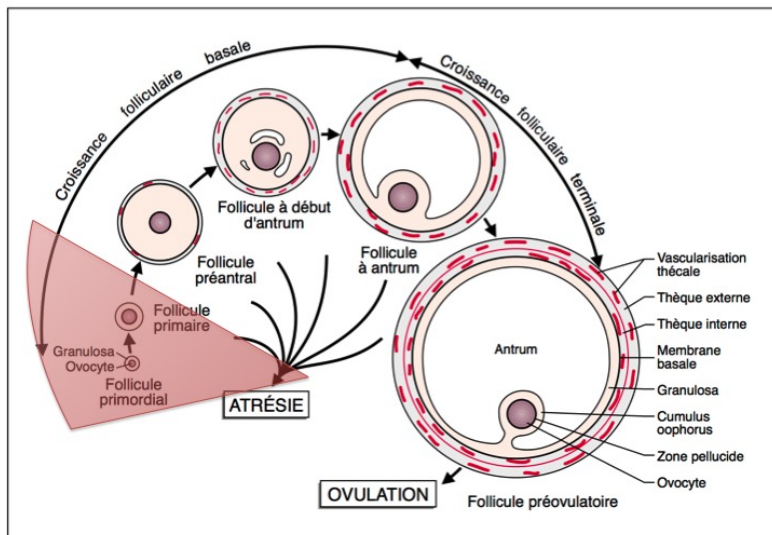
## Populations of follicles



Scaramuzzi et al., *Reprod. Fert. Dev.* 2011

- CEMRACS 2018 (summer school), C. Bonnet, K. Chahour

# Follicle initiation model



# Key features of follicle initiation

- Leave the **quiescent** phase (static reserve)
- A single layer of somatic cells
- Two types of cells :  
Flattened and Cuboid
- Irreversible transition from  
Flattened to Cuboid cells
- The follicle is "activated"  
when all cells have  
transitioned

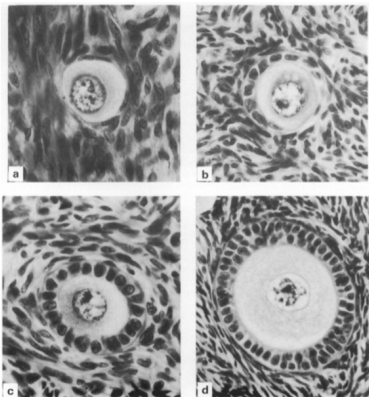


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# Stochastic model (CTMC)

- ↔ Two cell populations :  $F$  (flattened) and  $C$  (cuboid)
- ↔ Small number of cells : stochastic model with ponctual event, with density dependent rates.
- ↔ Initial Condition :  $F = F_0$  (parameter),  $C = 0$  ;  
Condition finale :  $F = 0$ ,  $C(F = 0) \geq F_0$  (output)

Events	Reaction	Intensity function
differentiation	$F \rightarrow C$	$\alpha F + \beta \frac{FC}{F+C}$
proliferation	$C \rightarrow C + C$	$\gamma C$

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- ↔ Retro-action of cuboid cells on the differentiation rate : is it relevant ?

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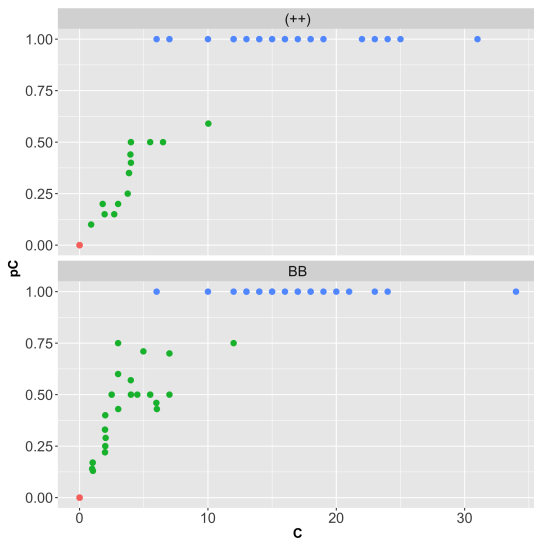
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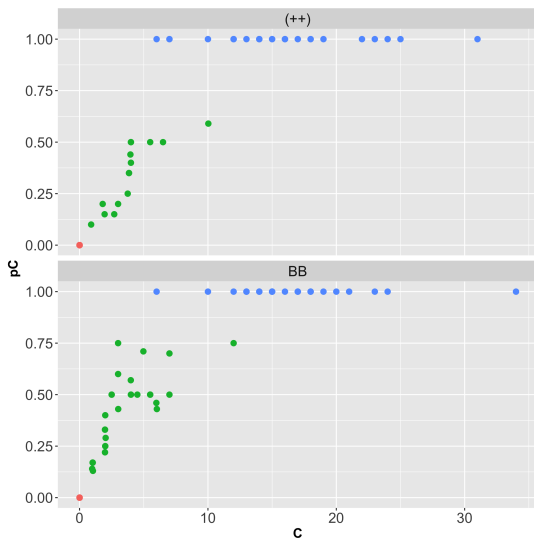
# Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus ( Courtesy of K. McNatty) : WT (++) vs Mutant (BB)

⇒ **Proportion of cuboid cells**  
 $p_C = C / (F + C)$  vs  
**number of cuboid cells C**

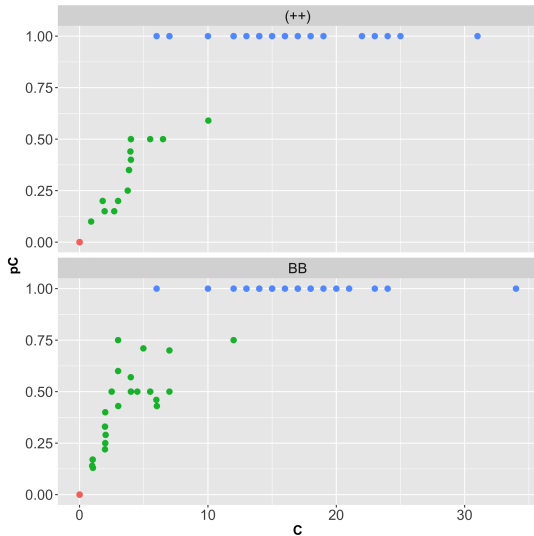
# Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Once activated, follicles have "fast" cell proliferation

⇒ **Are both differentiation et de proliferation process concomitant or successive ?**

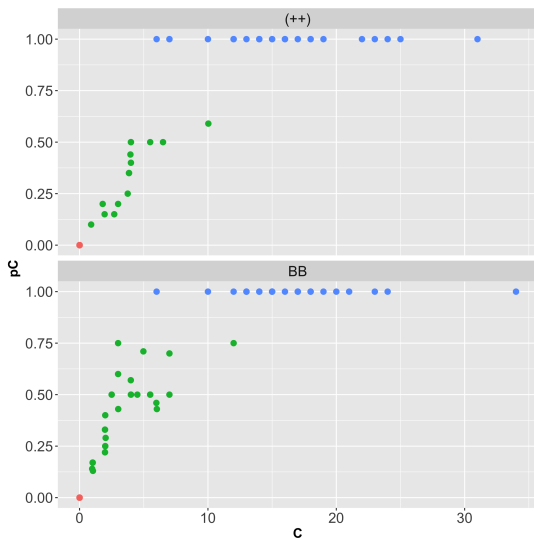
# Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Proportion of cuboid cells seems higher in mutant than WT, for a given number of cuboid cells.

⇒ **Is it coming from a kinetic difference?**

# Ex vivo data (snapshot data)



- Ex vivo data in sheep fetus WT vs BB
- Regulatory mechanism for this process are barely known.

⇒ **Is the transition of cell differentiation abrupt or more progressive ?**

Events	Reaction	Intensity function
differentiation	$F \rightarrow C$	$\alpha F + \beta \frac{FC}{F+C}$
prolifération	$C \rightarrow C + C$	$\gamma C$

- Theoretical study

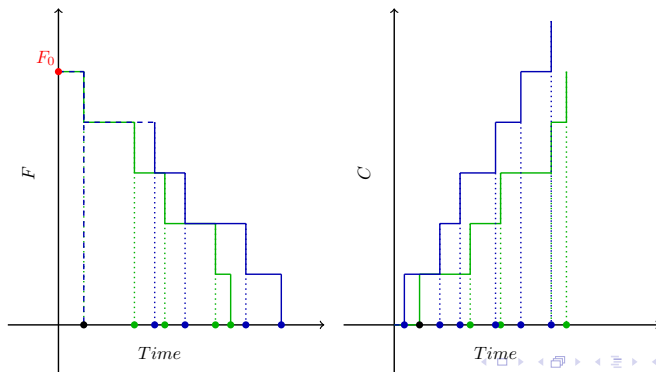
- ⇒ Statistics of the "transition" time  $\tau$  to reach  $F = 0$ .
- ⇒ Variability of final cuboid cells ( $\mathbb{E}[C_\tau] < \infty$  if  $\gamma < \alpha + \beta$ )
- ⇒ Impact of parameters e.g. on qualitative dynamics (progressive vs abrupt)



Robin et al. *Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation*, (submitted) arXiv :1903.01316

Events	Reaction	Intensity function
differentiation	$F \rightarrow C$	$\alpha F + \beta \frac{FC}{F+C}$
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- Theoretical study : stochastic bounds on  $\tau$  and finite state projection algorithm are obtained thanks to coupling arguments with linear processes



Events	Reaction	Intensity function
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- Theoretical study
- Parameter calibration :
  - $\Rightarrow$  Adimensionalize parameter ( $\alpha = 1, \beta \leftarrow \beta/\alpha, \gamma \leftarrow \gamma/\alpha$ )
  - $\Rightarrow$  Reformulation : cuboid cell number increase by 1 at each event  $\rightarrow$  it may be used as a "counter" instead of physical time :  $\mathbb{P}\{\exists t, (F(t), C(t)) = (f, c)\} = \mathbb{P}\{F(c) = f\}$
  - $\Rightarrow$  Likelihood :  $\prod_{i=1}^n \mathbb{P}\{F(c_i) = f_i\}$



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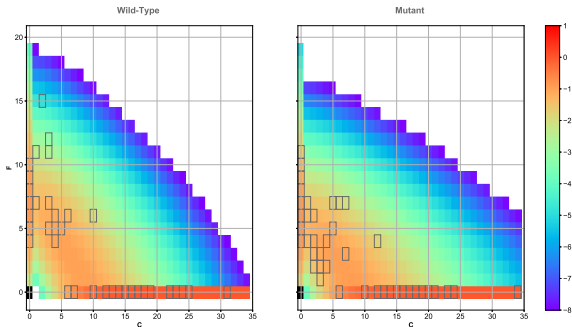
- Theoretical study
- Parameter calibration : lack of identifiability. Either  $\gamma \ll 1$  and  $\beta$  unconstrained, or  $\gamma > 1$  and  $\beta/\gamma \gg 1$



Robin et al. *Stochastic nonlinear model for somatic cell population dynamics during ovarian follicle activation*, (submitted) arXiv :1903.01316

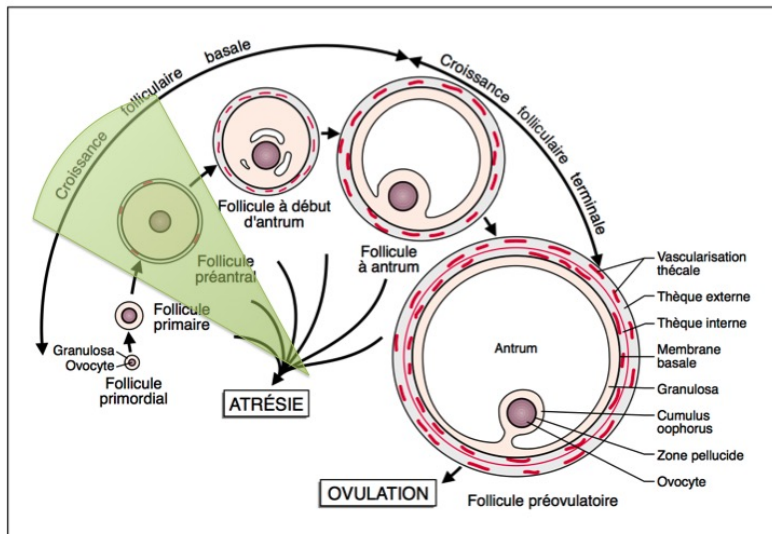


# Agreement to data



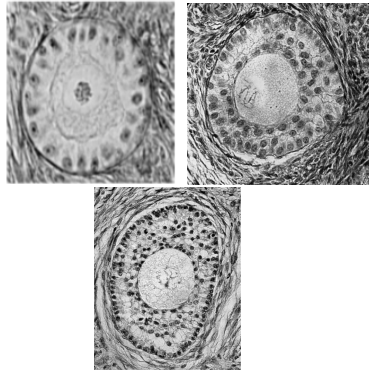
- ⇒ The model can capture both data sets
- ⇒ Lack of identifiability (non-conclusive on retro-action)
- ⇒ First differentiation, then proliferation (slightly more concomitant in mutant case)

# Basal growth model



# Key features of follicle basal growth

- Growth of a small follicle after initiation
- **Spherical Symmetry**
- Spatial structure of somatic cells in concentric **layers**
- Joint dynamic ovocyte **growth**  
Somatic cells **Proliferation**

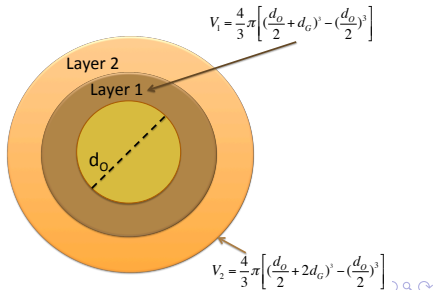
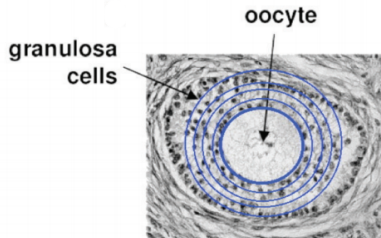


*Courtesy of Danielle Monniaux.*

# Geometric model : spatial compartment in successive layers

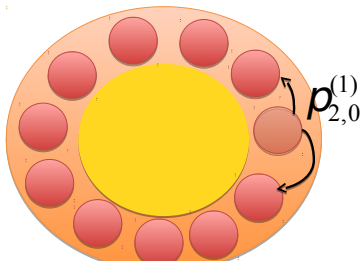
- Spherical somatic cells ( $d_G$ )
- Spherical ovocyte ( $d_o$ )
- Finite number of Layers ( $J$ )
- Spherical Follicle ( $d_f$ )  
 $\hookrightarrow d_f = d_o + 2Jd_G$

Somatic cells are supposed incompressible and migrate to successive layers.



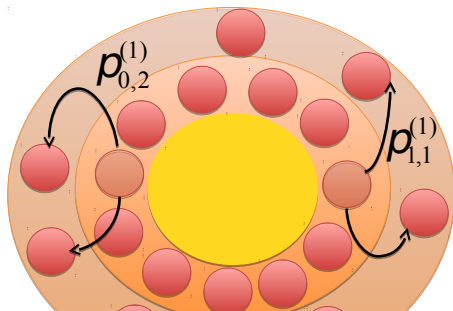
# Dynamical model (Multi-type Bellman-Harris Branching process)

- **Age** and **position** dependent division rate (cell cycle regulated by the ovocyte)
- At division, unidirectional motion **centrifugal**
- Cells are **independant** between each other (Unlimited layer capacity)



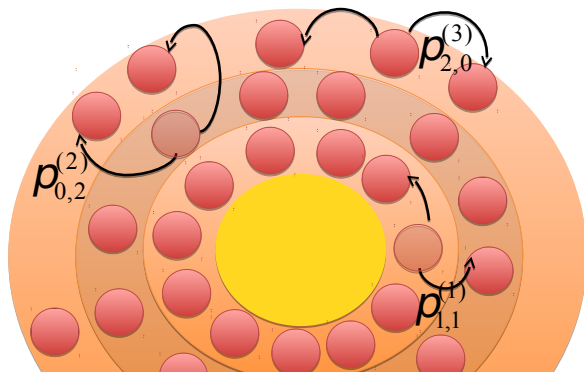
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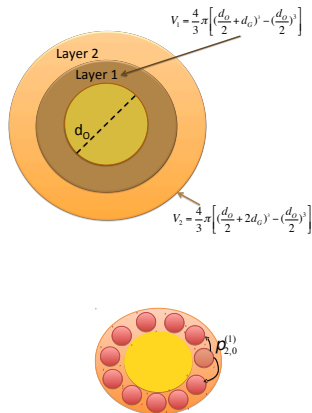


- The geometrical model allows a simple spatial description
- The model is linear and decomposable : exponential growth (under appropriate assumption), with a stable asymptotic spatial profile (with analytical first two moments) : there exists a unique  $\lambda > 0$  such that the process  $Z_t$  verifies

$$\lim_{t \rightarrow \infty} Z_t e^{-\lambda t} = \hat{Z} \quad (\text{in law})$$



Clément et al. *Analysis and Calibration of a Linear Model for Structured Cell Populations with Unidirectional Motion : Application to the Morphogenesis of Ovarian Follicles*, SIAM App. math, 2019





## Data

- We have counting data of somatic cells in snapshot data, morphological data (diameter) and *order of magnitude of transit times between follicle "type"*

	$t = 0$	$t = 20$	$t = 35$
#Data points	34	10	18
Total cell number	$113.89 \pm 57.76$	$885.75 \pm 380.89$	$2241.75 \pm 786.26$
Oocyte diameter ( $\mu m$ )	$49.31 \pm 8.15$	$75.94 \pm 10.89$	$88.08 \pm 7.43$
Follicle diameter ( $\mu m$ )	$71.68 \pm 13.36$	$141.59 \pm 17.11$	$195.36 \pm 23.95$

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⇒ Can we explain proliferation in concentric layers by a simple model of "division-migration"? Or do physical constraint play important role?

## Data

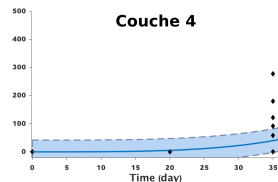
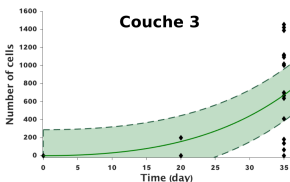
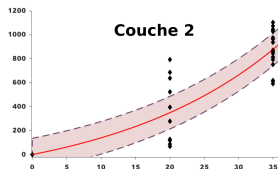
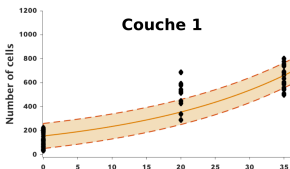
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- ⇒ Can we characterize the growth rate of a follicle and spatial repartition of somatic cells ?
- ⇒ What is the impact of spatial position of a somatic cell on its division rate ?

# Fitting results

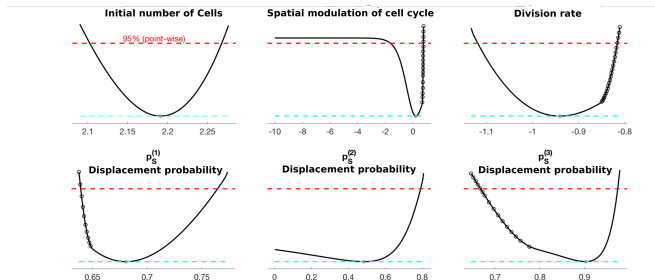
⇒ **Exponential** growth dominated by the first cell layer



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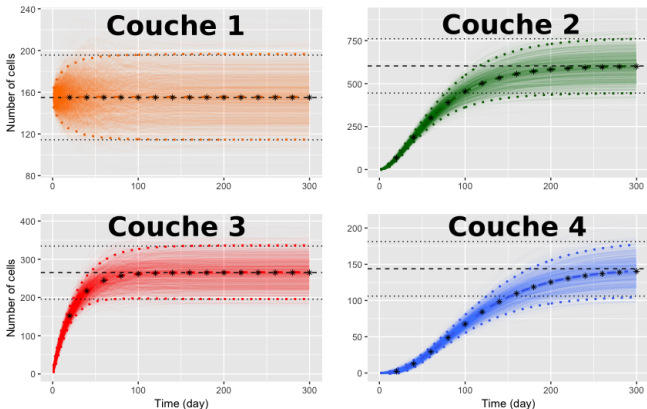
⇒ Parameter identifiability and doubling time quantification ( $\approx 16$  days) : Cell-cycle time ↗ with ovocyte distance



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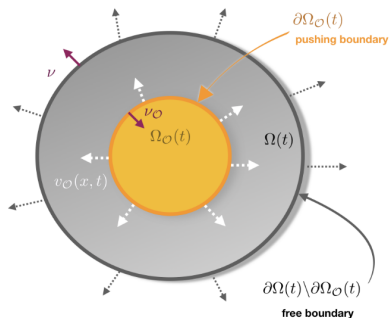
# Fitting results

⇒ Prediction of a stable spatial distribution (not observed in data)



Clément et al. *Analysis and Calibration of a Linear Model for Structured Cell Populations with Unidirectional Motion : Application to the Morphogenesis of Ovarian Follicles*, SIAM App. math, 2019

## More realistic model ?

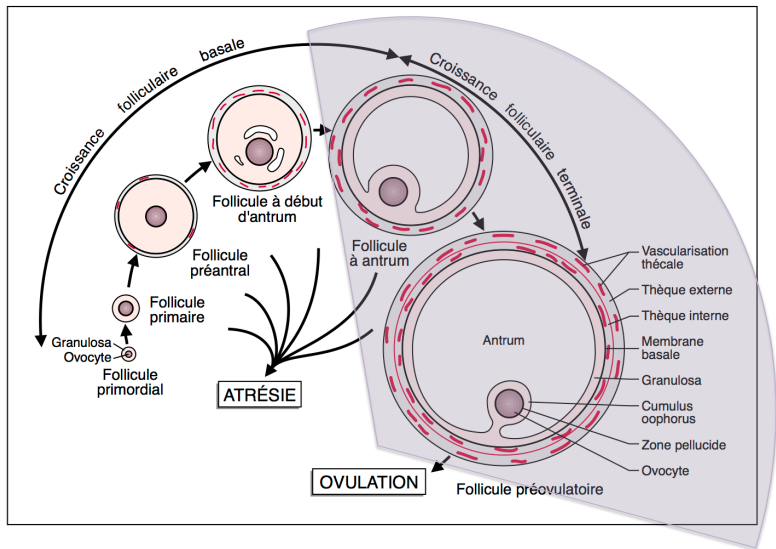


$\frac{\partial u}{\partial t} + \text{div}(\vec{\nabla} u) = b(x)u(t, x)$   
 for  $x \in \Omega(t)$  and with  $\vec{\nabla}$  linked  
 to the negative gradient of the  
 pressure, and the pressure related  
 to the density...

Under locally constant density  
 and spherical geometry, one  
 have :

$$\frac{d}{dt} (r_F(t) \text{vol}(\partial\Omega(t) \setminus \partial\Omega_O(t))) = \gamma \int_{\Omega(t)} b(x) dx + \frac{d}{dt} (r_O(t) \text{vol}(\partial\Omega_O(t)))$$

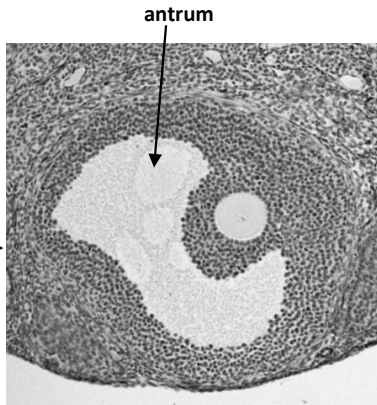
# Terminal growth model (work in progress)





# Terminal growth model (work in progress)

- Lost of spherical symmetry
- Joint Dynamic
  - Liquid-filled cavity formation and growth
  - Proliferation and differential of somatic cells
  - Morphogen gradient
- **Morphodynamic of the Liquid-filled cavity formation ?**
- **Differentiation vs proliferation : which regulation ?**
- **Role of the Liquid-filled cavity ?**



*Tertiary ( antral) follicle*

# Antrum growth model

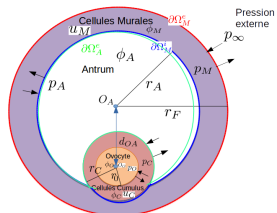
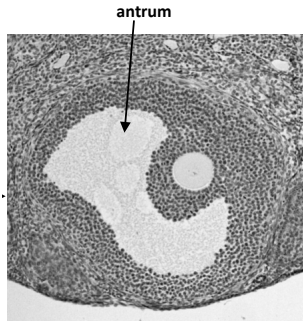
- Lost of spherical symmetry
- Joint Dynamic
  - Liquid-filled cavity formation and growth
  - Proliferation and differential of somatic cells
  - Morphogen gradient

⇒ "Advection-Diffusion-Reaction"  
PDE.

$$\begin{aligned} \frac{\partial \phi_A}{\partial t} + D\Delta\phi_A &= 0, x \in \Omega_A(t), \\ \frac{\partial u_M}{\partial t} + \operatorname{div}(\vec{v}_M u_M) &= R_M(u_M), x \in \Omega_M(t), \\ \frac{\partial u_C}{\partial t} + \operatorname{div}(\vec{v}_C u_C) &= R_C(u_C), x \in \Omega_C(t), \end{aligned}$$

+ Boundary conditions and constitutive laws

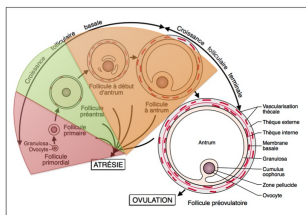
work in progress...



Tertiary ( antral) follicle

# Modeling ovarian folliculogenesis

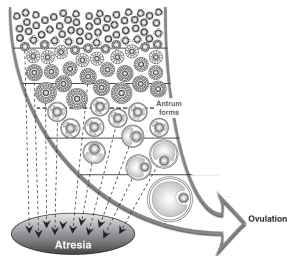
## Growth of a single follicle



Monniaux et al., M/S. 1999

- Thesis of F. Robin, (co-supervised. F. Clément)

## Populations of follicles

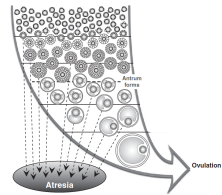


Scaramuzzi et al., *Reprod. Fert. Dev.* 2011

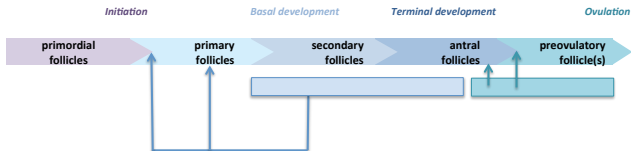
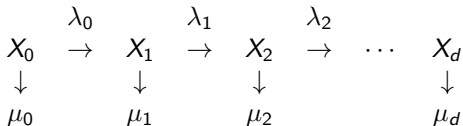
- CEMRACS 2018 (summer school), C. Bonnet, K. Cha-hour

# Modeling ovarian folliculogenesis on a lifespan timescale

- Compartment based model (CTMC)
- Non-linear interaction between follicles populations (endocrine and paracrine) via  $\lambda$ 's and  $\mu$ 's.
- Several time scales (slow initiation, fast growth)

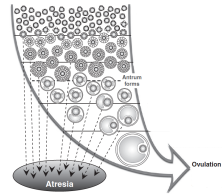


Scaramuzzi et al., *Reprod. Fert. Dev.* 2011



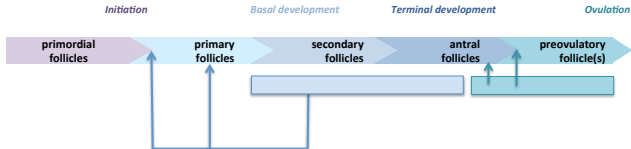
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Scaramuzzi et al., *Reprod. Fert. Dev.* 2011

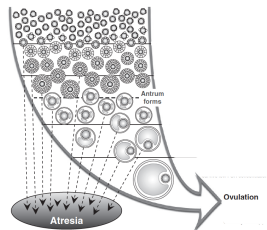
$$\begin{array}{ccccccc}
 & \varepsilon \lambda_0 & & \lambda_1 & & \lambda_2 & & \dots & & \lambda_d \\
 \frac{1}{\varepsilon} X_0 & \rightarrow & X_1 & \rightarrow & X_2 & \rightarrow & \dots & \rightarrow & X_d \\
 \downarrow & & \downarrow & & \downarrow & & & & \downarrow \\
 \varepsilon \mu_0 & & \mu_1 & & \mu_2 & & & & \mu_d
 \end{array}$$



# Modeling ovarian folliculogenesis on a lifespan timescale

⇒ When  $\varepsilon \rightarrow 0$  : (quasi-) stable distribution into maturity stages, driven by a slow deterministic decay of the static reserve (quiescent follicles)

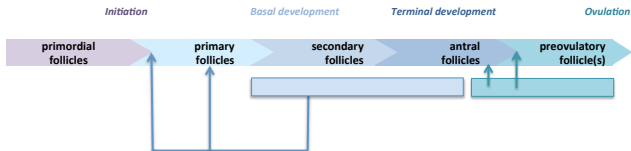
$$\begin{array}{ccccccc}
 & \varepsilon \lambda_0 & & \lambda_1 & & \lambda_2 & & \dots & & \lambda_d \\
 \frac{1}{\varepsilon} X_0 & \rightarrow & X_1 & \rightarrow & X_2 & \rightarrow & \dots & \rightarrow & X_d \\
 \downarrow & & \downarrow & & \downarrow & & & & \downarrow \\
 \varepsilon \mu_0 & & \mu_1 & & \mu_2 & & & & \mu_d
 \end{array}$$



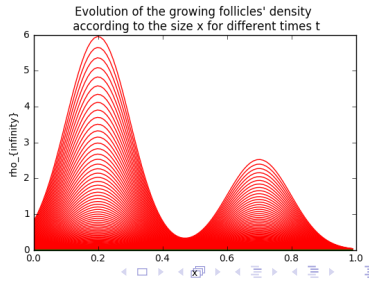
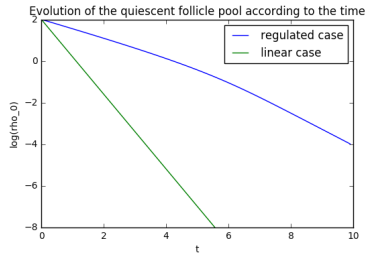
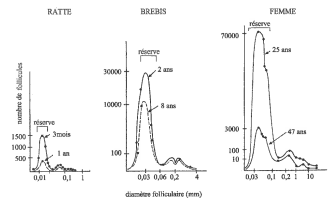
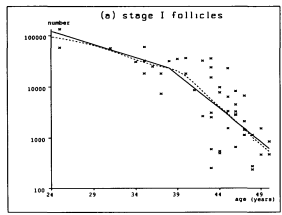
Scaramuzzi et al., *Reprod. Fert. Dev.* 2011



Bonnet, et al. *Multiscale population dynamics in reproductive biology : singular perturbation reduction in deterministic and stochastic models* preprint version of a proceeding of CEMRACS 2018 : arXiv :1903.08555



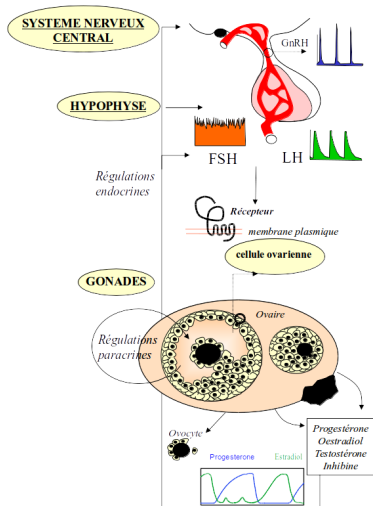
# Qualitative agreement with data



# Summary

## Population dynamics in ovarian folliculogenesis

- Somatic cells differentiation and proliferation during follicle initiation
- Somatic cells proliferation and migration during basal follicle growth
- Multiscale nonlinear dynamics shape the follicle population distribution into different maturity stages.



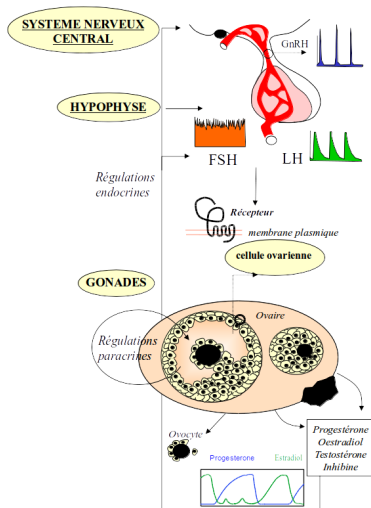


# Summary

## Population dynamics in ovarian folliculogenesis

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**Thank you for your attention !**



# Role of the Liquid-filled cavity ?

Species	Oocyte radius ( $\mu\text{m}$ )	Follicle radius when antrum first appears ( $\mu\text{m}$ )	Reference	Estimated voidage
Rat	32	100	Parkes (1931)	0.09
Mouse	35	100	Parkes (1931)	0.09
Horse	36	110	Dranacourt (1979)	0.14
Pig	38	200	Parkes (1931)	0.46
Human	40	200	McNatty (1978) and Peters & McNatty (1980)	0.46
Baboon	42	155	Parkes (1931)	0.33
Rabbit	42	125	Parkes (1931)	0.20
Sheep	47	150	Turnbull et al. (1977)	0.30
Buffalo	53	300	Kumar et al. (1997)	0.65
Ferret	54	115	Parkes (1931)	0.13
Range	32-54	100-300		0.09-0.65

Redding et al, *Mathematical modelling of oxygen transport-limited follicle growth*, Reproduction, 2007

- Antrum formation is driven by oxygen (and nutriment) accessibility of the oocyte
- Antrum size is driven by the need to increase the number of somatic cells (without increasing the thickness of the somatic layers) to supply estrogen production in agreement with body mass

**Table 1** The diameter of the mature follicle and characteristic weight in different mammalian species.

Follicle (mm)	Weight (kg)	Species	Ref.
0.42	0.03	Mouse	Griffin et al. (2006)
0.55	0.2-0.25	Albino rat	Sangha and Guraya (1989)
0.64	0.2	Hamster	Griffin et al. (2006)
2.8	2.7	Rabbit	Osteen and Mills (1980)
4	3	Cat	Izumi et al. (2012)
6	9-10	Beagle (dog)	Reynaud et al. (2009)
6	23	Sheep	Aurich(2011)
7.5	35	Serrana goat	Simões et al. (2006)
8	150	Gilt	Chiou et al. (2004)
7-12	48-84	Alpaca	Bravo et al. (1991)
7-12	130-200	Llama	Bravo et al. (1991)
16	250-800	Water buffalo	Taneja et al. (1996)
20	700	Cow	Evans (2003)
20	2700	Elephant	Lueders et al. (2011)
23	60	Human	Evans (2003)
20-25	800	Summatran rhinoceros	Hermes et al. (2007)
27-38	300-550	Camel dromedarius	Manjunatha et al. (2012)
30-34	1800	White rhinoceros	Hermes et al. (2007)
50	1000	Black rhinoceros	Hermes et al. (2007)
55	450	Horse	Aurich (2011)
120	1900	Indian rhinoceros	Hermes et al. (2007)

Bächler et al, *Species-specific differences in follicular antral sizes result from diffusion-based limitations on the thickness of the granulosa cell layer*, MHR, 2014